The Semi-individual Study in Air Pollution Epidemiology: A Valid Design as Compared to Ecologic Studies

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The assessment of long-term effects of air pollution in humans relies on epidemiologic studies. A widely used design consists of cross-sectional or cohort studies in which ecologic assignment of exposure, based on a fixed-site ambient monitor, is employed. Although health outcome and usually a large number of covariates are measured in individuals, these studies are often called ecological. We will introduce the term semi-individual design for these studies. We review the major properties and limitations with regard to causal inference of truly ecologic studies, in which outcome, exposure, and covariates are available on an aggregate level only. Misclassification problems and issues related to confounding and model specification in truly ecologic studies limit etiologic inference to individuals. In contrast, the semi-individual study shares its methodological and inferential properties with typical individual-level study designs. The major caveat relates to the case where too few study areas, e.g., two or three, are used, which render control of aggregate level confounding impossible. The issue of exposure misclassification is of general concern in epidemiology and not an exclusive problem of the semi-individual design. In a multicenter setting, the semi-individual study is a valuable tool to approach long-term effects of air pollution. Knowledge about the error structure of the ecologically assigned exposure allows consideration of the impact of ecologically assigned exposure on effect estimation. Semi-individual studies, i.e., individual level air pollution studies with ecologic exposure assignment, more readily permit valid inference to individuals and should not be labeled as ecologic studies. Key words: air pollution, cross-sectional study, ecologic fallacy, epidemiology, study design.

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A major purpose of epidemiologic research is the identification of health-comprising risk factors or exposures; such identification is a prerequisite for scientifically based public health policy and preventive action. Although epidemiologic methods are unable to assess directly biologic causal mechanisms, epidemiology nevertheless intends to establish causal relationships. When epidemiologic causal inference is applied to public health practice, the concept of a cause may not have the mechanistic quality of a cause in natural sciences. A cause in the field of public health may be social status, family disease history, nutritional habits, living in some mixture of (source related) air pollution, or smoking cigarettes. In this context, cause is action oriented and may be efficiently prevented well before any specific knowledge about the pathophysiologic mechanisms of disease induction or phenotypic disease expression is available. Examples of the successful history and application of epidemiology are the closing of the Broad Street Pump in the last century (1) to prevent cholera or the proof that smoking is a strong risk factor for a variety of diseases. According to this concept of cause, epidemiologic science may use indicator measures for the true unknown (biologic) cause. For example, Snow (1) used the water company as an indicator of the unknown causative agent, and Doll and Hill (2) used the number of cigarettes smoked—rather than any specific agent out of the complex toxic mixture of smoke—as a suitable proxy measure. This concept is particularly useful in the assessment of effects of complex causal factors such as mixtures of ambient air pollutants. Accordingly, the assessment of health effects of normal air pollution heavily relies on epidemiologic studies. In fact, in terms of long-term impact, epidemiology may be the only scientific approach to elucidate the causal effects.

Given that epidemiologic studies evaluate causality only indirectly through proxy exposures of varying specificity, it is important to have guidelines to infer causality based on epidemiologic studies. Similar to the traditional criteria of causality applied to the investigation of infectious agents (3), Hill (4) formulated such guidelines for epidemiology, namely as applied to cancer risk factors. With some modifications (5), this reasoning also applies to air pollution epidemiology. A major step in the process to assess causality relates to reviewing available studies and to select useful, i.e., etiologically valid, studies. In this step, epidemiologists usually apply some ranking of validity, with randomized trials being considered the best method and case studies or anecdotes having little value for etiologic inference (see Table 1). Depending on study content, the ranking order given in Table 1 may be different. In general, however, ecologic studies rank very low in this hierarchy.

Unfortunately, terminology in epidemiology is often used rather loosely (6). Although ecologic studies are considered to be of little use for etiologic inference, rather heterogeneous types of study designs are often labeled as ecologic. This is also the case in air pollution epidemiology. Given the policy and public health importance of the controversial question of causal inference from epidemiologic studies that assess the impact of normal ambient air pollution, this paper will 1) clarify the definition of truly ecologic studies; 2) introduce and define the term semi-individual study for a widely used type of air pollution study; and 3) discuss and compare major issues of the validity of both study designs. The introduction of a distinctive study design term is warranted, given the strong difference with regard to the inferential power of the two types of studies.

