SPECIAL ARTICLE

Assessment and Control for Confounding by Indication in Observational Studies

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In the evaluation of pharmacologic therapies, the controlled clinical trial is the preferred design. When clinical trial results are not available, the alternative designs are observational epidemiologic studies. A traditional concern about the validity of findings from epidemiologic studies is the possibility of bias from uncontrolled confounding. In studies of pharmacologic therapies, confounding by indication may arise when a drug treatment serves as a marker for a clinical characteristic or medical condition that triggers the use of the treatment and that, at the same time, increases the risk of the outcome under study. Confounding by indication is not conceptually different from confounding by other factors, and the approaches to detect and control for confounding — matching, stratification, restriction, and multivariate adjustment — are the same. Even after adjustment for known risk factors, residual confounding may occur because of measurement error or unmeasured or unknown risk factors. Although residual confounding is difficult to exclude in observational studies, there are limits to what this "unknown" confounding can explain. The degree of confounding depends on the prevalence of the putative confounding factor, the level of its association with the disease, and the level of its association with the exposure. For example, a confounding factor with a prevalence of 20% would have to increase the relative odds of both outcome and exposure by factors of 4 to 5 before the relative risk of 1.57 would be reduced to 1.00. Observational studies have provided important scientific evidence about the risks associated with several risk factors, including drug therapies, and they are often the only option for assessing safety. Understanding the methods to detect and control for confounding makes it possible to assess the plausibility of claims that confounding is an alternative explanation for the findings of particular studies. J Am Geriatr Soc 47:749–754, 1999.

Key words: observational studies; methods; confounding by indication; sensitivity analyses

In the evaluation of pharmacologic therapies, the controlled clinical trial is the preferred design because randomization generally produces groups whose probability of the outcome of interest is comparable.[1] With adequate sample sizes, randomization balances both known and unknown risk factors for the outcome. For many pharmacologic therapies, however, the results of randomized clinical trials are not available.[2] For instance, many of the clinical trials comparing the newer antihypertensive agents, including angiotensin-converting enzyme inhibitors and calcium channel blockers, with low-dose diuretic therapy in terms of outcomes such as myocardial infarction are just now in progress.[3] In the absence of clinical trials results, the alternative designs are observational epidemiologic studies.

A traditional concern about the validity of findings from epidemiologic studies is the possibility of bias from uncontrolled confounding. Case-control and cohort studies compare outcomes between groups with different exposures, and confounding arises when the groups under comparison differ in other ways than the exposure alone. These differences may include demographic factors, behaviors, clinical characteristics, medical conditions, or treatments. Some exposures are more liable to confounding than others. When the outcome is an unintended or unanticipated effect of the exposure — the unexpected thrombotic complications such as deep venous thrombosis and pulmonary embolism associated with the early oral contraceptives are a good example — confounding is less likely to occur than when the outcome is an intended effect of the exposure.[4,5]

The potential problem of intended effects is likely to arise when the exposure of interest is a medication or a medical procedure, and it is often called confounding by indication or, sometimes, channeling bias.[6–9] In the example of the association between myocardial infarction and the use of calcium channel blockers among hypertensive patients,[10] the argument runs as follows: calcium channel blockers are used to treat angina pectoris as well as hypertension; angina pec-

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toris is a major risk factor for myocardial infarction; because the use of calcium channel blockers is simply a marker for high-risk angina patients, the association between the use of calcium channel blockers and the incidence of myocardial infarction is, therefore, not a causal one. This argument, offered by a number of commentators,[11–14] describes perfectly the problem of confounding by indication. The purpose of this article is to describe several analytic approaches that make it possible in some observational studies of medication effects to detect and control for confounding by indication.

Definition and Analytic Approaches

Consider an observational study to determine whether a certain exposure affects the risk of a certain outcome. To be a confounder in this study, the factor must be associated with *both* the outcome and the exposure. Often, confounders are contributing causes of the outcome although other noncausal associations with the outcome status may also qualify: for example, if the factor affects recognition of the outcome. Factors whose association with the exposure derives solely from being a consequence of the exposure do not qualify as confounders; they may instead be mediating variables.

