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The effects of designation and volume of neonatal care on mortality and morbidity outcomes of very preterm infants in England: Retrospective population-based cohort study

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ABSTRACT

Objective: To examine the effects of designation and volume of neonatal care at the hospital of birth on mortality and morbidity outcomes in very preterm infants in a managed clinical network setting.

Design: A retrospective, population based analysis of operational clinical data using adjusted logistic regression and instrumental variables analyses.

Setting: 165 National Health Service neonatal units in England contributing data to the National Neonatal Research Database at the Neonatal Data Analysis Unit and participating in the Neonatal Economic, Staffing, and Clinical Outcomes Project.

Participants: 20,554 infants born at <33 weeks completed gestation (17,995 born at 27-32 weeks; 2,559 born at <27 weeks), admitted to neonatal care and either discharged or died, over the period 1st January 2009 to 31st December 2011.

Intervention: Tertiary designation or high volume neonatal care at the hospital of birth.

Outcomes: Neonatal mortality, any in-hospital mortality, surgery for necrotising enterocolitis, surgery for retinopathy of prematurity, bronchopulmonary dysplasia and postmenstrual age at discharge.

Results: Infants born at <33 weeks gestation and admitted to a high volume neonatal unit at the hospital of birth were at reduced odds of neonatal mortality (IV regression odds ratio [OR]: 0.70, 95% confidence interval [CI]: 0.53-0.92) and any in-hospital mortality (OR: 0.68, 95% CI: 0.54-0.85). The effect of volume on any in-hospital mortality was most acute amongst infants born at <27 weeks gestation (OR: 0.51, 95% CI: 0.33-0.79). A negative association between tertiary-level unit

designation and mortality was also observed with adjusted logistic regression for infant born at <27 weeks gestation.

Conclusions: High volume neonatal care provided at the hospital of birth may protect against in-hospital mortality in very preterm infants. Future developments of neonatal services should promote delivery of very preterm infants at hospitals with high volume neonatal units.

ARTICLE SUMMARY

Strengths and limitations of this study

- A national dataset consisting of the electronic patient records of a large majority of admissions to neonatal specialist care in England
- The analysis takes into account both observed and unobserved confounding
- A weakness is that the analysis is unable to disentangle the effects of the neonatal unit at the place of birth from subsequent transfers to other neonatal units

INTRODUCTION

Intense debate has revolved around the optimal organisation of neonatal critical care services. Numerous studies have suggested that the intensity and volume of neonatal care at the hospital of birth is negatively correlated with adverse clinical outcomes, including mortality.[1–11] This has contributed to calls for centralisation of neonatal services and the closure of smaller neonatal units.[2,11,12]

Following a review by the Department of Health in 2003, perinatal centres in England were reorganised into managed clinical networks (MCN).[13] MCNs provide some of the benefits of centralisation, but also strive to maintain equity and ease of access to services by keeping lower care level and lower volume neonatal units open, with provision for transfer to higher care level or higher volume units, if required.[13] Particular emphasis is placed on the importance of transferring women at risk of extremely preterm labour to tertiary centres before delivery. Consequently, most networks aim to transfer women at high risk of delivery at <27 weeks of gestation. We have previously shown that, since the formation of MCNs, both the proportion of low gestational age infants born in hospitals with higher designation neonatal units and their transfer rate between hospitals has increased significantly; however, it remains unclear what effect this has had on clinical outcomes.[14]

Studies that have examined the effects of neonatal unit designation or volume of neonatal care provided at the hospital of birth have shown that low designation level or volume is associated with increased rates of mortality,[1–10] decreased infection rate,[7] increased severe periventricular haemorrhage,[11] and increased bronchopulmonary dysplasia.[7] However, these studies were almost exclusively conducted in the United States where there is greater variability in neonatal unit volume—the highest volume units in the US are typically much larger than equivalent units in England—and there is no formal arrangements for MCNs. Results from similar studies using data from the UK are limited and based on data from 1998-9, prior to the formation of MCNs.[15,16] We are not aware of any studies that

have examined infant outcomes for neonatal specialist services in MCNs in relation to unit designation or volume. In addition, organisation of neonatal care differs between countries potentially affecting the generalisability of results from these systems; for example, in Germany neonatal services are markedly deregionalized whereas in Finland and Portugal there is a high degree of regionalization.[17]

Our aim in this study was to examine the effects of designation and volume of neonatal care provided at the hospital of birth on mortality and morbidity outcomes. We assess whether organisational factors remain determinants of clinical outcomes despite the goals of neonatal reorganisation that sought to ensure that vulnerable infants are not disadvantaged by their place of birth.

METHODS

Data source and study population

For the purpose of this empirical investigation, we extracted data from the National Neonatal Research Database (NNRD) for neonatal units participating the Neonatal Economic, Staffing, and Clinical Outcomes Project (NESCOP). The NNRD is held by the Neonatal Data Analysis Unit (NDAU), Imperial College, London, and was created from patient-level electronic records of all infants admitted to 168 of 173 neonatal units in England. Approval for data collection was obtained from the national research ethics service (reference REC 10/H0803/151) as well as the Caldicott Guardians of each NHS Trust. NESCOP included 165 centres providing perinatal care.; On behalf of NESCOP, the MRC EPICure studies carried out the Unit Profile Survey (UPS) during 2011, comprising a survey of English hospitals that provided onsite obstetric and neonatal services. We extracted records from the NNRD of all infants born in hospital at ≤32^{+6} weeks^{+days} gestation, admitted over the period 1st January 2009 to 31st December 2011 born at these units and who were discharged or died over the same period. We excluded infants who only received transitional care. Gestational age was determined by ultrasound scan.

Outcomes

We derived the following outcomes from the extracted data for use in the analyses: 28-day (neonatal) mortality, any in-hospital mortality, treatment for necrotising enterocolitis (NEC), treatment for retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD). We defined BPD as the requirement of supplementary oxygen for at least 28 days and at 36 weeks postmenstrual age (PMA).[18] We also examined PMA at discharge as a marker of length of stay; this was defined as the gestational age at birth plus the length of stay at final discharge from any neonatal unit or death. We defined the outcome to be one if the PMA at discharge was greater than 40 weeks and zero otherwise.

Covariates

To determine appropriate covariates, we reviewed previous prediction models for very preterm infants[19] and selected variables that a) were significant predictors of adverse sequelae, b) were available in our dataset and of high quality, and c) not confounded by the provision of neonatal care. The variables we included were: gestational age at birth, gestational age squared, birth weight z-score (birth weight standardised by gestational age week), and the following indicators: whether the mother received a full or partial course of antenatal steroids, sex, infant year of birth, and whether or not the mother came from an area within the lowest decile of the Index of Multiple Deprivation 2007 score.[20]

Statistical methods

We conducted two separate sets of analyses based on whether or not infants were admitted to a neonatal unit at the hospital of birth designated as: (i) a tertiary centre,[20] or (ii) high volume. For the latter, we defined volume according to the annual number of care days at any level of care provided to very preterm infants (≤32^{+6} weeks gestation). A 'high volume' unit was defined as one whose volume was in the top quartile of all neonatal units in the sample. ‘High volume’ was determined by quartile rather than an absolute care day threshold to facilitate comparison with other measures of volume in the sensitivity analyses.

A previous study that examined organisational characteristics of neonatal units also categorised volume using quartiles.[17] Dichotomising by upper quartile divided the infants between high and low volume units in approximately the same proportion as between tertiary and non-tertiary level units. To aid comparison with other studies, in particular from the US, and as a robustness check, `high volume' was also defined as 100 very low birth-weight (VLBW; <1,500g) admissions of infants born in the same hospital per annum.

We first conducted an unadjusted comparison of clinical characteristics and outcomes of infants by unit characteristics. Secondly, we estimated an adjusted model, and thirdly, we conducted an adjusted comparison using an instrumental variables methodology to account for unobserved confounding. In the absence of a randomised control trial, instrumental variables methodology acts as an *ex post* randomisation and enables us to estimate the 'causal effects' of designation and volume of neonatal care provided at the hospital of birth. The methodology involves the use of a variable, called an "instrument", which, in this context, needs to fulfil two criteria: 1) it should be strongly correlated with the characteristics of the neonatal unit at the hospital of birth; and 2) it should be uncorrelated with the outcomes of interest conditional on observed covariates and therefore uncorrelated with unobserved confounders.

For the instruments, we used indicators for the designated level of care of the nearest neonatal unit to the mother's residence, an indicator for whether it had surgical facilities, an indicator for whether it was high volume, the distance to the nearest neonatal unit, and the interactions of either the level of care indicators or high volume indicator with distance, giving nine instruments in total. Straight line distance was calculated from the population weighted centre of the mother's Lower Super Output Area to each hospital.[22]

These instrumental variables fulfil condition (1) if infants are more likely to be born in the hospital closest to the mother's residence. They will also fulfil condition (2) if the location of the mother's residence is uncorrelated with an infant's unobserved clinical risk. We tested for

a difference in observed characteristics by level and volume of the nearest neonatal unit. However, tertiary level and high volume units are more likely to be in urban areas that are socioeconomically deprived so we may expect to see more preterm and low birth weight infants being born in these areas.[23] We therefore also controlled for local deprivation when testing for a difference in means by nearest neonatal unit characteristics by estimating a linear regression of the observed variable of interest on the nearest neonatal unit characteristic and deprivation indicator and using an F-test to test the coefficient on the nearest neonatal unit characteristic variable.

As the outcomes are all binary logistic regression was used. In order to employ instrumental variables estimation in this framework, two stage residual inclusion (2SRI) was used.[24] The 2SRI method is explained in online Appendix A. The standard errors were adjusted for clustering within units.

Our baseline analyses examined infants born at ≤32^{+6} weeks gestation. We then conducted analyses on subsets of infants born at ≤26^{+6} weeks gestation or at 27^{+0}-32^{+6} weeks gestation; ≤26^{+6} weeks gestation is the cut-off used by perinatal networks for prioritising inter-unit transfers. 'Statistical significance', where discussed, refers to a 5% significance level in all cases.

Missing data and sensitivity analyses

Infants with missing outcomes data were excluded from the analyses, whilst those with missing covariate data were assigned a zero in the case of binary indicators. There were no infants with missing continuous covariates. We excluded all infants with any missing data as a further sensitivity analysis.

Separate sensitivity analyses, using our preferred method of instrumental variables logistic regression, also explored the effects of: (i) including unit random effects in the statistical models; (ii) removing infants who died from analyses of the morbidity and PMA at discharge outcomes and defining a new outcome of any in-hospital mortality and/or BPD; (iii) redefining

high volume as the top 25% of units in terms of intensive care days provided to ≤32^{+6} gestational week infants; (iv) redefining high volume as the top 25% of units in terms of number of ≤32^{+6} gestational week infants cared for; and (v) redefining high volume as at least 100 VLBW infants born in and admitted to the neonatal unit in the hospital per annum.

All analyses were carried out with R 2.14.2 and Stata 11.

RESULTS

In total, data for 20,554 infants born at ≤32^{+6} weeks gestation over the study period and admitted to a neonatal unit at the hospital of birth were extracted from the NNRD, 2,559 of whom were born at ≤26^{+6} weeks gestation. Table 1 provides descriptive statistics of the samples analysed.

In the sample, 9,466 (46.1%) infants were born in hospitals with a tertiary level neonatal unit and 9,541 (46.4%) were born in hospitals with a high volume neonatal unit. The cut-off for high volume was approximately 3,480 annual care days for infants born at ≤32^{+6} weeks gestation in each hospital. The total sample of 20,554 infants were born in 165 different hospitals, 44 (26.7%) of which had level three neonatal units, 81 (49.0%) level two neonatal units, and 39 (23.6%) level one neonatal units. There were 39 (23.6%) neonatal units classified as high volume, 30 (78.0%) of which were designated level three units; consequently, 14 of the 44 (31.8%) level three designated units were not classified as high volume. Among the 20,554 infants, 1,892 (9.2%) were born in hospitals with neonatal units that were classified as high volume but not tertiary level and 1,817 (8.8%) were born in hospitals with neonatal units classified as tertiary level but not high volume.

'Standard' adjusted results

Table 2 presents the estimated adjusted odds ratios associated with admission to either tertiary or high volume neonatal care the hospital of birth.

The standard logistic regressions did not reveal a statistically significant difference in the odds of mortality for very preterm infants admitted to tertiary level care at the hospital of birth compared to their counterparts admitted to non-tertiary level care. However, when considering only infants born at ≤26^{+6} weeks gestation, we found a reduction in the odds of neonatal mortality (OR: 0.65, 95% CI: 0.46-0.91, p=0.012), but not any in-hospital mortality.

A reduced odds of neonatal mortality was observed for infants born at ≤32^{+6} weeks gestation (OR: 0.73, 95% CI: 0.56-0.95, p=0.018) or at ≤26^{+6} weeks gestation (OR: 0.62, 95% CI: 0.44-0.87, p=0.006) and admitted to a high volume neonatal unit at the hospital of birth, but this was not replicated for infants born at 27^{+0}-32^{+6} weeks gestation. Infants born at ≤26^{+6} weeks gestation were also at reduced odds of any in-hospital mortality (0.71, 95% CI: 0.52-0.97, p=0.033) and increased odds of BPD (OR: 1.59, 95% CI: 1.18-2.14, p=0.002). There were no other statistically significant differences observed for the morbidity outcomes.

Instrument validity

The instruments were strongly correlated with the characteristics of the unit at the hospital of birth; 88.4% of infants whose nearest neonatal unit was designated level three were born in a hospital with a level three unit compared to only 22.5% of infants whose nearest neonatal unit was not designated level three. Table 3 shows descriptive statistics for the 20,554 very preterm infants by the designation and volume of the neonatal unit nearest to the mother's place of residence. After correcting for deprivation, there were no statistically significant differences in the observed covariates.

Instrumental variables logistic regression

Table 4 shows the estimated odds ratios using the instrumental variables logistic regressions. We found no significant differences in neonatal mortality between infants admitted to either tertiary or non-tertiary neonatal care at the hospital of birth. We did find an increased odds of treatment for ROP for very preterm infants born at 27^{+0}-32^{+6} weeks gestation born in a hospital with a tertiary level unit (OR: 2.17, 95% CI: 1.06-4.47, p=0.035).

In contrast to the effect of tertiary level care, admission to a high volume neonatal unit at the hospital of birth significantly reduced the odds of neonatal mortality (OR: 0.70, 95% CI: 0.53-0.92, p=0.011) and any in-hospital mortality (OR: 0.68, 95% CI: 0.54-0.85, p=0.001) in very preterm infants. These effects were most acute amongst infants born at ≤26^{+6} weeks gestation. In terms of morbidity, the only significant effect was found for BPD (OR: 1.78, 95% CI: 1.12-2.81, p=0.014) for infants born at ≤26^{+6} weeks gestation and admitted to high volume neonatal care at the hospital of birth.

