

Environmental Epidemiology: Challenges and Opportunities

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Epidemiology is struggling increasingly with problems with correlated exposures and small relative risks. As a consequence, some scholars have strongly emphasized molecular epidemiology, whereas others have argued for the importance of the population context and the reintegration of epidemiology into public health. Environmental epidemiology has several unique features that make these debates especially pertinent to it. The very large number of environmental exposures require prioritization, and the relative risks are usually very low. Furthermore, many environmental exposures can be addressed only by comparing populations rather than individuals, and the disruption of both local and global ecosystems requires us to develop new methods of study design. The population context is also very important to consider in risk management decisions because of the involuntary nature of most environmental exposures and the diversity of possible outcomes, both health- and nonhealth-related. Studies at the individual or molecular level tend to focus the research hypotheses and subsequent interventions at that level, even when research and interventions at other levels may be more appropriate. Thus, only by starting from the population and ecosystem levels can we ensure that these are given appropriate consideration. Although better research is needed at all levels, it is crucially important to choose the most appropriate level, or levels, of research for a particular problem. Only by conducting research at all these levels and by developing further methods to combine evidence from these different levels can we hope to address the challenges facing environmental epidemiology today. **Key words:** environmental health, epidemiology, methodology. *Environ Health Perspect* 109:1–5 (2001). [Online 27 November 2000]

<http://ehpnet1.niehs.nih.gov/docs/2001/109p1-5pekkanen/abstract.html>

Modern “risk factor” epidemiology may be facing its limits (1). Epidemiology often appears to be struggling with ever-larger problems with correlated exposures and small relative risks (2). This crisis has produced, for some, a stronger emphasis on molecular epidemiology (3). Other authors have argued that the best solution is for epidemiology to focus again on population and to reintegrate itself into public health (4,5). This “ecoepidemiology” approach involves conducting research at all possible levels of analysis, but the population level is fundamental in that it defines the key public health problems to be addressed and the population context in which these problems occur (6,7).

These issues have been debated extensively in the general epidemiology literature, but there has been less consideration of how these debates relate specifically to the current practice of environmental epidemiology. In fact, environmental epidemiology has several unique features that make this debate especially pertinent to it. These include the very large number of exposures, which occur in low concentrations in complex mixtures and often do not differ greatly among individuals within one area. Therefore, the relative risks are usually very low. Furthermore, the most important long-term environmental health problems are probably the indirect and long-term effects on local and global ecosystems,

which are only beginning to receive attention from environmental epidemiologists (8). In fact, most previous discussions (9) have not considered the ecosystem level, which is unique to environmental epidemiology. Besides the scientific issues, consideration of the population and ecosystem context is important in risk management decisions (10). Prevention of involuntary population exposures such as outdoor air pollution or environmental tobacco smoke involve scientific, practical, and ethical issues quite different from those involved in the prevention of “lifestyle” factors such as active tobacco smoking or diet.

Perhaps the most pertinent characteristic of environmental epidemiology is that, by definition, it focuses on the environment in which individuals live rather than on their personal characteristics or lifestyles. During the past centuries, environmental health and environmental epidemiology have achieved remarkable health gains by focusing on reducing the population’s exposure to contaminants in air, water, and soil. However, in the last decades, this focus has been changing to match developments in epidemiology and molecular biology. With increasing emphasis on individual exposures and susceptibility and on mechanisms, environmental epidemiologists are in danger of losing their population perspective of disease causation and prevention.

Environmental health problems can be approached on four different levels: the molecular, the individual, the population, or the ecosystem level (5,11). In this paper we first list briefly the main challenges to environmental epidemiology today and then discuss the advantages and disadvantages of these different “levels of approach” in addressing the challenges of environmental epidemiology. We conclude that the main environmental health problems need to be defined at the population and ecosystem levels, instead of allowing the available research methodology to define the problems that are considered most appropriate for study. Research and development of new research methods is needed at all levels, from the molecular to the ecosystem, but it is crucially important to choose the most appropriate level, or levels, of research for a particular environmental problem. Developing further our research methods and combining evidence from these various levels of research are the keys to addressing the current challenges to environmental health, and also provide significant opportunities for the development of the field.

