The heterogeneous effects of neonatal care: a model of endogenous demand for multiple treatment options based on geographical access to care

Neonatal units in the UK are organised into three levels, from highest Neonatal Intensive Care Unit (NICU), to Local Neonatal Unit (LNU) to lowest Special Care Units (SCU). We model the endogenous treatment selection of neonatal care unit of birth to estimate the average and marginal treatment effects of different neonatal designations on infant mortality, length of stay and hospital costs. We use prognostic factors, survival and hospital care use data on all preterm births in England for 2014-2015, supplemented by national reimbursement tariffs and instrumental variables of travel time from a geographic information system. The data were consistent with a model of demand for preterm birth care driven by physical access. In-hospital mortality of infants born before 32 weeks was 8.5% overall, and 1.7 percentage points lower for live births in hospitals with NICU or LNU compared to those with an SCU; differences estimated using instrumental variables were smaller and attributable to chance. We find imprecise differences in average total hospital costs by unit designation, with positive unobserved selection of those with higher unexplained absolute and incremental costs into NICU. Our results suggest a small but limited scope for improvement in infant mortality by increasing in-utero transfers based on unit designation alone.

Keywords: Endogeneity, Instrumental variables, control function, multiple treatments, geographical access, semi-parametric, average treatment effects, neonatal, seemingly unrelated regression equations; latent factor, policy evaluation

1 | INTRODUCTION

Preterm birth is accompanied by high risks of morbidity and neonatal mortality, and need for specialised neonatal care services. Since 2003 neonatal services in England are organised into managed clinical networks (DH 2003; Marlow et al. 2007) in which specialist care is centralised and low-level care is distributed across the network. These services are provided in neonatal units of three designated levels of specialisation: level 1 or Special Care units (SCU) look after infants needing level 1 care involving continuous monitoring of their breathing or heart rate, oxygen supply, tube feeding and recovery from phototherapy; level 2 or local neonatal units (LNU) can provide level 1 care as well as providing level 2 care such as short-term intensive care and support including continuous positive airway pressure (CPAP); level 3 or neonatal intensive care units (NICU) can provide level 1 and level 2 care and can additionally provide level 3 care for infants requiring ventilation, CPAP, and weighing <1kg. According to clinical guidelines, births of <28 weeks of gestational age (extremely preterm) should be cared for at a level 3 neonatal unit (NICE 2010). Nevertheless some extremely preterm infants are still born in hospitals with lower level units. Thus the relative effectiveness between neonatal unit designation levels is a key policy issue.

Estimating the relative effects of different designations on infant mortality requires inferring causality from observational data. Infant assignment to hospital of birth may be non-random, thereby confounding the observed mortality differences for true causal effects. Mothers of high-risk preterm infants may seek giving birth at designated level 3 units even among babies of the same gestational age and birthweight (Marlow et al. 2014). Instrument variables (IV) estimation is a method commonly used in economics to infer causality in observational studies (Wooldridge 2010) and increasingly used to estimate causal treatment effects in health service research (Garabedian et al. 2014).

Studies exploring the effects of neonatal unit designation at hospital of birth have shown that low-designated units are associated with increased rates of in-hospital mortality (Lasswell et al. 2010, Phibbs et al. 2007), although a recent study of very low-birthweight infants in California found no such association (Jensen and Lorch 2016). However, differences in organisation structure between UK neonatal services and other nationally funded neonatal services (Kelly et al. 2017), and the much larger neonatal units typical of the US, may limit the generalisability of results across countries. In the UK, Watson et al. estimated the causal effect of level 3 unit on infants born at ≤32 weeks using an instrumental variable (IV) approach and found no evidence that birth in NICU affects in-hospital mortality compared to lower unit designations (Watson et al. 2014a). They also found that higher nurse-to-patient ratios and higher per diem costs reduced infant mortality in NICUs (Watson et al. 2014b, Watson et al. 2017). However, none of these studies sought to analyse unobserved heterogeneity in treatment effects (Cornelissen et al. 2016).

The paper's methodological contribution is to develop an IV estimation framework with the first stage endogenous treatment choice modelled as a demand system, thus providing structural validation tests of identification with continuous geographical access, travel time, IVs. We test for unobserved heterogeneity in marginal treatment effects of NICU vs. other designations combined, and introduce a control function approach for estimating heterogeneous treatment effects with more than two treatment options. These methods are used to estimate the causal effects of preterm birth in a hospital with a SCU, LNU, or NICU, on in-hospital mortality, length of stay and hospital costs.

2 | Causal estimation approach

In this study our IV identification strategy is based on variation in travel time as measure of physical access to treatment. A systematic review of 187 comparative health effectiveness studies using an IV approach between 1993-2011 found that 65 studies had estimated mortality effects and, of these, 27 studies used travel distance (defined as straight line, Euclidean distance, or travel time) as instrumental variable, the second most common instrument after variation in regional treatment patterns (Garabedian et al. 2014).

In our context, IV estimation assumes that study subjects are a mix of high or low risk mothers that by chance live close to a particular unit. The IV estimates based on travel time or distance apply to mothers whose hospital designation at delivery is determined by the relative closeness of different hospital designations, and these mothers are known as 'compliers', because their randomly allocated 'treatment' (i.e. closest unit level) determines their place of delivery. Travel distance or time is a natural predictor of place of birth, and therefore candidate for instrument, as women prefer to deliver in a local unit (Hollowell et al 2016) and birthing units recommend avoiding excessive distances to limit the risk of out-of-hospital birth (Blondel, 2011). Previous distance-based IV studies have used differenced and absolute measures of distance or travel time as instruments in almost equal measure (Garabedian et al. 2014). In this study we use absolute travel times as the more accurate and less restrictive option for a set of IVs and validate them by comparing their actual and expected effects when interpreted as implicit access prices in a model of demand for treatment.

