Published in final edited form as:

Epidemiol Method. 2014 ; 3(1): 73–77. doi:10.1515/em-2014-0017.

Interaction – Epidemiology’s Brinkmanship

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Something is missing in VanderWeele and Knol’s extensive and remarkable review of the assessment and interpretation of interactions (VanderWeele and Knol, 2015). At which point does the analysis of interaction become incompatible with epidemiology? In an extreme scenario in which multiple exposures interact with one another, including all higher degree interactions, that is, in a model that is saturated with interactions, there is a different solution for each individual, and the basic tools of epidemiology, population thinking, and group comparisons, breakdown. The density of interactions is an indicator of complexity and complex hypotheses are something that epidemiology struggles with (Diez Roux, 2011).

We don’t need to resort to extreme scenarios to show the historically diffident attitude of epidemiology toward interactions, and more generally complexity. Isn’t it striking that in VanderWeele and Knol’s review (VanderWeele and Knol, 2015) all the examples deal with situations in which there is only one extra variable, interacting with (or modifying) the effect of one exposure? True, simplicity is a key feature of a didactic tutorial, but in this commentary, my aim is to show that the limitation to the simple case in which all the heterogeneity of an exposure effect is explained by splitting the studied population according to a third binary variable essentially is a reflection of epidemiology’s conflictive relationship with the concept of interaction.

This commentary broadly reviews what has been the role of interaction in epidemiologic thinking. In the seventeenth century, ignoring interaction was one of the fundamental conditions that permitted the emergence of population thinking (Morabia, 2013b). The scientists who, throughout the eighteenth and nineteenth centuries, steered away from interactions, adhering to simple causal frameworks limited to one exposure and one outcome (eventually with some confounders) are presently viewed as precursors of epidemiology, whereas those who had a complex vision of disease causation sometimes met dramatic failure. The interest of epidemiology for interaction resurfaced after 1945, when the so-called chronic disease epidemiologists timidly formulated hypotheses involving two-way interactions and evaluated them by stratification. Today, we may have reached the point at which the relation of epidemiology to interaction can be relaxed. The potential outcome framework may be more apt to deal with complexity than traditional modern epidemiologic approaches.

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1 The seventeenth century movement away from interactions

Historically, concepts of health and disease in all major civilizations of the world were complex in that they allowed for innumerable levels of interaction between the human body and all the elements of the universe (Morabia, 2014). Every individual was different and every case of disease had its specific determinants. These “antique holistic” ideas were based on assumptions of generalized interactions resulting in a different constellation of prognostic (the main concern of the physician) factors for each individual. It made therefore no sense to group and count. This complex vision of health and disease was incompatible with epidemiology.

A radical intellectual revolution took place in the first half of the seventeenth century. The essence of the new principles and scientific methodology proposed by Francis Bacon and René Descartes can be summarized in one watchword: Simplify! In practice, it meant analyzing one exposure-outcome association at a time and ignoring interactions when combining the effects of multiple individual exposures. This simplification away from holistic complexity was essential to transition from 4,000 years of individual thinking to population thinking in medicine and public health. Indeed, John Graunt’s analysis of 50-years worth of death records for London represents the first document we can undoubtedly place in the genealogic tree of epidemiology (Graunt, 1662; Morabia, 2013a).

2 The nineteenth century failure of interaction-based theories of disease causation

The idea that health and disease result from an interaction between individuals and their environments is so commonsensical that it took centuries for science to boldly ignore it for sake of efficiency. Throughout the eighteenth and nineteenth centuries, many modern scientists still adhered to causal frameworks allowing for interactions. The sanitarians, a heterogeneous group of people of the nineteenth century viewing life conditions of the poor as a main determinant of population health, believed that disease resulted from the interaction between miasms (stinking air factor) and innumerable personal susceptibility factors. For instance, if two people were exposed to the same air concentration of miasm and one contracted cholera and the other did not, it was because they differed in their individual susceptibility. This makes sense excluding the fact that the stench did not cause cholera. Moreover, theories based on miasm–individual interactions were purely speculative because no design existed in the pre-randomization era that could balance individual susceptibilities in the compared groups. Consider the two theories about the etiology of cholera, the miasm–elevation interaction and the germ–environment interaction. They were made by two of the main public health authorities of the nineteenth century, respectively, William Farr in Britain and Max von Pettenkofer in Germany. None had undergone population comparative tests and both theories resulted in unwanted, and in the second case, dramatic public health consequences.

2.1 Farr's miasm–elevation interaction

William Farr observed that the mortality from cholera was lower in localities located geographically higher above the sea level. The inverse association was monotonic and could be graphed as a pyramid with curvilinear sides, in which the mortality rates were plotted horizontally and centered, and the height of the pyramid was the geographical elevation (Morabia, 2014, p. 48). Thus, geographical elevation appeared to modify the association of miasm and cholera. This theory had potentially dangerous public health consequences since it suggested that in the presence of an outbreak of cholera, it was advantageous to escape to neighboring hills and mountains, at the risk (unsuspected by the miasmists) of disseminating the outbreak.

2.2 Max von Pettenkofer's germ–environment interaction

Max von Pettenkofer, the other public health giant of the century, had an explanation for Farr's elevation theory. He believed that the (still hypothetical, unobserved) cholera germ was innocuous until it underwent an underground transformation into a miasmatic gas. This transformation was more susceptible to occur in the smooth and porous ground of sea-level localities than in the rocky ground of more elevated localities. The resulting germ–environment interaction explained many traits of the population behavior of cholera epidemics. Pettenkofer's theory, like Farr's, led to inappropriate policy and was proved wrong in a dramatic natural experiment in Germany. In 1892 cholera broke out in Hamburg. The city was divided in two, a little bit as Berlin has been after World War II. The northern part of the city followed Pettenkofer's ideas and did not filter the drinking water. The other half followed the recommendation of the bacteriologist Robert Koch and filtered its drinking water, purifying it from the bacilli contaminating the Elbe, Hamburg's river, and water source. All the cholera deaths, all of them, occurred on the northern side of the city (Evans, 2005; Morabia, 2007).