Confounding by indication may arise when a drug treatment serves as a marker for a clinical characteristic or medical condition that triggers the use of the treatment and that, at the same time, increases the risk of the outcome under study. Confounding by indication is not conceptually different from confounding by other factors, and the approaches to control for confounding by indication are the same: matching, stratification, restriction, and multivariate adjustment.[15–18]

In a stratified analysis, for instance, the study population is divided into two groups according to the presence or absence of the potential confounding factor, and the association between the exposure and the outcome is examined separately within each stratum. Depending on the results of the stratified analysis, adjustment or restriction may be appropriate. Table 1 presents several hypothetical examples based on an unadjusted relative risk of 3. In example No. 1, the stratum-specific relative risks are both equal to the unadjusted relative risk of 3. Here, there is no confounding, and adjustment is not necessary. In examples No. 2 and No. 3, the stratum-specific relative risks are similar, and both are either higher or lower than 3. Confounding is present, and for each example, adjustment, which will produce a weighted average of the two stratum-specific relative risks, is appropriate.

In examples No. 4 and No. 5, the two stratum-specific relative risks are very different; the stratification factor appears to modify the effect of the treatment on the outcome, and the stratum-specific relative risks should not be combined. The alternatives are either to present the stratum-specific relative risks separately or to restrict the analysis to subjects who are free of the potential confounding factor. Confounding by indication simply cannot occur among subjects who do not have the potential confounding factor, and when the indication can be measured accurately, restriction of the analysis to subjects without the indication excludes the possibility of confounding by that indication.

A special form of restriction used to control for confounding by indication is the direct comparison of treatments that have the same indications. For instance, beta-blockers and calcium channel blockers are commonly used to treat both hypertension and angina, and in this instance, users of beta-blockers can serve as the reference group for users of calcium channel blockers. Even with this approach, confounding can still occur if the two groups differ in the severity of disease underlying the indication.

Illustration of the Analytic Approaches

The data used in this example come from a case-control study of patients with treated hypertension.[10] The setting was Group Health Cooperative of Puget Sound (GHC). During the study period, cases had a first fatal or nonfatal myocardial infarction, and controls were a stratified random sample of GHC enrollees without a myocardial infarction and matched to the cases on age, sex, and calendar year. Data collection included a review of medical records and telephone interviews with consenting subjects. The use of antihypertensive medications was assessed by data retrieved from the prospectively collected information in the computerized pharmacy database at GHC. The calcium channel blockers in use at GHC were short-acting agents. Odds ratios were used to estimate relative risks (RR).

In this case-control study, traditional risk factors such as current smoking (RR = 2.1), a history of diabetes (RR = 2.6), and the presence of clinical cardiovascular disease, mainly angina (RR = 2.1), were clearly associated with the risk of myocardial infarction. To be confounding factors in the association with myocardial infarction, these conditions must also be associated with the exposure, which was antihypertensive drug treatment. Although there was little asso-

Table 1. Hypothetical Effects of Stratification by a Potential Confounding Factor for an Association with a Crude (Unstratified) Relative Risk (RR) = 3*

	Stratification			
Example	Stratum I (Factor Present)	Stratum II (Factor Absent)	Adjust?	Comment
1	3.0	3.0	No	Crude and stratum-specific RRs are equal
2	1.9	2.1	Yes	Crude RR overestimates stratum-specific RRs
3	4.2	3.7	Yes	Crude RR underestimates stratum-specific RRs
4	1.0	6.1	No	Stratification factor modifies exposure effect
5	3.8	0.6	No	Stratification factor modifies exposure effect

* The relative risks are shown for each stratum of 5 hypothetical examples when the overall unadjusted and unstratified relative risk is 3.0. The stratification factor serves as a confounder when the crude RR consistently overestimates or underestimates the stratum-specific RRs (as in examples 2 and 3). The stratification factor serves as an effect modifier when stratum-specific RRs are clearly different (as in examples 4 and 5).

ciation between smoking and any of the drug treatments (see Table 2 in ref. 10), diabetes and cardiovascular disease were associated with several drug treatments.

