

A BRIEF ORIGINAL CONTRIBUTION

Factors Influencing the Optimal Control-to-Case Ratio in Matched Case-Control Studies

Sean Hennessy,¹ Warren B. Bilker,¹ Jesse A. Berlin,¹ and Brian L. Strom^{1,2}

Statistical power in matched case-control studies depends on both the correlation coefficient between cases and their matched controls (ϕ) and the prevalence of exposure among controls (P_0). To examine the hypothesis that the value of increasing the control-to-case ratio beyond 5 varies with both ϕ and P_0 , the authors estimated statistical power for a hypothetical case-control study under different assumptions. The effect of increasing the control-to-case ratio depended on ϕ and, to a lesser extent, on P_0 . The results suggest that investigators consider including more than five controls per case when either ϕ is greater than about 0.2 or P_0 is less than about 0.15. *Am J Epidemiol* 1999;149:195-7.

case-control studies; matched-pair analysis; statistics

Investigators planning case-control studies are usually advised to include no more than four or five controls per case because little statistical power is gained by further increasing this ratio (1, 2). While this rule may be appropriate in most situations, there are settings in which a higher control-to-case ratio may be desirable. Rothman (1) cites two such instances: 1) when the cost of including additional controls is negligible, and 2) when there is concern for sufficient numbers in stratified analyses.

The concern that additional controls per case may be needed for stratified analyses is of particular relevance in matched case-control studies, in which each case together with its matched controls constitutes a distinct stratum. In such instances, a given case contributes *no* information unless there is at least one matched control that is discordant on exposure status. The probability of discordance in exposure status between a case and any given matched control would therefore be expected to influence the optimal control-to-case ratio.

Statistical power calculations developed by Dupont (3) for matched case-control studies require the investigator to specify 1) the desired type I error rate, 2) the minimum odds ratio to be detected as statistically signif-

icant, 3) the estimated number of cases, 4) the control-to-case ratio, 5) the estimated prevalence of exposure in the control group (P_0), and 6) an estimate of ϕ , the correlation coefficient for exposure between cases and their matched controls. Although unfamiliar to many epidemiologists, ϕ has been used in the social sciences as a measure of agreement between dichotomous items (4). It is calculated using the equation $\phi = (\chi^2/N)^{1/2}$, where χ^2 is the uncorrected Pearson chi-square statistic from a two-by-two table, and N is the total number of observations (in a matched case-control study, this is the number of matched case-control pairs). To illustrate, table 1 presents a previously unpublished matched contingency table from a previously reported (5) case-control study of the effectiveness of Japanese encephalitis vaccine, with the exposure being defined as one (vs. zero) dose. The value of ϕ for this table is

TABLE 1. Data from a matched case-control study of the effectiveness of Japanese encephalitis vaccine, comparing two doses (exposed) with zero doses (unexposed)*,†

		Case		
		Exposed	Unexposed	Total
Control	Exposed	102	178	280
	Unexposed	57	550	607
Total		159	728	887

* Previously unpublished data from study reported in *Lancet* 1996;347:1583-6.

† Uncorrected Pearson's chi-square = 95.21.

Received for publication November 3, 1997, and accepted for publication June 8, 1998.

¹ Center for Clinical Epidemiology and Biostatistics, and Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA.

² Division of General Internal Medicine, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA.

$(95.21/887)^{1/2} = 0.33$ (exact 95 percent confidence interval 0.03–0.62). The values of ϕ (with exact 95 percent confidence intervals) for the two- and three-dose comparisons (each compared with zero doses) were 0.37 (0.06–0.68) and 0.58 (0.02–1.00), respectively.

