American Journal of Epidemiology

Vol. 181, No. 3
DOI: 10.1093/aje/kwu276
Advance Access publication:
January 14, 2015

Practice of Epidemiology

A Cautionary Note About Estimating Effects of Secondary Exposures in Cohort Studies

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Initially submitted April 24, 2014; accepted for publication September 11, 2014.

Cohort studies are often enriched for a primary exposure of interest to improve cost-effectiveness, which presents analytical challenges not commonly discussed in epidemiology. In this paper, we use causal diagrams to represent exposure-enriched cohort studies, illustrate a scenario wherein the risk ratio for the effect of a secondary exposure on an outcome is biased, and propose an analytical method for correcting for such bias. In our motivating example, maternal smoking (Z) is a cause of fetal growth restriction (X), which subsequently affects preterm birth (Y) (i.e., $Z \rightarrow X \rightarrow Y$); strong positive associations exist between both Z, X and X, Y; and enrichment for X increases its prevalence from 10% to 50%. In the X-enriched cohort, unadjusted and X-adjusted analyses lead to bias in the risk ratio for the total effect of Z on Y. After application of inverse probability weights, the bias is corrected, with a small loss of efficiency in comparison with a same-sized study without X-enrichment. With increasing interest in conducting secondary analyses to reduce research costs, caution should be employed when analyzing studies that have already been enriched, intentionally or unintentionally, for a primary exposure of interest. Causal diagrams can help identify scenarios in which secondary analyses may be biased. Inverse probability weights can be used to remove the bias.

bias (epidemiology); cohort studies; directed acyclic graph; epidemiologic methods; oversampling

Abbreviations: CI, confidence interval; IP, inverse probability.

Cohort studies are a central design in epidemiologic research, partly because they can allow for the assessment of a variety of exposure-outcome relationships. However, cohort studies are often enriched for a primary exposure of interest by design in order to improve cost-effectiveness (1). In general, enrichment entails oversampling 1 or more levels of the primary exposure and is sometimes referred to as "oversampling" or "exposure-dependent sampling" (2, 3).

Exposure enrichment may occur either by design or unintentionally. Examples of cohort studies intentionally exposure-enriched include registries of prenatal medication use alongside an unexposed reference population (4–6) and cohort studies of cancer patients and cancer-free controls (7, 8). While these studies can enhance comparability of classification procedures by including an internal reference group (9), the primary exposure distribution in the study cohort has been distorted. Matched cohort studies are also effectively exposure-enriched, as the ratio of exposed observations to unexposed observations is fixed by design. Although matching in cohort studies can effectively remove confounding at the design stage (10), the exposure enrichment remains in place. Studies can also oversample certain subpopulations unintentionally, thereby enriching the prevalence of specific exposures. Traditionally this has been an issue for all observational studies, but it has recently been a heightened concern with the advent of studies using Web-based recruitment, which could oversample populations with higher socioeconomic status due to their increased Internet access (11).

Exposure enrichment presents analytical challenges not commonly discussed in epidemiology. Chief among these is how to properly analyze exposure-enriched studies so as not to introduce bias when effects of secondary exposures are

evaluated. By "secondary exposure," we are referring to any exposure for the outcome of interest other than the primary (enriched) exposure of interest. Our objectives in this paper are to use causal diagrams (12) to represent primary exposure-enriched cohort studies, illustrate a scenario wherein the risk ratio for the average treatment effect of a secondary exposure is biased, and propose an analytical method for correcting for such bias. We will concentrate on a particular type of secondary exposure for which bias arises.