With diuretics used as the reference group, the use of beta-blockers and calcium channel blockers, both indicated for the treatment of angina, might be serving as markers of subjects with angina and convey a higher risk of myocardial infarction. Table 2 summarizes the analysis stratified on the presence or absence of previous clinical cardiovascular disease. Consider single drug users of beta-blockers. The unadjusted relative risk was 1.26. In the stratified analysis, the unadjusted relative risk was 1.83 among those with clinical cardiovascular disease and 1.00 among those without clinical cardiovascular disease. Several explanations are possible. First, it is conceivable, but unlikely,[19] that the use of beta-blockers has an adverse effect on patients with existing clinical cardiovascular disease. Second and more likely, this pattern of relative risks is also what one would expect to see when the use of a drug is serving as a marker of a clinical condition that itself carries an increased risk of the outcome.

This pattern of different risks across strata also appears among users of calcium channel blockers, both those with and those without diuretics. For this reason, restriction of the analysis to subjects who were free of clinical cardiovascular disease is appropriate when users of diuretics serve as the reference group. Adjustment for other potential confounding factors, including diabetes, smoking, and pretreatment blood pressures, had little effect on the relative risks observed among subjects free of clinical cardiovascular disease (last set of columns in Table 2).

The analysis presented in Table 3 is restricted to subjects who used beta-blockers or calcium channel blockers, two drugs that have the same indications. Here, the users of beta-blockers serve as the reference group. The unadjusted relative risk for users of calcium channel blockers was 1.78. Among subjects with and without cardiovascular disease, the relative risks were 1.69 and 1.52, respectively. These stratum-specific relative risks, both lower than 1.78, were similar, so restriction was not necessary, and adjustment was appropriate. The weighted average of the stratum-specific relative risks was 1.59. The difference between 1.78 and 1.59 represents the confounding caused by the modest association between the use of calcium channel blockers and the presence of clinical cardiovascular disease. Moreover, there was little additional confounding from other factors. After adjustment for the other confounding factors, the relative risk was 1.57 (95% CI, 1.21–2.04). Thus, adjustment for cardiovascular disease was adequate to control for confounding by indication in this example.

It is also possible for the dose of a drug to serve as a confounding factor. For example, subjects on higher doses of calcium channel blockers might have more severe high blood pressure. In analyses presented in the original paper,[10] users of low-dose beta-blockers served as the reference group, and increasing doses of calcium channel blockers were indeed associated with higher risks of myocardial infarction (trend $P = .003$). In contrast, increasing doses of beta-blockers were also associated with lower risks of myocardial infarction (trend $P = .035$). These dose-response findings, which went in opposite directions, made confounding by dose as a proxy for the severity of high blood pressure largely an implausible explanation.

Residual Confounding and Sensitivity Analyses

In particular studies, uncontrolled confounding may occur for several reasons. Some risk factors for an outcome may not have been identified. Among the known risk factors for an outcome, some may not have been measured for a variety of reasons, including cost and difficulty. Even after adjustment for known risk factors that are assessed in particular studies, residual uncontrolled confounding may occur insofar as the confounding factors are measured with error.[17,20,21] The possibility of residual uncontrolled confounding from known or unknown factors is difficult to exclude, and, as such, it is one of the main criticisms of observational studies.[14]

Table 2. Association Between Myocardial Infarction and Antihypertensive Drug Therapies Stratified on the Presence or Absence of Clinical Cardiovascular Disease (CVD): Single-Drug Users of Diuretics as Reference Group*