Sensitivity Analyses

The results from the sensitivity analyses are presented in Appendix B. There were 1,172 (5.7%) infants with missing data for antenatal steroids; there were no missing values for the other covariates. The results remained qualitatively similar when all infants with any missing data were excluded from the analyses (table B1).

The results remained robust to the inclusion of unit level random effects. We further excluded infants who died from the analyses of morbidity outcomes. This did not reveal any evidence of differences in the odds ratios except for the odds of treatment for ROP for infants admitted to tertiary level care at the hospital of birth (OR: 1.96, 95% CI: 1.15-3.32, p=0.013) (table B2). No evidence of an effect for the outcome defined as any in-hospital mortality and/or BPD was observed (table B2). Three alternative measures of volume were also used. In these sensitivity analyses, the odds of any in-hospital mortality remained significantly lower for very preterm infants admitted to a high volume unit at the hospital of birth (table B3 and B4). Only eight hospitals (4.8%) met the criteria of at least 100 VLBW infants per annum in any of the study years so that only a small proportion (6.5%) of the sample were inborn and admitted to these units. There is therefore imprecision around these results with wide confidence intervals; amongst these infants, the odds of any in-hospital mortality was significantly lower but not statistically significant (table B4).

DISCUSSION

We examined the effects of designation and volume of neonatal care provided at the hospital of birth on mortality and morbidity outcomes for very preterm infants in England. Our key finding was a consistent reduction in the odds of mortality for very preterm infants admitted to high volume neonatal units. We examined infants born at ≤26^{+6} weeks gestation and those born at 27^{+6}-32^{+6} weeks gestation separately to reflect transfer policy and found a statistically significant reduction in the odds of mortality in the former group only. Furthermore, we found differences in the odds of mortality outcomes between standard logistic regressions and our preferred instrumental variables approach. The standard logistic regressions were generally found to under-estimate the beneficial effects of high volume care on mortality outcomes. This was expected given the aim of MCNs to transfer high risk infants to high volume and designation units. With regards to morbidity outcomes, treatment for ROP was the only morbidity for which a statistically significant effect was observed across analyses. We found that infants born at 27^{+6}-32^{+6} weeks gestation in hospitals with tertiary level units were at increased odds of receiving treatment for ROP; however, only a very small number of these infants received treatment for ROP (86/17,995; 0.5%), suggesting the observed difference may not be clinically significant.

Our preferred instrumental variables methodology, in the absence of a randomised assignment of infants to units, enabled us to estimate the causal effects of designation and volume of neonatal care provided at the hospital of birth using observational data. This approach has been widely applied in other healthcare evaluations.[25] However, we can only identify one previous application of this methodology to the evaluation of perinatal outcomes.[7] Our findings agree with the findings of an US-based study that examined the separate effects of level and volume of neonatal care.[4] We also found a reduction in the odds of mortality when analysing the annual number of VLBW admissions of inborn infants—a measure frequently used in US studies of this nature.[2]

We acknowledge limitations to our study. First, instrumental variables methodology only identifies the effect of an intervention or treatment for those individuals whose assignment to

treatment is altered by the instrumental variable.[26] We do not know the effects for infants who would always be born in hospitals with a high level or volume neonatal unit despite the location of the mother's residence (see online Appendix A). Nevertheless, we demonstrated the validity of our instruments in meeting the required assumptions. Importantly, the assumptions required for an instrumental variables methodology are weaker than those required to support a "standard" analysis, which requires that infants are randomly assigned to hospitals of birth; otherwise the estimated odds ratios will be biased. Second, due to data limitations we cannot control for the effects of care and risk of death in the delivery suite at the hospital of birth. However, high volume delivery units have been shown to be associated with a reduced risk of neonatal mortality.[27,28] Since high volume delivery units are often found in hospitals with high volume neonatal care this would lead us to suspect that our analyses underestimate the benefits of birth in hospitals with high volume neonatal care.

Third, we are unable to disentangle the effects of the unit at the place of birth and subsequent transfers on final outcomes. We therefore cannot assess whether increasing the provision of transfers attenuates the increased odds of mortality associated with birth in hospitals without high volume neonatal care. While identification of acute neonatal transfers was possible from our data, identifying the effects of transfer on outcomes presents a number of difficult statistical issues. However, we expect that, if transfers reduce the odds of mortality, our effects presented in this paper underestimate the benefit of birth in a hospital with high level or volume neonatal care (see Appendix A for an extended discussion). A final limitation is that a small number of neonatal units in England (n=8) across MCNs do not contribute data to the NNRD and/or participate in NESCOP. The effect of also including data from these units on outcomes remains a topic for future enquiry.

An intervention that increases the proportion of very preterm infants born in hospitals with high volume neonatal units may involve increasing the proportion of in-utero transfers. Transfers of women prior to delivery are generally preferable because they are believed to

be both safer and less expensive than postnatal transfers of vulnerable infants.[29] However, a study in 2009 showed that almost one half of all in-utero transfer requests to the London Ambulance Service were unsuccessful for non-clinical reasons.[30] The effects of transfers within different organisational structures for neonatal care remains an important area for future research especially as the new Operational Delivery Networks will supersede the perinatal MCNs as part of the changes following the Health and Social Care Act (2012).[31]

In conclusion, instrumental variables methodology did not reveal evidence of a difference in mortality outcomes between very preterm infants admitted to either tertiary or non-tertiary neonatal care at the hospital of birth. However, we do provide evidence of reduced odds of mortality for very preterm infants admitted to high volume neonatal units at delivery hospitals. The effect of volume on neonatal outcomes is an important consideration for policy makers deciding the optimal organisation of neonatal specialist services.

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Contributors:

SW conceived the study; SW, WA, and SP contributed to developing the econometric methodology for the study; SW prepared the data for analysis; SW, WA, SP, NMa, AM, ED, and NMo contributed to covariate selection and interpretation of the results; SS managed the extraction and cleaning of NNRD variables; SW prepared the first draft of the paper; this and all subsequent drafts were reviewed and revised by all authors; all authors approved the final version submitted.

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Competing interests:

None declared.

Ethical approval:

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Table 1 Descriptive statistics for preterm infants born ≤32^{+6} weeks gestation by neonatal unit characteristic at the hospital of birth

	Designation of unit			Volume of unit[a]		
	Tertiary level unit	Non-tertiary level unit	p-value[b]	High volume unit	Non-high volume unit	p-value[b]
n (%)	9,466 (46.1)	11,088 (54.0)		9,541 (46.4)	11,013 (53.6)	
Gestation (weeks), mean (SD)	29.2 (2.5)	30.0 (2.1)	<0.001	29.3 (2.5)	29.9 (2.2)	<0.001
Birth weight (g), mean (SD)	1,313.9 (438.7)	1,451.9 (404.5)	<0.001	1326.6 (436.7)	1441.8 (409.4)	<0.001
Received full or partial course of antenatal steroids	6,394 (67.6)	7,262 (65.5)	0.002	6,330 (66.4)	7,326 (66.5)	0.790
Deprivation score bottom 10%	2,020 (21.4)	1,342 (12.1)	<0.001	1,730 (18.1)	1,632 (14.8)	<0.001
Male	5,048 (53.3)	5,397 (53.4)	0.756	5,093 (53.4)	5,892 (53.5)	0.863
Neonatal mortality	423 (4.5)	366 (3.3)	<0.001	394 (4.1)	395 (3.6)	0.043
Any in-hospital mortality	569 (6.0)	425 (3.8)	<0.001	527 (5.5)	467 (4.2)	<0.001
BPD[c]	3,695 (39.0)	2,856 (25.8)	<0.001	3,548 (37.2)	3,003 (27.3)	<0.001
Treatment for ROP	226 (2.4)	107 (1.0)	<0.001	195 (2.0)	138 (1.3)	<0.001
Surgery for NEC	167 (1.8)	123 (1.1)	<0.001	163 (1.7)	127 (1.2)	0.001
PMA[d] at discharge >40^{+0} weeks	1,292 (13.7)	848 (7.7)	<0.001	1,237 (13.0)	903 (8.2)	<0.001

All values are n (%) unless otherwise stated.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.

[b] Continuous variables were tested by t-test, categorical variables by chi-squared test.

[c] Bronchopulmonary dysplasia (BPD) defined as requirement of supplementary oxygen for at least 28 days post birth and at 36 weeks postmenstrual age.

[d] PMA at discharge = postmenstrual age at discharge, equal to gestational age at birth plus length of stay in weeks.

Table 2 Adjusted odds ratios for outcomes associated with admission to either tertiary or high volume neonatal care at the hospital of birth using a "standard" logistic regression model

	Tertiary neonatal unit			High volume neonatal unit[a]		
Outcome	**(1)** **≤32^{+6} weeks**	**(2)** **≤26^{+6} weeks**	**(3)** **27^{+0}-32^{+6} weeks**	**(4)** **≤32^{+6} weeks**	**(5)** **≤26^{+6} weeks**	**(6)** **27^{+0}-32^{+6} weeks**
Neonatal mortality	0.77 (0.59-1.00)	0.65* (0.46-0.91)	0.92 (0.69-1.22)	0.73* (0.56-0.95)	0.62** (0.44-0.87)	0.86 (0.65-1.14)
Any in-hospital mortality	0.91 (0.72-1.15)	0.78 (0.57-1.06)	1.06 (0.83-1.36)	0.83 (0.65-1.05)	0.71* (0.52-0.97)	0.96 (0.75-1.24)
BPD	1.23** (1.07-1.40)	1.50** (1.11-2.01)	1.17 (0.99-1.39)	1.11 (0.97-1.28)	1.59** (1.18-2.14)	1.02 (0.86-1.22)
Treatment for ROP	1.26 (0.91-1.75)	1.09 (0.76-1.57)	1.52 (0.91-2.55)	0.95 (0.68-1.32)	0.81 (0.56-1.17)	1.22 (0.71-2.09)
Surgery for NEC	1.05 (0.76-1.44)	0.89 (0.58-1.36)	1.17 (0.80-1.70)	1.05 (0.76-1.45)	0.94 (0.62-1.45)	1.11 (0.76-1.61)
PMA at discharge >40 weeks	1.17 (0.97-1.41)	1.09 (0.87-1.37)	1.19 (0.97-1.47)	1.13 (0.94-1.37)	1.11 (0.89-1.38)	1.11 (0.90-1.37)

Values are odd ratios (95% confidence interval). * p<0.05, ** p<0.01, *** p<0.001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.

Table 3 Descriptive statistics for the sample of preterm infants born ≤32^{+6} weeks gestation by designation of the neonatal unit nearest to maternal place of residence

	Unit level designation				Unit volume[a]			
	Nearest unit tertiary level	Nearest unit non-tertiary level	p-value[b]	p-value[c], controlling for deprivation	Nearest unit high volume	Nearest unit non-high volume	p-value[b]	p-value[c], controlling for deprivation
n (%)	7,167 (34.9)	13,387 (65.1)			7,357 (35.8)	13,197 (64.2)		
Gestation (weeks), mean (SD)	29.6 (2.4)	29.7 (2.3)	0.040	0.418	29.6 (2.4)	29.6 (2.3)	0.181	0.526
Birth weight (g), mean (SD)	1377.4 (429.2)	1394.2 (424.5)	0.007	0.262	1376.7 (426.7)	1394.8 (425.7)	0.004	0.111
Received Full or partial course of antenatal steroids	4,703 (65.6)	8,953 (66.9)	0.069	0.584	4,749 (64.6)	8,907 (67.5)	<0.001	0.052
Deprivation score -bottom 10%	1,751 (24.4)	1,611 (12.0)	<0.001	NA	1,476 (20.1)	1,886 (14.3)	<0.001	NA
Male	3,820 (53.3)	7,165 (53.5)	0.761	0.854	3,958 (53.8)	7,027 (53.3)	0.447	0.378
Birth in hospital with tertiary level unit	4,753 (88.4)	2,290 (22.5)	<0.001	<0.001	3,839 (69.5)	3,204 (31.9)	<0.001	<0.001
Birth in hospital with high volume unit	3,703 (68.9)	3,374 (33.1)	<0.001	<0.001	4,764 (86.3)	2,313 (23.0)	<0.001	<0.001

All values are n (%) and are a proportion of the column total unless otherwise stated.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.

[b] Continuous variables were tested by t-test, categorical variables by chi-squared test.

[c] P-value of F-test of coefficient on instrument from a regression of variable of interest on instrument and deprivation indicator.

Table 4 Adjusted odds ratios for outcomes associated with admission to either tertiary or high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model

	Tertiary neonatal unit			High volume neonatal unit[a]		
Outcome	**(1)** **≤32^{+6} weeks**	**(2)** **≤26^{+6} weeks**	**(3)** **27^{+0}-32^{+6} weeks**	**(4)** **≤32^{+6} weeks**	**(5)** **≤26^{+6} weeks**	**(6)** **27^{+0}-32^{+6} weeks**
Neonatal Mortality	0.87 (0.66-1.15)	1.01 (0.63-1.61)	0.82 (0.58-1.14)	0.70* (0.53-0.92)	0.54** (0.33-0.87)	0.80 (0.56-1.13)
Any in hospital mortality	0.85 (0.68-1.06)	0.95 (0.62-1.44)	0.84 (0.64-1.10)	0.68** (0.54-0.85)	0.51** (0.33-0.79)	0.80 (0.60-1.07)
BPD	1.19 (0.95-1.49)	1.04 (0.66-1.64)	1.17 (0.91-1.51)	1.05 (0.85-1.29)	1.78** (1.12-2.81)	0.96 (0.75-1.22)
Treatment for ROP	1.91* (1.16-3.14)	1.57 (0.83-2.96)	2.17* (1.06-4.47)	1.02 (0.60-1.73)	0.58 (0.29-1.15)	1.84 (0.83-4.05)
Surgery for NEC	1.17 (0.72-1.90)	0.81 (0.40-1.66)	1.34 (0.76-2.38)	1.26 (0.76-2.07)	1.11 (0.54-2.28)	1.35 (0.75-2.43)
PMA at discharge >40^{+0} weeks	0.95 (0.73-1.22)	0.83 (0.60-1.13)	0.97 (0.72-1.31)	0.92 (0.72-1.17)	1.04 (0.78-1.40)	0.86 (0.67-1.14)

Values are odd ratios (95% confidence interval). * p<0.05, ** p<0.01, *** p<0.001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation

Online Appendix A: Methodology

Instrumental variables

Description and interpretation

The instrumental variables methodology can be readily compared to a randomised controlled trial (RCT) for estimating the effects of a particular treatment on patient clinical outcomes. In this study we explore two possible 'treatments', a high level neonatal unit at the place of birth and high volume neonatal unit at the place of birth. Our study group is composed of infants admitted to neonatal care since we do not observe infants who died prior to admission. A RCT would have allowed us to estimate the effect of the treatment by comparing the effect for the treated group with that of a control group (those infants admitted to low level or low volume neonatal units at hospitals of birth). This assumes that the outcomes of the control group replicate what would have happened to the treated group had they been in the control group. This is called the *causal effect of the treatment*; in this case defined as the difference between the outcome for an infant born in a hospital with and admitted to a high level or high volume neonatal unit and the outcome for the same infant had that infant been born in a hospital and admitted to a low level or low volume neonatal unit. The latter outcome is a counter-factual and is not observed. For every infant, only one of the outcomes is observed.