MOTIVATING EXAMPLE

Scenario

To illustrate a secondary exposure analysis in a primary exposure-enriched cohort study design, we introduce a simple scenario in which a secondary exposure Z (maternal smoking) is a cause of primary exposure X (fetal growth restriction), which is a cause of Y (preterm birth). Figure 1A depicts such a scenario, where maternal smoking has an indirect causal effect on preterm birth through fetal growth restriction but has no direct effect on preterm birth and is therefore not a confounder of the fetal growth restriction–preterm birth association (assume for illustration purposes that this is the case). Given this scenario, consider a hypothetical cohort of pregnant women with a marginal population prevalence of fetal growth restriction (defined dichotomously) of 10%. Suppose, in the population under study, that maternal smoking has a prevalence of 50%, with a 16% prevalence of fetal growth restriction among mothers who smoke and a 4% prevalence among mothers who do not smoke (Z, X risk ratio = 4). The population risk of preterm birth is 13%, with the risk being 4 times higher among pregnant women with fetal growth restriction (40%) than among those without fetal growth restriction (10%) (Z, X risk ratio = 4). Therefore, the secondary exposure has a strong direct causal effect on the primary exposure, and the primary exposure has a strong direct causal effect on the outcome. The expected frequencies of maternal smoking, fetal growth restriction, and preterm birth in a simple random sample of this population ($n = 1{,}000$) are presented in Table 1 (left side).

Table 1 (right side) shows the expected frequencies of these same factors in a 50% primary exposure-enriched sample of the same size ($n = 1{,}000$): Exposure enrichment results in a 5-fold enrichment of fetal growth restriction from its marginal prevalence of 10% in the population to 50% in the study sample. Figure 1B depicts this exposure enrichment, in which the box around the indicator S denotes selection into the primary exposure-enriched cohort study, affected only by fetal growth restriction status.

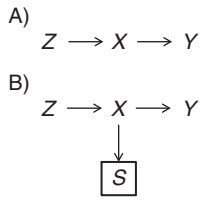

Figure 1. Causal diagrams for the example cohort study. A) Random sample; B) primary exposure-enriched sample. *S*, selection into the study; *X*, primary exposure (fetal growth restriction); *Y*, outcome (preterm birth); *Z*, secondary exposure (maternal smoking).

Table 1. Hypothetical Data From the Example Cohort Study[a]

	Random Sample			Primary Exposure-Enriched Sample		
	$Y=0$	$Y=1$	Total	$Y=0$	$Y=1$	Total
$X=1$						
$Z=1$	48	32	80	240	160	400
$Z=0$	12	8	20	60	40	100
Subtotal	60	40	100	300	200	500
$X=0$						
$Z=1$	378	42	420	210	23[b]	233
$Z=0$	432	48	480	240	27[c]	267
Subtotal	810	90	900	450	50	500
Total	870	130		750	250	

[a] X, primary exposure (fetal growth restriction); Y, outcome (preterm birth); Z, secondary exposure (maternal smoking).
[b] Rounded from $23.\bar{3}$.
[c] Rounded from $26.\bar{6}$.

Methods

Naive epidemiologic analysis of the average treatment effect of maternal smoking on preterm birth might proceed identically in Figures 1A and 1B; but if Figure 1B represents reality, then this analytical approach can result in bias. To demonstrate bias in the risk ratio under the study design shown in Figure 1A, we simulated a source population based on the distributions of maternal smoking, fetal growth restriction, and preterm birth in the expected random sample shown on the left side of Table 1. We then drew 50,000 samples of 1,000 participants under the 2 study designs (random sampling and 50% primary exposure-enriched sampling) and estimated the mean risk ratio, the mean standard error, and the Wald-type confidence interval coverage of the estimates using log binomial regression. Coverage was defined as the percentage of drawn samples with a 95% confidence interval that contained the true risk ratio, as determined from the risk ratio for Z, Y calculated from the expected frequencies for a random sample from Table 1 (left side).

RESULTS

Naive epidemiologic analysis

For the random-sample study design, the total effect of maternal smoking on preterm birth is modest, with a risk ratio of 1.33 (95% confidence interval (CI): 0.96, 1.84); this represents the true (casual) effect of Z on Y (Table 2). As expected from the causal diagram shown in Figure 1A, the effect of maternal smoking on preterm birth is null, and therefore biased, after adjustment for fetal growth restriction. In the 50%

Table 2. Risk Ratios From the Example Cohort Study for Causal Systems Based on Figure 1[a]