In addition, the continuous scale of both travel time and distance permits us to analyse how treatment effects vary across individuals with different unobserved propensities to use treatments, by estimating marginal treatment effects (MTE, Carneriro, Heckman and Vytlacil 2010), the continuous version of the 'local average treatment effect' (Imbens and Angrist 1994; Angrist and Pishcke 2001). Few studies in health economics have analysed treatment effect heterogeneity (Basu et al. 2007; Basu et al. 2014; Evans and Garthwaite 2012; Tyler-Brown et al. 2011) and this is an aspect we seek to address in this study.

Finally, the IV estimator implies a testable relationship between distance or travel time instruments and demand for the different treatment options. For example, Cutler evaluated heart services using difference in access (distance to hospital of each type) to intervention and control treatments as instruments (Cutler 2007). Watson similarly relied on IV estimation but only used information on the closest hospital and thus ignored instruments on alternative treatment options (i.e. when the closest unit was a non-NICU the characteristics of NICU were omitted and vice versa; Watson et al. 2014). We add to the literature by introducing a control function approach to extend the endogenous heterogeneous treatment effects model to ≥3 treatments.

3 | Methods

3.1 |Data

Data from the National Neonatal Research Database (NNRD) for years 2014 and 2015 were employed in the analysis. The NNRD contains selected information from the BadgerNet Neonatal Electronic Patient Record (https://www.clevermed.com/badgernet/badgernet-neonatal/) on all admissions to NHS neonatal units. Outcomes considered were any in-hospital mortality in the period from birth up to hospital discharge home or to a ward. Data available from the database include antenatal, delivery and neonatal treatments and outcomes. Neonatal unit level designation was taken from the 2015 National Neonatal Audit Programme report (RCPCH 2015). In our sample, 90%

of the 161 neonatal units in England gave permission to access NNRD data (100% of NICUs, 85% of LNUs, and 90% of SCUs). .

Expected fastest road travel times were calculated from a Geographic Information System (Maptitude® 2016) with MPMileCharter® add-in based on coordinates of postcode closest to the population-weighted centroids of the 2011 LSOA (there is one LSOA for each postcode in England) of the parents' residences and closest hospitals of each type and information on typical duration of journey on actual road grid. This created three IVs, i.e. three travel times for each individual, one per neonatal unit level. The 2015 Multiple Index of Deprivation (IMD) for each LSOA was obtained from the Office of National Statistics (ONS 2015). Ethical approval was obtained from the Neonatal Data Analysis Unit at Imperial College, London.

3.2 | Main outcome equation

Three types of infant outcomes are separately analysed: in-hospital mortality, length of hospital stay and associated reimbursement costs, and number of hospital days spent by the infant at three levels of critical care. The binary (mortality), continuous (costs) and discrete count (hospital days) scales of these outcomes required analysis using generalised linear models (Debb and Trivedi 2006) of individual infant outcomes as a function of place of birth (LNU and SCU) relative to a reference unit type (NICU),

$$Y_i = g(\beta_1 SCU_i + \beta_2 LNU_i + X_i'\delta + \lambda_1 l_{SCi} + \lambda_2 l_{LNi}) + v_i \quad (1)$$

where Y_i is an observed continuous or discrete outcome of infant i in the follow-up period up to hospital discharge, SCU_i is a binary variable equal to 1 if the neonatal unit of birth of infant i is SCU and 0 otherwise, and LNU_i is likewise defined for birth in LNU. The term $X_i'\delta$ stands for a linear vector of adjusting covariates commonly used in this literature (Gale et al. 2013, Cole et al. 2010, Manktelow et al. 2013, Ge et al. 2013, Tucker et al. 2002, Lorch et al. 2012; Appendix 0) including birthweight, gestational age, index of multiple deprivation, and number of pregnancies (plus a constant), with their respective coefficients δ.

The terms l_{SCi} and l_{LNi} are unobserved latent utility factors (section 3.3) for SCU and LNU, respectively, that serve to control for the endogeneity of SCU and LNU in Eq. 1, which occurs when coefficients $\lambda_1 \neq 0$ and $\lambda_2 \neq 0$. They account for possible unmeasured confounders, including prognostic factors e.g. congenital abnormalities that place infants at higher risks of neonatal adverse events including death. If, for example, women with high-risk pregnancies choose or are somehow determined by unmeasured factors to deliver at NICUs, a ('naïve') model excluding l_{SCi} and l_{LNi} will incorrectly attribute some of the systematic variation in outcomes to the SCU and LNU variables and likely result in biased estimates of β_{1i} and β_{2i}.

Assuming a mean zero error, $Ev_i = 0$,

$$g^{-1}(EY_i) = \beta_1 SCU_i + \beta_2 LNU_i + X_i'\delta + \lambda_1 l_{SCi} + \lambda_2 l_{LNi} \quad (2)$$

with $g^{-1}(EY)$ denoting the link function (logit or probit for mortality, log for costs, and log for days in hospital) evaluated at the mean of outcome Y, i.e., mortality status, costs, or days in hospital. Eq. 1 is estimated by maximum simulated likelihood, given a suitably chosen parametric distribution for v (binomial for mortality, normal for costs and negative binomial for days in hospital). We estimated

Eq. 1 using IV and control function methods, which required estimating a treatment choice model of the endogenous SCU and LNU binary variables as explained next.

3.3 | Instrumental variables

We evaluate the causal effects on infant outcomes of birth at LNU and SCU vs. NICU hospitals using the three available instruments of travel time to the closest hospital of each neonatal unit type, z_{SC}, z_{LN}, z_{IC}, for SCU, LNU and NICU respectively. At least two instruments were required for estimating treatment effects of the potentially endogenous SCU and LNU variables in Eq. (1) (rank condition; Wooldridge 2010). To be valid, the IVs have to determine the probability of delivering at a LNU and SCU (relevance condition), and be correlated with the outcome Y only through their association with LNU and SCU (conditional independence condition; Appendix 1 eq. 2).The individual may be born in one of three types of neonatal unit, a discrete treatment selection process which we analyse as a multinomial latent demand model where the neonatal unit level in the hospital of birth is the treatment option of maximum latent utility for the mother.