In the absence of a RCT we use an instrumental variables methodology which acts as an *ex post* randomisation. The purpose of an instrumental variable is to randomly assign infants to treatment and control groups. We assume that the mothers are taken to the nearest hospital for delivery. In order to use the characteristics of the nearest neonatal unit as instruments, we further assume that individuals in the population do not choose where they live on the basis of the level or volume of the nearest neonatal unit. This assumption needs to hold conditional on the other variables. For example, high volume units may be located in socioeconomically deprived areas where there are also a disproportionate number of very preterm infants. The instrument is valid provided we control for socioeconomic deprivation in our analyses so that the location of the mother's residence is not related to the level and volume of the nearest neonatal unit. In a RCT, the instrumental variable is the randomisation process itself.

We additionally assume that the effect of the treatment is heterogeneous since the effect of admission to a high level or high volume neonatal unit at the hospital of birth may be dependent on an infant's health.

As in the RCT setting, there are four types of individuals with respect to our treatment and instrumental variable:

Compliers: mothers who give birth in the nearest hospital regardless of whether it has a high level unit or not – if a mother lives near a high (low) level unit, then she gives birth in the hospital with a high (low) level unit.

Always-takers: mothers who always go to a hospital with a high level or high volume unit. This could be mothers who have been assessed to be better off having the baby in a high level unit and they go there regardless of the distance.

Never-takers: mothers who always go to a hospital with a low level or low volume unit. This could be because there is a policy that all mothers are taken to a low level unit without taking the risk into account and then infants are transferred after birth. This is unlikely and as such there are unlikely to be never-takers.

Defiers: women who do the opposite of compliers. There are unlikely to be mothers that fall into this group.

The only groups affected by the instrument are compliers and defiers. Since there are unlikely to be any defiers, the treatment effect estimated using an instrumental variables methodology is the effect of the treatment for compliers. This is known as the local average treatment effect (LATE).[1] There are two assumptions required for estimation of the LATE: i) that the effect of the treatment is either positive or negative for everyone, and ii) the probability of birth in a hospital with and admission to a high level or volume neonatal unit is greater the closer the mother lives to the unit. Both of these assumptions rule out defiers.

A "standard" analysis does not take into account the fact that treatment and control groups in an observational study may not be directly comparable.

Relationship to postnatal transfers

The previous discussion identifies how an instrumental variables methodology can be used to identify treatment effects in observational studies with a non-randomised treatment. An important part of the managed clinical network system in place in England is the provision of postnatal transfers. The question that this poses is whether postnatal transfers can be used to counteract the effect of a low volume neonatal unit at the place of birth. However, this requires identification of the effect of postnatal transfers among infants who were transferred had they not been transferred. There is not a valid control group for this. In particular, as this paper has demonstrated, the neonatal unit at the hospital of birth has an effect on the odds of mortality; the neonatal unit at the hospital of birth therefore has an effect on the probability of receiving a postnatal transfer. Hence, those infants who survive and receive a postnatal transfer will be observably and unobservably different from their counterparts not receiving a postnatal transfer.

In order to be able to identify the effect of postnatal transfers we could use an instrumental variables methodology. However, there is not a suitable candidate for an instrumental variable for postnatal transfer. A possible contender is the cot occupancy of the neonatal unit at the time of birth since this will increase the probability of transfer without affecting infant health. However, as the previous section discusses, an instrumental variables methodology identifies the treatment effect among compliers with the instrument. This group of infants is not of significant clinical interest as interest lies with those infants who may benefit from postnatal transfer to high level neonatal care regardless of the capacity of the current neonatal unit (always takers).

Technical description

The instrumental variables methodology requires two steps. Let y_i be a binary outcome equal to one if the infant i experiences the outcome and zero otherwise, D_i is a binary indicator equal to one if the unit at the hospital of birth was either high level or high volume and zero otherwise, x_i is a vector of variables explaining infant health outcomes up to the point of birth, and z_i is the vector of instruments. In the first step we estimate:

$$Pr(D_i | x_i, z_i) = logit(\lambda + x_i'\pi + z_i'\delta) \quad (1)$$

After estimating (1), the predicted values of the treatment are calculated as

$$\widehat{D}_i = logit(\hat{\lambda} + x_i'\hat{\pi} + z_i'\hat{\delta}) \quad (2)$$

where the hat indicates an estimated value. The residuals are obtained as $\hat{v}_i = D_i - \widehat{D}_i$.

The second stage is then

$$Pr(y_i | x_i, D_i, \hat{v}_i) = logit(\alpha + x_i'\beta + D_i\gamma + \hat{v}_i\rho) \quad (3)$$

The difference between the "standard" logistic regression and the instrumental variables logistic regression is the inclusion of $\hat{v}_i$.

References for Appendix A

[1] Imbens, G. & Angrist, J., 1994. Identification and estimation of local average treatment effects. *Econometrica: Journal of the Econometric Society*, 62(2), pp.467–475.

Online Appendix B: Results from sensitivity analyses

Table B1 Adjusted odds ratios for outcomes associated with admission to either tertiary or high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model; infants with missing data excluded

	Tertiary neonatal unit			High volume neonatal unit[a]		
Outcome	**(1) ≤32^{+6} weeks n=19,382**	**(2) ≤26^{+6} weeks n=2,452**	**(3) 27^{+0}-32^{+6} weeks n=16,930**	**(4) ≤32^{+6} weeks n=19,382**	**(5) ≤26^{+6} weeks n=2,452**	**(6) 27^{+0}-32^{+6} weeks n=16,930**
Neonatal Mortality	0·88 (0·67-1·17)	1·03 (0·63-1·69)	0·82 (0·59-1·14)	0·68** (0·52-0·90)	0·51** (0·31-0·84)	0·80 (0·57-1·11)
Any in hospital mortality	0·85 (0·67-1·08)	0·95 (0·61-1·47)	0·84 (0·64-1·11)	0·67** (0·53-0·84)	0·50** (0·32-0·79)	0·79 (0·59-1·05)
BPD	1·16 (0·93-1·44)	1·01 (0·64-1·61)	1·15 (0·90-1·46)	1·03 (0·84-1·26)	1·86** (1·17-2·97)	0·94 (0·74-1·18)
Treatment for ROP	1·93* (1·16-3·21)	1·76 (0·91-3·77)	1·94 (0·93-4·06)	1·04 (0·61-1·77)	0·63 (0·32-1·27)	1·79 (0·81-3·95)
Surgery for NEC	1·04 (0·63-1·73)	0·68 (0·32-1·45)	1·24 (0·68-2·24)	1·24 (0·73-2·09)	1·02 (0·48-2·16)	1·38 (0·75-2·54)
PMA at discharge >40^{+0} weeks	0·94 (0·73-1·22)	0·84 (0·60-1·18)	0·97 (0·71-1·32)	0·93 (0·73-1·19)	1·06 (0·78-1·46)	0·88 (0·66-1·16)

Values are odd ratios (95% confidence interval). * p<0·05, ** p<0·01, *** p<0·001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.

Table B2 Adjusted odds ratios for morbidities associated with admission to either tertiary or high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model; infants who died excluded from morbidity outcome

	Tertiary neonatal unit			High volume neonatal unit[a]		
Outcome	**(1) ≤32^{+6} weeks n=19,560**	**(2) ≤26^{+6} weeks n=1,987**	**(3) 27^{+0}-32^{+6} weeks n=17,573**	**(4) ≤32^{+6} weeks n=19,560**	**(5) ≤26^{+6} weeks n=1,987**	**(6) 27^{+0}-32^{+6} weeks n=17,573**
BPD	1·15 (0·88-1·52)	1·07 (0·30-3·80)	1·16 (0·88-1·52)	0·93 (0·72-1·22)	0·88 (0·25-3·04)	0·94 (0·72-1·22)
Treatment for ROP	1·96* (1·15-3·32)	1·73 (0·87-3·45)	2·13* (1·04-4·40)	0·93 (0·53-1·65)	0·49 (0·23-1·03)	1·80 (0·81-3·99)
Surgery for NEC	1·12 (0·66-1·90)	0·80 (0·36-1·76)	1·29 (0·71-2·33)	1·11 (0·65-1·89)	0·82 (0·37-1·82)	1·29 (0·70-2·38)
PMA >40^{+0} weeks	0·89 (0·67-1·19)	0·78 (0·53-1·15)	0·94 (0·69-1·28)	0·83 (0·63-1·08)	0·78 (0·53-1·13)	0·85 (0·63-1·13)
Any in-hospital mortality and/or BPD	1.13 (0.88-1.45)	N/A[b]	1.13 (0.88-1.45)	0.92 (0.72-1.17)	0.83 (0.24-2.86)	0.92 (0.72-1.17)

Values are odd ratios (95% confidence interval). * p<0·05, ** p<0·01, *** p<0·001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.
[b] Unable to estimate due to too few negative outcomes

Table B3 Adjusted odds ratios for outcomes associated with admission to high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model; alternative definitions of 'high volume'

	High volume defined as top 25% by number of intensive care days provided to infants ≤32^{+6} weeks			High volume defined as top 25% by number of ≤32^{+6} weeks births in hospital		
Outcome	**(1) ≤32^{+6} weeks**	**(2) ≤26^{+6} weeks**	**(3) 27^{+0}-32^{+6} weeks**	**(4) ≤32^{+6} weeks**	**(5) ≤26^{+6} weeks**	**(6) 27^{+0}-32^{+6} weeks**
Neonatal Mortality	0·73* (0·56-0·96)	0·73 (0·45-1·19)	0·71* (0·52-0·98)	0·81 (0·61-1·06)	0·78 (0·49-1·24)	0·82 (0·59-1·13)
Any in hospital mortality	0·67** (0·53-0·86)	0·65* (0·43-1·00)	0·69* (0·50-0·94)	0·75* (0·59-0·94)	0·69 (0·45-1·07)	0·79 (0·60-1·05)
BPD	0·98 (0·79-1·23)	1·28 (0·81-2·02)	0·93 (0·72-1·19)	1·09 (0·88-1·35)	1·41 (0·91-2·17)	1·02 (0·79-1·32)
Surgery for ROP	0·96 (0·56-1·57)	0·55 (0·28-1·06)	1·50 (0·66-3·43)	1·27 (0·76-2·13)	0·71 (0·36-1·42)	1·19 (0·88-4·14)
Surgery for NEC	1·16 (0·73-1·86)	1·11 (0·54-2·28)	1·22 (0·69-2·17)	1·10 (0·67-1·81)	0·95 (0·48-1·89)	1·15 (0·63-2·13)
PMA >40^{+0} weeks	0·81 (0·63-1·04)	0·87 (0·65-1·17)	0·78 (0·58-1·04)	0·86 (0·67-1·10)	0·88 (0·64-1·21)	0·83 (0·62-1·10)

Values are odd ratios (95% confidence interval). * p<0·05, ** p<0·01, *** p<0·001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

Table B3 Adjusted odds ratios for outcomes associated with admission to high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model; alternative definitions of 'high volume'

	High volume defined as top 25% by number of intensive care days provided to infants ≤32^{+6} weeks		
Outcome	**(1) ≤32^{+6} weeks**	**(2) ≤26^{+6} weeks**	**(3) 27^{+0}-32^{+6} weeks**
Neonatal Mortality	0.40 (0.03-4.96)	N/A[a]	0.74 (0.01-36.67)
Any in hospital mortality	0.28 (0.04-2.28)	1.18 (0.13-10.69)	0.52 (0.03-9.44)
BPD	1.95 (0.48-7.84)	0.29 (0.04-2.35)	1.10 (0.16-7.79)
Surgery for ROP	2.23 (0.17-29.70)	1.64 (0.07-40.08)	N/A[a]
Surgery for NEC	4.11 (0.29-58.79)	0.23 (0.00-26.25)	N/A[a]
PMA >40^{+0} weeks	0.54 (0.11-2.64)	0.40 (0.06-2.50)	0.45 (0.05-3.95)

Values are odd ratios (95% confidence interval). * p<0·05, ** p<0·01, *** p<0·001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a]Too few oberserved outcomes in treatment group to estimate

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **pages 1,4,5**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **pages 4,5**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Pages 6,7**
Objectives	3	State specific objectives, including any prespecified hypotheses **Pages 6,7**
Methods		
Study design	4	Present key elements of study design early in the paper **Pages 9-13**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Pages 7-9**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Pages 7-9, 12-13**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed ***N/A not a matched study***
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Pages 8,9**
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is

measurement		more than one group **Pages 8,9**
Bias	9	Describe any efforts to address potential sources of bias **Pages 9-13**
Study size	10	Explain how the study size was arrived at **Used whole eligible population (n=20,554)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Pages 7-13**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Pages 9-13**
		(*b*) Describe any methods used to examine subgroups and interactions **Pages 12-13**
		(*c*) Explain how missing data were addressed **Pages 12-13**
		(*d*) If applicable, explain how loss to follow-up was addressed N/A Cross-sectional study
		(*e*) Describe any sensitivity analyses **Pages 12-13**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Pages 13-17**
		(b) Give reasons for non-participation at each stage **Pages 16-17**
		(c) Consider use of a flow diagram **There were no non-participants, missing data are addressed in text and**

		methods
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Pages 13-15, table 1**
		(b) Indicate number of participants with missing data for each variable of interest **Pages 16-17**
		(c) Summarise follow-up time (eg, average and total amount) **N/A**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Pages 13-15, table 1**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Pages 9, 13-16, tables 1-4**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Pages 13-17, tables 2,4, appendix B**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Pages 17-22**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Pages 19-22**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,

		multiplicity of analyses, results from similar studies, and other relevant evidence **Pages 17-22**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Pages 17-22**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **N/A no specific funding**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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The effects of designation and volume of neonatal care on mortality and morbidity outcomes of very preterm infants in England: Retrospective population-based cohort study

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The effects of designation and volume of neonatal care on mortality and morbidity outcomes of very preterm infants in England: Retrospective population-based cohort study

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ABSTRACT

Objective: To examine the effects of designation and volume of neonatal care at the hospital of birth on mortality and morbidity outcomes in very preterm infants in a managed clinical network setting.

Design: A retrospective, population based analysis of operational clinical data using adjusted logistic regression and instrumental variables (IV) analyses.

Setting: 165 National Health Service neonatal units in England contributing data to the National Neonatal Research Database at the Neonatal Data Analysis Unit and participating in the Neonatal Economic, Staffing, and Clinical Outcomes Project.

Participants: 20,554 infants born at <33 weeks completed gestation (17,995 born at 27-32 weeks; 2,559 born at <27 weeks), admitted to neonatal care and either discharged or died, over the period 1st January 2009 to 31st December 2011.

