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Short Research Communication

Evaluating Epidemiological Evidence: A Simple Test

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Abstract

Epidemiological studies that investigate the relationships between health behaviors and diseases may be affected by both known and unknown confounding factors. Alcohol use is one of these behaviors that have been intensively investigated in epidemiological studies. This manuscript introduced a simple test that can identify confounded epidemiological studies. This approach is sensitive to both known and unknown confounders. It provides a new perspective to develop measures for evidence selection in the future.

Key words: evidence-based medicine; bias; epidemiology; causality; health behaviors

Some human behaviors are at least partly influenced by individuals' own health [1, 2]. For example people tend to quit or reduce their alcohol use when they experience ill health [3-5]. For cohort studies that investigate alcohol use and chronic disease outcomes, the influence of health on drinking behaviors could produce strong confounding effects which are difficult to block through multivariate analysis. It is impossible to tell whether the adjusted results are still manipulated by confounders or not. The following paragraphs will introduce a user-friendly test that tags confounded estimations.

The hypothesis that alcohol use at baseline affects mortality of chronic disease has been studied in many cohort studies [6]. Figure 1 employed the concept of casual diagrams developed by Pearl and Colleagues [7, 8] to illustrate the connections. It is hypothesized that Alcohol use at baseline (A2) affects mortality of chronic disease (E) through its biological effects on health after baseline (H3), and alcohol use before baseline (A1) affects mortality of chronic disease (E) through its biological effects on health at baseline (H2), which further affects health after baseline (H3). On the other hand, health influences people's drinking behaviors. In Figure 1, Health before baseline (H1) affects alcohol use before baseline (A1), and health at baseline (H2) affects alcohol use at baseline (A2). To investigate the effect of A2 on E, the confounding effects of H2 and other confounders (C) have to be blocked. If this hypothesis is tested in a randomized control trial, participants are randomly assigned to groups with different level of alcohol use since baseline. Randomization blocks confounding effects of health status and other factors, therefore any difference in mortality between groups is a result of difference in alcohol use. In cohort studies, alcohol use levels are self-determined. Multivariate analysis is conducted to block confounding effects of H2 and C. If effect of H2 and C is successfully blocked, the effect of A1 and H1 that passes through H2 will be blocked as well. This means for a given alcohol use level at baseline, the estimated risk will not be differed/affected by alcohol use before baseline (A1). In other words, the adjusted risk among participants with the same alcohol use level at baseline is expected to be the same regardless their alcohol use prior to baseline, if all confounding effects are removed. The mirror scenario in randomized controlled trial is that when testing the effects of a drug on a secondary event, possible confounding effect of prior medication use has to be removed (through randomization) [9]. Therefore within the same level of baseline alcohol use, any variation in adjusted risk estimates by prior alcohol use indicates the present of confounding ef-

fects. For example, most studies that compared the risk of chronic disease mortality between lifelong abstainers and former drinkers, observed risk difference between the two groups [6], and therefore the estimations from these studies are biased.

Data in Table 1 and Estimations in Table 2 provide a simple example to illustrate the general application of this confounding effect detection test. Let's assume that i) this study is to investigate the effect of a dietary supplement on the mortality; ii) the dietary supplement increases the mortality by 100%, so that the exposed-to-unexposed risk ratio equals to 2; iii) there were only three different risk levels at baseline: I1= 1 per 100 person years, I2=3 per 100 person years and I3= 5 per 100 person years. When randomization is applied, it is not necessary to control or stratify for the confounding effects, and the non-stratified exposed-to-unexposed risk ratio provides an unbiased estimate (Estimation 1).

If randomization is not available, non-stratified exposed-to-unexposed risk ratio produces a biased estimate (Estimation 2), and the presence of confounding effects will be detected by the test: the risk ratio by previous exposure status among non-users at baseline does not equal to 1 (= 1.25) (Test 1).

If the stratification of confounding effects is performed precisely, the confounding effects will be fully blocked (Estimation 3). In this case the risk ratio by previous exposure status among non-users at baseline equals to 1, which indicates the absence of residual confounding effects (Test 2).

