

Exercise on confounder evaluation

Daily folic acid supplementation around the time of conception is known to decrease risk of neural tube defects. Here we want to study the association between folic acid supplementation and neural tube defect using data from a case control study, where cases are mothers of infants with a neural tube defect and controls are mothers of infants with a birth defect thought to be unrelated to folic acid. The exposure of interest is presence vs. absence of daily intake of folic acid supplements. To simplify matters we assume that the only potential confounder of the association between folic acid and neural tube defects is variable C . We furthermore know that C is not an intermediate on the causal-path between folic acid and neural tube defect.

This exercise is based on the example described in: Hernan MA, Hernández-Dias S, Werler MM, and Mitchell AA. Causal Knowledge as a Prerequisite for Confounding Evaluation: An Application to Birth Defects Epidemiology. *Am J Epidemiol* 2002;155(2):176-84.

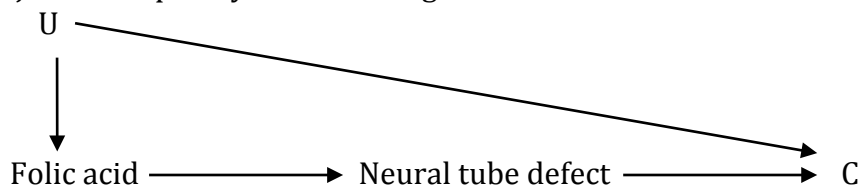
The following Table taken from the paper gives the actual observed numbers:

TABLE 4. Periconceptional folic acid supplementation ($E = 1$) and neural tube defects ($D = 1$), stratified by the covariate C , Slone Epidemiology Unit Birth Defects Study, 1992–1997

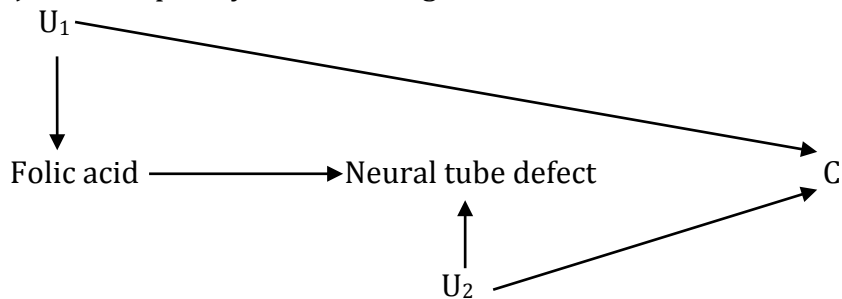
	$C = 1$		$C = 0$	
	$D = 1$	$D = 0$	$D = 1$	$D = 0$
$E = 1$	19	8	24	231
$E = 0$	100	46	94	658

1. Calculate the crude OR and the corresponding 95% confidence interval to see if folic acid seems to have an effect on the risk of neural tube defects
2. Calculate the Mantel-Haenzel estimate using C as confounder.
3. Investigate the association between folic acid and C for instance by calculating an appropriate OR along with the corresponding 95%-confidence interval.

4. Investigate the association between C and neural tube defect among unexposed mothers by calculating an appropriate OR along with the corresponding 95%-confidence interval.
5. Based on these observations, which analysis would be inclined to apply, the crude or Mantel-Haenzel based? Explain your reasoning.
6. What is the structural definition of a confounder, i.e. how it is visualized in a causal diagram?
7. If we assume the underlying causal structure between folic acid, neural tube defect and C to be as in the below figure. Which analysis is then the most appropriate, the crude or the adjusted? Explain your reasoning.



8. If we assume the underlying causal structure between folic acid, neural tube defect and C to be as in the below figure. Which analysis is then the most appropriate, the crude or the adjusted? Explain your reasoning.



9. If we assume the underlying causal structure between folic acid, neural tube defect and C to be as in the below figure. Which analysis is then the most appropriate, the crude or the adjusted? Explain your reasoning.



10. In the real application from the Hernan-paper, the potential confounder was stillbirth/therapeutic abortion. Make a DAG for this situation. Which analysis would you be inclined to apply, the crude or Mantel-Haenzel based? Explain your reasoning.