Intervention: Tertiary designation or high volume neonatal care at the hospital of birth.

Outcomes: Neonatal mortality, any in-hospital mortality, surgery for necrotising enterocolitis, surgery for retinopathy of prematurity, bronchopulmonary dysplasia and postmenstrual age at discharge.

Results: Infants born at <33 weeks gestation and admitted to a high volume neonatal unit at the hospital of birth were at reduced odds of neonatal mortality (IV regression odds ratio [OR]: 0.70, 95% confidence interval [CI]: 0.53-0.92) and any in-hospital mortality (IV regression OR: 0.68, 95% CI: 0.54-0.85). The effect of volume on any in-hospital mortality was most acute amongst infants born at <27 weeks gestation (IV regression OR: 0.51, 95% CI: 0.33-0.79). A negative association

between tertiary-level unit designation and mortality was also observed with adjusted logistic regression for infant born at <27 weeks gestation.

Conclusions: High volume neonatal care provided at the hospital of birth may protect against in-hospital mortality in very preterm infants. Future developments of neonatal services should promote delivery of very preterm infants at hospitals with high volume neonatal units.

ARTICLE SUMMARY

Strengths and limitations of this study

- A national dataset consisting of the electronic patient records of a large majority of admissions to neonatal specialist care in England
- The analysis takes into account both observed and unobserved confounding
- A weakness is that the analysis is unable to disentangle the effects of the neonatal unit at the place of birth from subsequent transfers to other neonatal units

INTRODUCTION

Intense debate has revolved around the optimal organisation of neonatal critical care services. Numerous studies have suggested that the intensity and volume of neonatal care at the hospital of birth is negatively correlated with adverse clinical outcomes, including mortality.[1–11] This has contributed to calls for centralisation of neonatal services and the closure of smaller neonatal units.[2,11,12]

Following a review by the Department of Health in 2003, perinatal centres in England were reorganised into managed clinical networks (MCN).[13] MCNs provide some of the benefits of centralisation, but also strive to maintain equity and ease of access to services by keeping lower care level and lower volume neonatal units open, with provision for transfer to higher care level or higher volume units, if required.[13] Particular emphasis is placed on the importance of transferring women at risk of extremely preterm labour to tertiary centres before delivery. Consequently, most networks aim to transfer women at high risk of delivery at <27 weeks of gestation. We have previously shown that, since the formation of MCNs, both the proportion of low gestational age infants born in hospitals with higher designation neonatal units and their transfer rate between hospitals has increased significantly; however, it remains unclear what effect this has had on clinical outcomes.[14]

Studies that have examined the effects of neonatal unit designation or volume of neonatal care provided at the hospital of birth have shown that low designation level or volume is associated with increased rates of mortality,[1–10] decreased infection rate,[7] increased severe periventricular haemorrhage,[11] and increased bronchopulmonary dysplasia.[7] However, these studies were almost exclusively conducted in the United States where there is greater variability in neonatal unit volume—the highest volume units in the US are typically much larger than equivalent units in England—and there are no formal arrangements for MCNs. Results from similar studies using data from the UK are limited and based on data from 1998-9, prior to the formation of MCNs.[15,16] We are not aware of any studies that

have examined infant outcomes for neonatal specialist services in MCNs in relation to unit designation or volume. In addition, organisation of neonatal care differs between countries potentially affecting the generalisability of results from these systems; for example, in Germany neonatal services are markedly deregionalised whereas in Finland and Portugal there is a high degree of regionalization.[17]

Our aim in this study was to examine the effects of designation and volume of neonatal care provided at the hospital of birth on mortality and morbidity outcomes. We assess whether organisational factors remain determinants of clinical outcomes despite the goals of neonatal reorganisation that sought to ensure that vulnerable infants are not disadvantaged by their place of birth.

METHODS

Data source and study population

For the purpose of this empirical investigation, we extracted data from the National Neonatal Research Database (NNRD) for neonatal units participating the Neonatal Economic, Staffing, and Clinical Outcomes Project (NESCOP). The NNRD is held by the Neonatal Data Analysis Unit (NDAU), Imperial College, London, and was created from patient-level electronic records of all infants admitted to 168 of 173 neonatal units in England. Approval for data collection was obtained from the national research ethics service (reference REC 10/H0803/151) as well as the Caldicott Guardians of each NHS Trust. NESCOP included 165 centres providing perinatal care. On behalf of NESCOP, the MRC EPICure studies carried out the Unit Profile Survey (UPS) during 2011, comprising a survey of English hospitals that provided onsite obstetric and neonatal services. We extracted records from the NNRD of all infants born in participating centres at ≤32^{+6} $weeks^{+days}$ gestation, admitted over the period 1st January 2009 to 31st December 2011, and who were discharged or died over the same period. We excluded infants who only received transitional care (n=5), which was

defined according to English Department of Health's Healthcare Resource Group (HRG4) code "XA04Z".[18] Gestational age was determined by ultrasound scan.

Outcomes

We derived the following outcomes from the extracted data for use in the analyses: 28-day (neonatal) mortality, any in-hospital mortality, surgery for necrotising enterocolitis (NEC), treatment for retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD). We defined BPD as the requirement of supplementary oxygen for at least 28 days and at 36 weeks postmenstrual age (PMA).[19] We also examined PMA at discharge as a marker of length of stay; this was defined as the gestational age at birth plus the length of stay at final discharge from any neonatal unit or death. We defined the outcome to be one if the PMA at discharge was greater than 40 weeks and zero otherwise.

Covariates

To determine appropriate covariates, we reviewed previous prediction models for very preterm infants[20] and selected variables that a) were significant predictors of adverse sequelae, b) were available in our dataset and of high quality, and c) not confounded by the provision of neonatal care. The variables we included were: gestational age at birth, gestational age squared, birth weight z-score (birth weight standardised by gestational age week), and the following indicators: whether the mother received a full or partial course of antenatal steroids, sex, infant year of birth, and whether or not the mother came from an area within the lowest decile of the Index of Multiple Deprivation 2007 score.[21]

Statistical methods

We conducted two separate sets of analyses based on whether or not infants were admitted to a neonatal unit at the hospital of birth designated as: (i) a tertiary centre,[22] or (ii) high volume. For the latter, we defined volume according to the annual number of care days at any level of care provided to very preterm infants (≤32^{+6} weeks gestation). A 'high volume'

unit was defined as one whose volume was in the top quartile of all neonatal units in the sample. 'High volume' was determined by quartile rather than an absolute care day threshold to facilitate comparison with other measures of volume in the sensitivity analyses. A previous study that examined organisational characteristics of neonatal units also categorised volume using quartiles.[17] Dichotomising by upper quartile divided the infants between high and low volume units in approximately the same proportion as between tertiary and non-tertiary level units. To aid comparison with other studies, in particular from the US, and as a robustness check, `high volume' was also defined as 100 very low birth-weight (VLBW; <1,500g) admissions of infants born in the same hospital per annum.

We first conducted an unadjusted comparison of clinical characteristics and outcomes of infants by unit characteristics. Secondly, we estimated an adjusted model, and thirdly, we conducted an adjusted comparison using an instrumental variables methodology to account for unobserved confounding. In the absence of a randomised control trial, instrumental variables methodology acts as an *ex post* randomisation and enables us to estimate the 'causal effects' of designation and volume of neonatal care provided at the hospital of birth. The methodology involves the use of a variable, called an "instrument", which, in this context, needs to fulfil two criteria: 1) it should be strongly correlated with the characteristics of the neonatal unit at the hospital of birth; and 2) it should be uncorrelated with the outcomes of interest conditional on observed covariates and therefore uncorrelated with unobserved confounders.

For the instruments, we used indicators for the designated level of care of the nearest neonatal unit to the mother's residence, an indicator for whether it had surgical facilities, an indicator for whether it was high volume, the distance to the nearest neonatal unit, and the interactions of either the level of care indicators or high volume indicator with distance, giving nine instruments in total. Straight line distance was calculated from the population weighted centre of the mother's Lower Super Output Area to each hospital.[23]

These instrumental variables fulfil condition (1) if infants are more likely to be born in the hospital closest to the mother's residence. They will also fulfil condition (2) if the location of the mother's residence is uncorrelated with an infant's unobserved clinical risk. We tested for a difference in observed characteristics by level and volume of the nearest neonatal unit. However, tertiary level and high volume units are more likely to be in urban areas that are socioeconomically deprived so we may expect to see more preterm and low birth weight infants being born in these areas.[24] We therefore also controlled for local deprivation when testing for a difference in means by nearest neonatal unit characteristics by estimating a linear regression of the observed variable of interest on the nearest neonatal unit characteristic and deprivation indicator, and using an F-test to test the coefficient on the nearest neonatal unit characteristic variable.

As the outcomes are all binary logistic regression was used. In order to employ instrumental variables estimation in this framework, two stage residual inclusion (2SRI) was used.[25] The 2SRI method is explained in online Appendix A. The standard errors were adjusted for clustering within units.

Our baseline analyses examined infants born at ≤32^{+6} weeks gestation. We then conducted analyses on subsets of infants born at ≤26^{+6} weeks gestation or at 27^{+0}-32^{+6} weeks gestation; ≤26^{+6} weeks gestation is the cut-off used by perinatal networks for prioritising inter-unit transfers. 'Statistical significance', where discussed, refers to a 5% significance level in all cases.

Missing data and sensitivity analyses

Infants with missing outcomes data were excluded from the analyses, whilst those with missing covariate data were assigned a zero in the case of binary indicators. There were no infants with missing continuous covariates. We excluded all infants with any missing data as a further sensitivity analysis.

Separate sensitivity analyses, using our preferred method of instrumental variables logistic regression, also explored the effects of: (i) including unit random effects in the statistical models; (ii) removing infants who died from analyses of the morbidity and PMA at discharge outcomes and defining a new outcome of any in-hospital mortality and/or BPD to account for possible bias caused by infants dying prior to experiencing the morbidity outcome; (iii) redefining high volume as the top 25% of units in terms of intensive care days provided to $\leq 32^{+6}$ gestational week infants; (iv) redefining high volume as the top 25% of units in terms of number of $\leq 32^{+6}$ gestational week infants cared for; and (v) redefining high volume as at least 100 VLBW infants born in and admitted to the neonatal unit in the hospital per annum.

All analyses were carried out with R 2.14.2 and Stata 11.

RESULTS

In total, data for 20,554 infants born at $\leq 32^{+6}$ weeks gestation over the study period and admitted to a neonatal unit at the hospital of birth were extracted from the NNRD, 2,559 of whom were born at $\leq 26^{+6}$ weeks gestation. Table 1 provides descriptive statistics of the samples analysed.

In the sample, 9,466 (46.1%) infants were born in hospitals with a tertiary level neonatal unit and 9,541 (46.4%) were born in hospitals with a high volume neonatal unit. The cut-off for high volume was approximately 3,480 annual care days for infants born at $\leq 32^{+6}$ weeks gestation in each hospital. The total sample of 20,554 infants were born in 165 different hospitals, 44 (26.7%) of which had level three neonatal units, 81 (49.0%) level two neonatal units, and 39 (23.6%) level one neonatal units. There were 39 (23.6%) neonatal units classified as high volume, 30 (78.0%) of which were designated level three units; consequently, 14 of the 44 (31.8%) level three designated units were not classified as high volume. Among the 20,554 infants, 1,892 (9.2%) were born in hospitals with neonatal units that were classified as high volume but not tertiary level and 1,817 (8.8%) were born in hospitals with neonatal units classified as tertiary level but not high volume.

'Standard' adjusted results

Table 2 presents the estimated adjusted odds ratios associated with admission to either tertiary or high volume neonatal care at the hospital of birth.

The standard logistic regressions did not reveal a statistically significant difference in the odds of mortality for very preterm infants admitted to tertiary level care at the hospital of birth compared to their counterparts admitted to non-tertiary level care. However, when considering only infants born at ≤26^{+6} weeks gestation, we found a reduction in the odds of neonatal mortality (OR: 0.65, 95% CI: 0.46-0.91, p=0.012), but not any in-hospital mortality.

For infants admitted to a high volume neonatal unit at the hospital of birth, a reduced odds of neonatal mortality was observed for those born at ≤32^{+6} weeks gestation (OR: 0.73, 95% CI: 0.56-0.95, p=0.018) and at ≤26^{+6} weeks gestation (OR: 0.62, 95% CI: 0.44-0.87, p=0.006) , but this was not replicated for infants born at 27^{+0}-32^{+6} weeks gestation. Those infants born at ≤26^{+6} weeks gestation were also at reduced odds of any in-hospital mortality (0.71, 95% CI: 0.52-0.97, p=0.033) and increased odds of BPD (OR: 1.59, 95% CI: 1.18-2.14, p=0.002) compared to their counterparts admitted to a non-high volume neonatal unit at the hospital of birth. There were no other statistically significant differences observed for the morbidity outcomes.

Instrument validity

The instruments were strongly correlated with the characteristics of the unit at the hospital of birth; 88.4% of infants whose nearest neonatal unit was designated level three were born in a hospital with a level three unit compared to only 22.5% of infants whose nearest neonatal unit was not designated level three. Table 3 shows descriptive statistics for the 20,554 very preterm infants by the designation and volume of the neonatal unit nearest to the mother's place of residence. After correcting for deprivation, there were no statistically significant differences in the observed covariates.

Instrumental variables logistic regression

Table 4 shows the estimated odds ratios using the instrumental variables logistic regressions. We found no significant differences in neonatal mortality between infants admitted to either tertiary or non-tertiary neonatal care at the hospital of birth. We did find an increased odds of treatment for ROP for very preterm infants born at 27^{+0}-32^{+6} weeks gestation born in a hospital with a tertiary level unit (OR: 2.17, 95% CI: 1.06-4.47, p=0.035).

In contrast to the effect of tertiary level care, admission to a high volume neonatal unit at the hospital of birth significantly reduced the odds of neonatal mortality (OR: 0.70, 95% CI: 0.53-0.92, p=0.011) and any in-hospital mortality (OR: 0.68, 95% CI: 0.54-0.85, p=0.001) in very preterm infants. These effects were most acute amongst infants born at ≤26^{+6} weeks gestation. In terms of morbidity, the only significant effect was found for BPD (OR: 1.78, 95% CI: 1.12-2.81, p=0.014) for infants born at ≤26^{+6} weeks gestation and admitted to high volume neonatal care at the hospital of birth.

Sensitivity Analyses

The results from the sensitivity analyses are presented in Appendix B. There were 1,172 (5.7%) infants with missing data for antenatal steroids; there were no missing values for the other covariates. The results remained qualitatively similar when all infants with any missing data were excluded from the analyses (table B1).

