



## Invited Commentary

### Invited Commentary: Multilevel Analysis of Individual Heterogeneity—A Fundamental Critique of the Current Probabilistic Risk Factor Epidemiology

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In this issue of the *Journal*, Dundas et al. (*Am J Epidemiol.* 2014;180(2):197–207) apply a hitherto infrequent multilevel analytical approach: multiple membership multiple classification (MMMC) models. Specifically, by adopting a life-course approach, they use a multilevel regression with individuals cross-classified in different contexts (i.e., families, early schools, and neighborhoods) to investigate self-reported health and mental health in adulthood. They provide observational evidence suggesting the relevance of the early family environment for launching public health interventions in childhood in order to improve health in adulthood. In their analyses, the authors distinguish between specific contextual measures (i.e., the association between particular contextual characteristics and individual health) and general contextual measures (i.e., the share of the total interindividual heterogeneity in health that appears at each level). By doing so, they implicitly question the traditional probabilistic risk factor epidemiology including classical “neighborhood effects” studies. In fact, those studies use simple hierarchical structures and disregard the analysis of general contextual measures. The innovative MMMC approach properly responds to the call for a multilevel eco-epidemiology against a widespread probabilistic risk factors epidemiology. The risk factors epidemiology is not only reduced to individual-level analyses, but it also embraces many current “multilevel analyses” that are exclusively focused on analyzing contextual risk factors.

analysis of variance; cross-classified multilevel models; family; life course; neighborhood; probabilistic approach; risk factors; school

Abbreviations: MMMC, multiple membership multiple classification; VPC, variance partition coefficient.

The article by Dundas et al. (1) in this issue of the *Journal* is, so far, one of the few in social epidemiology that, by adopting a life-course approach, applies modern multiple membership multiple classification (MMMC) multilevel models (2, 3) to disentangle contextual components of interindividual heterogeneity in health (4–6). A limited number of similar investigations have also been performed in educational research (7, 8).

By adopting a life-course approach, the authors apply a cross-classified multilevel regression analysis to estimate the contributions of families, early-life schools, and neighborhoods to adult self-reported health and mental health. The authors properly distinguish between general contextual measures (i.e., the share of the total interindividual heterogeneity in health that appears at the family, school, and area

levels) and specific contextual measures (i.e., the association between particular characteristics of those contexts and individual health) (9–11). When it comes to general contextual influences, the authors found that the variance partition coefficients (VPCs) for the school (VPC = 0.2%) and the area of residence (VPC = 0.1%) were almost null, so at the time and place of the study, those environments appeared rather irrelevant for understanding individual differences in adult health. Similarly, the specific contextual associations of the socioeconomic characteristics of the areas and schools were tiny. Therefore, both the specific and the general contextual measures indicated that the accuracy of the area- and school-level constructs for discriminating between adults with or without impaired health was also very low (12, 13). However, the general contextual influences of the family level seemed

to be more relevant (VPC = 10%), as was the familial social class (odds ratio = 2.23 for social class IV vs. I), even if the magnitude of this specific contextual association also conveyed a very low discriminatory accuracy.

The study by Dundas et al. (1) gives observational evidence suggesting the relevance of the early family environment for launching public health interventions in childhood in order to improve health in adulthood. This investigation joins several others (4–6, 9, 10, 14, 15) in questioning classical “neighborhood effects” studies that, by using simple hierarchical structures, consider merely the analysis of specific contextual associations (i.e., contextual “risk factors”) but disregard the analysis of general contextual influences.

The MMMC study design applied by Dundas et al. (1) and previously by other authors (4–6), is an innovative contribution that properly responds to the call for a multilevel “eco-epidemiologic” way of thinking (16) against a widespread risk factors epidemiology. Paradoxically, this probabilistic risk factors epidemiology is not only reduced to individual-level analyses but also embraces many current “multilevel analyses” that neglect interindividual heterogeneity and are focused exclusively on the analysis of contextual risk factors.

Having said that, I bear the ambition of giving a condensed overview on some key—but contradictory—conceptual approaches coexisting today in epidemiology. I will use this framework to argue for an increased use of the MMMC study design in epidemiology.

### RISK FACTORS, INDIVIDUAL HETEROGENEITY, AND THE TYRANNY OF THE MEANS

Today, most epidemiologic work habitually crystalizes in simple measures of association like the relative risk or the odds ratio, indicating that the average disease risk is higher or lower in 1 group of people (e.g., the exposed) compared with another (e.g., the nonexposed). Hundreds of biological, genetic, lifestyle, social, and environmental conditions appear to increase the risk of different diseases. Beyond the perils of medicalization (17), stigmatization, overtreatment, side effects of treatment, and others, the honest expectation is that knowledge of risk factors will improve our capacity to discriminate with accuracy between the individuals who will develop the disease and those who will not in order to provide targeted preventive treatment. Nevertheless, during recent years a number of relevant publications (12, 18–23) have pointed out that measures of association alone are unsuitable for this discriminatory purpose. In fact, what we normally consider to be a strong association between a risk factor and a disease (e.g., a relative risk of 10) is related to a rather low capacity of the risk factor to discriminate between cases and noncases of disease in the population (12, 20).