Challenges

As noted above, environmental epidemiology focuses on the health effects of environmental factors that are outside the immediate control of the individual (2). In industrialized countries, environmental epidemiologists often must assess a large number of low-level intercorrelated exposures, which often occur in complex mixtures. In that respect environmental epidemiology is similar to nutritional epidemiology, except that environmental exposures usually are involuntary and do not differ significantly among individuals within one area. A typical example is contamination of community drinking water supplies, which affects all residents more or less equally.

The relative increases in disease risks due to environmental exposures usually are very

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This work was conducted in New Zealand, with funding from the Academy of Finland and Foundation for Allergy Research.

Received 14 February 2000; accepted 25 August 2000.

low, typically below 1.5 (12). In addition, most chronic diseases of interest in environmental epidemiology, have other, much stronger determinants than the environmental exposure. This leads to problems with controlling for confounding. Therefore, research findings often have been inconclusive. This is especially true for several new areas of research, such as electromagnetic fields and cancer, but is true even for several classical environmental health problems, such as passive smoking and radon. Thus, the future of environmental epidemiology often is seen as primarily involving even more research on these same exposures, using more powerful research methods (12).

Many of the problems of environmental epidemiology become especially severe during local field investigations in response to acute public health problems, such as a cluster of cancer in a neighborhood or around a point source (13). In this situation, the level of exposure is often low and may have happened in the distant past. Often there is no clear hypothesis, the small number of residents gives sufficient power to detect only relative risks that are unrealistically high in the environmental setting, or the latency period may be insufficient. Case-control studies done in this situation, where the outcome is a chronic disease such as cancer, usually have been disappointing (14) because it is rarely possible to reconstruct personal exposures accurately. Furthermore, environmental epidemiologists may be unprepared to address other health outcomes and issues of public concern, such as psychological effects, aesthetic values, social disruption, or effects on property values which may be the main concern of the public (14,15).

The large number of environmental exposures means that environmental epidemiology, more than many other fields of epidemiology, needs to prioritize the issues to be studied. The current emphasis on molecular epidemiology means that a hypothesis may be chosen for study simply because a new methodology has become available, rather than because the hypothesis is important for science or public health (16). Such an approach can lead to the neglect of other, potentially much greater public health problems, such as the long-term effects of environmental decisions on local and global ecosystems (17).

Ultimately, the survival of the human race depends on the survival of the global ecosystem, the atmosphere, arable land, ocean fisheries, freshwater supplies, and biodiversity (11). These systems are increasingly taxed by overconsumption, overpopulation, and wasteful technologies. The best-known examples are the depletion of ozone in the upper atmosphere and climatic warming.

Ozone protects the earth from excessive ultraviolet (UV) radiation, which increases the risk of skin cancer and cataracts. Climatic warming may be associated with a large variety of effects, such as an increased number of deaths from heat waves and other weather extremes, spread of infectious diseases, declining crops, and major societal disruption from loss of habitable land through flooding (17). To increase understanding of the potential health consequences of these changes, environmental epidemiologists must develop new methods of study and new interdisciplinary collaborations.

Opportunities

We consider the above challenges to environmental epidemiology in light of recent debates about the future of epidemiology generally, and particularly the importance of identifying the appropriate "level of approach" in epidemiologic research. We consider these issues by discussing, in turn, each of the four possible levels of approach.

As noted above, environmental health problems can basically be approached at four different levels, the molecular, the individual, the population, or the ecosystem level (5,11). Because epidemiologic research always involves population and most studies involve measurements at a variety of levels, these divisions are arbitrary and there are no strict lines of demarcation separating the different levels of study (7). Also other divisions could be used, e.g., immediate versus long-term effects (18). Nevertheless, most researchers focus primarily on one of these levels of study.