The results remained robust to the inclusion of unit level random effects. We further excluded infants who died from the analyses of morbidity outcomes. This did not reveal any evidence of differences in the odds ratios except for the odds of treatment for ROP for infants admitted to tertiary level care at the hospital of birth (OR: 1.96, 95% CI: 1.15-3.32, p=0.013) (table B2). No evidence of an effect for the outcome defined as any in-hospital mortality and/or BPD was observed (table B2). Three alternative measures of volume were also used. In these sensitivity analyses, the odds of any in-hospital mortality remained significantly lower for very preterm infants admitted to a high volume unit at the hospital of

birth (table B3 and B4). Only eight hospitals (4.8%) met the criteria of at least 100 VLBW infants per annum in any of the study years so that only a small proportion (6.5%) of the sample was inborn and admitted to these units. There is therefore imprecision around these results with wide confidence intervals; amongst these infants, the odds of any in-hospital mortality was significantly lower but not statistically significant (table B4).

DISCUSSION

We examined the effects of designation and volume of neonatal care provided at the hospital of birth on mortality and morbidity outcomes for very preterm infants in England. Our key finding was a consistent reduction in the odds of mortality for very preterm infants admitted to high volume neonatal units. We examined infants born at ≤26^{+6} weeks gestation and those born at 27^{+6}-32^{+6} weeks gestation separately to reflect transfer policies and found a statistically significant reduction in the odds of mortality in the former group only. Furthermore, we found differences in the odds of mortality outcomes between standard logistic regressions and our preferred instrumental variables approach. The standard logistic regressions were generally found to under-estimate the beneficial effects of high volume care on mortality outcomes. This was expected given the aim of MCNs to transfer high risk infants to high volume and designation units. With regards to morbidity outcomes, treatment for ROP was the only morbidity for which a statistically significant effect was observed across analyses. We found that infants born at 27^{+6}-32^{+6} weeks gestation in hospitals with tertiary level units were at increased odds of receiving treatment for ROP; however, only a very small number of these infants received treatment for ROP (86/17,995; 0.5%), suggesting the observed difference may not be clinically significant.

Our preferred instrumental variables methodology, in the absence of a randomised assignment of infants to units, enabled us to estimate the causal effects of designation and volume of neonatal care provided at the hospital of birth using observational data. This approach has been widely applied in other healthcare evaluations.[26] However, we can only

identify one previous application of this methodology to the evaluation of perinatal outcomes.[7] Our findings agree with the findings of an US-based study that examined the separate effects of level and volume of neonatal care.[4] We also found a reduction in the odds of mortality when analysing the annual number of VLBW admissions of inborn infants—a measure frequently used in US studies of this nature.[2]

We acknowledge limitations to our study. First, instrumental variables methodology only identifies the effect of an intervention or treatment for those individuals whose assignment to treatment is altered by the instrumental variable.[27] We do not know the effects for infants who would always be born in hospitals with a high level or volume neonatal unit despite the location of the mother's residence (see online Appendix A). Nevertheless, we demonstrated the validity of our instruments in meeting the required assumptions. Importantly, the assumptions required for an instrumental variables methodology are weaker than those required to support a "standard" analysis, which requires that infants are randomly assigned to hospitals of birth; otherwise the estimated odds ratios will be biased. Second, due to data limitations we cannot control for the effects of care and risk of death in the delivery suite at the hospital of birth. However, high volume delivery units have been shown to be associated with a reduced risk of neonatal mortality.[28,29] Since high volume delivery units are often found in hospitals with high volume neonatal care this would lead us to suspect that our analyses underestimate the benefits of birth in hospitals with high volume neonatal care.

Third, we are unable to disentangle the effects of the unit at the place of birth and subsequent transfers on final outcomes. We therefore cannot assess whether increasing the provision of transfers attenuates the increased odds of mortality associated with birth in hospitals without high volume neonatal care. While identification of acute neonatal transfers was possible from our data, identifying the effects of transfer on outcomes presents a number of difficult statistical issues. However, we expect that, if transfers to high volume units reduce the odds of mortality, our effects presented in this paper underestimate the benefit of birth in a hospital with high level or volume neonatal care (see Appendix A for an

extended discussion), although neonatal transport itself may have negative effects on infant health outcomes.[30,31] A final limitation is that a small number of neonatal units in England (n=8) across MCNs do not contribute data to the NNRD and/or participate in NESCOP. The effect of also including data from these units on outcomes remains a topic for future enquiry.

An intervention that increases the proportion of very preterm infants born in hospitals with high volume neonatal units may involve increasing the proportion of in-utero transfers. Transfers of women prior to delivery are generally preferable because they are believed to be both safer and less expensive than postnatal transfers of vulnerable infants.[32] However, a study in 2009 showed that almost one half of all in-utero transfer requests to the London Ambulance Service were unsuccessful for non-clinical reasons.[33] Furthermore, studies from other countries, including Portugal, Finland, and the United States, have shown that in more regionalised systems as many as 90-95% of very preterm or very low birth weight infants are born in hospitals with tertiary designation neonatal units.[10,34,35] The effects of transfers within different organisational structures for neonatal care remains an important area for future research especially as the new English Operational Delivery Networks will supersede the perinatal MCNs as part of the changes following the Health and Social Care Act (2012).[36]

In conclusion, instrumental variables methodology did not reveal evidence of a difference in mortality outcomes between very preterm infants admitted to either tertiary or non-tertiary neonatal care at the hospital of birth. However, we do provide evidence of reduced odds of mortality for very preterm infants admitted to high volume neonatal units at delivery hospitals. The effect of volume on neonatal outcomes is an important consideration for policy makers deciding the optimal organisation of neonatal specialist services.

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Contributors:

SW conceived the study; SW, WA, and SP contributed to developing the econometric methodology for the study; SW prepared the data for analysis; SW, WA, SP, NMa, AM, ED, and NMo contributed to covariate selection and interpretation of the results; SS managed the extraction and cleaning of NNRD variables; SW prepared the first draft of the paper; this and all subsequent drafts were reviewed and revised by all authors; all authors approved the final version submitted.

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None declared.

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Data Sharing Statement:

No additional data available. Statistical code is available from the corresponding author.

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Table 1 Descriptive statistics for preterm infants born ≤32^{+6} weeks gestation by neonatal unit characteristic at the hospital of birth

	Designation of unit			Volume of unit[a]		
	Tertiary level unit	Non-tertiary level unit	p-value[b]	High volume unit	Non-high volume unit	p-value[b]
n (%)	9,466 (46.1)	11,088 (54.0)		9,541 (46.4)	11,013 (53.6)	
Gestation (weeks), mean (SD)	29.2 (2.5)	30.0 (2.1)	<0.001	29.3 (2.5)	29.9 (2.2)	<0.001
Birth weight (g), mean (SD)	1,313.9 (438.7)	1,451.9 (404.5)	<0.001	1326.6 (436.7)	1441.8 (409.4)	<0.001
Received full or partial course of antenatal steroids	6,394 (67.6)	7,262 (65.5)	0.002	6,330 (66.4)	7,326 (66.5)	0.790
Deprivation score bottom 10%	2,020 (21.4)	1,342 (12.1)	<0.001	1,730 (18.1)	1,632 (14.8)	<0.001
Male	5,048 (53.3)	5,397 (53.4)	0.756	5,093 (53.4)	5,892 (53.5)	0.863
Neonatal mortality	423 (4.5)	366 (3.3)	<0.001	394 (4.1)	395 (3.6)	0.043
Any in-hospital mortality	569 (6.0)	425 (3.8)	<0.001	527 (5.5)	467 (4.2)	<0.001
BPD[c]	3,695 (39.0)	2,856 (25.8)	<0.001	3,548 (37.2)	3,003 (27.3)	<0.001
Treatment for ROP	226 (2.4)	107 (1.0)	<0.001	195 (2.0)	138 (1.3)	<0.001
Surgery for NEC	167 (1.8)	123 (1.1)	<0.001	163 (1.7)	127 (1.2)	0.001
PMA[d] at discharge >40^{+0} weeks	1,292 (13.7)	848 (7.7)	<0.001	1,237 (13.0)	903 (8.2)	<0.001

All values are n (%) unless otherwise stated.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.

[b] Continuous variables were tested by t-test, categorical variables by chi-squared test.

[c] Bronchopulmonary dysplasia (BPD) defined as requirement of supplementary oxygen for at least 28 days post birth and at 36 weeks postmenstrual age.

[d] PMA at discharge = postmenstrual age at discharge, equal to gestational age at birth plus length of stay in weeks.

Table 2 Adjusted odds ratios for outcomes associated with admission to either tertiary or high volume neonatal care at the hospital of birth using a "standard" logistic regression model

	Tertiary neonatal unit	High volume neonatal unit[a]				
Outcome	**(1)** **≤32^{+6} weeks**	**(2)** **≤26^{+6} weeks**	**(3)** **27^{+0}-32^{+6} weeks**	**(4)** **≤32^{+6} weeks**	**(5)** **≤26^{+6} weeks**	**(6)** **27^{+0}-32^{+6} weeks**
Neonatal mortality	0.77 (0.59-1.00)	0.65* (0.46-0.91)	0.92 (0.69-1.22)	0.73* (0.56-0.95)	0.62** (0.44-0.87)	0.86 (0.65-1.14)
Any in-hospital mortality	0.91 (0.72-1.15)	0.78 (0.57-1.06)	1.06 (0.83-1.36)	0.83 (0.65-1.05)	0.71* (0.52-0.97)	0.96 (0.75-1.24)
BPD	1.23** (1.07-1.40)	1.50** (1.11-2.01)	1.17 (0.99-1.39)	1.11 (0.97-1.28)	1.59** (1.18-2.14)	1.02 (0.86-1.22)
Treatment for ROP	1.26 (0.91-1.75)	1.09 (0.76-1.57)	1.52 (0.91-2.55)	0.95 (0.68-1.32)	0.81 (0.56-1.17)	1.22 (0.71-2.09)
Surgery for NEC	1.05 (0.76-1.44)	0.89 (0.58-1.36)	1.17 (0.80-1.70)	1.05 (0.76-1.45)	0.94 (0.62-1.45)	1.11 (0.76-1.61)
PMA at discharge >40 weeks	1.17 (0.97-1.41)	1.09 (0.87-1.37)	1.19 (0.97-1.47)	1.13 (0.94-1.37)	1.11 (0.89-1.38)	1.11 (0.90-1.37)

Values are odd ratios (95% confidence interval). * p<0.05, ** p<0.01, *** p<0.001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.

Table 3 Descriptive statistics for the sample of preterm infants born ≤32^{+6} weeks gestation by designation of the neonatal unit nearest to maternal place of residence

	Unit level designation	Unit volume[a]						
	Nearest unit tertiary level	Nearest unit non-tertiary level	p-value[b]	p-value[c], controlling for deprivation	Nearest unit high volume	Nearest unit non-high volume	p-value[b]	p-value[c], controlling for deprivation
n (%)	7,167 (34.9)	13,387 (65.1)			7,357 (35.8)	13,197 (64.2)		
Gestation (weeks), mean (SD)	29.6 (2.4)	29.7 (2.3)	0.040	0.418	29.6 (2.4)	29.6 (2.3)	0.181	0.526
Birth weight (g), mean (SD)	1377.4 (429.2)	1394.2 (424.5)	0.007	0.262	1376.7 (426.7)	1394.8 (425.7)	0.004	0.111
Received Full or partial course of antenatal steroids	4,703 (65.6)	8,953 (66.9)	0.069	0.584	4,749 (64.6)	8,907 (67.5)	<0.001	0.052
Deprivation score -bottom 10%	1,751 (24.4)	1,611 (12.0)	<0.001	NA	1,476 (20.1)	1,886 (14.3)	<0.001	NA
Male	3,820 (53.3)	7,165 (53.5)	0.761	0.854	3,958 (53.8)	7,027 (53.3)	0.447	0.378
Birth in hospital with tertiary level unit	4,753 (88.4)	2,290 (22.5)	<0.001	<0.001	3,839 (69.5)	3,204 (31.9)	<0.001	<0.001
Birth in hospital with high volume unit	3,703 (68.9)	3,374 (33.1)	<0.001	<0.001	4,764 (86.3)	2,313 (23.0)	<0.001	<0.001

All values are n (%) and are a proportion of the column total unless otherwise stated.
[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.
[b] Continuous variables were tested by t-test, categorical variables by chi-squared test.
[c] P-value of F-test of coefficient on instrument from a regression of variable of interest on instrument and deprivation indicator.

Table 4 Adjusted odds ratios for outcomes associated with admission to either tertiary or high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model

	Tertiary neonatal unit	High volume neonatal unit[a]				
Outcome	**(1)** $\leq 32^{+6}$ **weeks**	**(2)** $\leq 26^{+6}$ **weeks**	**(3)** 27^{+0}-32^{+6} **weeks**	**(4)** $\leq 32^{+6}$ **weeks**	**(5)** $\leq 26^{+6}$ **weeks**	**(6)** 27^{+0}-32^{+6} **weeks**
Neonatal Mortality	0.87 (0.66-1.15)	1.01 (0.63-1.61)	0.82 (0.58-1.14)	0.70* (0.53-0.92)	0.54** (0.33-0.87)	0.80 (0.56-1.13)
Any in hospital mortality	0.85 (0.68-1.06)	0.95 (0.62-1.44)	0.84 (0.64-1.10)	0.68** (0.54-0.85)	0.51** (0.33-0.79)	0.80 (0.60-1.07)
BPD	1.19 (0.95-1.49)	1.04 (0.66-1.64)	1.17 (0.91-1.51)	1.05 (0.85-1.29)	1.78** (1.12-2.81)	0.96 (0.75-1.22)
Treatment for ROP	1.91* (1.16-3.14)	1.57 (0.83-2.96)	2.17* (1.06-4.47)	1.02 (0.60-1.73)	0.58 (0.29-1.15)	1.84 (0.83-4.05)
Surgery for NEC	1.17 (0.72-1.90)	0.81 (0.40-1.66)	1.34 (0.76-2.38)	1.26 (0.76-2.07)	1.11 (0.54-2.28)	1.35 (0.75-2.43)
PMA at discharge >40^{+0} weeks	0.95 (0.73-1.22)	0.83 (0.60-1.13)	0.97 (0.72-1.31)	0.92 (0.72-1.17)	1.04 (0.78-1.40)	0.86 (0.67-1.14)

Values are odd ratios (95% confidence interval). * p<0.05, ** p<0.01, *** p<0.001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at $\leq 32^{+6}$ weeks gestation

The effects of designation and volume of neonatal care on mortality and morbidity outcomes of very preterm infants in England: Retrospective population-based cohort study

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ABSTRACT

Objective: To examine the effects of designation and volume of neonatal care at the hospital of birth on mortality and morbidity outcomes in very preterm infants in a managed clinical network setting.

Design: A retrospective, population based analysis of operational clinical data using adjusted logistic regression and instrumental variables (IV) analyses.

Setting: 165 National Health Service neonatal units in England contributing data to the National Neonatal Research Database at the Neonatal Data Analysis Unit and participating in the Neonatal Economic, Staffing, and Clinical Outcomes Project.

Participants: 20,554 infants born at <33 weeks completed gestation (17,995 born at 27-32 weeks; 2,559 born at <27 weeks), admitted to neonatal care and either discharged or died, over the period 1st January 2009 to 31st December 2011.

