Invited Commentary

Invited Commentary: The Action in the Interaction and Exposure Modification

David C. Christiani

* Correspondence to Dr. David C. Christiani, Harvard School of Public Health, 665 Huntington Avenue, Building I, Room 1401, Boston, MA 02115 (e-mail: dchris@hsph.harvard.edu).

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The study of disease variability in populations is a goal of modern epidemiology. Because most common diseases arise out of a combination of factors and events (exposures, heritability, comorbidities, and chance), developing simple models of characterizing joint events is a daunting task. Dr. Weinberg argues successfully in this issue of the Journal (Am J Epidemiol. 2012;175(7):602–605) that additive null models can capture pure forms of independent causal effects in studies of rare conditions. Moreover, the concept of exposure modification, which characterizes most gene-environment interactions reported to date, is introduced. More cross-talk between biologists and epidemiologists is needed to tackle key issues in chronic disease etiology, and the argument for the use of parsimonious joint models in epidemiology is convincing.

environmental health; epidemiology; gene-environment interaction; joint effects

Abbreviations: PAF, population attributable fraction; PAR, population attributable risk.

In her thoughtful Commentary, Dr. Weinberg (1) discusses several very important points about causes of disease in the context of considering the characteristics of interactions in epidemiologic research. The main premise of her paper is that the public health community has posed the wrong questions in studying and, it follows, in trying to control chronic disease. Her first point addresses the age-old question about how much disease is caused by environment versus genetic susceptibility. She makes the point that population attributable risk (PAR) is often misunderstood, mainly because the PAR may exceed 1 when there are overlapping sets of causes of disease, such as phenylketonuria, where both genetic and environmental factors are necessary. Indeed, there are situations less extreme but common, where more than one disease determinant can result in sums over 100%: Smoking and occupational exposure also come to mind (environment-environment), as well as chronic beryllium disease (gene-environment) or glucose-6-phosphate dehydrogenase disease (gene-environment). I agree with her point that, although not intuitive, we have to recognize that, in complex diseases, PAR may commonly add to greater than 100%.

However, it is also important to note that we must give policymakers clear direction and distillation of epidemiologic research, lest our advice sound like double speak. The term “population attributable risk” has been described as the reduction in incidence that would be observed if the population were entirely unexposed, compared with its current (actual) exposure pattern (2). There remains some ambiguity in terminology. Population attributable risk is often simply called “attributable risk,” and the latter term is most often associated with the above PAR definition. However, some epidemiologists use “attributable risk” when referring to the “excess risk,” also called the risk difference or rate difference. Greenland and Robins (3) distinguished between excess fraction (what epidemiologists usually calculate as “population attributable risk” or “population attributable fraction” (PAF)) and etiologic fraction in 1988. “Etiologic fraction” is the proportion of the cases in which the exposure had played a causal role in its development, that is, for the amount of the disease that was actually caused by the exposure. Even if someone may have the disease if unexposed, it may be that the exposure was, in fact, what ended up causing the disease for that particular individual (competing risks), and thus that person would be included in the numerator of the etiologic fraction, in contrast to the excess fraction, that is, the proportion of the cases occurring among an exposed population...
that is in excess in comparison with the unexposed. Although the 2 concepts are not mutually exclusive, the etiologic fraction is not estimable without significant biologic knowledge or assumptions; hence, what is commonly calculated as the PAR or PAF corresponds to Greenland and Robins’ “excess fraction.”

For effective public health interventions, these concepts need to be translated from computer to community. I agree with Dr. Weinberg that the PAR and PAF are commonly misused but also point out that the PAR remains important to public health policy formation. For example, it is reasonable to explain to a regulator that elimination of lead from products in the community, all else remaining the same, will result in a quantifiable decrease in neurodevelopmental abnormalities in children. However, lead exposure and toxicity exist along a continuum, not just among high (vs. low) exposed children, and hence I agree with Dr. Weinberg that it may be more difficult to explain the proportion of children likely to be affected unless some exposure threshold (e.g., 10 μg/dL) is chosen. Where cutoffs or suggested thresholds have not been proven, such as asbestos exposure and malignant mesothelioma risk, the PAR concept usually defaults to an exposed versus nonexposed characterization. Perhaps these practical problems with PAR underscore more the need for accurate exposure assessment and estimation of exposure-response relations than with the concept of PAR per se.

