LETTERS TO THE EDITOR

RE: RESIDUAL CONFOUNDING

In John Last's A Dictionary of Epidemiology (1), as defined in the last (third) edition, the term "residual confounding" is used to describe unmeasured confounding. Specifically, the definition for residual confounding states:

Potential confounding by factors or variables not yet considered in the analysis; these may be directly observable or not; in the latter case, they are latent residual confounders. (1, p. 146)

This dictionary, sponsored by the International Epidemiological Association, is due for revision, and we propose that this definition should be revised. It is unclear from the definition as currently worded how residual confounding differs from just confounding. Kleinbaum et al. (2) refer to residual confounding as both the lack of proper covariates and the effect of not sufficiently detailed information.

It seems to us more appropriate to define residual confounding as the confounding which remains after unsuccessful attempts to adjust for it. The sources of residual confounding would then be both insufficiently detailed information (also stemming from improper categorization) and misclassification of the variable. Marshall and Hastrup (3) suggest the term "resonance" for the latter situation, which we do not find appealing.

Following our suggestion, residual confounding becomes a variable-specific concept, as opposed to both variable- and model-specific concepts. A more specific concept is needed to convey the fact that we only rarely have the information needed to fully adjust for confounding. A word is needed to describe the difference between theoretical effect estimates after complete confounder control and the empirical effect estimates after our attempts to control. "Residual confounding" could serve this purpose.

REFERENCES


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Editor’s note: The editors of the Journal asked Drs. Marshall and Hastrup if they wished to respond to this letter from Drs. Olsen and Basso, but they chose not to do so.

RE: “MALE PESTICIDE EXPOSURE AND PREGNANCY OUTCOME”

In the abstract of their paper, Savitz et al. (1) write: “No associations were found between farm chemicals and... altered sex ratio.” However, as the authors noted, “there was a consistent observation of reduced sex ratio (OR = 0.8) for men who did not report using protective equipment.” Yet, these are the very births of interest. The numbers of independent births in this category are not given, but they may be estimated on the assumption that the extent of overlap (viz., of being included in more than one category of chemical exposure) is the same for offspring of fathers who do, and do not, use protective equipment. On this assumption, one would estimate totals of about 165 male births and 197 female births. This sex ratio is significantly different from an expected white birth sex ratio of 0.514 (2) (chi-square = 4.9, p < 0.03).

I suggest that, taken in conjunction with existing data that relate offspring sex ratio to paternal exposure (later adduced in this note), these data of Savitz et al. (1) may be interpreted as indicative of an effect of male pesticide exposure.

Savitz et al. (1) also cite two reports (3, 4) that have addressed dibromochloropropane (DBCP), a proven cause of male fertility. In regard to these reports, Savitz et al. state that the one report (3) "has not been replicated" in the other report (4) "indicating a decrease in the proportion of male offspring." Yet, these two reports are by the same group of workers and deal with the same set of data—so the question of replication does not arise. In fact, however, the same group of workers, who originally reported six male offspring and 11 female offspring fathered by men during exposure, later reported four males and 15 females sired during the fathers’ recovery period (5). So, in that sense, replication has been reported.

There are further reports that associate low offspring sex ratios with paternal exposure to a number of agents, e.g., borates (6), vinclozolin (7), and non-ionizing radiation (8). Moreover, it has been reported (9) that men treated with methyltestosterone (or other agents which increase testosterone levels in men) produce highly significant excesses of male offspring (9).

However, the most persuasive data linking parental chemical exposures to offspring sex ratio relate to dioxin. I have adduced very substantial quantities of data to support the hypothesis that a low testosterone/gonadotropin ratio in men is associated with the production of excess daughters (10). Egeland et al. (11) noted that dioxin is associated with such a
hormone profile in men and I accordingly predicted (12) that exposure to dioxin would be associated with the production of excess female offspring. This hypothesis has since been confirmed (13).

To summarize, there are a number of forms of male exposure which are associated with significantly low offspring sex ratios. These have been replicated in the case of DBCP and non-ionizing radiation. In regard to DBCP, dioxin, and methyltestosterone, the known hormonal effects of the chemicals are consistent with my hypothesis that the testosterone/gonadotropin ratio in mammalian parents at the time of conception is causally and positively related to the offspring sex ratio (proportion male).

I suggest that offspring sex ratio is a useful non-invasive alternative to sperm counts and hormone assays as a monitor of male reproductive hazard.

THE AUTHORS REPLY

We thank Dr. James for his observations regarding our study (1). As noted in our article (2), the consistent finding of a male deficit for births fathered by men who did not use protective equipment is impressive. The reason we did not tabulate the summary measure for “any chemical exposure” with and without use of protective equipment was that the heterogeneity of exposures associated with such diverse chemical applications was thought to be less informative than the results for specific types of chemical applications. However, in response to Dr. James’s inquiry, we did analyze “any chemical” with and without use of protective equipment. As noted, in making his calculation based on published results, the assumption was made that overlap based on multiple types of chemical application was similar for those who did and did not use protective equipment. For reasons that are not at all clear, there were actually more men who had applied pesticides for multiple purposes among those who used protective equipment (1,184 actual births vs. 2,370 estimated by summing across types of chemical application, for a ratio of 0.4995) than among those who did not use protective equipment (370 births vs. a sum across categories of 682, for a ratio of 0.5425). This small disparity leads to a much smaller male deficit than that estimated by Dr. James, with 181 males and 189 females born to men who did not use protective equipment, for a risk ratio of 0.97 (95 percent confidence interval 0.86–1.10).

Nevertheless, the examination of sex ratio for each type of chemical application among men who did and did not use protective equipment is more likely to be valid, though less precise, than the result for the aggregate of chemical applications. We agree that at least this component of our results lends very modest support to the hypothesis that male chemical exposures may reduce the proportion of male offspring. Other data cited by Dr. James (1) make this case much more strongly than our results.

REFERENCES

10. James WH. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels at the time of conception. J Theor Biol 1996;180:271–86.

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