3.4 Demand for hospital type for a very preterm birth

In order to model the endogenous multinomial treatment selection, we define ICU*, LNU*, SCU* as the corresponding latent utilities of birth at the three neonatal unit levels:

$$SCU_i^* = \theta_3 z_{SCi} + \theta_2 z_{LNi} + \theta_1 z_{ICi} + X_i'\gamma_{SC} + \epsilon_{SCi} \quad (3)$$

$$LNU_i^* = \alpha_3 z_{SCi} + \alpha_2 z_{LNi} + \alpha_1 z_{ICi} + X_i'\gamma_{LN} + \epsilon_{LNi}$$

$$ICU_i^* = \pi_3 z_{SCi} + \pi_2 z_{LNi} + \pi_1 z_{ICi} + X_i'\gamma_{IC} + \epsilon_{ICi}$$

where

$$\epsilon_{ji} = W_i'\omega_j + \upsilon_{ji} \quad j = \{SC, LC, IC\}$$

are linear indices of unmeasured demand attributes (W) that are prognostic factors in outcome equation (2) plus an independently distributed random error (υ), while other Greek symbols are coefficients to be estimated. Birth occurs in the unit type of maximum utility:

$$SCU_i = 1 \; if \; SCU_i^* > ICU_i^* \; and \; SCU_i^* > LNU_i^*,$$

$$SCU_i = 0 \qquad otherwise;$$

$$LNU_i = 1 \; if \; LNU_i^* > ICU_i^* \; and \; LNU_i^* > SCU_i^*,$$

$$LNU_i = 0 \qquad otherwise;$$

birth in a NICU occurs when SCU=0 and LNU=0.

We expect $\theta_3<0$, $\alpha_2<0$, and $\pi_1<0$, whilst the coefficients of remaining instrumental variables are expected to be positive or zero. The coefficients of the multinomial choice model of Eq. 3 are not identifiable (Train 2003, p. 26-27). Subtracting the utility of a reference option, say, ICU_i^* from each equation in Eq. 3, results in an identifiable system of two independent equations of differenced utility for SCU and LNU relative to the utility of NICU:

$$\widetilde{SCU}_i^* = \tilde{\theta}_3 z_{SCi} + \tilde{\theta}_2 z_{LNi} + \tilde{\theta}_1 z_{ICi} + X_i' \tilde{\gamma}_{SC} + \tilde{\epsilon}_{SCi} \quad (4a),$$

$$\widetilde{LNU}_i^* = \tilde{\alpha}_3 z_{SCi} + \tilde{\alpha}_2 z_{LNi} + \tilde{\alpha}_1 z_{ICi} + X_i' \tilde{\gamma}_{LN} + \tilde{\epsilon}_{LNi} \quad (4b)$$

where utility differences depend on the three instruments, one for travel time to the closest unit of each type, and the Greek symbols denote the estimable coefficients. The accents denote coefficients transformed by subtracting the corresponding coefficient in the NICU latent equation, and $\tilde{\epsilon}_{LNi}$ and $\tilde{\epsilon}_{SCi}$ are the error terms in the propensity equations after subtracting the error in the NICU latent equation. We expect the own-'access price' effect to be negative ($\tilde{\alpha}_2$<0 and $\tilde{\theta}_3$<0), and the cross-price of access to NICU effect to be positive ($\tilde{\alpha}_1 >$0 and $\tilde{\theta}_1 > 0$). In contrast, the expected signs of $\tilde{\alpha}_3$ and $\tilde{\theta}_2$ are ambiguous a priori (Appendix 1). Birth in NICU (ICU=1) occurs when $\widetilde{SCU}_i^*$<0 in 4a and $\widetilde{LNU}_i^*$<0 in 4b, otherwise, birth occurs in a lower level unit (ICU=0). The case of birth at LNU (LNU=1) and SCU (SCU=1) are defined analogously.

Our control function approach for estimating Eq. 2 (Debb and Trivedi 2006), uses equations 4a & 4b and,

$$\tilde{\epsilon}_{LNi} \equiv \epsilon_{LNi} - \epsilon_{ICi} = W'(\omega_{LN} - \omega_{IC}) + \upsilon_{LNi} - \upsilon_{ICi} \equiv l_{LNi} + \tilde{\upsilon}_{LNi}$$

$$\tilde{\epsilon}_{SCi} \equiv \epsilon_{SCi} - \epsilon_{ICi} = W'(\omega_{SC} - \omega_{IC}) + \upsilon_{SCi} - \upsilon_{ICi} \equiv l_{SCi} + \tilde{\upsilon}_{SCi} \quad (5)$$

where l_{LNi} and l_{SCi} are the values of unobserved indirect utility factors affecting the neonatal outcome Y in Eq. 2. We assume that these terms are distributed standard normal across mothers, and integrate them out of the likelihood function using simulation methods. To derive the likelihood we assume that $\tilde{\upsilon}_{LNi}$ and $\tilde{\upsilon}_{SCi}$ are independently identically extreme-value distributed error terms that are independent from l_{LNi} and l_{SCi} and whose joint distribution implies a multinomial logit treatment choice probability function of the linear indices of covariates and unobserved factors in 4a & 4b (Appendix 2).

In addition, we estimate the multinomial probit treatment choice model (Roodman 2011) that relaxes the independence of irrelevant alternatives (IIA) assumption of the multinomial logit model by allowing the indirect utility equations 4a and 4b to be correlated (Train 2003). In sensitivity analysis we impose the exclusion restrictions on 4a and 4b that all instrument coefficients other than θ_3, α_2, and π_1 equal zero, i.e. $\widetilde{SCU}_i^* = \theta_3 z_{SCi} - \pi_1 z_{ICi} + X_i' \tilde{\gamma}_{SC} + \tilde{\epsilon}_{SCi}$, $\widetilde{LNU}_i^* = \alpha_2 z_{LNi} - \pi_1 z_{ICi} + X_i' \tilde{\gamma}_{LN} + \tilde{\epsilon}_{LNi}$, to address possible issues of identification with this model (Keane 1992; Appendix 1).