Levels of Variable Measurement

A major tool in epidemiologic research consists of the measurement of a large set of variables to be used in analytic models. These variables may be categorized as dependent or outcome variables, independent exposure variables, and independent covariates, which represent confounding and effect-modifying factors that bias or modify the association between exposure and outcome. The availability of accurate measurements for all variables is a prerequisite for a valid study. Two levels of measurement of these variables have to be distinguished, and all variables, within one single study, may be measured on either one or both levels: 1) individual level, and 2) aggregate or ecological level. This concept is a simplification to the extent that individuals are perceived as the smallest unit and aggregation happens across these smallest units (7).

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ologic perspective, the definition of the smallest unit is arbitrary; subjects may be considered an aggregation of organs, which are an aggregation of cells, which, in turn, may be subdivided in functional units of cells, etc. (7). The concept is helpful, however, and has a direct correlate in public health and preventive policy aimed at disease prevention.

Table 2 illustrates the major measurement level combinations across all three categories of variables used in epidemiologic studies, namely the exposure, outcome, and covariates.

Table 2 is an extension of the table presented by Susser (8), who did not include covariates. Accordingly, cells 1 and 4 can be considered unmixed (outcome and exposure), whereas the other two cells describe studies in which the levels of measurement of variables are mixed.

The usual purpose of causal epidemiologic studies relates to the enhancement of the understanding of risk factors for morbidity or mortality in individuals. For the purpose of etiologic inference on the individual level, it is usually assumed that at least outcome and exposure are measured on the individual level (cell 4), and there is little controversy about the general validity of this concept as applied in individual-level studies. The other three cells, 1–3, are not identified by clearly distinct terms to describe study designs; these cells might often be called ecological, whereas only cell 1 is ecologic in the classical sense, with all variables being measured at the group level. The assessment of long-term health effects of ambient air pollution cannot solely rely on purely individual-level studies (cell 4) because it is not feasible to obtain individual lifetime exposure histories by direct measurement. As a consequence, most such studies are mixed study designs (cell 3) in which exposure is assigned at the group level—most frequently based on a central ambient monitor (9–13). The question, in terms of etiologic inference, is whether this mixed study design provides a stronger basis for individual inference than does a truly ecologic study.

The Truly Ecologic Study Design
Studies based on group measures for all variables (cell 1) are unambiguously defined as ecological studies. Accordingly, in A Dictionary of Epidemiology by Last (6), the ecologic study is defined as "a study in which the units of analyses are populations or groups of people, rather than individuals.” The primary reason for such studies is not the mere interest in effects of contextual, ecologic variables but rather the unavailability of individual level data. Based on aggregated or group data, ecologic correlation or regression coefficients may be derived, which in turn may be expressed as relative risk (14). A typical truly ecologic study may compare morbidity or mortality rates, considered as health outcome, across different communities or populations. The analysis might assess associations of these rates with an ecologic exposure measure such as the prevalence of some risk factor, e.g., the smoking prevalence among these populations.

This basic concept of ecological studies is generally used in all major epidemiology textbooks, which usually refer at the same time to the ecologic fallacy as a major concern (15). The ecologic fallacy is defined as a type—or rather a family—of biases, i.e., aggregation bias or ecologic bias, to which the ecologic study is considered to be uniquely prone. The fallacy (bias) stems from making inferences on individual risks based on group-level associations, which is in fact (as shown below) an inadequate basis for such inference. These studies usually are said to be of interest only in the generation of hypotheses (16–18). The major limitations of this design were described nearly half a century ago by Robinson (15) who introduced the concept of ecologic fallacy. However, important properties of this design have been characterized only relatively recently (19–22); important details, which were not addressed in earlier publications, have been identified (23–26) and must be considered in judgments about the validity of purely ecological studies with regard to etiologic inference at the level of individuals.

The Semi-individual Air Pollution Study
Although several important ecological studies have been carried out to evaluate the health effects of long-term exposure to ambient air pollutants, the bulk of more recent studies involves cross-sectional studies in which health and functional outcomes in individuals are compared across regions, with the same exposure being assigned to all individuals within a region. In some cases, cross-sectional evaluations are supplemented by longitudinal follow-up (9), but exposure assignment remains at the group level at all times. These studies are not characterized by cell 1 (truly ecologic studies) nor cell 4 (purely individual-level studies) presented in Table 2, i.e., they do not fit the truly ecological design; we define these types of study as semi-individual studies.