The second question addressed by Dr. Weinberg is extremely important and has implications for those of us who study gene-environment interactions. This question is whether we should use additive or multiplicative models for assessing gene-environment interaction. She argues that, for rare diseases, 2 causal factors acting through completely different pathways would have a joint effect that is expected to be additive. Hence, independent risks combine additively if they are small (but not if they are large). Because most common gene variant-environmental exposure interactions are likely to represent joint effects between risks of small to modest size, it would seem reasonable to use additivity as the null formulation in these studies.

Gene-environment interaction has been described from both statistical and biologic points of view. Statistical interaction is a model-dependent approach, and its presence is scale dependent, for example, on a multiplicative scale or an additive scale (4). In toxicology, on the other hand, interaction refers to causation from the biologic action of 2 or more factors to produce or prevent an effect (4). Rothman et al. (5) argued that the additive effect model is the best model for interaction between 2 factors that are part of different causal mechanisms. Although many authors have suggested that the multiplicative model is more appropriate if the primary goal is to study disease etiology and is suitable for factors affecting the same mechanism or stage of a multistage process (6), neither the multiplicative nor the additive model is necessarily the default for disease etiology. Most human studies are not able to identify or measure all the intervening variables and their effects on the occurrence of disease (7). There are restrictions, therefore, in inferring biologic interactions based on statistical assessment, particularly when the underlying biology is unknown. Yet, the concept of additive interactions based on biology is important in epidemiology for predicting disease based on an individual’s profile of risk factors and for planning intervention. Researchers can focus the search for gene-environment interactions on genes that plausibly share the same biologic pathway as the exposures and assess the exposure effects in disease risk within subgroups of specific genotypes. This leads to the discussion of effect modification or, more aptly put by Dr. Weinberg, “exposure modification.”

Many of the examples of gene-environment interactions in the literature are actually examples of what epidemiologists usually call effect modification. Dr. Weinberg gives several representative examples of what she calls “exposure modification,” which in this context I believe is an improvement on the concept of effect modification. She defined exposure modification as occurring when the effects of an exposure vary by levels of another factor, the modifier, which may be a genetic variant (that may alter the biologically effective dose after an exposure), another exposure factor (that varies the internal dose by altering the exposure or internal dose), or age (that may alter metabolism and hence the internal or biologically effective dose after an exposure).

A good example of exposure modification is bladder cancer. A pooled analysis including 4 case-control studies conducted in 4 European countries suggested that NAT2 acetylation status is not a risk factor for bladder cancer per se but modulates the carcinogenic effects of cigarette smoke (probably the arylamine component) or occupational exposure to arylamines (8).

Does the choice of a null additive versus multiplicative model matter much? Dr. Weinberg reminds us that, if the association between both factors of interest and outcome is small, it matters little which model to use, as the additive approximates the multiplicative. The choice becomes important only when large magnitudes of association are at play, such as occupational asbestos exposure and cigarette smoking (where both have large associations), or at least 1 factor has a strong association, such as the bladder cancer case.

Finally, I agree with Dr. Weinberg that concern for relevance to public health should drive our science, and that means our choice of models. We need more cross-talk between the basic biologic sciences and epidemiologists. The relevance of discovering the reasons (environmental, genetic) for variability in disease occurrence is crucial and becomes more complicated as we study environmental mixtures, multiple single-nucleotide polymorphisms, and genes. In this quest, we should be open to the use of parsimonious joint models in advancing our understanding of the causes of disease.

The call for more multidisciplinary cooperation (dare say, interaction) between toxicology and epidemiology is not new in the realm of environmental health. Several years ago, a report from the National Research Council, *Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment*, called for, among other things, the incorporation of toxicogenomic data to identify, understand the mechanisms of, and characterize the extent of genetic and epigenetic influences on variations in human susceptibility to the toxic effects of chemicals, with the eventual goal of improving certainty around the assumptions used in the regulatory processes to address population variability (9).
Dr. Weinberg shows us that the real action is asking the right question about interaction and exposure modification.

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Author affiliations: Harvard School of Public Health, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts.

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REFERENCES