3.5 |In-hospital mortality

The endogenous treatment model was specified as a logit outcome with multinomial logit treatment control function (Debb and Trivedi 2006) and, alternatively, as a probit outcome with multinomial probit treatment (Roodman 2011; Appendix 2). We present results in terms of marginal effects.

3.6 |Costs and length of stay

Reimbursement cost and length of hospital stay were analysed as linear outcomes with endogenous multinomial logit (Debb and Trivedi 2006) or probit treatment (Roodman 2011). Reimbursement costs were calculated by multiplying the number of days at each level of care (section 3.7) by the corresponding English 2015 per diem (HRG) tariff. We also estimated heterogeneous treatment effects in correlated random coefficients models (Card 2001), by limited information maximum likelihood (Aakvik, Heckman and Vytalacil 2005; Appendix 2).

3.7 | Inpatient days by level of care

We estimated the effect of neonatal unit designation on the number of days at British Association of Perinatal and Maternity (BAPM) levels of care 1, 2 and 3 separately, which together accounted for 98% of total LOS (the 'super spell' including any post-natal transfer) in our sample. This analysis used a negative binomial endogenous multinomial logit treatment model. We present treatment effect estimates in terms of incidence rate ratios and marginal effects (Appendix 2).

We estimate the MTE of NICU vs. non-NICU birth (Carneiro, Heckman and Vitlacil 2011; Cornelissen et al. 2016) on mortality and the logarithm of hospital costs using a linear endogenous binary treatment model. These analyses use a Gaussian family with an identity link, i.e. a linear probability model for mortality and log linear model for costs. The treatment indicators SCU and LNU in (1) are replaced by a treatment indicator, ICU, equal to 1 when SCU=0 and LNU=0 and 0 otherwise. Also, the strong assumption that the latent factors enter linearly in (1) is relaxed by replacing them with a non-parametric function $K_Y(p)$ of the 'resistance to NICU' treatment or propensity score (p):

$$EY_i = X_i'\delta_{Y0} + X_i'(\delta_{Y1} - \delta_{Y0})p_i + K_Y(p_i) \quad (6)$$

The MTE is the derivative of (6) with respect to p,

$$MTE_i \equiv \frac{\partial EY_i}{\partial p} = X_i'(\delta_{Y1} - \delta_{Y0}) + \partial K_Y(p)/\partial p$$

MTEs are estimated semi-parametrically (Brave and Walstrum 2014) and plotted relative to p. We estimate alternative MTEs under the parametric probit treatment choice model (Appendix 3).

We tested for the existence of unobserved selection by prognosis (H0: $\rho_1 = 0$), where infants who have worse unobserved prognosis may be more likely to be born in NICU than infants with better prognosis, and selection by returns (H0: $\partial K_Y(p)/\partial p = 0$ in (6) or $\sigma_1\rho_1 - \sigma_0\rho_0 = 0$ in (7)), where infants with unobserved characteristics predisposing them to benefit more from treatment are more likely to be born in NICU (Appendix 3).

Standard errors are calculated using the method by White (1980), to account for clustering of infants in hospitals, except for MTEs, which are estimated at the mean of covariates X, using the bootstrap percentile method. Stata code illustrating the implementation of main analyses is provided in Appendix 4.

4 | RESULTS

4.1 | Distribution of sample characteristics by geographical access

Data on 14,727 live births at less than 32 weeks' gestation were available from the NNRD, 12,990 of which had complete data on infant and hospital characteristics for analysis, with 303 observations having invalid data values. Of the 12,687 remaining observations, 1650 (13%) individuals had no travel time to the closest SCU or LNU hospitals data and were excluded from the analysis. The remaining sample included 11,037 patients from 154 hospitals, of which 11 were hospitals that delivered at least 100 infants weighing <1500 g per year on average during the study period ('high-volume'); all of these hospitals were ICU and 42% (2377) of the 5595 infants born in a NICU level were delivered in a high-volume hospital. Fifteen infants were born in a hospital without a neonatal unit and were transferred ex-utero to the closest neonatal unit in the network (14 to SCU, 1 to LNU);

they were analysed according to the level of these units. In-hospital mortality in the analysis sample was 8.52% (8.43% including missing travel time data cases).

There are no systematic differences in most descriptive characteristics of the analysed sample across travel time to NICU tertiles (Table 1). In addition to the exposure variables (delivery at NICU, LNU and SCU), systematic differences arise only for deprivation of residence, unknown delivery mode and suggest the need to control for possible confounding by these variables in our analyses. Similar results were obtained for tables in terms of travel times to LNU and SCUs and in London (Appendix 5).

Table 1 Sample characteristics by travel time to NICUs (% unless stated otherwise)

	All available observations (N=12,687)			**Excluding cases with missing travel time to LNU or SCU data (N=11,037)**		
	Lower tertile N=4,191	**Medium tertile N=4,185**	**High tertile N=4,311**	**Lower tertile N=3,855**	**Medium tertile N=3,500**	**High tertile N=3,682**
Died	8.26	8.89	8.14	8.40	9.17	8.04
Discharged home	87.30	84.49	81.52	87.16	85.77	86.77
Discharged ward	1.29	1.53	2.07	1.37	1.66	2.01
Last record: transferred to another hospital/unit	2.94	4.56	7.66	2.88	3.20	3.02
Unknown destination	0.21	0.55	0.60	0.18	0.20	0.16
Gestational age at birth (weeks), mean (SD)	28.41 (2.37)	28.43 (2.33)	28.47 (2.30)	28.38 (2.38)	28.46 (2.33)	28.53 (2.29)
Birthweight (kg), mean (SD)	1.19 (0.38)	1.20 (0.38)	1.21 (0.39)	1.18 (0.38)	1.20 (0.38)	1.22 (0.39)
Foetus 2+	25.84	27.60	27.70	26.04	27.49	27.59
Female sex	46.36	45.16	46.69	46.46	44.80	45.95
Residence: Most deprived quintile[1]	47.67	29.49	21.76	49.55	30.36	22.44
Residence: 2nd most deprived quintile[1]	23.00	24.35	21.87	22.65	23.74	21.27
Residence: 3-5 least deprived quintile[3]	29.33	46.16	56.36	27.80	45.90	56.29
Caesarean delivery	48.34	50.75	51.54	48.50	51.14	51.54
Spontaneous vaginal	37.06	36.92	36.67	37.15	36.46	36.85
Unknown delivery mode	4.84	3.70	0.00	4.77	3.74	0
Delivery at NICU	81.53	42.39	26.70	83.24	43.00	23.93
Delivery at LNU	13.36	47.22	58.76	11.47	46.11	60.81
Delivery at SCU	5.11	10.39	14.54	5.29	10.89	15.26
Delivery at high volume[2]	32.38	19.52	10.69	34.42	19.40	10.08