Below we concentrate on scientific issues involving epidemiologic research and risk assessment, but these issues are also crucially important in risk management decisions and interventions. Although all of the various levels of epidemiologic research are important, the population and ecosystem levels are fundamental in that they define the key public health problems to be addressed. Studies done at the different levels have their own advantages and disadvantages, but these are specific to the problem that is being addressed. Thus, it is important to conduct environmental epidemiology studies at the appropriate level or levels for the problem under consideration. To address the current challenges to environmental health, we must develop methods to conduct research and combine evidence from these various levels of research.

Micro-Level

The most basic level of analysis in epidemiologic research has been termed the "micro-level" (19), and is typified by the current emphasis on "molecular epidemiology." Traditionally, the existence of risks

from specific exposures (e.g., tobacco smoke, air pollution) has been established in individual-level and population-level studies, whereas micro-level studies have been used subsequently to determine the etiologic mechanism. However, there is currently a strong movement to routinely use molecular markers to assess exposure and individual susceptibility, and as early markers of outcome in epidemiologic studies (3). This reductionist approach may lead to excessive focus on single substances and characteristics of individuals, whereas the sources of pollutants, other substances in the mixture, and characteristics of the exposed population are easily ignored.

Of course, more accurate and sensitive measures of exposure, outcome, and susceptibility have the potential to increase the power of epidemiologic studies by increasing the relative risks observed, e.g., through the reduction of nondifferential information bias (3) and/or confounding. Furthermore, knowledge of the molecular mechanisms underlying the association between exposure and disease also enhances the biological plausibility of the observed association. This could in turn lead to stronger inferences on causality and improvements in our ability to undertake traditional risk assessment. Such studies can also give feedback to regulatory toxicology on the plausibility of the extrapolations from the animal data. This is an important activity because epidemiologic studies can address only very few exposures, which means that most environmental risk assessment will be based solely on toxicologic studies.

However, because molecular markers are very expensive, studies using them usually have very small sample sizes. The power of the study thus may actually be less than with conventional questionnaires: Precision may be reduced, and validity may also be compromised because control of confounding may be impossible. For example, a recent study compared the types of gene mutations in 12 newborns born to mothers with passive tobacco exposure during pregnancy with 12 nonexposed newborn, but in the analyses no other characteristics of the mothers or newborns were considered (20). Also, the biomarkers currently available are often poorly validated and in many instances inferior to standard questionnaires (3,16). A typical example is the association of smoking or occupational exposures with cancer risk: Questionnaires or work histories give a good estimate of the long-term cumulative exposure, whereas biomarkers tend to reflect only recent exposure.

Better exposure markers in theory can be used to attempt to separate the effects of single chemicals in complex mixtures. However, in practice the effects of a single chemical are often impossible to disentangle

because the various exposures are strongly correlated and the exposure that has been measured may actually stand as a marker for the whole mixture. Typically, exposures to single chemicals are measured because a biological marker is available, and individual differences in metabolism of specific chemicals may mean that a biomarker of a specific chemical may be a very poor marker of exposure to other chemicals in the mixture, which may be more etiologically relevant (16). In such a situation, it may be more useful to study and regulate the mixture, e.g., emissions from diesel vehicles, than to attempt the impossible task of identifying the individual etiologically relevant constituent, if it exists.

Furthermore, the limited number of molecular markers available means that often the methods available, not the problem at hand, determine the exposures and outcomes that will be studied. Most exposures are associated with multiple outcomes, and an overemphasis on a few outcomes that are considered “most important” may produce invalid exposure standards for other outcomes (21).

Individual Level

Most of epidemiologic research in the few past decades has been individual “risk factor” epidemiology. This approach has had remarkable successes, such as discovering the association between smoking and lung cancer or discovering the main preventable risk factors of coronary heart disease. Lately this approach has come under strong attack. Some have argued that all the main risk factors that can be discovered using questionnaires and crude biological markers have already been found and that we need more sensitive and specific biomarkers of exposure, susceptibility, and outcome to refine our knowledge about disease mechanisms and risks (1). Other authors have argued that the best way forward is for epidemiology to regain its focus on population (4,5).

