ing. However, the evidence seems to suggest strongly that it is rather a case of "both/and."

Finally, the question remains: Does it really matter what causes lung cancer? Certainly, tobacco smoking is a major contributory factor to lung cancer and to other diseases and should be eradicated from society. However, tobacco has also been skillfully exploited as a smokescreen which has distracted attention from the air pollution associated with our uncritical (and still increasing) dependence upon motor vehicles.

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In accordance with Journal *policy, Dr. Vandenbroucke was asked if he wished to respond to Dr. Wolff's letter but chose not to do so.*

RE: "CASE-CONTROL STUDIES OF ENVIRONMENTAL INFLUENCES IN DISEASES WITH GENETIC DETERMINANTS, WITH AN APPLICATION TO ALZHEIMER'S DISEASE"

Breitner et al. (1) recently reported apparently counterintuitive results concerning the estimation of relative risks from case-control studies of diseases of genetic origin. They assumed that disease occurs only in a genetically susceptible subpopulation, but that within this group, the risk of disease differs between those exposed to an environmental risk factor and those unexposed. They showed that, under these circumstances, a case-control study in which controls are drawn from the whole population (not just from susceptibles) is expected to yield an odds ratio for the risk factor which is greater than the ratio of the risk for exposed susceptibles to that for unexposed susceptibles. They noted that this finding is in apparent conflict with the results of Khoury et al. (2), which suggest that the effect of the risk factor will be diluted in a total-population case-control study. The results presented by Breitner et al. may lead the reader to the erroneous conclusion that the strength of the exposure-disease association is overestimated. Here we wish to show that this paradox is due to the breakdown of the "rare disease" assumption in the circumstances Breitner et al. considered, but that these circumstances have little relevance to epidemiologic research.

The argument of Breitner et al. omits the crucial dimension of time. Their figure 1 (1, p. 248) refers to cross-sectional sampling of a population. The proportions x/se and $y/s\bar{e}$ measure prevalences in the exposed and unexposed sections of the genetically susceptible population, and r refers to the ratio of these prevalences. Breitner et al. show that the odds ratio in a study of prevalent cases and total-population controls overestimates r. However, a different impression is given when the strength of the exposure-disease association among susceptibles is measured by the ratio of prevalence odds rather than proportions. Table 1 shows this odds ratio for the range of situations considered in Breitner et al.'s table 2 (1, p. 250).

TABLE 1. Odds ratios in the genetically susceptible population hypothesized by Breitner et al. (1)*

			Odds ratio		
			$r = 2$	$r = 5$	$r = 8$
$s = 0.10$					
	$e = 0.10$				
		$t = 0.02$	2.04	5.31	8.73
		$t = 0.10$	2.22	7.22	14.22
		$t = 0.50$	12.00		
	$e = 0.50$				
		$t = 0.02$	2.03	5.14	8.26
		$t = 0.10$	2.15	5.80	9.51
		$t = 0.50$	4.00	25.00	64.00
	$e = 0.90$				
		$t = 0.02$	2.02	5.09	8.16
		$t = 0.10$	2.12	5.49	8.86
		$t = 0.50$	3.11	9.76	16.48
$s = 0.25$					
	$e = 0.10$				
		$t = 0.02$	2.04	5.31	8.73
		$t = 0.10$	2.22	7.22	14.22
		$t = 0.50$	12.00		
	$e = 0.50$				
		$t = 0.02$	2.03	5.14	8.26
		$t = 0.10$	2.15	5.80	9.51
		$t = 0.50$	4.00	25.00	64.00
	$e = 0.90$				
		$t = 0.02$	2.02	5.09	8.16
		$t = 0.10$	2.12	5.49	8.86
		$t = 0.50$	3.11	9.76	16.48
$s = 0.50$					
	$e = 0.10$				
		$t = 0.02$	2.04	5.31	8.73
		$t = 0.10$	2.22	7.22	14.22
		$t = 0.50$	12.00		
	$e = 0.50$				
		$t = 0.02$	2.03	5.14	8.26
		$t = 0.10$	2.15	5.80	9.51
		$t = 0.50$	4.00	25.00	64.00
	$e = 0.90$				
		$t = 0.02$	2.02	5.09	8.16
		$t = 0.10$	2.12	5.49	8.86
		$t = 0.50$	3.11	9.76	16.48

* Data from table 2 of Breitner et al. (1, p. 250).