[1] Ranked by the index of multiple deprivation of residential postcode. [2] Defined as born in hospital delivering more than 100 infants with <1500 g birthweight per year during the study period. SD: Standard deviation.

4.2 | Demand (choice) model–first stage

Table 2 presents estimates obtained from multinomial probit and multinomial logit models for the probability of birth in LNU (second and fourth columns) and the probability of birth at SCU (third and fifth columns), adjusted for covariates. The signs of these coefficients are consistent with our a priori expectations. The two coefficients with ambiguous expectations a priori, the cross-price effects of access to SCU in the LNU equation and to LNU in the SCU equation are negative with p>0.10, suggesting that the effect of travel time to LNU on the utility of SCU, and vice versa, is equal to or smaller than its effect on the utility of NICU (eq. 4a, and $b). The probability of birth in a LNU level facility was positively related with longer travel times to the closest NICU, and with longer travel times to the closest SCU, whereas being negatively related with longer travel times to the closest LNU facility. The price elasticity of demand decreases with level of specialisation, with NICU care being the least responsive option to an increase in its own travel-time price of access. Birth at SCU is nine times as responsive to travel time to NICU as it is to travel time to LNU (0.61 vs. 0.07).

Table 2 Linear index coefficients of instruments in IV multinomial treatment models

	Multinomial probit		**Multinomial logit**		**Elasticities (multinomial logit)**		
Instrumental variable	Birth at LNU†	Birth at SCU†	Birth at LNU†	Birth at SCU†	Birth at ICU	Birth at LNU	Birth at SCU
	N= 11,037	N= 11,037	N= 11,037	N= 11,037			
Minimum travel time (mins) to NICU	0.063*** (0.006)	0.075*** (0.024)	0.087*** (0.009)	0.076*** (0.013)	-1.34 (-1.72, -0.97)	0.80 (0.58, 1.02)	0.61 (0.06, 1.16)
Minimum travel time (mins) to LNU	-0.064*** (0.008)	-0.034 (0.021)	-0.109*** (0.013)	-0.026 (0.016)	0.69 (0.47, 0.92)	-1.55 (-1.96, -1.14)	0.07 (-0.49, 0.63)
Minimum travel time to SCU	-0.014 (0.009)	-0.112 (0.105)	-0.003 (0.012)	-0.152*** (0.017)	0.27 (-0.07, 0.60)	0.13 (-0.24, 0.51)	-4.14 (-4.95, -3.33)
Wald F test Ho: all instruments have no effect	188***	36***	153***	172***	N/A	N/A	N/A
Correlation across equations (ρ_{13})	0.82**		Not allowed				

†1=yes; 0=no equation. *Controlled covariates: Age and age squared at birth, birthweight, birthweight squared, sex, deprivation of residence, foetus no. N/A: Not applicable. *p< 0.10 ** p<0.05 ***p<0.01.N/A: Not applicable. *p< 0.10 ** p<0.05 ***p<0.01. Statistical inferences based on robust standard errors adjusting for clustering of observations by hospital. Figures in parentheses are standard errors except under elasticities, which are 95% CI.*

4.3 | Estimates of in-hospital mortality

Table 3 summarises the estimated marginal effects of birth at LNU vs NICU and birth at SCU vs. NICU in the naïve single equation probit model (second column) and corresponding average treatment effects of the IV model that adjusts for unobserved confounding (third column). In the naïve probit model birth in a SCU is associated with a 1.7 percentage point higher risk of neonatal death than birth in NICU (p=0.09), while LNU with 0.4 percentage point excess risk over NICU (p=0.54). In the IV model, the respective estimates are 0.1 (p=0.96) and 1.2 (p=0.23) under a probit specification.

According to the IV model diagnostic statistics, the hypothesis that birth at SCU is exogenous cannot be rejected at p=0.05. Results were similar for logit specifications.

Similar results were obtained in the subgroup of infants born at less than 28 weeks' gestation (Appendix 5).

Table 3 Causal effects on mortality of birth in LNU & SCU relative to ICU in infants born at <32 weeks

	Naïve	**IV**		**Naïve**	**IV**
	Probit regression	**Probit with endogenous multinomial probit treatment**	**Probit with endogenous multinomial probit treatment – with exclusion restrictions**	**logit regression**	**Logit with endogenous multinomial logit treatment**
Birth at LNU ([0,1] range)	0.004 (0.007)	0.012 (0.010)	0.013 (0.009)	0.006 (0.008)	0.012 (0.010)
Birth at SCU ([0,1] range)	0.017* (0.010)	0.001 (0.015)	-0.001 (0.015)	0.020* (0.010)	0.003 (0.017)
ρ_{12}, λ_1		-0.04	-0.06		-0.202
ρ_{13}, λ_2		0.07	0.12		0.391
ρ_{23}		0.82*	0.20		
Instrument strength: Wald F test statistic (3 degrees of freedom)	N/A	LNU equation: 191*** SCU equation: 34***	LNU equation: 200*** SCU equation: 98***	N/A	LNU equation: 171*** SCU equation: 151***
N	**11,037**	**11,037**	**11,037**	**11,037**	**11,037**
Hausman test z statistic of H0: no endogeneity LNU treatment variable	N/A	-0.63	-1.23	N/A	-1.0
Hausman test z statistic of H0: no endogeneity SCU treatment variable	N/A	0.77	1.32	N/A	1.1
z statistic: no correlation between utility equations (IIA)	N/A	1.82*	0.59		
Test z statistic Ho: valid over-identifying restriction of minimum travel time to NICU	N/A	-0.42	0.26	N/A	0.59