If the stratification for confounding effect is not performed correctly, there will be residual confounding effects (Estimation 4). The presence of confounding effects will be detected by the test: the risk ratio by previous exposure among non-users at baseline does not equal to 1 (= 1.14) (Test 3).

Furthermore, it is rarely possible to assume that all confounding factors are known or measured in a given observational study. However this test can detect the effects of confounding factors without identifying these factors, and therefore it is effective towards unknown confounding factors.

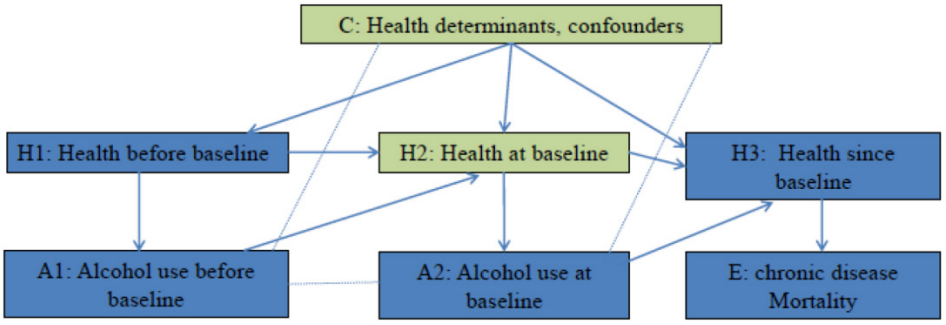

Figure 1. Testing the hypothesis: does alcohol use at baseline affect the mortality of chronic disease? Arrow line: Causal association, the direction of arrow indicates the cause-to-outcome direction. Dot line without arrow: Correlation

Table 1. Data for demonstration

Risk level at baseline	Exposure before baseline	Exposure at baseline			
		non-user		user	
		person-years	cases	Person-years	cases
Randomization in place (corresponding to Estimation 1)					
I1	non-user	10000	100	10000	200
	user	15000	150	15000	300
	Subtotal	25000	250	25000	500
I2	non-user	7500	225	7500	450
	user	7500	225	7500	450
	Subtotal	15000	450	15000	900
I3	non-user	2500	125	2500	250
	user	7500	375	7500	750
	Subtotal	10000	500	10000	1000
Non-randomized, Correct stratification of confounding effects (corresponding to Estimation 2, 3)					
I1	non-user	6000	60	14000	280
	user	6000	60	24000	480

	Subtotal	12000	120	38000	760
I2	non-user	7500	225	7500	450
	user	7500	225	7500	450
	Subtotal	15000	450	15000	900
I3	non-user	4000	200	1000	100
	user	12000	600	3000	300
	Subtotal	16000	800	4000	400
Non-randomized, Incorrect stratification of confounding effects (corresponding to Estimation 4)					
I1	non-user	6000	60	14000	280
	user	6000	60	24000	480
	Subtotal	12000	120	38000	760
I2 and I3	non-user	11500	425	8500	550
	user	19500	825	10500	750
	Subtotal	31000	1250	19000	1300

Table 2. Estimations of risk ratios based on data in table 1

Estimation 1	[(500+900+1000)/(25000+15000+10000)]/[(250+450+500)/(25000+15000+10000)]=2
Estimation 2	[(760+900+400)/(38000+15000+4000)]/[(120+450+800)/(12000+15000+16000)]=1.13
Test 1	[(60+225+600)/(6000+7500+12000)]/[(60+225+200)/(6000+7500+4000)]=1.25
Estimation 3	(760/38000)/(120/12000)=2; (900/15000)/(450/15000)=2; (400/4000)/(800/16000)=2; Weighted estimate = 2
Test 2	(60/6000)/(60/6000)=1; (225/7500)/(225/7500)=1; (600/12000)/(200/4000)=1.
Estimation 4	(760/38000)/(120/12000)=2; (1300/19000)/(1250/31000)=1.69; Weighted estimate= 1.74.
Test 3	(60/6000)/(60/6000)=1; (825/19500)/(425/11500)=1.14.

Competing Interests

The author has declared that no competing interest exists.

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