	Mean RR for the *Z*-*Y* Relationship	95% CI[b]	Mean SE[c]	Coverage, %[d]
Random sample				
Unadjusted (true effect)	1.33	0.96, 1.84	0.167	95
X-adjusted	1.00	0.72, 1.40	0.169	61
Primary exposure-enriched sample				
Unadjusted	1.60	1.24, 2.05	0.128	70
X-adjusted	1.00	0.79, 1.28	0.123	39
Weighted[e]	1.33	0.90, 1.96	0.198	95

Abbreviations: CI, confidence interval; RR, risk ratio; SE, standard error.
[a] *X*, primary exposure (fetal growth restriction); *Y*, outcome (preterm birth); *Z*, secondary exposure (maternal smoking).
[b] 95% CIs were calculated using mean log RR ± (1.96 × mean log SE) and then exponentiated for tabular display.
[c] SE of the log RR.
[d] Coverage was based on sampling of 50,000 simulations, each of size 1,000.
[e] Robust variance estimate.

exposure-enriched design, the unadjusted analysis of the effect of maternal smoking on preterm birth, which is conditioned on S by design, is also biased. Specifically, the risk ratio is 1.60 (95% CI: 1.24, 2.05), which is larger than the true total effect of 1.33. Additionally, as expected based on the causal diagram shown in Figure 1B, in the exposure-enriched design the risk ratio for the effect of maternal smoking on preterm birth adjusted for fetal growth restriction is null and therefore biased. Consequent to these biased estimates of effect is poor coverage of the true (causal) effect of Z on Y by the 95% confidence interval (Table 2).

Proposed solution

In our example, by conditioning on selection into the 50% enriched sample by design, the prevalences of maternal smoking, fetal growth restriction, and preterm birth all increase to an extent that the relationship between maternal smoking and preterm birth is artificially inflated (see Appendix for a proof illustrating this bias). This may seem counterintuitive, as conditioning on a descendent proxy would typically bias results toward the null with respect to the total causal effect (13). However, in situations such as our example—where all depicted relationships are positive, primary exposure enrichment goes from 10% to 50%, and conditioning is achieved by restriction to a certain subpopulation ($S = 1$)—then conditioning on a descendent proxy of X changes the distribution of all variables and can lead to upward bias. The direction and magnitude of bias appears to be a function of the direction and size of component effects, as well as the level of enrichment. Further study is needed to fully explore these relationships.

To correct this bias due to enrichment, we then apply stabilized inverse probability (IP) weights to the 50% exposure-enriched sample to create a reweighted sample with expected frequencies of maternal smoking, fetal growth restriction, and preterm birth identical to the random sample. The IP weights are defined as $w = P(S = 1)/P(S = 1 \mid X = x)$, where the denominator addresses bias and represents the sampling fraction given x and the numerator addresses efficiency and scales the weights so that the weighted sample sums to the observed sample size ($n = 1{,}000$). In our 50% enrichment example, the sampling fraction for observations with $X = 1$ was $500/(0.1N)$—that is, 500 exposed observations were selected among the 10% of the source population N with fetal growth restriction. The sampling fraction for observations with $X = 0$ was $500/(0.9N)$—that is, 500 unexposed observations were selected among the 90% of the source population without fetal growth restriction. Then the inverse of each sampling fraction was taken and multiplied by the scaling factor ($1{,}000/N$) so that sample weights summed to 1,000. Importantly, the actual size of the source population isn't necessary for calculating w, because N cancels. However, the proportion of the source population with the primary exposure is required. See Appendix Table 1 for details regarding stratum-specific IP weight calculations.

The IP-weighted risk ratio, which corrects for the exposure enrichment, is unbiased for the total effect of maternal smoking on preterm birth and results in a confidence interval which is slightly wider (95% CI: 0.90, 1.96) than that from the random sample (95% CI: 0.96, 1.84) (Table 2). Robust standard errors or bootstrapping is required to provide appropriate estimates of precision for IP-weighted estimates (14).