*Controlled covariates: Age and age squared at birth, birthweight, birthweight squared, sex, deprivation of residence, foetus no. N/A: Not applicable. *p< 0.10 ** p<0.05 ***p<0.01.N/A: Not applicable. *p< 0.10 ** p<0.05 ***p<0.01. Statistical inferences based on robust standard errors (in parentheses) adjusting for clustering of observations by hospital.*

Our main results (reproduced in Table 4 column a) were robust to excluding socio-economic and including mode of delivery covariates, and to variation in the specification of the endogenous treatment model. Moreover, tests on the estimated correlations between the random error terms of the multinomial treatment equations and the mortality equation do not reject the null hypothesis that birth at LNU and birth at SCU are exogenous in the mortality equation at p=0.05 under bothlogit and probit specifications.

Table 4 Robustness check: marginal effects on mortality of birth in LNU & SCU relative to ICU

	Multinomial probit treatment model			**Multinomial logit treatment model**		
	(a)	**(b)**	**(c)**	**(d)**	**(e)**	**(f)**
Birth at LNU (difference [0,1] range)	0.012 (0.010)	0.009 (0.010)	0.011 (0.010)	0.012 (0.010)	0.010 (0.010)	0.011 (0.010)
Birth at SCU (difference [0,1] range)	0.001 (0.015)	-0.003 (0.015)	0.000 0.015)	0.003 (0.017)	-0.000 (0.017)	0.003 (0.017)
Included Covariates?						
Gestational age (GA), GA squared	Yes	Yes	Yes	Yes	Yes	Yes
birthweight, birthweight squared	Yes	Yes	Yes	Yes	Yes	Yes
Infant's sex	Yes	Yes	Yes	Yes	Yes	Yes
Foetus number	Yes	Yes	Yes	Yes	Yes	Yes
Quintiles of multiple deprivation index	Yes	No	Yes	Yes	No	Yes
Mode of delivery and labour	No	No	Yes	No	No	Yes
Instrument strength: Wald F test statistic (3 degrees of freedom)	LNU equation: 191*** SCU equation: 34***	LNU equation: 190*** SCU equation: 38***	LNU equation: 188*** SCU equation: 36***	LNU equation: 171*** SCU equation: 151***	LNU equation: 167*** SCU equation: 146***	LNU equation: 172*** SCU equation: 154***
N	**11,037**	**11,037**	**11,037**	**11,037**	**11,037**	**11,037**
z statistic of H0: no endogeneity LNU treatment	-0.63	-0.38	-0.57	-1.05	-0.82	-1.01
z statistic of H0: no endogeneity SCU treatment	0.77	0.92	0.77	1.06	1.20	1.04

*N/A: Not applicable. *p< 0.10 ** p<0.05 ***p<0.01.N/A: Not applicable. *p< 0.10 ** p<0.05 ***p<0.01. Statistical inferences based on robust standard errors (in parentheses) adjusting for clustering of observations by hospital.*

The IV estimates will not apply to those mothers who deliver in NICUs regardless of the distance or time required to travel from home to their closest NICU. For example, high-risk mothers with history of preterm birth may be booked in for birth at a hospital with a NICU in spite of it not being their closest hospital; the so-called *always takers* of the intervention (birth at NICU) regardless of travel time. The IV estimates will also not apply to high-risk mothers who are not transferred to higher level units because of their infants' poor life prospects; the so-called *never takers* of birth at NICU. The proportion of *always takers* in our dataset appears to be higher than the proportion of *never takers*: 732 (22%) of those mothers who would need more time to reach their closest NICU than to reach their closest LNU and their closest SCU would still deliver at a NICU; in contrast, only 56 (1.5%) and 388 (8.9%) mothers whose closest (minimum travel time) hospital was a NICU delivered in a SCU and LNU, respectively. The analysis of MTE of birth at hospitals with NICUs vs. hospitals with a

lower-designation neonatal unit produced treatment effect estimates with 95% CI crossing zero throughout the unobserved resistance to NICU treatment (Appendix 6).