In light of the above background, there is a growing realization that epidemiologic risk factor research is not as effective as might be hoped because most established risk factors actually have very low discriminatory accuracy (12, 20, 23, 24). This insight was already declared at the end of the last century, and in 1998 Davey Smith commented that clinical trials “have not, however, answered the question of which individuals actually benefit from medical interventions.”

Therefore, he proposed the identification of those individuals as “the key issue in clinical research for the next millennium” (25, p. 294).

The development of the Human Genome Organisation, as well as the creation of large biobanks, has raised new hope regarding the identification of better risk predictors and, thereby, an improved understanding of the determinants of health and disease. Unfortunately, this hope has not yet been fulfilled and, consequently, a gloomy but real prospect is being considered in epidemiology (26). This discouraging outlook is based not only on the low “value added” of novel versus established risk factors; there is also explicit evidence that knowledge of traditional risk factors like, for instance, hypertension or hypercholesterolemia, does not improve the discriminatory accuracy of risk predictions that are based exclusively on simple demographic variables like age (27).

In an effort to find a hopeful solution to the gloomy prospect, it is being argued that measures of association such as the odds ratio are inappropriate as guides for individual risk prediction, but that these measures are—and should only be—intended for population-level inferences (23, 26). So, after the first decade of the new millennium, Davey Smith stated that,

Chance leads to averages being the only tractable variables in many situations, and this is why epidemiology makes sense as a science. We should embrace the effects of chance, rather than pretend to be able to discipline them (26, p. 556).

Rockhill, in a seminal article (23 p. 124), also develops these concepts and affirms that,

The distinction between questions about group averages and questions about mechanisms of individual events can be framed by an analogy to coin-flipping. ‘Did more heads than expected arise in the repeated tossing of this coin?’ is a question readily answered by recourse to the binomial probability model. The question of why a particular flip resulted in heads rather than tails is a mechanistic question not answerable through reference to the statistical model.

This perspective assumes a probabilistic approach that conceives the individual risk as the expression of a stochastic or “chance” phenomenon that cannot be determined at the individual level and, therefore, is best estimated by the average risk in the population (e.g., the group exposed to the risk factor). If we adopt a stochastic perspective, these opinions are of radical relevance because they discredit the suitability of statistical and epidemiologic methods for the determination of specific individual causal effects, which is actually a major task in current epidemiology (28).

A deeper reflection on the ideas of Davey Smith and Rockhill shows that they force an epistemological paradox. In a first step, these authors accept a mechanistic approach for determining individual risk. Thereafter, they conclude that specific individual risk cannot be determined by epidemiologic methods. Finally, as a solution, they proposed a probabilistic population approach that considers individual risk as a stochastic phenomenon. Thus, the classic question is whether the individual risk is a stochastic or “chance” phenomenon that can be estimated only by a population average risk, or if individual risk conveys specific mechanisms that can be

determined. In this query, I share the opinions of Zernicka-Goetz and Huang (29), that science (epidemiology included) is interested in identifying causal mechanisms, but a logical contradiction of the stochastic viewpoint is that a stochastic phenomenon is, by definition, not causal. Therefore, it is most reasonable to think that the mechanism underlying an individual response might be very complex and difficult to determine, so it might appear to be a stochastic phenomenon. In fact, the origin of individual heterogeneity may have a stochastic component (e.g., meiotic recombination) or be very complex (e.g., chaotic determinism, epigenetic mechanisms), but once this heterogeneity is established, it can be studied. Therefore, rather than vindicating the “chance” approach, we should recognize our current ignorance, and that our lack of knowledge could be amended by a better understanding of individual responses in different contexts. This insight is, I believe, the *sine qua non* of science, and it needs to be considered when planning strategies of prevention under the principle of *primum non nocere*. In simple words, let us say that smoking increases the risk of cancer by a relative risk of 10. From the “chance” approach, the interpretation is that one’s risk will be multiplied, on average, by 10 if one smokes. However, the fact is that smoking does not homogeneously increase the risk by a factor of 10 in all individuals. There are individuals who are resilient and individuals with cancer who do not smoke. Increased knowledge will help to identify the susceptible individual. Nevertheless, quitting smoking can be recommended to everyone (even in the resilient cases) because it confers many advantages, and this prevention does no harm. On the other hand, pharmacological treatment of risk factors for all people seems less appropriate because of the perils of side effects, medicalization, etc.

The imposition of the average group value on the individual is the rule in (probabilistic) epidemiology, and it has been called the “tyranny of the means” (30, 31) or the “mean centric approach” (32). Not only a problem in social epidemiology (9–11, 33), this issue has also been discussed in political science (32, 34) and evolutionary biology (35). The key concept is that common measures of average association correspond to abstractions that do not represent the heterogeneity of individual effects. This idea points to the study of interindividual heterogeneity around group averages as fundamental for understanding the effect of an exposure (e.g., a risk factor) in the population. Analogous ideas were already described in the 19th century by Claude Bernard (36) and later by Hogben and Sim (37), as well as by modern clinical epidemiologists (38, 39) promoting “*n*-of-1” design. The same notion also lies behind the current movement toward personalized (or stratified) medicine (40). Individual heterogeneity of responses is, obviously, the underlying reason for the low discriminatory accuracy of many “risk factors.”