These are always greater than the values tabulated by Breitner et al., which are odds ratios computed in the entire population. Thus, if an odds ratio measure is used throughout, the exposure effect measured in the total population is an attenuated version of that applying among susceptibles. This is in accord with the results of Khoury et al. (2). However, because the rare disease assumption breaks down within the pool of susceptibles, r is less than both odds ratios. A case-control study would estimate the odds ratio in the total population, and this overestimates r.

There is no real conflict between the results of Breitner et al. and those of Khoury et al.; there is merely a difference of view as to which measure of effect is most relevant. The calculations of Breitner et al. are relevant only if the aim is to compare prevalences using a case-control study of prevalent cases. The problems of such comparisons are well known. In particular, the ratio

of prevalences may only be taken as an estimate of risks (cumulative incidences) under very restrictive assumptions concerning mortality and migration. These are unlikely to hold in the case of Alzheimer's disease. In the cross-sectional sampling model considered by Breitner et al., it is incorrect to refer to r as a "relative risk," and restating their argument in terms of cumulative incidences would be realistic only for a synthetic retrospective study within a prospective follow-up study of a cohort. In this case, follow-up would usually have to be very long for the rare disease assumption to be violated—even for susceptibles.

The study design, which is of greater practical importance, is that in which incident cases are compared with age-matched controls. Here it is necessary to consider the time dimension, and by considering a sufficiently fine stratification of the time scale, the applicability of the rare disease assumption may be guaranteed: The odds ratio in the case-control study estimates the rate ratio in the study base (see, for example, Greenland et al. (3)). In the case where disease only occurs in a proportion of the population, the rate ratio in the total population will be attenuated with respect to the rate ratio among susceptibles. The odds ratios given by a properly conducted case-control study will simply reflect this. If it is possible to stratify by susceptibility—for example, by carrying out case-control studies in disease-discordant monozygotic twins—then we are targeting larger odds ratios and have a correspondingly greater chance of a positive finding. Thus, the power comparisons shown in Breitner et al.'s figure 3 (1, p. 252) are no more or less than we would expect.

Finally, we note that, for many important risk factors, studies in monozygotic twins run the risk of "overmatching." The example given by Breitner et al. of controlling for genetic confounding of the relation between Protestant/Catholic religious denomination and Alzheimer's disease would only be successful if we could find sufficient numbers of monozygotic twins who were discordant with respect to both disease and religion—a tall order!

In our table, some odds ratios have been omitted, since these situations correspond to inadmissable choices of parameter values. The corresponding odds ratios (including a value of −38.67) should also be omitted from table 2 of Breitner et al.

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THE AUTHORS REPLY

We thank Drs. Clayton and van Duijn for their observations (1). Evidently, Drs. Clayton and van Duijn misunderstood our paper (2) as implying that the tendency of the odds ratio occasionally to overestimate relative risk results from heterogeneity of genetic risk in the population. They observe that any such overestimation results instead from a breakdown of the "rare disease" assumption, a phenomenon that is already familiar. We agree. To the extent that the odds ratio does occasionally overestimate the relative risk among susceptibles, we argued that "this problem appears to be a special case of the well known inadequacy of the case-control method where prevalence is high . . . The bias in the odds ratio [then] appears to result despite . . . not because of . . . the condition of heterogeneous genetic risk" (2, p. 253). The central point of our paper was that even "under hypothetical conditions where a predisposing genotype is absolutely required for disease expression, the odds ratio provides a reasonable approximation of the relative risk among susceptibles" (2, p. 253)—i.e., that the most extreme sort of heterogeneity of genetic risk in the population itself produces no practical distortion in case-control studies of environmental influences, either in biased odds ratios or in reduced power. Although apparently "counter-intuitive," these conclusions rely on explicitly stated assumptions and a formal algebraic development which, to the best of our knowledge, was correct. Parenthetically, we also noted that Alzheimer's disease is not "rare," particularly among elderly relatives of cases. Therefore, case-control studies of Alzheimer's disease may be one instance in which breakdown of the "rare disease" assumption is of practical relevance.