

## Accepting the Limits of Ecologic Studies: Drs. Greenland and Robins Reply to Drs. Piantadosi and Cohen

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We thank Drs. Piantadosi (1) and Cohen (2) for their comments on our commentary (3). Because we and Dr. Piantadosi agree on virtually all the methodological points we raised, we will focus our reply on Dr. Cohen's comments. Before doing so, however, we wish to make one point of clarification regarding the mathematical findings (cited by Dr. Piantadosi (1)) that ecologic and individual-level associations will generally disagree if the exposure and covariate are correlated within groups, and at the individual level there is exposure-covariate interaction (effect modification) on the linear regression scale. The resulting disagreement is usually interpreted as indicating that ecologic bias is present. Nevertheless, when such disagreement occurs, it is at least logically possible that the true effect under study is closer to the ecologic association than the individual-level association (as in example 1 of our paper). In other words, mere disagreement between ecologic and individual-level results is not a demonstration that the ecologic results are invalid, for individual-level results are themselves subject to many biases. Only external considerations of possible biases and biology enable researchers to rationally prefer one set of results to another.

Unfortunately, Dr. Cohen goes beyond these points to assert that "the ecologic fallacy" (which is really a family of biases including ecologic confounding and cross-level bias) does not apply to testing a linear-no threshold theory (that is, testing whether disease incidence varies linearly with exposure dose). We continue to maintain that his assertion is wrong. Indeed, in

our paper, we show that both cross-level bias and ecologic confounding can bias tests of the linear-no threshold theory. For instance, example 5 of our paper (3) is an illustration in which

- 1) there is *no* radon effect, linear or otherwise; *but*
- 2) due to residual ecologic confounding, the ecologic test of the linear-no threshold hypothesis is grossly biased toward rejecting the hypothesis in favor of a *negative* association, even after confounder adjustment (just like that seen in the studies by Cohen (4) and Cohen and Colditz (5)); and
- 3) the test of the theory using individual-level data from the same population would be valid.

Furthermore, our example 8 can represent a study in which

- 1) a linear-no threshold model is correct, with positive dose-response;
- 2) there is no ecologic confounding; yet
- 3) due to potentially severe cross-level bias from the individual-level exposure-smoking interaction, the ecologic test of the linear-no threshold hypothesis could be grossly biased toward rejecting the hypothesis in favor of a negative association; and
- 4) the test of the theory using individual-level data from the same population would be valid.

Why does Cohen continue to claim the ecologic fallacy is not possible in testing a linear-no threshold theory, when we have shown that it *is* possible? We suspect it is

because he has amassed certain ancillary data bearing on the extent of biases in his studies, and has concluded that the biases are probably small in his studies. He may be right about his studies, although there are reasons to doubt this (1, 6). Regardless of the validity of his results, his arguments are completely context-specific (that is, specific to his studies of radon and lung cancer), and do not generalize beyond that context in any mathematical fashion, despite his claims to the contrary.

In his comment (2), Cohen makes further assertions that we regard as wrong or misleading. For example, he asserts that the dependence of lung-cancer risk on cigarettes that we used in our example 3 "is grossly inconsistent with available information on that subject." In fact, the dependence we used *is* consistent with the data on smoking and lung cancer used by other authors (7), and the rate ratio for the effect of one pack per day in our examples is only  $\exp[0.1(20)] = 7.4$ , less than that seen in most studies.

Early in his comment, Cohen fails to distinguish between ecologic measurements of confounders and actual confounder levels when he claims "good data are available on about a hundred potential confounding factors" in his study. Contrary to his implications, the actual data he has are mostly county-level summaries, which are not sufficient to create internally homogeneous strata. For example, stratification of counties on median income does not create strata within which the counties have homogenous income distributions.

The ecologic summaries used by Cohen are chiefly unadjusted means and percentages (4, 5). As we tried to emphasize in our commentary (3), even when used for stratification, such summaries can be inadequate for confounder control, especially when nonlinear dependencies and interactions are present (as with cancer incidence). Furthermore, even with no misclassification of the exposure or confounder, it is possible for adjusted tests and estimates to be more biased than the crude tests and estimates (as

shown in example 4 of our commentary). This is true, regardless of whether adjustment is carried out by stratification or regression methods. All of Cohen's results are logically subject to such concerns.

Cohen is correct when he asserts that statistical uncertainty is not a major factor in his studies, whereas such uncertainty is usually important in individual-level studies. We do, however, find misleading his use of the phrase "statistically valid" to refer to the number of standard errors an estimate is from the null. A test is statistically valid if the test rejects at no more than its nominal (stated) alpha level when the null hypothesis is correct (8). The distance of a point estimate from the null value is no indication of validity, since it is as much a function of bias as it is of true effects.

In our commentary (3) and previous work (e.g., 9) cited therein, we have criticized earlier arguments given by Cohen in defense of ecologic studies, including those he has presented here (2). Having done so, we find ourselves in agreement with Cohen on two general points. First, the potential problems of ecologic studies should not lead one to overlook any analogous problems in individual-level studies. Cohen is wrong in stating that *every* problem we discuss applies to individual-level studies of lung cancer risk (for example, there can be no cross-level bias in such studies); nonetheless, he is correct in pointing out that limitations of individual-level measurements threaten the validity of individual-level studies, as well as the ecologic studies that depend on these measurements (although the biases produced by these limitations can be very different in ecologic and individual-level studies (10)).

Second, we agree that ecologic studies should not be rejected automatically. We say this, even though *any* ecologic study is potentially vulnerable to ecologic biases. For, regardless of the flaws in Cohen's defense, the logical possibility of a bias in his (or any) study should not be taken as evidence that the bias is actually present. To paraphrase Cohen's conclusion, *any* study,

ecologic or not, should be judged only after careful consideration of its merits and any relevant background information.

All study designs have inherent limitations: this is true even of randomized trials, which can suffer from noncompliance, loss to follow-up, and biased ascertainment. Ecologic studies have and will continue to serve valuable functions, such as screening potential risk factors when no strong factors have been discovered. In studies of contagious diseases, for which ecologic effects (such as herd immunity) can be paramount, ecologic data will remain essential (11). It thus seems to us that the major problem with the ecologic design is not its limitations, but rather the relatively poor understanding of those limitations. Too often, as in Cohen's comment (2), it is implied that control of available ecologic variables is likely to remove most or all of the ecologic biases. But, as we have attempted to show in our examples, ecologic biases may persist or even be worse after control of ecologic variables (3, 9, 12). One solution to this problem is to obtain individual-level data by conducting surveys within the ecologic units, and then combine these data with the ecologic data in a hybrid analysis (13). Of course, the survey data must be of reasonable quality and must be combined with the ecologic data in an appropriate manner in order to realize the potential benefits of the hybrid analysis.

In closing, we wish to point out that our commentary was intended as a general discussion of ecologic studies; the radon-lung cancer controversy served only as a source of examples. Nonetheless, Dr. Cohen's focus on the controversy leads us to make the following observations: There have now been numerous ecologic studies of indoor radon and lung cancer. Stidley and Samet (6) reviewed 15 such studies; they judged that seven showed a positive association, six showed no association, and two (including Cohen's) showed a negative association. Stidley and Samet discussed the shortcomings of each of these studies and argued that

*none* of them (including Cohen's) have provided reliable information on the radon-lung cancer association. This is a considerably more pessimistic view than Cohen's.

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