DISCUSSION

Estimation of the total effect of a secondary exposure in a cohort study enriched for a primary exposure can result in bias. This situation may be encountered in cohort studies that are secondarily analyzed for causes of the primary exposure. This bias is a consequence of controlling for an intermediate variable (or by study design its descending proxy, such as S in Figure 1B) and is a type of overadjustment bias (13), also referred to as "virtual collider bias" (15–18) due to unmeasured exogenous factors affecting the intermediate. As a result of primary exposure enrichment, the study cohort no

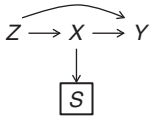

Figure 2. Causal diagram for the example cohort study representing the primary exposure-enriched sample with the addition of a direct effect of the secondary exposure on the outcome. *S*, selection into the study; *X*, primary exposure (fetal growth restriction); *Y*, outcome (preterm birth); *Z*, secondary exposure (maternal smoking).

longer represents the source population for the secondary analysis. IP weights based on sampling fractions can correct for this bias. When implementing exposure-enriched cohort studies, secondary analyses should be considered in the design phase so that sampling fractions can be estimated, which will allow for the appropriate application of IP weights.

The simple scenario we present can be further complicated if the secondary exposure also has a direct effect on the outcome, as shown in Figure 2. In this scenario, the unadjusted risk ratio in the exposure-enriched sample can be biased when estimating the total effect of the secondary exposure on the outcome, because the indirect effect operating through the primary exposure has been altered by design. Adjustment for the primary exposure will completely block the indirect effect, potentially leading to a total effect estimate that is biased toward the null. This is similar to the scenario depicted in Figure 1B; however, in that scenario, adjusting for the primary exposure completely nullified the effect of secondary exposure on the outcome, since the only path depicted was indirect.

In addition, there may also exist U, an unmeasured confounder of the primary exposure–outcome relationship, which is depicted in Figure 3. In this scenario, adjustment for X not only blocks the indirect path from Z to Y but also opens up a biasing path between Z and Y (via U) because of conditioning on X, which is a collider on the path $Z - X - U - Y$. For many primary exposure-enriched studies, key confounders of the primary exposure–outcome relationship will have been well-measured, so that bias due to unmeasured confounders is probably minor; however, this diagram points out that confounders of the primary exposure–outcome relationship may also need to be included in the analysis of a secondary exposure.

There are, of course, scenarios other than the ones we present above. For instance, the secondary exposure may operate through mechanisms that are completely independent of the primary exposure, and in such cases accounting for the primary exposure enrichment by IP weights will be unnecessary. The secondary exposure could also share a common cause with the primary exposure, making the primary exposure a potential confounder of the secondary exposure–outcome relationship. However, given that one never knows the true underlying diagram, one may wish to explore the impact of accounting for selection by use of IP weights in a sensitivity analysis.

In practice, exposure enrichment is achieved through study selection procedures. These include both the sampling frame designation and the study participation rates. Various methods are available for oversampling rare exposures using a multistage screening approach (2). When descriptive statistics for a specific population are the objective, the study cohort is often reweighted so that it is representative of the entire sampling frame. This can be accomplished by using IP weights (19) to rescale the sample observations. Here, we advocate the use of these IP weights for etiological analyses as well when the exposure of interest is a cause of the exposure which was used to enrich the study. IP weights have been similarly proposed for reweighting of case-control studies when additional outcomes are of interest (20); however, IP weighting may not be as efficient as some recently developed methods (21). These new methods have yet to be translated to the cohort study setting in which a secondary exposure is of interest. Alternative epidemiologic methods of selection bias correction may also be useful for removing bias in studies with exposure-enriched designs, such as the application of selection ratios (based on conditional selection probabilities) (22), probabilistic bias analysis (23), doubly robust estimation (24), and Heckman-type selection models (25).

Here, we present an example in which the study cohort is not representative of the source population for the secondary exposure. The value of representativeness in epidemiologic research has been questioned recently, with Rothman et al. (26) going so far as to say that representativeness should be avoided for the sake of enhancing internal validity. Here we have demonstrated an example in which an altered primary exposure distribution leads to incorrect inference about the magnitude of association between a secondary exposure and an outcome. Because secondary analyses are widespread as a cost-savings strategy in epidemiology, caution should be used when examining predictors or indications for a primary exposure that may itself have been enriched through study selection procedures.