Intervention: Tertiary designation or high volume neonatal care at the hospital of birth.

Outcomes: Neonatal mortality, any in-hospital mortality, surgery for necrotising enterocolitis, surgery for retinopathy of prematurity, bronchopulmonary dysplasia and postmenstrual age at discharge.

Results: Infants born at <33 weeks gestation and admitted to a high volume neonatal unit at the hospital of birth were at reduced odds of neonatal mortality (IV regression odds ratio [OR]: 0.70, 95% confidence interval [CI]: 0.53-0.92) and any in-hospital mortality (IV regression OR: 0.68, 95% CI: 0.54-0.85). The effect of volume on any in-hospital mortality was most acute amongst infants born at <27 weeks gestation (IV regression OR: 0.51, 95% CI: 0.33-0.79). A negative association

between tertiary-level unit designation and mortality was also observed with adjusted logistic regression for infant born at <27 weeks gestation.

Conclusions: High volume neonatal care provided at the hospital of birth may protect against in-hospital mortality in very preterm infants. Future developments of neonatal services should promote delivery of very preterm infants at hospitals with high volume neonatal units.

ARTICLE SUMMARY

Strengths and limitations of this study

- A national dataset consisting of the electronic patient records of a large majority of admissions to neonatal specialist care in England
- The analysis takes into account both observed and unobserved confounding
- A weakness is that the analysis is unable to disentangle the effects of the neonatal unit at the place of birth from subsequent transfers to other neonatal units

INTRODUCTION

Intense debate has revolved around the optimal organisation of neonatal critical care services. Numerous studies have suggested that the intensity and volume of neonatal care at the hospital of birth is negatively correlated with adverse clinical outcomes, including mortality.[1–11] This has contributed to calls for centralisation of neonatal services and the closure of smaller neonatal units.[2,11,12]

Following a review by the Department of Health in 2003, perinatal centres in England were reorganised into managed clinical networks (MCN).[13] MCNs provide some of the benefits of centralisation, but also strive to maintain equity and ease of access to services by keeping lower care level and lower volume neonatal units open, with provision for transfer to higher care level or higher volume units, if required.[13] Particular emphasis is placed on the importance of transferring women at risk of extremely preterm labour to tertiary centres before delivery. Consequently, most networks aim to transfer women at high risk of delivery at <27 weeks of gestation. We have previously shown that, since the formation of MCNs, both the proportion of low gestational age infants born in hospitals with higher designation neonatal units and their transfer rate between hospitals has increased significantly; however, it remains unclear what effect this has had on clinical outcomes.[14]

Studies that have examined the effects of neonatal unit designation or volume of neonatal care provided at the hospital of birth have shown that low designation level or volume is associated with increased rates of mortality,[1–10] decreased infection rate,[7] increased severe periventricular haemorrhage,[11] and increased bronchopulmonary dysplasia.[7] However, these studies were almost exclusively conducted in the United States where there is greater variability in neonatal unit volume—the highest volume units in the US are typically much larger than equivalent units in England—and there are~~is~~ no formal arrangements for MCNs. Results from similar studies using data from the UK are limited and based on data from 1998-9, prior to the formation of MCNs.[15,16] We are not aware of any studies that

have examined infant outcomes for neonatal specialist services in MCNs in relation to unit designation or volume. In addition, organisation of neonatal care differs between countries potentially affecting the generalisability of results from these systems; for example, in Germany neonatal services are markedly deregionalis~~z~~ed whereas in Finland and Portugal there is a high degree of regionalization.[17]

Our aim in this study was to examine the effects of designation and volume of neonatal care provided at the hospital of birth on mortality and morbidity outcomes. We assess whether organisational factors remain determinants of clinical outcomes despite the goals of neonatal reorganisation that sought to ensure that vulnerable infants are not disadvantaged by their place of birth.

METHODS

Data source and study population

For the purpose of this empirical investigation, we extracted data from the National Neonatal Research Database (NNRD) for neonatal units participating the Neonatal Economic, Staffing, and Clinical Outcomes Project (NESCOP). The NNRD is held by the Neonatal Data Analysis Unit (NDAU), Imperial College, London, and was created from patient-level electronic records of all infants admitted to 168 of 173 neonatal units in England. Approval for data collection was obtained from the national research ethics service (reference REC 10/H0803/151) as well as the Caldicott Guardians of each NHS Trust. NESCOP included 165 centres providing perinatal care. On behalf of NESCOP, the MRC EPICure studies carried out the Unit Profile Survey (UPS) during 2011, comprising a survey of English hospitals that provided onsite obstetric and neonatal services. We extracted records from the NNRD of all infants born in participating ~~hospital~~ centres at ≤32^{+6} weeks^{+days} gestation, admitted over the period 1st January 2009 to 31st December 2011, ~~born at these units~~ and who were discharged or died over the same period. We excluded infants who only received transitional care (n=5), which was defined according to English Department of Health's

Healthcare Resource Group (HRG4) code "XA04Z".[18] Gestational age was determined by ultrasound scan.

Outcomes

We derived the following outcomes from the extracted data for use in the analyses: 28-day (neonatal) mortality, any in-hospital mortality, ~~treatment~~ surgery for necrotising enterocolitis (NEC), treatment for retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD). We defined BPD as the requirement of supplementary oxygen for at least 28 days and at 36 weeks postmenstrual age (PMA).[198] We also examined PMA at discharge as a marker of length of stay; this was defined as the gestational age at birth plus the length of stay at final discharge from any neonatal unit or death. We defined the outcome to be one if the PMA at discharge was greater than 40 weeks and zero otherwise.

Covariates

To determine appropriate covariates, we reviewed previous prediction models for very preterm infants[2019] and selected variables that a) were significant predictors of adverse sequelae, b) were available in our dataset and of high quality, and c) not confounded by the provision of neonatal care. The variables we included were: gestational age at birth, gestational age squared, birth weight z-score (birth weight standardised by gestational age week), and the following indicators: whether the mother received a full or partial course of antenatal steroids, sex, infant year of birth, and whether or not the mother came from an area within the lowest decile of the Index of Multiple Deprivation 2007 score.[210]

Statistical methods

We conducted two separate sets of analyses based on whether or not infants were admitted to a neonatal unit at the hospital of birth designated as: (i) a tertiary centre,[220] or (ii) high volume. For the latter, we defined volume according to the annual number of care days at any level of care provided to very preterm infants (≤32^{+6} weeks gestation). A 'high volume'

unit was defined as one whose volume was in the top quartile of all neonatal units in the sample. 'High volume' was determined by quartile rather than an absolute care day threshold to facilitate comparison with other measures of volume in the sensitivity analyses. A previous study that examined organisational characteristics of neonatal units also categorised volume using quartiles.[17] Dichotomising by upper quartile divided the infants between high and low volume units in approximately the same proportion as between tertiary and non-tertiary level units. To aid comparison with other studies, in particular from the US, and as a robustness check, `high volume' was also defined as 100 very low birth-weight (VLBW; <1,500g) admissions of infants born in the same hospital per annum.

We first conducted an unadjusted comparison of clinical characteristics and outcomes of infants by unit characteristics. Secondly, we estimated an adjusted model, and thirdly, we conducted an adjusted comparison using an instrumental variables methodology to account for unobserved confounding. In the absence of a randomised control trial, instrumental variables methodology acts as an *ex post* randomisation and enables us to estimate the 'causal effects' of designation and volume of neonatal care provided at the hospital of birth. The methodology involves the use of a variable, called an "instrument", which, in this context, needs to fulfil two criteria: 1) it should be strongly correlated with the characteristics of the neonatal unit at the hospital of birth; and 2) it should be uncorrelated with the outcomes of interest conditional on observed covariates and therefore uncorrelated with unobserved confounders.

For the instruments, we used indicators for the designated level of care of the nearest neonatal unit to the mother's residence, an indicator for whether it had surgical facilities, an indicator for whether it was high volume, the distance to the nearest neonatal unit, and the interactions of either the level of care indicators or high volume indicator with distance, giving nine instruments in total. Straight line distance was calculated from the population weighted centre of the mother's Lower Super Output Area to each hospital.[232]

These instrumental variables fulfil condition (1) if infants are more likely to be born in the hospital closest to the mother's residence. They will also fulfil condition (2) if the location of the mother's residence is uncorrelated with an infant's unobserved clinical risk. We tested for a difference in observed characteristics by level and volume of the nearest neonatal unit. However, tertiary level and high volume units are more likely to be in urban areas that are socioeconomically deprived so we may expect to see more preterm and low birth weight infants being born in these areas.[243] We therefore also controlled for local deprivation when testing for a difference in means by nearest neonatal unit characteristics by estimating a linear regression of the observed variable of interest on the nearest neonatal unit characteristic and deprivation indicator, and using an F-test to test the coefficient on the nearest neonatal unit characteristic variable.

As the outcomes are all binary logistic regression was used. In order to employ instrumental variables estimation in this framework, two stage residual inclusion (2SRI) was used.[254] The 2SRI method is explained in online Appendix A. The standard errors were adjusted for clustering within units.

Our baseline analyses examined infants born at ≤32^{+6} weeks gestation. We then conducted analyses on subsets of infants born at ≤26^{+6} weeks gestation or at 27^{+0}-32^{+6} weeks gestation; ≤26^{+6} weeks gestation is the cut-off used by perinatal networks for prioritising inter-unit transfers. 'Statistical significance', where discussed, refers to a 5% significance level in all cases.

Missing data and sensitivity analyses

Infants with missing outcomes data were excluded from the analyses, whilst those with missing covariate data were assigned a zero in the case of binary indicators. There were no infants with missing continuous covariates. We excluded all infants with any missing data as a further sensitivity analysis.

Separate sensitivity analyses, using our preferred method of instrumental variables logistic regression, also explored the effects of: (i) including unit random effects in the statistical models; (ii) removing infants who died from analyses of the morbidity and PMA at discharge outcomes and defining a new outcome of any in-hospital mortality and/or BPD to account for possible bias caused by infants dying prior to experiencing the morbidity outcome; (iii) redefining high volume as the top 25% of units in terms of intensive care days provided to $\leq 32^{+6}$ gestational week infants; (iv) redefining high volume as the top 25% of units in terms of number of $\leq 32^{+6}$ gestational week infants cared for; and (v) redefining high volume as at least 100 VLBW infants born in and admitted to the neonatal unit in the hospital per annum.

All analyses were carried out with R 2.14.2 and Stata 11.

RESULTS

In total, data for 20,554 infants born at $\leq 32^{+6}$ weeks gestation over the study period and admitted to a neonatal unit at the hospital of birth were extracted from the NNRD, 2,559 of whom were born at $\leq 26^{+6}$ weeks gestation. Table 1 provides descriptive statistics of the samples analysed.

In the sample, 9,466 (46.1%) infants were born in hospitals with a tertiary level neonatal unit and 9,541 (46.4%) were born in hospitals with a high volume neonatal unit. The cut-off for high volume was approximately 3,480 annual care days for infants born at $\leq 32^{+6}$ weeks gestation in each hospital. The total sample of 20,554 infants were born in 165 different hospitals, 44 (26.7%) of which had level three neonatal units, 81 (49.0%) level two neonatal units, and 39 (23.6%) level one neonatal units. There were 39 (23.6%) neonatal units classified as high volume, 30 (78.0%) of which were designated level three units; consequently, 14 of the 44 (31.8%) level three designated units were not classified as high volume. Among the 20,554 infants, 1,892 (9.2%) were born in hospitals with neonatal units that were classified as high volume but not tertiary level and 1,817 (8.8%) were born in hospitals with neonatal units classified as tertiary level but not high volume.

'Standard' adjusted results

Table 2 presents the estimated adjusted odds ratios associated with admission to either tertiary or high volume neonatal care at the hospital of birth.

The standard logistic regressions did not reveal a statistically significant difference in the odds of mortality for very preterm infants admitted to tertiary level care at the hospital of birth compared to their counterparts admitted to non-tertiary level care. However, when considering only infants born at ≤26^{+6} weeks gestation, we found a reduction in the odds of neonatal mortality (OR: 0.65, 95% CI: 0.46-0.91, p=0.012), but not any in-hospital mortality.

For infants admitted to a high volume neonatal unit at the hospital of birth, ~~A~~a reduced odds of neonatal mortality was observed for ~~infants~~ those born at ≤32^{+6} weeks gestation (OR: 0.73, 95% CI: 0.56-0.95, p=0.018) and~~or~~ at ≤26^{+6} weeks gestation (OR: 0.62, 95% CI: 0.44-0.87, p=0.006) ~~and admitted to a high volume neonatal unit at the hospital of birth~~, but this was not replicated for infants born at 27^{+0}-32^{+6} weeks gestation. Those ~~i~~infants born at ≤26^{+6} weeks gestation were also at reduced odds of any in-hospital mortality (0.71, 95% CI: 0.52-0.97, p=0.033) and increased odds of BPD (OR: 1.59, 95% CI: 1.18-2.14, p=0.002) compared to their counterparts admitted to a non-high volume neonatal unit at the hospital of birth. There were no other statistically significant differences observed for the morbidity outcomes.

Instrument validity

The instruments were strongly correlated with the characteristics of the unit at the hospital of birth; 88.4% of infants whose nearest neonatal unit was designated level three were born in a hospital with a level three unit compared to only 22.5% of infants whose nearest neonatal unit was not designated level three. Table 3 shows descriptive statistics for the 20,554 very preterm infants by the designation and volume of the neonatal unit nearest to the mother's place of residence. After correcting for deprivation, there were no statistically significant differences in the observed covariates.

Instrumental variables logistic regression

Table 4 shows the estimated odds ratios using the instrumental variables logistic regressions. We found no significant differences in neonatal mortality between infants admitted to either tertiary or non-tertiary neonatal care at the hospital of birth. We did find an increased odds of treatment for ROP for very preterm infants born at 27^{+0}-32^{+6} weeks gestation born in a hospital with a tertiary level unit (OR: 2.17, 95% CI: 1.06-4.47, p=0.035).

In contrast to the effect of tertiary level care, admission to a high volume neonatal unit at the hospital of birth significantly reduced the odds of neonatal mortality (OR: 0.70, 95% CI: 0.53-0.92, p=0.011) and any in-hospital mortality (OR: 0.68, 95% CI: 0.54-0.85, p=0.001) in very preterm infants. These effects were most acute amongst infants born at ≤26^{+6} weeks gestation. In terms of morbidity, the only significant effect was found for BPD (OR: 1.78, 95% CI: 1.12-2.81, p=0.014) for infants born at ≤26^{+6} weeks gestation and admitted to high volume neonatal care at the hospital of birth.

Sensitivity Analyses

The results from the sensitivity analyses are presented in Appendix B. There were 1,172 (5.7%) infants with missing data for antenatal steroids; there were no missing values for the other covariates. The results remained qualitatively similar when all infants with any missing data were excluded from the analyses (table B1).

