**THE SECOND AUTHOR REPLIES**

In his letter, Gordon (1) raises questions concerning the findings of our prospective cohort study of breastfeeding and respiratory illness (2) based on his unproven speculations about the etiology of respiratory illnesses in children. In a series of previous letters to the editor, he has advanced a "mechanical theory" for the occurrence of respiratory and gastrointestinal illnesses in infants. His proposed "some syndrome"—that "pooling of liquids in the middle ear, with secondary reflux down the eustachian tubes into the stomach and lungs, [causes] gastroenteritis and pneumonia" (1, p. 427)—seems implausible. While his theory may not have been "refuted," it is hardly established and is not well supported by a broad understanding of pathogenic mechanisms of respiratory infection in infants. Our paper (2) offers strong evidence for a role of breastfeeding in lowering the risk of respiratory illnesses in infants during the first 6 months of life, and the findings have no relevance to Gordon's speculations.

**REFERENCES**


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**RE: “DISTINGUISHING THE EFFECTS OF MATERNAL AND OFFSPRING GENES THROUGH STUDIES OF ‘CASE-PARENT TRIADS’” AND “A NEW METHOD FOR ESTIMATING THE RISK RATIO IN STUDIES USING CASE-PARENTAL CONTROL DESIGN”**

The recent papers by Wilcox et al. (1) and Sun et al. (2), which appeared in the same issue of the *Journal*, both discuss inference based on genetic studies of cases and their parents. The intrepid reader who attempts to read both articles may reasonably be confused as to how they relate to each other, if at all.

Sun et al. (2) describe the "case-parental control" design, wherein one studies cases and genetically matched controls consisting of the nontransmitted parental alleles, put together to form a hypothetical individual. Wilcox et al. (1) do not form these hypothetical controls but instead focus on the multinomial distribution of triads made up of cases and their two parents. In fact, the designs are identical: Both methods genotype cases and their parents. There is a one-to-one equivalence between table 1 of Sun et al. and table 1 of Wilcox et al., except that in the paper by Wilcox et al., the triads in which all three individuals carry a single copy of the variant allele are included as a single cell, whereas in the paper by Sun et al., the subcounts in which the inherited variant came from the mother versus the father have been (artificially) distinguished (though they are later summed), netting 16 rather than 15 cells for their multinomial. Thus, while they are conceptualized differently, both the designs and the data structures are identical.

One conceptual problem that arises when the case-parent triad design is thought of as a case-control method is that one may assume it is odds ratios that are being estimated and that these are interpretable as relative risks only under a rare disease assumption. In fact, what is being estimated here are relative risks, regardless of whether the disease is rare or common.

The analytic techniques proposed in the two papers are somewhat different. Wilcox et al. (1) allow for two causal scenarios: one where effects are maternally mediated (scenario B) and one where effects are related to the inherited gene (scenario A). Thus, the overlapping advice related to analysis is confined to situations in which one assumes that scenario B is not a plausible causal mechanism. Restricting attention to scenario A, Sun et al. (2) propose noniterative methods of analysis, whereas Wilcox et al. apply a log-linear model, which requires an iterative maximum likelihood fit but can be easily fitted with widely available software such as SAS. The method described by Wilcox et al. for their scenario A is in fact identical to the maximum likelihood estimation (MLE) technique considered by Sun et al., who show via simulations that MLE is more efficient (and less biased) than the other three methods considered. We have pointed out elsewhere (3) that MLE (conditional on parental genotype), first proposed by Schaid and Sommer (4), is mathematically equivalent to our log-linear modeling method under scenario A.

An inconsequential difference between the two papers is that Sun et al. (2) do not assume genetic mating symmetry, whereas Wilcox et al. (1) do. For example, in the paper by Wilcox et al., it is assumed that couples in which the father is homozygous for the variant allele and the mother is heterozygous are just as frequent in the population as couples in which the father is heterozygous and the mother homozygous. However, in the context of scenario A (but not scenario B), this assumption can easily be relaxed by using nine stratum parameters in place of the six specified in Wilcox et al.'s table 1.

One interesting point made by Sun et al. (2) is that one can carry out inference under scenario A even with missing parents. However, we caution that the proposed estimation methods require that the parents be missing at random, or the cell probabilities given (e.g., in Sun et al.'s table 5) may not be correct. A general maximum likelihood method that allows for missing parents has since been described by Weinberg (5).

**REFERENCES**


*Am J Epidemiol* Vol. 150, No. 4, 1999
Kleven et al. (1) recently reported results of an acquired immunodeficiency syndrome (AIDS) risk group validation study. They inferred that heterosexual risk was validated in 82 percent of the cases originally so classified and in 22 percent of men and 60 percent of women among cases originally reported as having no identified risk factor. They verified AIDS risk classification at six US sites by using information obtained mainly from medical records; details on the information distilled were not presented. The report by Klevens et al. may be misnamed, given that it is more a reliability study than a validity study (i.e., people may reliably provide the same false information repeatedly). A rigorous reliability study requires multiple methods of querying respondents rather than recording of unchallenged (2) medical chart entries. In a study of adolescents, use of computer-assisted questionnaires resulted in reported prevalences of homosexual activity that were up to seven times greater than those obtained through conventional methods (3).

A persuasive validation study would demand a multi-method search for invalidation of patients' self-reports, particularly given the literature on misreporting of sexual and drug use histories (4, 5). When epidemiologists in Chicago, Illinois, conducted a similar validation study (one that the authors failed to cite) by using various combinations of record reviews and personal interviews (of medical providers and patients themselves or their proxies), they reclassified 69 percent of originally "heterosexual" or unidentified risk cases into nonheterosexual categories (6). A yet more rigorous validation study requires additional investigative methods (5), including measures of response bias and physical and serologic (7) markers of injection drug use and anal intercourse. It is likely that use of such additional methods would dramatically reduce the number of insufficiently researched cases assigned to the heterosexual group.

AIDS case categories used by the Centers for Disease Control and Prevention (CDC) are asymmetrical and ambiguous. The "heterosexual" category fails to capture crucial transmission efficiency differences between vaginal intercourse and anal intercourse, and "men who have sex with men" is a cumbersome construct used to avoid the neutral term "homosexual" (and is less specific than "men who have sex with men") in the elucidation of modes of AIDS transmission, the dual danger of patients' misreporting their drug and sex histories and of misleading language is compounded by this CDC classification system. Deficiencies in risk factor assessment—whether a consequence of patient recall, misunderstanding, or lying or of interviewer vagueness or timidity—can yield inflated "heterosexual" or "unidentified" risk factor counts, because these can be used as default categories. Patients who report heterosexual contact may be pleading guilty to a lesser charge—not only because admitting to illicit drug use or anal or homosexual intercourse may be pejorative but also because, quite literally, injection drug use is illegal at all six sites studied, homosexual anal intercourse is illegal at three (four including California prisons), and heterosexual anal intercourse is illegal at two (8). Consistent with the contentious CDC approach, Klevens et al. (1) interpret the dearth of identified risk factors among the vast majority of nominated heterosexual partners as evidence of secondary transmission, ignoring the possibility that it may simply be evidence of the low validity of self-reported information. The widespread use of the confounded CDC classification system may have produced a spurious, albeit still quite small, "heterosexual epidemic."

REFERENCES


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