	All subjects			With CVD			Without CVD				
	Unadjusted			Unadjusted			Unadjusted			RF Adjusted	
Drug	Case	Cntl	RR	Case	Cntl	RR	Case	Cntl	RR	RR	95% CI
Diuretics	124	541	1.00	25	89	1.00	99	452	1.00	1.00	(reference)
β-blockers											
Alone	89	308	1.26	38	74	1.83†	51	234	1.00	1.09	0.74–1.63
With diuretics	52	221	1.03	18	60	1.07	34	161	0.96	0.97	0.62–1.52
Calcium-channel blockers											
Alone	101	236	1.87‡	45	66	2.43‡	56	170	1.50†	1.58	1.04–2.39
With diuretics	66	108	2.67‡	42	48	3.11‡	24	60	1.83†	1.70	0.97–2.99
ACE inhibitors											
Alone	45	188	1.04	13	29	1.60	32	159	0.92	1.01	0.62–1.62
With diuretics	15	80	0.82	5	14	1.27	10	66	0.69	0.66	0.32–1.37

* Abbreviations: RR = relative risk, estimate from the odds ratio; RF = risk factor; CVD = cardiovascular disease; CI = confidence interval; Cntl = controls. The last column of RRs was adjusted for age, gender, calendar year, smoking, diabetes, pre-treatment systolic blood pressure, duration of hypertension, physical activity and education.

† $P < 0.05$.

‡ $P < 0.01$.

Table 3. Association Between Myocardial Infarction and Antihypertensive Drug Therapies Stratified on the Presence or Absence of Clinical Cardiovascular Disease (CVD): β-Blockers as Reference Group*

	All subjects			With CVD			Without CVD			All Subjects CVD adjusted	
Drug	Case	Cntl	RR	Case	Cntl	RR	Case	Cntl	RR	RR	95% CI
β-blockers	161	623	1.00	64	155	1.00	97	468	1.00	1.00	(reference)
Ca channel blockers	223	485	1.78†	128	183	1.69†	95	302	1.52†	1.59	1.25–2.02

* Abbreviations: RR = relative risk, estimate from the odds ratio; CVD = cardiovascular disease; Cntl = controls; CI = confidence interval; Ca-channel blockers = calcium-channel blockers. Additional adjustment for risk factors as well as CVD reduced the association from 1.59 down to 1.57 (95% CI = 1.21–2.04).
† $p < 0.01$.

While this possibility of residual confounding often looms large, there are limits to what this "unknown" confounding can explain. The degree of confounding depends in a predictable way on the prevalence of the putative confounding factor, the level of its association with the disease, and the level of its association with the exposure. Using methods adapted from Rosenbaum and Rubin,[22,23] Table 4 summarizes the effects of an unknown confounding factor with prevalences of 20 and 40%. This unknown factor can represent a single unknown or unmeasured factor, or it can be thought of as incorporating the uncontrolled residual confounding that might result from measurement error in a known risk factor.

In the case-control study,[10] the risk of myocardial infarction in users of calcium channel blockers, compared with

Table 4. Sensitivity Analysis of the Effect of an Unknown Confounding Factor on the Association Between the Risk of Myocardial Infarction and the Use of Calcium Channel Blockers (RR = 1.57) for Two Hypothetical Prevalences*

Prevalence of unknown confounder = 40%

Relative odds of the use of CCBs	Relative odds of myocardial infarction										
	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
1.0	1.57	1.57	1.57	1.57	1.57	1.57	1.57	1.57	1.57	1.57	1.57
1.5	1.57	1.51	1.47	1.43	1.41	1.39	1.37	1.36	1.35	1.34	1.33
2.0	1.57	1.46	1.40	1.35	1.31	1.27	1.25	1.23	1.21	1.19	1.18
2.5	1.57	1.43	1.35	1.28	1.23	1.19	1.16	1.14	1.11	1.09	1.07
3.0	1.57	1.41	1.31	1.24	1.18	1.14	1.10	1.07	1.04	1.02	1.00
3.5	1.57	1.39	1.28	1.20	1.14	1.09	1.05	1.02	0.99	0.97	0.95
4.0	1.57	1.38	1.25	1.17	1.11	1.06	1.01	0.98	0.95	0.93	0.90
4.5	1.57	1.36	1.24	1.15	1.08	1.03	0.98	0.95	0.92	0.89	0.87
5.0	1.57	1.35	1.22	1.13	1.06	1.00	0.96	0.92	0.89	0.86	0.84
5.5	1.57	1.34	1.21	1.11	1.04	0.98	0.94	0.90	0.87	0.84	0.82
6.0	1.57	1.34	1.19	1.10	1.02	0.97	0.92	0.88	0.85	0.82	0.80