The results remained robust to the inclusion of unit level random effects. We further excluded infants who died from the analyses of morbidity outcomes. This did not reveal any evidence of differences in the odds ratios except for the odds of treatment for ROP for infants admitted to tertiary level care at the hospital of birth (OR: 1.96, 95% CI: 1.15-3.32, p=0.013) (table B2). No evidence of an effect for the outcome defined as any in-hospital mortality and/or BPD was observed (table B2). Three alternative measures of volume were also used. In these sensitivity analyses, the odds of any in-hospital mortality remained significantly lower for very preterm infants admitted to a high volume unit at the hospital of

birth (table B3 and B4). Only eight hospitals (4.8%) met the criteria of at least 100 VLBW infants per annum in any of the study years so that only a small proportion (6.5%) of the sample wasere inborn and admitted to these units. There is therefore imprecision around these results with wide confidence intervals; amongst these infants, the odds of any in-hospital mortality was significantly lower but not statistically significant (table B4).

DISCUSSION

We examined the effects of designation and volume of neonatal care provided at the hospital of birth on mortality and morbidity outcomes for very preterm infants in England. Our key finding was a consistent reduction in the odds of mortality for very preterm infants admitted to high volume neonatal units. We examined infants born at ≤26^{+6} weeks gestation and those born at 27^{+6}-32^{+6} weeks gestation separately to reflect transfer policiesy and found a statistically significant reduction in the odds of mortality in the former group only. Furthermore, we found differences in the odds of mortality outcomes between standard logistic regressions and our preferred instrumental variables approach. The standard logistic regressions were generally found to under-estimate the beneficial effects of high volume care on mortality outcomes. This was expected given the aim of MCNs to transfer high risk infants to high volume and designation units. With regards to morbidity outcomes, treatment for ROP was the only morbidity for which a statistically significant effect was observed across analyses. We found that infants born at 27^{+6}-32^{+6} weeks gestation in hospitals with tertiary level units were at increased odds of receiving treatment for ROP; however, only a very small number of these infants received treatment for ROP (86/17,995; 0.5%), suggesting the observed difference may not be clinically significant.

Our preferred instrumental variables methodology, in the absence of a randomised assignment of infants to units, enabled us to estimate the causal effects of designation and volume of neonatal care provided at the hospital of birth using observational data. This approach has been widely applied in other healthcare evaluations.[265] However, we can

only identify one previous application of this methodology to the evaluation of perinatal outcomes.[7] Our findings agree with the findings of an US-based study that examined the separate effects of level and volume of neonatal care.[4] We also found a reduction in the odds of mortality when analysing the annual number of VLBW admissions of inborn infants—a measure frequently used in US studies of this nature.[2]

We acknowledge limitations to our study. First, instrumental variables methodology only identifies the effect of an intervention or treatment for those individuals whose assignment to treatment is altered by the instrumental variable.[276] We do not know the effects for infants who would always be born in hospitals with a high level or volume neonatal unit despite the location of the mother's residence (see online Appendix A). Nevertheless, we demonstrated the validity of our instruments in meeting the required assumptions. Importantly, the assumptions required for an instrumental variables methodology are weaker than those required to support a "standard" analysis, which requires that infants are randomly assigned to hospitals of birth; otherwise the estimated odds ratios will be biased. Second, due to data limitations we cannot control for the effects of care and risk of death in the delivery suite at the hospital of birth. However, high volume delivery units have been shown to be associated with a reduced risk of neonatal mortality.[287,298] Since high volume delivery units are often found in hospitals with high volume neonatal care this would lead us to suspect that our analyses underestimate the benefits of birth in hospitals with high volume neonatal care.

Third, we are unable to disentangle the effects of the unit at the place of birth and subsequent transfers on final outcomes. We therefore cannot assess whether increasing the provision of transfers attenuates the increased odds of mortality associated with birth in hospitals without high volume neonatal care. While identification of acute neonatal transfers was possible from our data, identifying the effects of transfer on outcomes presents a number of difficult statistical issues. However, we expect that, if transfers to high volume units reduce the odds of mortality, our effects presented in this paper underestimate the benefit of birth in a hospital with high level or volume neonatal care (see Appendix A for an

extended discussion),~~,~~ a ~~A~~lthough~~,~~ neonatal transport itself may have negative effects on infant health outcomes.[30,31] ~~-~~A final limitation is that a small number of neonatal units in England (n=8) across MCNs do not contribute data to the NNRD and/or participate in NESCOP. The effect of also including data from these units on outcomes remains a topic for future enquiry.

An intervention that increases the proportion of very preterm infants born in hospitals with high volume neonatal units may involve increasing the proportion of in-utero transfers. Transfers of women prior to delivery are generally preferable because they are believed to be both safer and less expensive than postnatal transfers of vulnerable infants.[32~~29~~] However, a study in 2009 showed that almost one half of all in-utero transfer requests to the London Ambulance Service were unsuccessful for non-clinical reasons.[3~~0~~] Furthermore, studies from other ~~regions~~countries, including Portugal, Finland, and the United States, have shown that in more regionalised systems as many as 90-95% of very preterm or very low birth weight infants are born in hospitals with tertiary designation neonatal units.[10,34,35] The effects of transfers within different organisational structures for neonatal care remains an important area for future research especially as the new English Operational Delivery Networks will supersede the perinatal MCNs as part of the changes following the Health and Social Care Act (2012).[3~~1~~]

In conclusion, instrumental variables methodology did not reveal evidence of a difference in mortality outcomes between very preterm infants admitted to either tertiary or non-tertiary neonatal care at the hospital of birth. However, we do provide evidence of reduced odds of mortality for very preterm infants admitted to high volume neonatal units at delivery hospitals. The effect of volume on neonatal outcomes is an important consideration for policy makers deciding the optimal organisation of neonatal specialist services.

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Contributors:

SW conceived the study; SW, WA, and SP contributed to developing the econometric methodology for the study; SW prepared the data for analysis; SW, WA, SP, NMa, AM, ED, and NMo contributed to covariate selection and interpretation of the results; SS managed the extraction and cleaning of NNRD variables; SW prepared the first draft of the paper; this and all subsequent drafts were reviewed and revised by all authors; all authors approved the final version submitted.

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Competing interests:

None declared.

Ethical approval:

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Data Sharing Statement:

No additional data available. Statistical code is available from the corresponding author.

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Table 1 Descriptive statistics for preterm infants born ≤32^{+6} weeks gestation by neonatal unit characteristic at the hospital of birth

	Designation of unit			Volume of unit[a]		
	Tertiary level unit	Non-tertiary level unit	p-value[b]	High volume unit	Non-high volume unit	p-value[b]
n (%)	9,466 (46.1)	11,088 (54.0)		9,541 (46.4)	11,013 (53.6)	
Gestation (weeks), mean (SD)	29.2 (2.5)	30.0 (2.1)	<0.001	29.3 (2.5)	29.9 (2.2)	<0.001
Birth weight (g), mean (SD)	1,313.9 (438.7)	1,451.9 (404.5)	<0.001	1326.6 (436.7)	1441.8 (409.4)	<0.001
Received full or partial course of antenatal steroids	6,394 (67.6)	7,262 (65.5)	0.002	6,330 (66.4)	7,326 (66.5)	0.790
Deprivation score bottom 10%	2,020 (21.4)	1,342 (12.1)	<0.001	1,730 (18.1)	1,632 (14.8)	<0.001
Male	5,048 (53.3)	5,397 (53.4)	0.756	5,093 (53.4)	5,892 (53.5)	0.863
Neonatal mortality	423 (4.5)	366 (3.3)	<0.001	394 (4.1)	395 (3.6)	0.043
Any in-hospital mortality	569 (6.0)	425 (3.8)	<0.001	527 (5.5)	467 (4.2)	<0.001
BPD[c]	3,695 (39.0)	2,856 (25.8)	<0.001	3,548 (37.2)	3,003 (27.3)	<0.001
Treatment for ROP	226 (2.4)	107 (1.0)	<0.001	195 (2.0)	138 (1.3)	<0.001
Surgery for NEC	167 (1.8)	123 (1.1)	<0.001	163 (1.7)	127 (1.2)	0.001
PMA[d] at discharge >40^{+0} weeks	1,292 (13.7)	848 (7.7)	<0.001	1,237 (13.0)	903 (8.2)	<0.001

All values are n (%) unless otherwise stated.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.

[b] Continuous variables were tested by t-test, categorical variables by chi-squared test.

[c] Bronchopulmonary dysplasia (BPD) defined as requirement of supplementary oxygen for at least 28 days post birth and at 36 weeks postmenstrual age.

[d] PMA at discharge = postmenstrual age at discharge, equal to gestational age at birth plus length of stay in weeks.

Table 2 Adjusted odds ratios for outcomes associated with admission to either tertiary or high volume neonatal care at the hospital of birth using a "standard" logistic regression model

	Tertiary neonatal unit	High volume neonatal unit[a]				
Outcome	**(1)** **≤32^{+6} weeks**	**(2)** **≤26^{+6} weeks**	**(3)** **27^{+0}-32^{+6} weeks**	**(4)** **≤32^{+6} weeks**	**(5)** **≤26^{+6} weeks**	**(6)** **27^{+0}-32^{+6} weeks**
Neonatal mortality	0.77 (0.59-1.00)	0.65* (0.46-0.91)	0.92 (0.69-1.22)	0.73* (0.56-0.95)	0.62** (0.44-0.87)	0.86 (0.65-1.14)
Any in-hospital mortality	0.91 (0.72-1.15)	0.78 (0.57-1.06)	1.06 (0.83-1.36)	0.83 (0.65-1.05)	0.71* (0.52-0.97)	0.96 (0.75-1.24)
BPD	1.23** (1.07-1.40)	1.50** (1.11-2.01)	1.17 (0.99-1.39)	1.11 (0.97-1.28)	1.59** (1.18-2.14)	1.02 (0.86-1.22)
Treatment for ROP	1.26 (0.91-1.75)	1.09 (0.76-1.57)	1.52 (0.91-2.55)	0.95 (0.68-1.32)	0.81 (0.56-1.17)	1.22 (0.71-2.09)
Surgery for NEC	1.05 (0.76-1.44)	0.89 (0.58-1.36)	1.17 (0.80-1.70)	1.05 (0.76-1.45)	0.94 (0.62-1.45)	1.11 (0.76-1.61)
PMA at discharge >40 weeks	1.17 (0.97-1.41)	1.09 (0.87-1.37)	1.19 (0.97-1.47)	1.13 (0.94-1.37)	1.11 (0.89-1.38)	1.11 (0.90-1.37)

Values are odd ratios (95% confidence interval). * p<0.05, ** p<0.01, *** p<0.001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.

Table 3 Descriptive statistics for the sample of preterm infants born ≤32^{+6} weeks gestation by designation of the neonatal unit nearest to maternal place of residence

	Unit level designation	Unit volume[a]						
	Nearest unit tertiary level	Nearest unit non-tertiary level	p-value[b]	p-value[c], controlling for deprivation	Nearest unit high volume	Nearest unit non-high volume	p-value[b]	p-value[c], controlling for deprivation
n (%)	7,167 (34.9)	13,387 (65.1)			7,357 (35.8)	13,197 (64.2)		
Gestation (weeks), mean (SD)	29.6 (2.4)	29.7 (2.3)	0.040	0.418	29.6 (2.4)	29.6 (2.3)	0.181	0.526
Birth weight (g), mean (SD)	1377.4 (429.2)	1394.2 (424.5)	0.007	0.262	1376.7 (426.7)	1394.8 (425.7)	0.004	0.111
Received Full or partial course of antenatal steroids	4,703 (65.6)	8,953 (66.9)	0.069	0.584	4,749 (64.6)	8,907 (67.5)	<0.001	0.052
Deprivation score -bottom 10%	1,751 (24.4)	1,611 (12.0)	<0.001	NA	1,476 (20.1)	1,886 (14.3)	<0.001	NA
Male	3,820 (53.3)	7,165 (53.5)	0.761	0.854	3,958 (53.8)	7,027 (53.3)	0.447	0.378
Birth in hospital with tertiary level unit	4,753 (88.4)	2,290 (22.5)	<0.001	<0.001	3,839 (69.5)	3,204 (31.9)	<0.001	<0.001
Birth in hospital with high volume unit	3,703 (68.9)	3,374 (33.1)	<0.001	<0.001	4,764 (86.3)	2,313 (23.0)	<0.001	<0.001

All values are n (%) and are a proportion of the column total unless otherwise stated.
[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.
[b] Continuous variables were tested by t-test, categorical variables by chi-squared test.
[c] P-value of F-test of coefficient on instrument from a regression of variable of interest on instrument and deprivation indicator.

Table 4 Adjusted odds ratios for outcomes associated with admission to either tertiary or high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model

	Tertiary neonatal unit	High volume neonatal unit[a]				
Outcome	**(1)** $\leq 32^{+6}$ **weeks**	**(2)** $\leq 26^{+6}$ **weeks**	**(3)** 27^{+0}-32^{+6} **weeks**	**(4)** $\leq 32^{+6}$ **weeks**	**(5)** $\leq 26^{+6}$ **weeks**	**(6)** 27^{+0}-32^{+6} **weeks**
Neonatal Mortality	0.87 (0.66-1.15)	1.01 (0.63-1.61)	0.82 (0.58-1.14)	0.70* (0.53-0.92)	0.54** (0.33-0.87)	0.80 (0.56-1.13)
Any in hospital mortality	0.85 (0.68-1.06)	0.95 (0.62-1.44)	0.84 (0.64-1.10)	0.68** (0.54-0.85)	0.51** (0.33-0.79)	0.80 (0.60-1.07)
BPD	1.19 (0.95-1.49)	1.04 (0.66-1.64)	1.17 (0.91-1.51)	1.05 (0.85-1.29)	1.78** (1.12-2.81)	0.96 (0.75-1.22)
Treatment for ROP	1.91* (1.16-3.14)	1.57 (0.83-2.96)	2.17* (1.06-4.47)	1.02 (0.60-1.73)	0.58 (0.29-1.15)	1.84 (0.83-4.05)
Surgery for NEC	1.17 (0.72-1.90)	0.81 (0.40-1.66)	1.34 (0.76-2.38)	1.26 (0.76-2.07)	1.11 (0.54-2.28)	1.35 (0.75-2.43)
PMA at discharge >40^{+0} weeks	0.95 (0.73-1.22)	0.83 (0.60-1.13)	0.97 (0.72-1.31)	0.92 (0.72-1.17)	1.04 (0.78-1.40)	0.86 (0.67-1.14)

Values are odd ratios (95% confidence interval). * p<0.05, ** p<0.01, *** p<0.001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at $\leq 32^{+6}$ weeks gestation

Online Appendix A: Methodology

Instrumental variables

Description and interpretation

The instrumental variables methodology can be readily compared to a randomised controlled trial (RCT) for estimating the effects of a particular treatment on patient clinical outcomes. In this study we explore two possible 'treatments', a high level neonatal unit at the place of birth and high volume neonatal unit at the place of birth. Our study group is composed of infants admitted to neonatal care since we do not observe infants who died prior to admission. A RCT would have allowed us to estimate the effect of the treatment by comparing the effect for the treated group with that of a control group (those infants admitted to low level or low volume neonatal units at hospitals of birth). This assumes that the outcomes of the control group replicate what would have happened to the treated group had they been in the control group. This is called the *causal effect of the treatment*; in this case defined as the difference between the outcome for an infant born in a hospital with and admitted to a high level or high volume neonatal unit and the outcome for the same infant had that infant been born in a hospital and admitted to a low level or low volume neonatal unit. The latter outcome is a counter-factual and is not observed. For every infant, only one of the outcomes is observed.

