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Invited Commentary

Invited Commentary: When Case-Control Studies Came of Age

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In his 1976 paper "Estimability and Estimation in Case-Referent Studies" (*Am J Epidemiol*. 1976;103(2):226–235), Miettinen weaved together a patchwork of new ideas into a coherent view of case-control studies. His article spurred theoretical development in epidemiologic methods and became a platform for teaching about some key concepts in epidemiologic study design.

case-control study; epidemiologic methods; estimation; rate ratio; risk ratio

By 1976, when "Estimability and Estimation in Case-Referent Studies" was published (1), case-control studies had become common, but their theoretical underpinnings had yet to be clearly elucidated. Today, we conceptualize case-control studies as streamlined versions of cohort studies. The case-control design improves efficiency by sampling from the persons or person-time that gave rise to the cases rather than collecting data from all of that experience. The control-group sample allows estimation of the prevalence of exposure and covariates more efficiently than does a complete census of the source population, with only a slight reduction in precision.

A perusal of basic epidemiology texts from 4 decades ago reveals just a glimmer of present-day insights into the theory of case-control study design. In that era, the case-control study design was described in most textbooks as a "retrospective study" or a "case-history study" and considered more of a quick and dirty approach to epidemiologic research than a legitimate study design. For example, in one textbook, the "retrospective study" was relegated to the final pages and described with this theoretical foundation: "Careful consideration must also be given to the selection of a control group; the important principle is that the controls should resemble the cases closely except for the presence of the disease under study" (2, pp. 314–315). Epidemiologists now understand this advice to be incorrect, although it was common then, was often repeated in classrooms, and even today may still have currency among amateur epidemiologists. It is an example of a false analogy: In a cohort study, it would be reasonable to say that an unexposed cohort should resemble the exposed cohort closely except for the presence of the exposure. It was reasoned by analogy that in a case-control study, because the controls were the comparison series for the cases, they should be just like the cases apart from having disease. It took new theoretical insights, largely influenced by Miettinen, to reach the understanding that the control series should not be like the cases; instead, it should be like the population from which the cases arise. Of course, hindsight has great acuity, and I cite this example only to illustrate the conceptual level of understanding about case-control studies that was prevalent when Miettinen wrote this paper.

Although historical examples of case-control studies can be found from before the 20th century, many credit Janet Lane-Claypon as the author of the first formal case-control study, which was published in 1926 (3). However, it was not until 1950, with the publication of the landmark case-control studies on smoking and lung cancer by Wynder and Graham (4), Doll and Hill (5), and Levin et al. (6), that the case-control design gained impetus. Within a year, Jerome Cornfield (7) introduced the odds ratio and showed that it was an estimator of the risk ratio in case-control studies. Nonetheless, Cornfield's paper left gaps. For example, it did not distinguish between rates and risks, and it led to the widespread belief that the odds ratio could serve as an estimator of relative risk only if one could assume that the disease is rare. "Relative risk" was an ambiguous term; we now understand that it can refer to the ratio of risks or the ratio of incidence rates (and in some circumstances, the ratio of prevalences). In Cornfield's day, the distinction between risks and rates was largely submerged. It is a historical curiosity, explained by Vandenbroucke (8), that the distinction (between risk and rate) was well known to William Farr in the mid-19th century but was later forgotten, at least among epidemiologists, until it was reintroduced in the 1970s (9).

Miettinen's 1976 paper was rich with content that made it a watershed development in the understanding of case-control studies. As the title suggests, Miettinen addressed several measures that might be estimable from a case-control study and discussed how to estimate them. He meticulously distinguished rates from risk and explained why the rare disease assumption discussed by Cornfield was only applicable to a particular type of case-control study in which the cases are ascertained after the end of the entire risk period of interest and controls are sampled from among those who did not become cases, a design nowadays called a cumulative case-control study. In the paper, Miettinen discussed estimation of incidence density ratio (he used the term "incidence density" to describe "incidence rate"), explaining how the rare disease assumption was not needed for case-control studies in which the incidence density ratio was estimated. The paper also addressed how the incidence density ratio could be estimated from a study of either incident or prevalent cases; however, with prevalent cases, it was necessary to assume that the duration of illness was unrelated to the exposure. Another issue discussed was the estimation of the risk ratio (Miettinen's term for this was "cumulative incidence ratio") and the etiologic fraction, as well as exposure-specific estimation. These ideas laid a strong theoretical foundation for the case-control study.

In Appendix 1, Miettinen also introduced a controversial method for estimating confidence intervals. This was the method of test-based confidence limits, a simple approach that capitalized on the connection between statistical tests of a null hypothesis and the calculation of confidence limits. This procedure was easy to apply but had theoretical drawbacks, because the confidence intervals were found to have coverage levels that departed from nominal levels (10, 11). Miettinen argued that the coverage levels were not as important as the proximity of the approximate limits to exact limits (12); however, with the advent of programmable calculators and personal computers that enabled quick calculation of exact confidence limits, test-based limits ultimately conferred little advantage and did not gain traction either theoretically or practically.

Miettinen did not discuss matched case-control designs in that paper. Presumably the sweep of the paper was broad enough without introducing the issue of matching, which for case-control studies brought considerable added complexity. Nonetheless, the role of matching in case-control studies was something that he had already elaborated in detail in a series of papers that stemmed from his doctoral thesis in biostatistics at the University of Minnesota, which was completed in 1968 (13–16). Later, Greenland and Thomas (17) noted that his proposed density-sampling design involved time-matching and therefore required taking that matching into account in the analysis to obtain unbiased results.

With his paper, Miettinen introduced the neologism "case-referent studies" in place of the more traditional and popular term case-control studies. As noted above, the term case-control itself was not universally used in the 1970s, but it was rapidly gaining acceptance. Miettinen had used the term case-control in several of his earlier papers, but he switched to case-referent here. Some epidemiologists still use case-referent, but the term case-control is the one more commonly used by epidemiologists today. Similarly, his introduction of the term incidence density for incidence rate is still occasionally used, but most epidemiologists use the term incidence rate.

Not surprisingly, some of Miettinen's observations were anticipated in earlier literature. For example, several authors had used control sampling directly from the population from which the cases arose and thus did not need a rare disease assumption (18, 19). However, Miettinen drew ideas together in a concise and elegant elaboration of some key elements of modern epidemiologic theory that is likely to be read by many future generations of epidemiologists.

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