In a semi-individual design, a broad range of individual level data is available for all subjects. Questionnaire data and extensive measurements, such as lung function or other objective assessments, are usually obtained. Issues that relate to measurements of health outcome and covariates are identical to the usual individual-level design.

It is not possible, however, to measure individual dose of air pollutants received at the target organ nor is it even feasible to measure personal exposure to concentrations of pollutants over long periods. Thus, pollutant-specific exposure is assigned on an ecologic level, with the use of data from a fixed site monitor located within some acceptable distance to the study population. Therefore, all subjects living around a monitor receive the same value of exposure. In contrast to the true situation at the individual level, within-region variability of exposure cannot be captured with this approach. Adequate ranges of exposure are therefore determined by the selection of people from several different areas.

Inferential Validity of Truly Ecological and Semi-individual Studies
The two study designs have inherently different properties with regard to inferential validity. In the context of this discussion, let us assume that the strongest inference in air pollution epidemiology targets individuals; thus, the final aim of ecological and semi-individual studies, similar to other designs, may be the understanding of exposure–outcome associations on an individual level rather than on the group level. This restriction is reasonable and corresponds to the
typical situation of many ecologic studies that are undertaken as surrogate versions of individual-level studies (16).

**Confounding.** In individual-level studies, a variable must be a risk factor for the outcome and also must be independently associated with the exposure of interest in order to induce confounding (16). Thus, only risk factors of the health outcome under investigation may potentially confound results. Accordingly, the availability of measurements of these other risk factors—or some proxy measure—allow statistical control or at least reduction of potential confounding. Covariates may confound results in either direction; therefore, multivariate adjustment minimizes both spurious associations of exposure and outcome and false negative results. It is crucial, therefore, to measure as many relevant secondary risk factors as possible and to include their assessment in the study design. This is particularly important in environmental epidemiology where relative risk estimates over the observed range of exposure tend to be small, i.e., close to or below 2.0 (27). Hence, uncontrolled confounding, especially by factors with large effects on the outcome, would have more relevance for the occurrence of false negative or spurious results. Due to the requirement that a confounder be a risk factor, the issue of potential confounding is predictable from state-of-the-art knowledge. In general, and mainly in the situation where only few risk factors of some outcome have been established, it can be estimated how strongly some other unknown risk factor would have to be to produce a spurious exposure–outcome association (28,29).

In truly ecological studies, however, the situation of confounding is rather different. In an ecological design, the true individual-level exposure–outcome association may be distorted not only by some uncontrolled other risk factor of the outcome but by any other covariate (19). More specifically, any factor that is directly or indirectly related to the grouping process may act as confounder. As a consequence, and in contrast to the individual-level study, no a priori statement about the effect of potential confounders can be made in an ecological study. This results in an unpredictable situation in the ecological design compared to the individual-level study, where subject matter knowledge permits the minimization of sources of confounding. This problem of a virtually unlimited number of potential confounders stands in contrast to the limited availability of measured group-level covariates and the lack of data on factors on the individual level that may have confounded the grouping in ecologic studies.

For example, a recent truly ecological study used land-use patterns in 104 electoral wards as proxy measure for industrial air pollution and correlated these patterns with standardized mortality data (SMR) (30). Ward-level social indicators were the only factors for which the authors could control, and confounding could not be adequately addressed.

Furthermore, there is no symmetry between ecologic and individual-level studies with regard to confounding: a true uncontrolled risk factor may indeed confound an individual-level analysis but may have no impact on the ecologic estimate, or vice versa (29). In other words, whatever information one might have about exposure–outcome–confounder associations on an individual level, i.e., true ecologic pathways, will not enhance the judgment about potential confounders on the ecological level.

In the semi-individual study, a broad range of individually measured variables are usually available; thus, confounding may clearly be controlled. Statistical methods have been established to deal adequately with such a hybrid set of individual variables and ecologic exposure assignment (31). These issues correspond much more to the situation encountered in an individual-level study.

One might envision a semi-individual study in which regional factors correlate in unpredictable and potentially uncontrollable ways with the area of residence. If the area of residence is used to estimate exposure to ambient air pollution, then confounding may be present. For example, access to outdoor sport facilities and, as a consequence, exposure to ambient air pollution may be different in highly industrialized regions compared to less developed areas. In a semi-individual study with very few comparison groups such as two- or three-site studies (32,33), uncontrolled factors may have large impact on the exposure–effect estimates. However, in a semi-individual study, increase of the number of study sites reduces this problem (31) because it is less likely that some unmeasured factor covaries with the group-level exposure across the entire range of multiple study sites. In contrast, in truly ecologic studies, the increase in number of groups does not completely resolve methodological limitations unless misclassification of exposure is minimal (20).