A focus on individual-level studies and personal exposures has often created and reflected the assumption that only these most proximate causes of disease risk are “real” causes (18). Therefore, hypotheses are formulated mainly on the individual level, and interventions tend to focus on individual susceptibility and personal habits while other exposures and determinants of exposure are considered “fixed” and thus not susceptible to intervention. This approach is problematic in epidemiology in general (9), but is particularly inappropriate in environmental epidemiology because of the involuntary and widespread nature of many exposures.

In environmental epidemiology the focus is moving from ecologic studies to individual-level studies. In the early days of

environmental epidemiology, much of the research focused on comparisons of health between a polluted and a nonpolluted area. It is well known that such studies are very susceptible to the ecologic fallacy. Therefore, better individual-level studies with careful exposure assessment (22) and new, innovative designs, such as the case–crossover design (23), clearly have been needed. Such studies have also significantly advanced the understanding of environmental health problems (24).

The ecologic fallacy involves drawing wrong conclusions on individual-level associations between exposure and disease from a study done at the population level. However, fallacious conclusions can also be drawn at the individual level from individual-level studies, if relevant population-level variables are excluded. Corresponding fallacies exist also when inferences are drawn at the population level (25). Any study focusing on a single level can fall prey to these fallacies when information at a different level, which is crucial to the understanding of the problem being investigated, is ignored.

As discussed below, an excessive focus on the individual or the micro-level can lead us to focus our research and subsequent interventions on hypotheses generated at these levels and not on the main environmental health problems. In addition, not all hypotheses can be studied at the individual level. A focus on personal exposures may also ignore long-term, indirect effects. For example, to reduce the exposure of the residents living near the factories, most factories in Western Europe at first were equipped with long stacks, instead of reducing emissions. This has contributed to the current problems with transboundary pollution in Western Europe and to global climatic change.

Population Level

The main environmental health problems must be defined at the population, or ecosystem, level. In the most simple terms this means calculating population-attributable risks based on the prevalence of exposure and expected health effects derived from individual-level studies. This activity is important especially in environmental health due to the very large number of low-level exposures, and is routinely done in risk assessment. However, reliance only on individual-level studies neglects the population context in which these exposures are occurring and also neglects exposures that are uniform within a population, but may be important determinants of disease. This has occurred in the epidemiology of asthma, where much effort has been spent on studying the importance of air pollution and allergens (26); standardized

comparisons among populations are now revealing major international differences in the prevalence of asthma that are not explained by these factors (27), but are more consistent with the protective role of some infant infections on the etiology of asthma. To discover such effects, we need to do comparisons among populations as part of a multilevel research process.

At least three different types of variables can be separated at the population or ecologic level: aggregate, environmental, and global variables (28). Aggregate variables are summaries of variables originally measured at the individual level, such as average income or proportion of smokers. Environmental variables are physical characteristics of the place in which members of each group live. Environmental epidemiology focuses mostly on such variables. Many environmental exposures are so universal—such as exposure through community water supply (29) or long-term average exposure to air pollution (30) or hours of sunlight exposure—that measurements done at the community level give a fair approximation of the exposure at the individual level. In such situations, studies comparing individuals will not achieve sufficient contrast in exposure, so comparisons among populations are needed. Global variables are characteristics of groups, organizations, or ecosystems—e.g., herd immunity to infections produced by vaccination or the existence of a specific law—that have no analogue at the individual level, unlike the aggregate and environmental variables. Global variables can be studied only at the population level.

Population-level studies include purely ecologic studies (in which the unit of investigation is the population rather than the individual), but also include studies involving a mix of population-, individual-, and micro-level analyses (31). Ecologic variables can affect individual health either directly or through some known individual-level characteristics or they can modify the effect of the individual-level risk factors (32). An example of such effect modification is the effect of arsenic on cancer risk, where results from one population, in this case Taiwan, may not be generalizable to other countries due to differences in metabolism or diet (33). To separate these effects we need to collect data both at the population and the individual level, and possibly also at the micro-level. This can be done using a two-stage design, where detailed individual-level information is collected at least from subsamples of the populations (34). This has been done in epidemiologic studies on the effects on mortality of long-term exposure to air pollution, where air pollution exposure has been measured at the population level, but detailed data on lifestyle and

other factors have been measured at the individual level (30).