Prevalence of unknown confounder = 20%

Relative odds of the use of CCBs	Relative odds of myocardial infarction										
	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0
1.0	1.57	1.57	1.57	1.57	1.57	1.57	1.57	1.57	1.57	1.57	1.57
1.5	1.57	1.52	1.49	1.47	1.45	1.44	1.42	1.41	1.41	1.40	1.39
2.0	1.57	1.49	1.43	1.39	1.36	1.33	1.31	1.30	1.28	1.27	1.26
2.5	1.57	1.46	1.38	1.33	1.29	1.25	1.23	1.21	1.19	1.17	1.16
3.0	1.57	1.43	1.34	1.28	1.23	1.19	1.16	1.13	1.11	1.09	1.08
3.5	1.57	1.41	1.31	1.23	1.18	1.14	1.10	1.07	1.05	1.03	1.01
4.0	1.57	1.39	1.28	1.20	1.14	1.09	1.05	1.02	1.00	0.97	0.96
4.5	1.57	1.37	1.25	1.17	1.10	1.05	1.01	0.98	0.95	0.93	0.91
5.0	1.57	1.36	1.23	1.14	1.07	1.02	0.98	0.94	0.92	0.89	0.87
5.5	1.57	1.35	1.21	1.11	1.05	0.99	0.95	0.91	0.88	0.86	0.84
6.0	1.57	1.33	1.19	1.09	1.02	0.97	0.92	0.89	0.85	0.83	0.81

* CCB = calcium-channel blockers Stronger associations of the unknown confounder with the disease and the outcome are indicated by increasing relative odds, and a relative odds of 1 means no association. The tables list the estimated RR after adjustment for an unknown confounding factor that has various levels of associations with the disease and the exposure. For an unknown confounder that (1) has a prevalence of 20%, (2) doubles the odds of a myocardial infarction, and (3) doubles the odds of using CCBs, adjustment for such a confounder would reduce estimated relative risk from 1.57 down to 1.43.

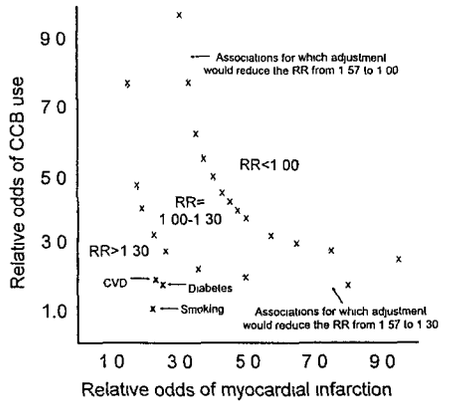

Figure 1. Effect of adjustment for an unknown confounder on a relative risk (RR) of 1.57. The short-dashed line represents the association of the unknown confounder with various combinations of the myocardial infarction and calcium channel blocker use required to move an RR of 1.57 down to 1.00. The long-dashed line represents the associations required to move the RR of 1.57 down to 1.30, which would have remained statistically significant at the .05 level. Levels of associations with myocardial infarction and calcium channel blocker use (CCB) use (respectively) for typical risk factors such as a history of diabetes (2.5 and 1.8), current smoking (2.2 and 1.04), and clinical cardiovascular disease (2.3 and 2.0) are marked on the figure.

