

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 counterfactual 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:

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

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

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

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

The second stage is then

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

The difference between the "standard" logistic regression and the instrumental variables logistic regression is the inclusion of \widehat{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.