It is also well known that observational multilevel analysis—like most observational studies—suffers from problems of exchangeability between the groups being compared, which calls into question the causal validity of both general and specific observational contextual measures (41–44). However, the critical points concerning the “tyranny of the means” can also be applied to experimental randomized controlled trials estimating the average causal effect of a treatment

because they are used as the best estimation of the individual causal effect (45). We need to be aware that in all epidemiologic studies—including randomized controlled trials—the variance ( $\sigma^2$ ) is not a measure of probabilistic uncertainty (as sometimes interpreted) but, instead, it expresses a natural phenomenon that corresponds to the underlying interindividual heterogeneity of responses (46, 47). Probabilistic uncertainty is quantified by the standard error, so the natural interindividual heterogeneity ( $\sigma^2$ ) may be large but probabilistically estimated with high precision (i.e., a low standard error of the  $\sigma^2$ ), if the sample size is large.

#### MULTILEVEL ANALYSIS OF INDIVIDUAL HETEROGENEITY IN ECO-EPIDEMIOLOGY

Besides the methodological critique of Rockhill and Davey Smith (24–26) and their paradoxical promotion of a population-based stochastic approach, in the last decades many other authors have reacted against an unbalanced individualistic risk factor epidemiology on the basis of a more sociological perspective (16, 48–50). For instance, under the name of eco-epidemiology, Susser and Susser (16) recovered and expanded the classic multilevel approach based on Rose’s seminal distinction between “causes of individual cases” and “causes of population incidence” (51). Eco-epidemiology conveys a multilevel perspective of analysis that goes from molecules and individuals to populations. Nevertheless, the distinction between individual and population levels of risk is still not well recognized. For instance, studies investigating population risk, as well as those explicitly focused on individual risk, are based on probabilistic comparisons of average group risks, which makes it difficult to distinguish between causes of population incidence and causes of individual cases. Rose’s ideas are highly relevant but need a better conceptual elaboration and statistical operationalization.

An appropriate operationalization of the eco-epidemiologic approach can be obtained by multilevel regression analysis focused on the interpretation of the natural interindividual heterogeneity (i.e., variance) (5, 9, 33, 52, 53) or by analogous methodologies (15). In this multilevel framework, the “effect” of being influenced by a higher level like, for instance, the family, the neighborhood, or the school can be considered as a general contextual effect (9). This general influence is not properly operationalized by measuring differences between average risks. Rather, the general influence of the context is better quantified by measuring the share of the total interindividual heterogeneity that appears at that specific level (33). A suitable measure for this purpose is, for instance, the VPC (33, 53–55), obtained from multilevel regression analyses, but we can also apply other approaches like the median odds ratio (56) or the pairwise odds ratio (15) and even measures inspired by the idea of discriminatory accuracy (13). In any case, we arrive at similar substantive conclusions.

From a multilevel perspective, it is worthwhile to realize that, in contrast to repeated intraindividual measurements that are always perfectly nested within individuals, individuals are normally included in a complex structure of contexts that changes not only across life but also every day (9, 57).

Furthermore, although the individual body is a highly coherent system with easily identifiable boundaries (i.e., the skin), most of the supra-individual levels we investigate are arbitrarily defined, and their boundaries may not successfully capture the true context that is influencing health (9). This problem is difficult to solve but is better handled by multi-level regression analyses applying MMMC study designs (2, 3).

Multilevel analyses of individual heterogeneity should be an analytical standard in epidemiology, but they are still relatively uncommon. This situation might express an implicit reluctance toward the underlying “determinism” of this kind of analyses. In fact, many epidemiologists become confused when they observe a “significant” association between contextual variables and individual health along with tiny general contextual influences (e.g., VPC close to 0%) (10). Whereas a statistically significant association is always relevant in the probabilistic approach, it may not be relevant in multilevel analyses of individual heterogeneity. This apparent paradox can be solved if we realize that the idea of quantifying general contextual influences by using, for instance, the VPC, is completely analogous to the concept of discriminatory accuracy developed in other fields of epidemiology like the study of risk factors and biomarkers (12, 13, 31). It is well recognized that many risk factors and novel biomarkers are not so useful because they have a very low discriminatory accuracy even if they are “significantly” associated with diseases (12).

In conclusion, we need to embrace eco-epidemiology and reject a reductionist and idealized risk factors perspective that considers only probabilistic average associations at any level. For this purpose, we need to develop an epidemiology based on longitudinal multilevel analyses of heterogeneity that includes repeated measurements within individuals (45, 58), as well as individuals in different cross-classified contexts and multiple memberships (1, 2, 4–8). This approach will increase the discriminatory accuracy and, thereby, the causal strength of observational “risk factors” by identifying the individuals or homogeneous groups of individuals who are actually susceptible to an exposure. Simultaneously, we will be able to quantify possible general contextual influences at different levels across time. The study by Dundas et al. (1) is a step in the right direction (4–8).

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