users of beta-blockers, was 1.57 after adjustment for confounding factors that were measured. Table 4 represents the influence of adjustment for a hypothetical unknown confounding factor on this association (RR = 1.57) according to the strength of its association with the risk of myocardial infarction (columns) and according to the strength of its association with the use of calcium channel blockers (rows). For instance, adjustment for an unknown confounding factor that doubled the relative odds of myocardial infarction and doubled the relative odds of the use of calcium channel blockers would decrease the relative risk from 1.57 to 1.40 if its prevalence was 40% and to 1.43 if its prevalence was 20%. With a prevalence of 20%, the unknown confounding factor would have to increase the relative odds of disease by a factor of 5 and simultaneously increase the odds of exposure by a factor of 4 in order for adjustment to remove completely (RR = 1.00) the association between calcium channel blockers and myocardial infarction in the case-control study. In this study, we believe that plausible confounding factors with such high levels of associations are unlikely to be present. In these data, for instance, major risk factors such as smoking, diabetes, and clinical cardiovascular disease increased the risk of myocardial infarction by a factor of only 2.1 to 2.6.

Notice that in the first row and the first column of each part of Table 4, the relative risk remains constant at 1.57. This invariance illustrates the point that to be a confounder, the potential confounding factor has to be associated both with the exposure and with the outcome. Factors that are unassociated (RR = 1.00) with either the exposure or the outcome cannot be confounding factors. For any prevalence, the degree of the associations determines the level of confounding.

Figure 1 illustrates the effects of adjustment for an unknown confounding factor with a prevalence of 20% on a relative risk of 1.57. The short-dashed line is an isobar that connects the combinations of associations with myocardial infarction and use of calcium channel blockers required to reduce the relative risk from 1.57 to 1.00. The long-dashed line connects the combinations required to reduce the relative risk from 1.57 to 1.30. Given its standard error, a relative risk of 1.30 is the lowest that would be statistically significant at $P = .05$. Thus, any unknown or unmeasured confounding factor whose associations with the myocardial infarction and calcium channel blocker use place it below and to the left of the long-dashed line would have reduced the relative risk from 1.57 to a value larger than 1.30. Similarly, any confounding factor whose associations place it above and to the right of the short-dashed line would have reduced the relative risk from 1.57 to a value less than 1.0. The levels of associations for typical risk factors, including diabetes, smoking, and cardiovascular disease, are shown in Figure 1. In other words, individual unknown or unmeasured confounding factors similar in prevalence and predictive power to these major risk factors would have had little or no effect on the interpretation of the association between the use of calcium channel blockers and the risk of myocardial infarction in this study.

Concluding Observations

Several commentators have suggested that the mere possibility of unmeasured or unknown confounding requires relative risks of 3 — or even 7 — before the findings of observational studies can be believed.[14,24] These hypothetical unknown confounding factors would need to have extraordinarily large associations with the outcome and the exposure to move a relative risk from 7 down to 1. As illustrated in Figure 1, a confounding factor with a prevalence of 20% would have to increase the relative odds of both outcome and exposure by factors of 4 to 5 before the relative risk of 1.57 would be reduced to 1.00.

The findings of observational studies can, of course, be affected by other biases. Selective misclassification, when present for either the exposure or the outcome, represents a serious threat to validity. Other problems in the design or analysis can have important effects on the results. Selection bias is an example. In another case-control study of calcium channel blockers and myocardial infarction,[25] the authors applied entry criteria that were different for the cases and the controls. Insofar as this difference in entry criteria affected their findings, selection bias remains an alternative explanation for their findings.

Despite their potential problems, observational studies have provided important scientific evidence about the risks associated with a number of risk factors, including medications such as beta-agonists,[26] exogenous estrogens,[27–30] and nonsteroidal anti-inflammatory agents.[31,32] Observational epidemiologic studies are often the only option for assessing safety. Although concern about potential confounding is both important and appropriate, approaches to detecting and controlling confounding are available, and, indeed, there are mathematical limits to what unmeasured or unknown confounding can explain. As Walker and Stampfer suggest,[9] confounding represents "an alternative storyline." Given the data and the analysis presented, readers need to assess seriously the plausibility of the alternative storylines.[33]

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