**Misclassification of exposure.** One of the most intriguing limitations of the ecologic design relates to misclassification of variables, particularly nondifferential misclassification of exposure (20,21,34).

Exposure variables, as with any other variables, are subject to measurement errors in all study designs. Ideally, exposure measurement errors in an individual-level study will be a random property of the assessment, i.e., uncorrelated to the true disease status or level of exposure. This situation is described as nondifferential misclassification. In contrast to differential misclassification, in which errors in exposure depend on disease status or level of exposure, nondifferential misclassification of exposure often elicits predictable impact on effect estimation in individual-level studies (16,35). For exposures measured on a continuous scale (e.g., number of cigarettes smoked), random error in exposure often will yield an underestimate of the true exposure–outcome association, unless in some specific cases in which continuous data are converted into ordinal or nominal categories, which may induce differential misclassification despite random errors in the original variable (36,37). In most cases, however, nondifferential misclassification has qualitatively predictable implications on the effect estimation. Furthermore, other studies or investigations on a subgroup may indicate sensitivity and specificity of some misspecified measure of exposure. Such information may be suitable to adjust the observed effects or to at least estimate the degree and direction of distortion due to the misclassification (38).

As demonstrated by Brenner et al. (20), the situation described for individual-level studies strongly diverges from the issues encountered in truly ecologic studies. As an empirical example, the authors used ecologic (geographic) data to assess the effect size of smoking on the risk of dying due to lung cancer, a risk function well established from many individual-level studies. The ecologic outcome measures were lung cancer mortality rates of 30 administrative districts in Germany in 1976–1980, which were correlated with the corresponding smoking prevalence assessed in 1976. In this example, the ecologic fallacy applies if we were to use the ecologic risk estimates of smoking on lung cancer as the risk in individuals. Similar to the individual-level study, it is obvious that smoking prevalence is an exposure measure with some degree of misclassification. Specificity and sensitivity of this prevalence measure are unknown and, in contrast to the individual-level data, are not assessable. This is particularly true for the prevalence of an exposure measure that changes over time and is associated with an outcome with a long latency period. Brenner et al. (20) show that cancer relative risk estimates vary grossly and depend on the assumed sensitivity and specificity of the exposure measure, i.e., the smoking prevalence within each district. Rate ratios for smoking ranged from a meaningless negative value of -20.3 up to 315; if sensitivity and

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specificity were varied between 0.8 and 1.0 [see Table 8 in Brenner et al. (20)]. In other words, unless true assumptions were made for sensitivity and specificity of the exposure classification, the ecologic analyses did not even adequately describe the direction of the relationship. As mentioned, these true values remain largely undefined and, therefore, no knowledge-based adjustment of the ecologic effect estimate can be implemented. It is this empirical presentation that makes the strongest argument against the use of purely ecologic studies in the process of causal inference. The point of Brenner et al. (20) is reinforced by the paper of Richardson et al. (39), which shows that inference at the level of the individual based on ecological studies can only be judged a posteriori, i.e., after the establishment of the individual-level cause–effect association. Their work compares relative risk estimates derived from ecologic and individual studies, with smoking as risk factor. The authors demonstrate that ecological estimates of smoking-related lung cancer risk are similar to those derived from cohort studies. However, ecological analyses substantially overestimate bladder cancer risk, whereas ecologic estimates failed to capture any risk of smoking for esophageal cancer (39).

The implications of exposure misclassification in the semi-individual setting are different from those summarized for purely ecologic studies (20). Two important differences are of note.

First, exposure measures in a truly ecologic study, e.g., smoking prevalence, are bounded between 0 and 100%. The ecologic relative risk estimates implicitly consist of extrapolations over the (usually unobserved) total range of exposure (14). In addition, as mentioned above, sensitivity and specificity of this exposure measure are crucial sources of uncontrollable bias. In contrast, semi-individual air pollution studies use exposure values measured on a continuous, unbounded scale. It is not sensitivity/specificity that must be considered as sources of bias but rather the degree of exposure misclassification of individuals on this continuous scale around the group mean level of exposure.

