I–6.

Olli Miettinen: Confounding and Effect-Modification. American Journal of Epidemiology 1974; 100:350–353.

Miettinen's "Confounding and Effect-Modification" is noteworthy for introducing what may be Miettinen's most widely used neologism, "effect modification," and for carefully distinguishing the concept from confounding. The quantitative aspects of this distinction were appreciated by Simpson nearly a quarter of a century previously (see his article in Part II), but a detailed consideration of the causal aspects of these phenomena was not given until Miettinen.

The article was written in response to a brief note by Fisher and Patil [1974], which was in turn inspired by an earlier article by Miettinen. The earlier articles were concerned with issues far afield from effect modification and so are not reproduced here. Indeed the issue debated among these authors—whether one should routinely consider confounding conditional on other controlled factors—is still an open one. But it is Miettinen's criteria for confounding and his definition of the term "effect modification" that need to be put in an historical perspective.

Among the criteria for confounding by a covariate (p. 351), items 1–3 are now generally employed, and indeed are often used as a definition of a confounder (i.e., a covariate, predictive of illness among the unexposed and associated with exposure, but not an intermediate variable) (see, e.g., Schlesselman [1982]). Item 4 has not, however, held up under scrutiny: a covariate whose apparent relation to exposure or illness is solely the result of measurement error need not be a confounder [Greenland and Robins, 1985]. And item 5 has been criticized and abandoned by Miettinen himself [Miettinen and Cook, 1981]: among other things, absence of a covariate-illness relation in the data at hand need not imply absence of confounding by the covariate.

With regard to "effect modification"—variation in the chosen effect parameter across levels of a covariate—the term seems somewhat ambiguous, for it suggests a changing biologic process. In fact, as Miettinen notes in point 3 on page 352, when effects are present, presence or absence of effect modification depends on the measure of effect one uses, even if the biological mechanism that produces the effect is invariant. Effect modification is thus no more than a special type of statistical interaction, and should not be confused with biological interaction or "synergy." Given this, a more precise term for the phenomenon would be "effect-measure modification."

One minor technical note: the "Zelen test" of uniformity of the odds ratio, given by Miettinen on page 352, has since been shown to be invalid [Halperin et al., 1977]; for valid tests see, e.g., Schlesselman [1982], or Rothman [1986].

References:

Fisher L, Patil K. Matching and unrelatedness. Am J Epidemiol 1974; 100:347–349.
Greenland S, Robins JM. Confounding and misclassification. Am J Epidemiol 1985; 122:495–506.
Halperin M, Ware JH, Byar DP, et al. Testing for interaction in an I × J × K contingency table. Biometrika 1977; 64:271–275.
Miettinen OS, Cook EF. Confounding: essence and detection. Am J Epidemiol 1981; 114:593–603.
Rothman KJ. *Modern Epidemiology*. Boston: Little, Brown, 1986.
Schlesselman JJ. *Case-control Studies: Design, Conduct, Analysis*. New York: Oxford University Press, 1982.