A variant of the pure ecologic studies is the time-series studies, which have produced major breakthroughs in air pollution epidemiology (30). In this design, data are aggregated over time, not over area as in most ecologic designs, and the association between daily average levels of air pollution and daily average mortality or morbidity in the area is then analyzed. Because the same population is being compared over time, only variables that change from day to day in parallel with the air pollution levels can confound the association between air pollution and mortality. Therefore, as most individual-level risk factors are not confounders and the numbers involved are very large, time-series analyses can detect very small relative risks (35). Time-series studies can also be done at the individual level by, for example, following up a panel of asthmatics with daily measurements of symptoms and lung function (30). In panel studies, exposure is usually measured at the population level by a centrally located monitor, but can be supplemented by measurements of personal exposure (36). Panel studies can be analyzed by aggregating the data over time or by multi-level modeling simultaneously considering the individual and the group level.

In addition to these scientific issues relevant to risk assessment, consideration of the population context is particularly important in studies intended for risk management, such as local field investigations. In these situations, researchers tend to narrow down the study and focus on a specific substance and a single “hard” end point, such as cancer, whereas the main concerns of the public may be broader, including issues such as noise, annoyance, or decrease in property values. Negative findings from studies of narrowly defined exposures and end points, done without insufficient power, are easily misinterpreted to mean there is “no risk” in general. On the other hand, positive results from a study often invite more studies because one study is not considered sufficient to establish causality (37). Therefore, it is important to start from the problem at hand and not let the methods determine the problem. Guidelines for community participation are also required (10) and it is important to be explicit on the limitations of epidemiologic studies (37). This does not mean that studies should not be done of specific exposures and end points, but rather that these cannot substitute for investigating and acting on broader issues of community concern.

Ecosystem Level

Besides considering the direct human health effects of environmental exposures, it is also

important to consider the long-term and indirect threats to human health from the disruption of the local, regional, and global ecosystems (8,11). This requires development of new methodologies, such as a systems-based approach, that are quite different from the usual epidemiologic techniques and always require interdisciplinary collaborations. Several such interdisciplinary initiatives have been made recently with regard to the concept of ecosystem health, which attempts to integrate the biophysical, societal, economic, and human health dimensions of ecosystems (38).

The challenge of ecosystem-level analyses is to incorporate evidence from several fields of research into one assessment. Chan et al. (39) have proposed an integrated assessment framework on the effect of global climatic change on the spread of infectious diseases, which is one of the most cited health effects of climatic change. The framework is composed of the effects of the predicted climatic change on the vectors and pathogens, on ecology, and on the society. These changes and their interconnections in turn produce changes in human physiology and morbidity. Such frameworks allow identification of potentially important research gaps and a better understanding of the whole system.

One approach to combining evidence from several fields is mathematical modeling. One of the first truly integrative models analyzes the effect of different climatic scenarios on the future risk of malaria (40). The model is based on estimated transmission potential of malaria, which was modeled as a function of the human-biting rate of the mosquitoes, human susceptibility, mosquito susceptibility, daily survival probability of the mosquito, and incubation period of the parasite inside the mosquito (40). All but the last of these depend on the mosquito species and three out of five depend on temperature. As mosquitoes breed on standing water, a minimum level of rainfall is also required. For simplicity, the model was estimated only for the 18 main species of mosquitoes and only for *Plasmodium vivax* and *P. falciparum*; the current world distribution of mosquitoes was assumed to stay constant. Combining this information with scenarios of future population growth suggests that in 2080 an estimated 450 million additional people are at risk of malaria due to climatic change.

