9.4 A French cohort study of screening for PDA

During fetal life there's no point having all of the blood that the heart is pumping go to the lungs, because the fetus is not breathing. Therefore, in fetal life blood bypasses the lungs through a blood vessel called the ductus arteriosus, which connects the pulmonary artery to the aorta. Once the baby is born, the ductus is supposed to close, but sometimes that doesn't happen, especially in preterm babies, and they have a **patent ductus arteriosus** (PDA). Whether or not to treat PDAs with medicine or surgery and even whether to look for them is controversial. Roze et al (1) examined whether screening for PDA with ultrasound in the first 3 days affected treatment for PDA and in-hospital mortality among infants born (very prematurely) at 24-28 weeks' gestation. They used propensity matching to compare outcomes among 605 infants who were screened and 605 infants who were not, matching on the propensity score for screening. From the abstract:

> RESULTS Among the 1513 preterm infants with data available to determine exposure, 847 were screened for PDA and 666 were not; 605 infants from each group could be paired. Exposed infants were treated for PDA more frequently during their hospitalization than nonexposed infants (55.1%vs 43.1%; odds ratio [OR], 1.62 [95%CI, 1.31 to 2.00] …Exposed infants had a lower hospital death rate (14.2%vs 18.5%; OR, 0.73 [95%CI, 0.54 to 0.98]; ARR, 4.3 [95% CI, 0.3 to 8.3]).

a. PDA treatment was significantly more common among the "exposed" (screened) infants. Why didn't the propensity matching lead to equal numbers of treated infants in the two groups? [2]

The intention of propensity matching was to assemble screened and unscreened groups at comparable risk of being screened, based on measured covariates (available BEFORE screening). The group that was screened would be expected to have more PDA diagnoses made and treated, because screening finds PDAs.

b. Many infants in both groups did not have a PDA diagnosed. Should diagnosis of PDA have been included in the propensity score? Why or why not? [2]

No. As noted above, the propensity score should only include variables available at the time the decision to screen was made. The diagnosis of PDA presumably came later. Because the benefit of screening would likely come from diagnosing PDAs, we would not want to control for diagnosis of PDA because that might adjust away the benefit of screening.

c. Before matching the exposed infants (those who were screened) had higher propensity scores than the unexposed infants. Why would that be the case? [2]

This is exactly what you would expect if screening was not randomly assigned: measured covariates to some extent were able to predict screening. Those covariates are used to create the propensity score.

d. To supplement their propensity analysis, the authors also did an instrumental variable analysis, using neonatal unit preference for early screening (in quartiles) as the instrument for actual screening. An alternative approach would be to use screening itself as an instrument for PDA treatment in the propensity-matched groups.

i. If we used this latter approach, what would we need to assume about the relation between PDA treatment, screening, and in-hospital mortality? (Hint: You can assume that PDA treatment is the exposure, screening is the instrument and mortality is the outcome.) [2]

We would need to assume that PDA screening is associated with PDA treatment and that any association between screening and mortality is only via screening increasing the likelihood of PDA treatment. (Screening does not affect PDA mortality directly and the PDA-Mortality relation is not confounded.)

ii. (Extra credit) If the assumption(s) above are valid, what would the estimated effect of PDA treatment on mortality need to be to yield the 4.3% absolute risk reduction observed by the authors for PDA screening? (Hint: the answer is an absolute risk reduction and you can calculate it from numbers above.)

This is just like the calculation for the effect of the deposit-based smoking cessation intervention in footnote 3 of Chapter 9. We divide the observed risk reduction associated with the instrument (in this case a 4.3% absolute risk difference between those who were and were not screened) by the difference in proportions that actually received the treatment of interest (treatment for PDA):

4.3%/(55.1%-43.1%) = 35.8%.

Note that this absolute risk reduction seems implausibly large, suggesting either that the point estimate for the ARR is too high (the 95% CI goes down to an ARR of 0.3%) or that at least one of the assumptions of the instrumental variable analysis might not be valid. (For example, because screening was not randomly assigned, perhaps hospitals performing screening were also doing other good things not captured by measured covariates.)

iii. (Extra credit) To which subset of treated infants would that estimate apply?

Those who received the PDA treatment as a result of having been screened for PDA.

REFERENCES

1. Roze JC, Cambonie G, Marchand-Martin L, Gournay V, Durrmeyer X, Durox M, et al. Association Between Early Screening for Patent Ductus Arteriosus and In-Hospital Mortality Among Extremely Preterm Infants. JAMA. 2015;313(24):2441-8.