3 Advantages of the contagion theory

In contrast to miasmist theories, successful epidemiologic endeavors of the nineteenth century ignored interactions and performed comparisons between groups that were either exposed or unexposed to what was considered to be the unique determinant of disease.

Chronologically, Pierre Louis's comparison of pneumonia patients isolated the role of bloodletting in explaining mortality (Louis, 1836); Ignaz Semmelweis's 1848 comparisons of delivery clinics in the General Hospital of Vienna isolated the role of hand transmission in explaining maternal mortality from puerperal fever (Carter, 1983); John Snow's comparison of clients of the London water companies isolated the role of water transmission in explaining mortality from cholera (Snow, 1855). These studies eluded much of the complexity that kept miasmists away from group comparisons.

4 The third variable

The question of interaction resurfaced in the 1950s to explain the heterogeneity of effects between populations rather than the heterogeneity of susceptibility to disease between individuals. These interactions could be evaluated in case–control and cohort studies, but

remained limited to the relatively simple situation of one exposure, one outcome, and a third variable.

Chronologically, Stocks and Campbell tested whether there could be an interaction between the two major suspected causes to the lung cancer epidemic, air pollution, and tobacco (Stocks and Campbell, 1955). Wynder suggested there was interaction between alcohol, tobacco, and oral cancer (Rothman and Keller, 1972; Wynder et al., 1957). Lilienfeld (1961) and Tokuhashi and Lilienfeld (1963) discussed gene– environment interaction. Arguably the most famous case of interaction was published by Hammond et al. (1979) showing an additive but not multiplicative interaction between tobacco smoking and occupational exposure to asbestos fibers with respect to lung cancer mortality. Mervyn Susser, in his 1966 lectures published in 1973 as a book, “Causal Thinking in the Health Sciences,” recognized that the only causal models which could be evaluated were those which “simplified the multiple interactions and reciprocities discernible in any ecological model” (Susser, 1973, p. 31).

In the 1970s the *American Journal of Epidemiology* published several contributions to a debate about whether interactions should be assessed at the additive or multiplicative scale. The 1980 conclusion was “We believe that the controversy surrounding the concept of interaction can be laid to rest with specification of the context in which the interaction is being evaluated. Four broad contexts can be distinguished: statistical, biological, public health, and individual decision-making. Each has different implications for the evaluation of interaction” (Rothman et al., 1980, p. 467). The choice of a model was deemed “arbitrary” in statistical contexts, “unnecessary” in biological contexts, still departure from additivity of rate differences had to prevail in the public health and individual decision-making contexts. As an illustration of a “public health interaction,” the paper gave the recently published example of tobacco, asbestos, and lung cancer, in which there is departure of the joint effect from the sum of rate differences but not from the product of rate ratios (Hammond et al., 1979).

In the 1980s, Ruth Ottman characterized different types of two-way interactions (Ottman, 1990, 1996). Most telling of the context and implementation of interaction in epidemiologic research is that the methods available in the epidemiologic literature to compute statistical power for interaction did not go beyond the third variable scenario (Smith and Day, 1984).

5 Potential outcome frameworks

Besides notable exceptions (Darroch, 1997; Koopman, 1977), the rest of the history is well covered in VanderWeele and Knol’s tutorial (VanderWeele and Knol, 2015). In the 1980s, the newly imported potential outcome framework (POF) facilitated the progression of the *concept* (as opposed to the methods of assessment) of interaction in epidemiology. It provided VanderWeele the notation to lay out the distinction between effect modification and interaction (VanderWeele, 2009). The use of the four individual types of potential outcome pairs for a dichotomous treatment described by Copas in 1973 (Copas, 1973) also helps grasping the comparability issues entailed in interactions (Hernan and Robins, 2015, in press).

The POF, because of its defining feature at the individual level, seems to hold the potential of tackling more complex questions involving multiple levels of interaction/effect modification, such as those simultaneously involving environmental, genetic, and epigenetic causes. As a result, there is probably more construction on the site of epidemiologic interactions than there has ever been in the past.

6 Conclusions

A complete historical review should comprise the influence on epidemiology of other close-by, social and medical (e.g. genetics (Haldane, 1946)) sciences concerned by and struggling with interactions. There is also a parallel evolution of the biostatistical approach to interaction, in particular with respect to the statistical tests of interaction and the statistical power calculations. VanderWeele and Knol's tutorial (VanderWeele and Knol, 2015) covers a wider ground than my commentary but, again, I am making a modest attempt to accentuate a conceptual issue that the tutorial does not address.

Historically, deciding whether there is effect heterogeneity in populations, and the extent of this heterogeneity has been dictated more by our ability to deal with complexity than by the complexity of the studied reality. It is therefore important to stress that the question which opened this commentary, that is, "at which point does the analysis of interaction become incompatible with epidemiology?", has no exact mathematical solution. Paraphrasing Vanderbroucke's statement about confounding (Vanderbroucke, 2004), interaction has to do with the logic of scientific reasoning and has no statistical or analytic solution. This is why experimenting with interaction will always flirt with epidemiologic brinkmanship.

Acknowledgment

I thank Zoey Laskaris for her comments on a previous version of the manuscript.

Research funding: Supported by a grant from the National Library of Medicine, 1G13LM010884.

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