In the absence of a RCT we use an instrumental variables methodology which acts as an *ex post* randomisation. The purpose of an instrumental variable is to randomly assign infants to treatment and control groups. We assume that the mothers are taken to the nearest hospital for delivery. In order to use the characteristics of the nearest neonatal unit as instruments, we further assume that individuals in the population do not choose where they live on the basis of the level or volume of the nearest neonatal unit. This assumption needs to hold conditional on the other variables. For example, high volume units may be located in socioeconomically deprived areas where there are also a disproportionate number of very preterm infants. The instrument is valid provided we control for socioeconomic deprivation in our analyses so that the location of the mother's residence is not related to the level and volume of the nearest neonatal unit. In a RCT, the instrumental variable is the randomisation process itself.

We additionally assume that the effect of the treatment is heterogeneous since the effect of admission to a high level or high volume neonatal unit at the hospital of birth may be dependent on an infant's health.

As in the RCT setting, there are four types of individuals with respect to our treatment and instrumental variable:

Compliers: mothers who give birth in the nearest hospital regardless of whether it has a high level unit or not – if a mother lives near a high (low) level unit, then she gives birth in the hospital with a high (low) level unit.

Always-takers: mothers who always go to a hospital with a high level or high volume unit. This could be mothers who have been assessed to be better off having the baby in a high level unit and they go there regardless of the distance.

Never-takers: mothers who always go to a hospital with a low level or low volume unit. This could be because there is a policy that all mothers are taken to a low level unit without taking the risk into account and then infants are transferred after birth. This is unlikely and as such there are unlikely to be never-takers.

Defiers: women who do the opposite of compliers. There are unlikely to be mothers that fall into this group.

The only groups affected by the instrument are compliers and defiers. Since there are unlikely to be any defiers, the treatment effect estimated using an instrumental variables methodology is the effect of the treatment for compliers. This is known as the local average treatment effect (LATE).[1] There are two assumptions required for estimation of the LATE: i) that the effect of the treatment is either positive or negative for everyone, and ii) the probability of birth in a hospital with and admission to a high level or volume neonatal unit is greater the closer the mother lives to the unit. Both of these assumptions rule out defiers.

A "standard" analysis does not take into account the fact that treatment and control groups in an observational study may not be directly comparable.

Relationship to postnatal transfers

The previous discussion identifies how an instrumental variables methodology can be used to identify treatment effects in observational studies with a non-randomised treatment. An important part of the managed clinical network system in place in England is the provision of postnatal transfers. The question that this poses is whether postnatal transfers can be used to counteract the effect of a low volume neonatal unit at the place of birth. However, this requires identification of the effect of postnatal transfers among infants who were transferred had they not been transferred. There is not a valid control group for this. In particular, as this paper has demonstrated, the neonatal unit at the hospital of birth has an effect on the odds of mortality; the neonatal unit at the hospital of birth therefore has an effect on the probability of receiving a postnatal transfer. Hence, those infants who survive and receive a postnatal transfer will be observably and unobservably different from their counterparts not receiving a postnatal transfer.

In order to be able to identify the effect of postnatal transfers we could use an instrumental variables methodology. However, there is not a suitable candidate for an instrumental variable for postnatal transfer. A possible contender is the cot occupancy of the neonatal unit at the time of birth since this will increase the probability of transfer without affecting infant health. However, as the previous section discusses, an instrumental variables methodology identifies the treatment effect among compliers with the instrument. This group of infants is not of significant clinical interest as interest lies with those infants who may benefit from postnatal transfer to high level neonatal care regardless of the capacity of the current neonatal unit (always takers).

Technical description

The instrumental variables methodology requires two steps. Let y_i be a binary outcome equal to one if the infant i experiences the outcome and zero otherwise, D_i is a binary indicator equal to one if the unit at the hospital of birth was either high level or high volume and zero otherwise, x_i is a vector of variables explaining infant health outcomes up to the point of birth, and z_i is the vector of instruments. In the first step we estimate:

$$Pr(D_i | x_i, z_i) = logit(\lambda + x_i'\pi + z_i'\delta) \quad (1)$$

After estimating (1), the predicted values of the treatment are calculated as

$$\widehat{D}_i = logit(\hat{\lambda} + x_i'\hat{\pi} + z_i'\hat{\delta}) \quad (2)$$

where the hat indicates an estimated value. The residuals are obtained as $\hat{v}_i = D_i - \widehat{D}_i$.

The second stage is then

$$Pr(y_i | x_i, D_i, \hat{v}_i) = logit(\alpha + x_i'\beta + D_i\gamma + \hat{v}_i\rho) \quad (3)$$

The difference between the "standard" logistic regression and the instrumental variables logistic regression is the inclusion of $\hat{v}_i$.

References for Appendix A

[1] Imbens, G. & Angrist, J., 1994. Identification and estimation of local average treatment effects. *Econometrica: Journal of the Econometric Society*, 62(2), pp.467–475.

Online Appendix B: Results from sensitivity analyses

Table B1 Adjusted odds ratios for outcomes associated with admission to either tertiary or high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model; infants with missing data excluded

	Tertiary neonatal unit			High volume neonatal unit[a]		
Outcome	**(1) ≤32^{+6} weeks n=19,382**	**(2) ≤26^{+6} weeks n=2,452**	**(3) 27^{+0}-32^{+6} weeks n=16,930**	**(4) ≤32^{+6} weeks n=19,382**	**(5) ≤26^{+6} weeks n=2,452**	**(6) 27^{+0}-32^{+6} weeks n=16,930**
Neonatal Mortality	0·88 (0·67-1·17)	1·03 (0·63-1·69)	0·82 (0·59-1·14)	0·68** (0·52-0·90)	0·51** (0·31-0·84)	0·80 (0·57-1·11)
Any in hospital mortality	0·85 (0·67-1·08)	0·95 (0·61-1·47)	0·84 (0·64-1·11)	0·67** (0·53-0·84)	0·50** (0·32-0·79)	0·79 (0·59-1·05)
BPD	1·16 (0·93-1·44)	1·01 (0·64-1·61)	1·15 (0·90-1·46)	1·03 (0·84-1·26)	1·86** (1·17-2·97)	0·94 (0·74-1·18)
Treatment for ROP	1·93* (1·16-3·21)	1·76 (0·91-3·77)	1·94 (0·93-4·06)	1·04 (0·61-1·77)	0·63 (0·32-1·27)	1·79 (0·81-3·95)
Surgery for NEC	1·04 (0·63-1·73)	0·68 (0·32-1·45)	1·24 (0·68-2·24)	1·24 (0·73-2·09)	1·02 (0·48-2·16)	1·38 (0·75-2·54)
PMA at discharge >40^{+0} weeks	0·94 (0·73-1·22)	0·84 (0·60-1·18)	0·97 (0·71-1·32)	0·93 (0·73-1·19)	1·06 (0·78-1·46)	0·88 (0·66-1·16)

Values are odd ratios (95% confidence interval). * p<0·05, ** p<0·01, *** p<0·001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.

Table B2 Adjusted odds ratios for morbidities associated with admission to either tertiary or high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model; infants who died excluded from morbidity outcome

	Tertiary neonatal unit			High volume neonatal unit[a]		
Outcome	**(1) ≤32^{+6} weeks n=19,560**	**(2) ≤26^{+6} weeks n=1,987**	**(3) 27^{+0}-32^{+6} weeks n=17,573**	**(4) ≤32^{+6} weeks n=19,560**	**(5) ≤26^{+6} weeks n=1,987**	**(6) 27^{+0}-32^{+6} weeks n=17,573**
BPD	1·15 (0·88-1·52)	1·07 (0·30-3·80)	1·16 (0·88-1·52)	0·93 (0·72-1·22)	0·88 (0·25-3·04)	0·94 (0·72-1·22)
Treatment for ROP	1·96* (1·15-3·32)	1·73 (0·87-3·45)	2·13* (1·04-4·40)	0·93 (0·53-1·65)	0·49 (0·23-1·03)	1·80 (0·81-3·99)
Surgery for NEC	1·12 (0·66-1·90)	0·80 (0·36-1·76)	1·29 (0·71-2·33)	1·11 (0·65-1·89)	0·82 (0·37-1·82)	1·29 (0·70-2·38)
PMA >40^{+0} weeks	0·89 (0·67-1·19)	0·78 (0·53-1·15)	0·94 (0·69-1·28)	0·83 (0·63-1·08)	0·78 (0·53-1·13)	0·85 (0·63-1·13)
Any in-hospital mortality and/or BPD	1.13 (0.88-1.45)	N/A[b]	1.13 (0.88-1.45)	0.92 (0.72-1.17)	0.83 (0.24-2.86)	0.92 (0.72-1.17)

Values are odd ratios (95% confidence interval). * p<0·05, ** p<0·01, *** p<0·001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a] High volume was defined as being in the top quartile of units by number of care days provided to infants born at ≤32^{+6} weeks gestation.
[b] Unable to estimate due to too few negative outcomes

Table B3 Adjusted odds ratios for outcomes associated with admission to high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model; alternative definitions of 'high volume'

	High volume defined as top 25% by number of intensive care days provided to infants ≤32^{+6} weeks			High volume defined as top 25% by number of ≤32^{+6} weeks births in hospital		
Outcome	**(1) ≤32^{+6} weeks**	**(2) ≤26^{+6} weeks**	**(3) 27^{+0}-32^{+6} weeks**	**(4) ≤32^{+6} weeks**	**(5) ≤26^{+6} weeks**	**(6) 27^{+0}-32^{+6} weeks**
Neonatal Mortality	0·73* (0·56-0·96)	0·73 (0·45-1·19)	0·71* (0·52-0·98)	0·81 (0·61-1·06)	0·78 (0·49-1·24)	0·82 (0·59-1·13)
Any in hospital mortality	0·67** (0·53-0·86)	0·65* (0·43-1·00)	0·69* (0·50-0·94)	0·75* (0·59-0·94)	0·69 (0·45-1·07)	0·79 (0·60-1·05)
BPD	0·98 (0·79-1·23)	1·28 (0·81-2·02)	0·93 (0·72-1·19)	1·09 (0·88-1·35)	1·41 (0·91-2·17)	1·02 (0·79-1·32)
Surgery for ROP	0·96 (0·56-1·57)	0·55 (0·28-1·06)	1·50 (0·66-3·43)	1·27 (0·76-2·13)	0·71 (0·36-1·42)	1·19 (0·88-4·14)
Surgery for NEC	1·16 (0·73-1·86)	1·11 (0·54-2·28)	1·22 (0·69-2·17)	1·10 (0·67-1·81)	0·95 (0·48-1·89)	1·15 (0·63-2·13)
PMA >40^{+0} weeks	0·81 (0·63-1·04)	0·87 (0·65-1·17)	0·78 (0·58-1·04)	0·86 (0·67-1·10)	0·88 (0·64-1·21)	0·83 (0·62-1·10)

Values are odd ratios (95% confidence interval). * p<0·05, ** p<0·01, *** p<0·001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

Table B3 Adjusted odds ratios for outcomes associated with admission to high volume neonatal care at the hospital of birth using an instrumental variable logistic regression model; alternative definitions of 'high volume'

	High volume defined as top 25% by number of intensive care days provided to infants ≤32^{+6} weeks		
Outcome	**(1) ≤32^{+6} weeks**	**(2) ≤26^{+6} weeks**	**(3) 27^{+0}-32^{+6} weeks**
Neonatal Mortality	0.40 (0.03-4.96)	N/A[a]	0.74 (0.01-36.67)
Any in hospital mortality	0.28 (0.04-2.28)	1.18 (0.13-10.69)	0.52 (0.03-9.44)
BPD	1.95 (0.48-7.84)	0.29 (0.04-2.35)	1.10 (0.16-7.79)
Surgery for ROP	2.23 (0.17-29.70)	1.64 (0.07-40.08)	N/A[a]
Surgery for NEC	4.11 (0.29-58.79)	0.23 (0.00-26.25)	N/A[a]
PMA >40^{+0} weeks	0.54 (0.11-2.64)	0.40 (0.06-2.50)	0.45 (0.05-3.95)

Values are odd ratios (95% confidence interval). * p<0·05, ** p<0·01, *** p<0·001

BPD=Bronchopulmonary Dysplasia, PMA at discharge=postmenstrual age at discharge, equal to gestational age at birth plus the length of stay in weeks. Models are adjusted for gestational age, gestational age squared, birthweight z score, use of antenatal steroids, gender, infant year of birth and deprivation.

[a]Too few oberserved outcomes in treatment group to estimate

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **pages 1,4,5**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **pages 4,5**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Pages 6,7**
Objectives	3	State specific objectives, including any prespecified hypotheses **Pages 6,7**
Methods		
Study design	4	Present key elements of study design early in the paper **Pages 9-13**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Pages 7-9**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Pages 7-9, 12-13**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed ***N/A not a matched study***
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Pages 8,9**
Data sources/	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is

1

1

measurement		more than one group **Pages 8,9**
Bias	9	Describe any efforts to address potential sources of bias **Pages 9-13**
Study size	10	Explain how the study size was arrived at **Used whole eligible population (n=20,554)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Pages 7-13**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Pages 9-13**
		(*b*) Describe any methods used to examine subgroups and interactions **Pages 12-13**
		(*c*) Explain how missing data were addressed **Pages 12-13**
		(*d*) If applicable, explain how loss to follow-up was addressed N/A Cross-sectional study
		(*e*) Describe any sensitivity analyses **Pages 12-13**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Pages 13-17**
		(b) Give reasons for non-participation at each stage **Pages 16-17**
		(c) Consider use of a flow diagram **There were no non-participants, missing data are addressed in text and**

		methods
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Pages 13-15, table 1**
		(b) Indicate number of participants with missing data for each variable of interest **Pages 16-17**
		(c) Summarise follow-up time (eg, average and total amount) **N/A**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Pages 13-15, table 1**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Pages 9, 13-16, tables 1-4**
		(*b*) Report category boundaries when continuous variables were categorized **N/A**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **Pages 13-17, tables 2,4, appendix B**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Pages 17-22**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Pages 19-22**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,

		multiplicity of analyses, results from similar studies, and other relevant evidence **Pages 17-22**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Pages 17-22**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **N/A no specific funding**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.