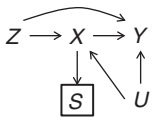

Figure 3. Causal diagram for the example cohort study representing the primary exposure-enriched sample with the additions of a direct effect of the secondary exposure on the outcome and a confounder of the primary exposure and the outcome. *S*, selection into the study; *X*, primary exposure (fetal growth restriction); *Y*, outcome (preterm birth); *Z*, secondary exposure (maternal smoking).

ACKNOWLEDGMENTS

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This work was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, US National Institutes of Health (E.F.S. and K.A.A.); the National Institute of Allergy and Infectious Diseases, US National Institutes of Health (grant R01-AI 100654 to S.R.C.); the Chercheur National Award from the Fonds de Recherche en Santé du Quebec (R.W.P.); and core support provided to the Montreal Children's Hospital Research Institute from the Fonds de Recherche en Santé du Quebec (R.W.P.).

We are grateful for the comments and suggestions provided by investigators and postdoctoral fellows in the Epidemiology Branch of the Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

A preliminary version of this analysis was presented at the 47th Annual Meeting of the Society for Epidemiologic Research, Seattle, Washington, June 24–27, 2014.

Conflict of interest: none declared.

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(Appendix follows)

APPENDIX

Here we present a mathematical proof of potential bias in the *Z*-*Y* relationship when analysis is restricted to $S = 1$ (S = selection into the study; Y = outcome; Z = secondary exposure). This potential bias may arise in situations where the relationship between Z and Y in a subpopulation is not equivalent to that in the whole population. For a detailed mathematical derivation of how the conditional covariance of Z and Y given S can result in bias, see the eAppendix "Conditional Covariance of E and D Given M" in the paper by Schisterman et al. (13).

Since $f(y|z)$ equals

$$f(y|z,S=1)P(S=1)+f(y|z,S=0)P(S=0) \quad \text{(A1)}$$

and the expected value is defined as

$$\int yf(y|z)dy = \int yf(y|z,S=1)P(S=1)dy + \int yf(y|z,S=0)P(S=0)dy,$$

then

$$\int yf(y|z)dy = P(S=1)\int yf(y|z,S=1)dy + P(S=0)\int yf(y|z,S=0)dy. \quad \text{(A2)}$$

Since

$$E(y|z) = \int yf(y|z)dy \quad \text{(A3)}$$

$$E(y|z,S=1) = \int yf(y|z,S=1)dy \quad \text{(A4)}$$

$$E(y|z,S=0) = \int yf(y|z,S=0)dy, \quad \text{(A5)}$$

by substituting equations A3–A5 into equation A2, we have

$$E(y|z) = P(S=1)E(y|z,S=1) + P(S=0)E(y|z,S=0).$$

Therefore, only when $P(S=0)=0$ does $E(y|z)$ equal $E(y|z,S=1)$; otherwise, $E(y|z) \neq E(y|z,S=1)$.

Appendix Table 1. Example Cohort Study Data and Calculation of the Inverse Probability Weight[a]

Z	*X*	*Y*	Random Sample	Exposure-Enriched Sample	IP Weight, *w*[b]
0	0	0	432	240	9/5
0	0	1	48	27[c]	9/5
0	1	0	12	60	1/5
0	1	1	8	40	1/5
1	0	0	378	210	9/5
1	0	1	42	23[d]	9/5
1	1	0	48	240	1/5
1	1	1	32	160	1/5
Total			1,000	1,000	

Abbreviation: IP, inverse probability.

[a] *S*, selection into the study; *X*, primary exposure (fetal growth restriction); *Y*, outcome (preterm birth); *Z*, secondary exposure (maternal smoking).

[b] The IP weight *w* was calculated as $P(S=1)/P(S=1|X=x)$, where $P(S=1)$ is estimated as n/N and $P(S=1|X=x)$ is estimated as $n_x/(p_xN)$, and where n_x and p_x are the number sampled with $X=x$ and the probability of $X=x$, respectively.

[c] Rounded from $26.\bar{6}$.

[d] Rounded from $23.\bar{3}$.