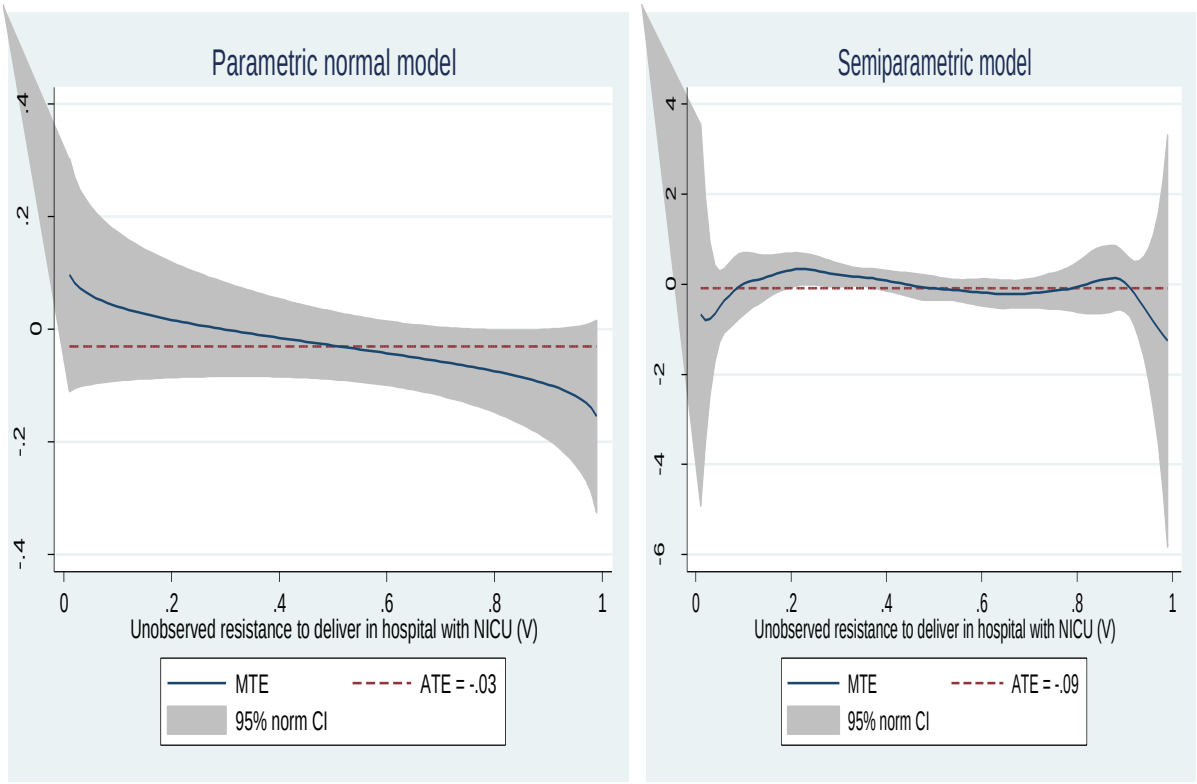
4.4 | Estimates on length of stay and costs

The estimated total duration of the neonatal hospital stay including hospital transfers (i.e. the 'super spell') of an infant born in NICU, LNU and SCU was, respectively 66, 66, and 67 days (differences: SCU vs NICU 1.0, p=0.76; LNU vs. NICU 0.6, p=0.81; Appendix 7 Table A7.1). The reimbursement cost of birth was respectively £42,776, £44,854 and £43,220 per infant (NICU minus LNU, -£2078 [95% CI: -5551,1396]; NICU minus SCU, -£444 [-4690,3802]). The results for reimbursement cost and LOS (Appendix 7 Table A7.1) are robust to varying the covariates (available from the authors).

Different test results for homogeneous effects were obtained for LNU ($p<0.05$) and SCU ($p>0.05$) using a control function approach. Unobserved characteristics that led mothers to prefer LNU over ICU were also associated with lower in-hospital costs; e.g. conditional on covariates, mothers in the top 16 percent LNU utility ranking cost under £4634 less than the average. Moreover, individuals with below-average unobserved LNU utility factors (i.e. ceteris paribus above-average NICU utility, eq. 4b) have above-average returns (cost savings vs. NICU) with LNU (Appendix 6).

Parametric normal MTE for NICU vs non-NICU had 95% CI that crossed zero (H0: no positive selection into NICU by non-observably more costly patients, p=0.001; more incrementally costly patients, p=0.17) (Appendix 7). Semi-parametric analysis reveals, however, that mothers who delivered in NICU despite having the 20 to 40 percentile lowest predicted probabilities of doing so ('unobserved resistance' on the x-axes in Figure 1) have the highest incremental costs relative to a non-NICU birthplace.

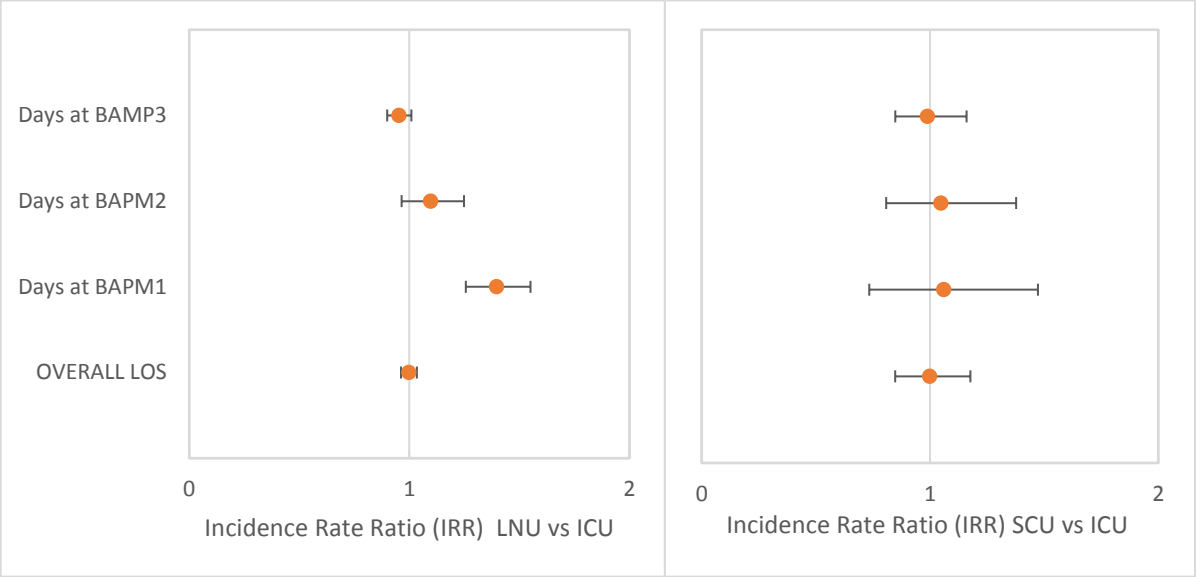
Figure 1. Marginal Treatment Effects on hospital reimbursement costs (in logarithms) of level 3 vs. lower designation hospital



Notes: Parametric model was estimated as log linear model and a probit model for NICU vs.non-NICU birth under the Potential outcomes framework. The x-axis depicts the unobserved resistance to treatment, V in Appendix 3, which equals the predicted probability of treatment in the first stage choice model. Semiparametric model is the local IV estimator (Heckman and Vytlacil 1999) as implemented by Brave and Walstrum (Brave and Walstrum 2014).