Second, in air pollution epidemiology, geographic grouping may be considered as grouping according to the exposure, X. As shown by Langbein and Lichtman (24), cross-level bias may be prevented if the grouping process is based on X.

In the semi-individual study, the impact of exposure misclassification depends on the error structure; there is no conceptual difference compared to the individual-level study in which exposure may always be measured with some error. The semi-individual design may follow a Berkson type error structure where

\[ X = Z + E \]

with X being the true (unknown) personal exposure and Z the ecologically assigned value (i.e., the group mean concentration from a fixed monitor), assuming the error term \( E \) to be independent of Z, with mean zero and constant variance (40). In this case, in a bivariate model, no bias occurs in the regression coefficient of group data.

On the other hand, if the surrogate measure Z is assumed to reflect the true (unknown) individual exposure X, with some random error E (independent of X, with mean zero and constant variance), the error structure is referred to as classical error:

\[ Z = X + E \]

In this case, the exposure–effect estimates in a bivariate, individual-level model always will be biased toward the null value. In other words, true effects will be underestimated. Thus, the direction of the bias is predictable, and the effect estimates from the semi-individual study remains interpretable. This predictability is in strong contrast to the properties of a truly ecologic study noted above.

It must be emphasized that predictability of bias holds only if the error structure is in fact classical (41). As shown formally by Wahcholder (40), bias could be quite unpredictable under a more general error structure than those described as classical and the Berkson-type. Wahcholder (40) presents the range of bias to be expected in relation to the correlation of the measurement error with the true and proxy measure of exposure. Thus, the question arises whether the assumption of Berkson-error or classic error may hold in the situation of multicenter, cross-sectional air pollution studies. In a pilot study on long-term effects of lifetime ozone exposure on pulmonary flow measures (42), we assessed both an ecologic ambient concentration and an effective exposure measure, which also considered personal time–activity information. Based on this exposure estimate, we concluded that the effect estimates for ozone on measures of lung function remained unchanged whether we used the lifetime ecologic exposure value or the effective exposure. The latter measure is considered to be closer to the true individual exposure. Other studies suggest that the semi-individual design results in underestimation of the effects of air pollution. In a simulation study, Navidi and Lurmann (43) formally showed that proxy measures of exposure (fixed site monitor data, microenvironmental exposure assignment, and personal exposure sampling) gave smaller effect estimates than those based on true exposure. There is indirect evidence from epidemiologic studies to support these observations. Ostro et al. (44) reported that the estimated effect of particle acidity on occurrence of cough increased by 43% when time–activity data were used to adjust the ecological exposure estimate. Similarly, Neas et al. (45) observed larger acute effects of ambient ozone on peak flow if concentrations were weighted by time spent outdoors. In the Seventh Day Adventist Study, risk estimates of particular matter increased after accounting for hours spent indoors (46).

**Regression coefficient (β) and correlation coefficient (ρ) estimates.** The between-group slope, β, of the aggregate exposure X [e.g., the smoking prevalence of different cities (20), or the percent industrial land use in electoral wards (30)] on the aggregate outcome Y [e.g., the lung cancer mortality rates (20) or the SMR (30)] reflects the true (individual) relationship between X and Y, i.e., the within-group slope \( β_w \), only if there are no group effects (βg) present. Otherwise, β is a weighted average of both the between-group effects and the true within-group \( β_w \), i.e., the individual-level effects of smoking on risk of lung cancer (25). In the usual situation of an ecologic study, \( β_w \) is unknown and \( β_g \) cannot be specified. The ecologic fallacy or cross-level bias occurs if β is taken as an estimate of \( β_w \), despite the presence of grouping effects (i.e., βg ≠ 0). Neither direction nor size of the distortion of β from the true estimate \( β_w \) can be predicted. Unless effects of the grouping process are clearly defined for other covariates, the distortion cannot be controlled.

Although the situation is similar for the correlation coefficient ρ, this statistic has the additional disadvantage of being distorted even if no group effects are present; therefore, they are usually considered to be inadequate statistics in ecologic studies.