A more direct application of the usual epidemiologic approach to the global level is the predicted effect of the changes in global fossil fuel combustion on levels of outdoor particulate air pollution, which in turn have been associated with increased mortality and morbidity (41). The model uses information on projected changes in CO₂ emissions and

the use of different fossil-fuels in four sectors, i.e., electric utility, residential/commercial, industrial, and transportation, in nine global regions. Future levels of particulate air pollution are estimated based on large-scale air-dispersion models developed for the United States. Estimated long-term average levels of particulate air pollution, in combination with the estimated sizes of the populations at risk, was then used to estimate number of premature deaths based on estimates from epidemiologic studies. According to this model, an estimated 8 million avoidable deaths would occur between 2000 and 2020 under the business-as-usual scenario, when compared with the climate-policy scenario.

Integrating evidence from several fields of research can be an extremely complex task. However, few alternatives are appropriate to tackle the long-term health effects of ecosystem change. Epidemiologists obviously are key members in working groups doing such integrative assessments and modeling efforts. In addition, new empirical studies are also needed on the links between health and climatic condition (39), such as the studies on the health effects of the El Niño oscillation (42), which resemble future climatic changes.

Conclusions

With increasing emphasis on individual exposures and susceptibility and on mechanisms, environmental epidemiologists risk losing their population perspective of disease causation and prevention. This shift has paralleled the developments in epidemiologic research in general (4,5). In environmental epidemiology, where many of the exposure-disease associations are weak, well-conducted individual-level studies have in many situations been important to establish more firmly the causal associations between specific exposures and specific diseases (24). However, individual- and micro-level analyses will not be able to address many of the most important challenges that environmental epidemiology currently faces, and can lead to a poor choice of hypotheses, poor research, and poor risk management.

An excessive focus on the individual or the micro-level can lead us to focus our research on hypotheses generated at these levels and not on the main environmental health problems. In addition, many relevant environmental exposures are practically universal or are characteristics of the population, not the individual, so they can be studied only by comparing populations rather than individuals. The involuntary nature of most environmental exposures and the multitude of outcomes, both health- and nonhealth-related, also necessitates consideration of the

context of exposure and the characteristics and values of the exposed population (10). Finally, the human impact of local and global ecosystems and the ultimate dependence of humans on ecosystems requires us to study the indirect and long-term effects on environmental decisions (17,43).

Therefore, it is important not to focus only on the individual level, but to conduct environmental epidemiology studies at the appropriate level or levels for the problem under consideration. Although ecologic studies have been criticized, they can produce important results. This has recently been shown by studies on the international differences in the prevalence of asthma (27), which have revolutionized our thinking about asthma and by the time-series studies, which have done the same with regard to ambient air pollution (30). Therefore, there is a clear need to develop better methods for population-level and ecosystem-level studies in parallel with development of better methods for individual-level studies (23). We also need better methods for combining information from different levels, such as combining individual and population levels in multilevel analyses (44) or through study of gene-environment interactions. The task becomes even more challenging when the ecosystem level is also considered, and the first steps in this task have already been taken (39–41). The complexity of the problems requires multidisciplinary collaboration of epidemiologists not only with toxicology, environmental hygiene, and medicine, but also with ecology, social sciences, meteorology, and systems analysis, and with other scientists.

A good example is research on health effects of particulate air pollution, which has included intensive epidemiologic studies on the individual level, time-series studies, and population comparisons together with toxicologic research (30). Recently, scientists have also recognized that both particulate pollution and the most important causes of climatic warming are produced by the same process—burning of fossil fuels (41). Therefore, the solution to the problem with particulate pollution in the long run cannot focus solely on reducing the particulate emissions by technical means; it is also important to convert away from burning of fossil fuel. This emphasizes the need to consider all possible short- and long-term effects of environment emissions at all levels: molecular, individual, population, and ecosystem.

In conclusion, the main environmental health problems must be defined at the population and ecosystem levels, instead of allowing the available research methodology

to define the problems that are considered most appropriate for study. Better research and development of new research methods is needed at all levels, from the molecular to the ecosystem level, but it is crucially important to choose the most appropriate level or levels of research for a particular environmental problem. The different levels should, however, not be considered competitive, but rather complementary (45). Only by considering all of these levels and by developing further our methods to combine evidence from these different levels can we hope to respond satisfactorily to the challenges facing environmental epidemiology today.

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