While birth at lower level units results in very preterm infants spending the same total number of days in hospital as they would if born at a NICU, birth at LNU results in more intensive care (BAPM 1) days (IRR 1.40, 95% CI: 1.26,1.55) and fewer specialised intensive care (BAPM 3) days (IRR 0.95, 95% CI: 0.90,1.01) relative to what would happen if the same infant were born in ICU (or SCU; Figure 2). Birth at SCU results in similar numbers of inpatient days of treatment at the three levels of care relative to birth at NICU (Appendix 9).

Figure 2 Causal Incidence rate ratios for number of hospital days at the three levels of care LNU, SCU vs ICU



Notes: Coefficient estimates and 95% CI from negative binomial regression models with endogenous multinomial logit treatment for number of days spent at each level of care (See Appendix 2). Fur separate models were estimated, one for each outcome measure (Overall LOS or 'superspell', BAPM1 days, BAPM 2 days, BAPM 3 days). Model estimated by the control function approach (Debb and Trivedi 2006).

5 | DISCUSSION

Our study found that the occurrence of very preterm births outside NICUs was consistent with a model of demand for preterm birth care driven by physical access. Using data on physical access as instrumental variables produced a 0.9-1.3 percentage points lower mortality in NICU and SCU relative to LNU. In contrast, in the simple naïve model with common prognostic covariates, in-hospital mortality was 1-2 percentage points lower in hospitals with NICU or LNU compared to those with an SCU. The 95% CI of all these estimated differences crosses zero, suggesting they are due to chance alone.

We found that our data were compatible with a mortality model in which there is no unobserved confounding. In cases without such confounding, the IV method is inefficient relative to simple regression analysis and may lead to incorrect inferences (Wooldridge 2010). However, we have a

priori reasons to suspect endogeneity is present e.g. from selective choice of NICU by pregnancies with risk factors not recorded in our data, and our instruments were found to be strong and valid. Therefore the likely treatment effect for designated units lies with the IV results. Moreover, there is no evidence of an increase in the total length of the infant stay in these neonatal units or cost to commissioners when these outcomes are analysed unadjusted for the competing death risk. Since there are few 'never NICU takers', our IV estimates may be interpreted as the treatment effect on the NICU-untreated (Angrist and Pischke 2009). Thus our results suggest that increases of in-utero transfers from lower unit designations alone are unlikely to bring large improvements in in-hospital mortality (Gale et al. 2012a,b).

Our study also exploited continuous instruments to analyse the heterogeneity in treatment effects on mortality and costs. Our results failed to reject the hypothesis that there is no residual unobservable self-selection of women into NICU according to neonate severity or expected mortality risk reduction at conventional significance levels; however, it is possible that a larger sample would have rejected it. In terms of costs, there is evidence of unobservable self-selection of complex (i.e. more costly) cases into NICU hospitals and of negative selection by returns as some infants with the highest additional costs relative to non-NICU care are prone to be born in NICU hospital for reasons unrelated to birthweight, gestational age, socio-economic status, number of pregnancies and sex.

We found a significant causal reduction in the number of hospital days spent under the most intensive care level (BAPM 1) that was accompanied by an increase in the number of days under lower care intensity (BAPM 3) with NICU relative to LNU. While the associated net effect on overall reimbursement costs to the NHS is apparently zero, and we did not find the mortality benefits documented by Marlow and colleagues (Marlow et al. 2014), these results suggest nevertheless that birth at NICU would reduce neonatal morbidity among those currently born in LNU. Further research that investigates this question is warranted using measures of neonatal morbidity including ventilator days; bronchopulmonary dysplasia; intraventricular haemorrhage, particularly the severe grades 3-4; late-onset infection; necrotizing enterocolitis; and retinopathy of prematurity, particularly severe stages 3 and above.

A limitation of our analysis is that the IV method requires the assumption that travel time to the closest neonatal unit did not affect infant mortality by means other than through its role in determining the level of the neonatal unit of the hospital of birth. It is possible that longer travel time to a NICU increased the chance of in-hospital mortality among those infants delivered in a NICU due to delays in receiving the required specialised care. However, we would expect these effects, if present, to be secondary to the effects of travel time on mortality that are due to exposure to the level of care of the neonatal unit of birth.

Our measure of mortality, in-hospital infant death, did not include stillbirths, which exceed neonatal deaths in England (2952 versus 1721 annually, ONS 2015). Another limitation of our dataset is its lacking information on antenatal steroid use (ANS), which may account for the poorer mortality results for the SCUs as these use less steroids (RCPCH 2017). Watson et al. using the same database reported that covariates, including ANS, were evenly distributed between level 3 and non-level 3 born very preterm infant groups, after controlling for the lowest decile of index of multiple deprivation (Watson et al. 2015). We thus expect any omitted variable bias from ANS in our analysis, after controlled for quintiles of socioeconomic deprivation, to be limited. Low socio-economic status is itself linked to an increased risk of preterm births through low maternal weight and smoking (Taylor-Robinson et al. 2011). Therefore, any unmeasured differences in socio-economic status that are not captured by our multiple deprivation measure may have confounded our results also.

Future work should investigate differences in mortality and costs between high and low-volume NICUs since a high volume of births may be more influential on neonatal mortality and outcomes than a high designation level of unit (Jensen and Lorch 2015). Our findings comprise 42% of NICU infants born in high-volume units in our sample.

Supplementary files

Appendix 0 – Covariates included in the analysis

Appendix 1 – Identification of the instrumental variable estimator

Appendix 2 – Main outcome equation models

Appendix 3 – Marginal Treatment Effect analysis

Appendix 4 – Stata code to implement the main analyses

Appendix 5 – Distribution of sample characteristics by travel time to SCU and LNU

Appendix 6 – Main results for extremely preterm births

Appendix 7 – Results on LOS and reimbursement costs for VPT births

Appendix 8 – Results on inpatient days by level of care for VPT births

Appendix 9 – Results on marginal treatment effects

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