**Model specification.** In a purely ecologic setting, the options for model specification are limited with regard to the functional form of an association and are prone to model specification bias (22). The ecologic theorem implies that the ecologic relation is linear if individual-level disease rates follow a linear relationship across exposure, X, and covariate levels, C. The additivity, however, may be inadequate on the individual level and/or important covariate data may not be available at the ecologic level; therefore, group level estimates are subject to undefined errors (22). As Greenland (22) states, none of the problems of the ecologic theorem are strictly specific to ecologic studies, but implications for bias are different.
Finally, it often may be the case that the ecologic averages of exposure, $X$, and covariates, $C$, may be adjusted averages that are based on different and often unknown standardization procedures (47). For example, one may use published smoking prevalence of different countries as an ecologic exposure measure, which might be an adjusted prevalence. The weights used for the adjustments may differ across countries, and detailed information regarding the distribution of weighted factors used in adjustment may be unknown. Lack of a common standardization is a further source of bias in ecological studies that has no counterpart in individual-level studies (47).

The major limitations of purely ecological studies are summarized in Table 3. As discussed by Greenland et al. (19), it is only under rather rare conditions that no ecologic bias occurs. This is the case only if all of the following criteria are met: 1) the background rate of the outcome, i.e., among unexposed, does not vary across ecologic groups; 2) exposure effects do not vary across groups; and 3) there is no confounding within groups (19).

Strategies have been proposed to minimize the problems inherent in ecologic studies that are used for individual level inference, e.g., choosing smaller units of analysis and increasing the number and homogeneity (with regard to exposure and covariates) of groups (23). Greenland (22) has suggested the inclusion of geographic areas with homogeneous within-area exposure and a broad exposure distribution across groups. He also has emphasized the need to use comparably standardized variables. Regression coefficients, which are less likely to be biased upward, should be reported rather than correlation coefficients, which have properties that make them more unpredictable (25). Despite the application of such strategies, unpredictable (in terms of direction) bias may persist in such studies and limit their inferential value (25).

### Conclusion

The crucial methodological problems of purely ecological studies are qualitatively and quantitatively different from individual-level studies (Table 3). The validity of ecological studies for individual-level causal inference is strongly limited due to the important issues raised above. The problems related to nondifferential exposure misclassification may be considered the strongest argument against the use of the ecological studies as an inferential tool.

On the other hand, the semi-individual design, often applied in a cross-sectional setting, shares mostly the same methodologic properties as individual-level studies. The problem of exposure misclassification is similar to that in individual-level studies, where proxy measures of exposure such as job title are used. In contrast to the ecologic study, the semi-individual study is based inherently on individuals. Thus, one may deal efficiently with methodological problems of the ecologic exposure assignment at the level of study planning or analyses. Major options are inclusion of personal modifiers of exposure, such as time-activity patterns, the consideration of microenvironmental exposure data, the use of samples of personal exposure assessment, or appropriate multi-level data modeling (37). Another design approach may make efficient use of the widespread networks of air monitoring stations in some geographical areas: subjects may be selected from very large areas with no a priori restriction on the number of cities. In this case, the ecologic exposure values are assigned individually, using data from the closest monitor station (48). Such cross-sectional approaches may yield important scientific insights, and we suggest that, in the field of air pollution epidemiology, the cohort design may not be, by default, a uniformly superior method (49).

In summary, the strong inferential limitations of ecological studies do not apply to the semi-individual multisite design, with an exposure measured on an unbounded continuous scale. In terms of crucial methodological problems that relate directly to validity and inference, ecological and semi-individual studies should, therefore, be regarded as different entities. The inferential properties of semi-individual studies do not fundamentally differ from those of individual-level studies, and it is a misconception to criticize semi-individual air pollution studies on the base of problems encountered in truly ecological studies.

Given the widespread and well-supported criticism against individual inference from truly ecological studies, it is appropriate to use a distinct terminology for the valuable semi-individual study design, which is widely and efficiently used in air pollution epidemiology.

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### Table 3. Limit on causal inference in ecologic studies that do not apply to the semi-individual and individual-level studies.

| Methodological concern | Specific situation in truly ecologic studies* |
|------------------------|---------------------------------------------|
| Confounding            | Any variable related to grouping process may confound, not only risk factors for outcome |
| Regression and correlation coefficients | Weighted average of between-group and individual-level effects Uncontrollable distortion |
| Model specification   | Source of undefined errors Individual level function cannot be assessed Limited number of (ecologic) modeling variables available Available ecologic variables may be adjusted to different (unknown) standards |
| Misclassification      | Deleterious effects on measures of associations Requires unavailable estimates of specificity/sensitivity of ecologic exposure measures Direction and size of bias unpredictable |

*Issues are qualitatively and quantitatively different from same concerns encountered in semi-individual and individual-level studies.
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