How can investigators who are planning a matched case-control study estimate ϕ , given that few studies report either the value of ϕ or the matched tables that would allow readers to calculate ϕ ? Dupont (3) recommends using a value of 0.2 if a data-based estimate for ϕ is unavailable. However, as shown above, there may be situations in which ϕ may be substantially higher, although this is difficult to know in advance. Interestingly, in the previously cited case-control study, the high observed values of ϕ did not translate into lack of association between exposure and disease. The matched odds ratios were as follows: 0.20 (95 percent confidence interval 0.07–0.56) for one dose and 0.025 (95 percent confidence interval 0.004–0.14) for two doses (the matched odds ratio for three doses was not calculable because of a zero cell) (5). Thus, contrary to intuition, a high degree of correlation in exposure between cases and their matched controls did not result in a lack of association between exposure and disease.

We were interested in learning how the optimal control-to-case ratio is affected by the degree of correlation in exposure between cases and their matched controls. In particular, we hypothesized that the amount of information provided by increasing the control-to-case ratio beyond five would increase as a function of

ϕ . As well, we were interested in examining what effect, if any, P_0 had on the optimal control-to-case ratio.

MATERIALS AND METHODS

Using typical values for the parameters that determine statistical power, we examined the effect of increasing the control-to-case ratio for different values of 1) ϕ and 2) prevalence of exposure among controls (P_0). In particular, we examined the estimated statistical power to detect an odds ratio of 3 in a hypothetical matched case-control study of 50 cases, specifying a type I error rate of 5 percent, and varying ϕ , P_0 , and the control-to-case ratio. We used the computer program developed by Dupont and Plummer (6) to estimate statistical power.

RESULTS AND DISCUSSION

As expected, for a given P_0 and a fixed number of cases and controls, ϕ has a large effect on statistical power (figure 1). Also as expected, the gains in statistical power resulting from increasing the control-to-case ratio increased as ϕ increased (figure 1); that is, the power curves flatten more gradually as ϕ increased. For example, if ϕ is 0.1, the estimated statistical power increases only from 89 percent to 92 percent (an absolute increase of 3 percentage points) when the control-to-case ratio is increased from 5 to 10. In most situations, it is unlikely that this small

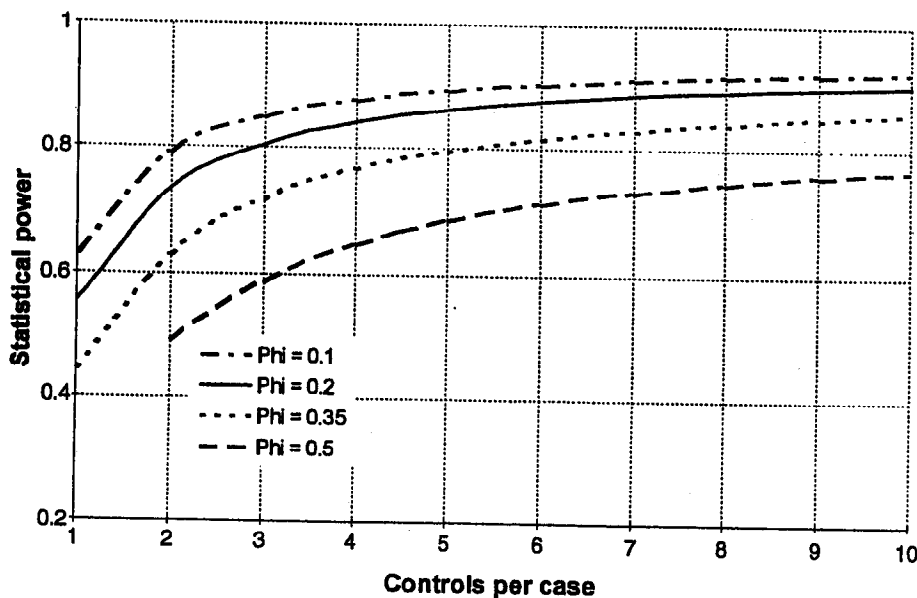


FIGURE 1. Estimated statistical power for a hypothetical matched case-control study with $\alpha = 0.05$, the probability of exposure in the control group = 0.2, and odds ratio = 3 (produced using software described in *Control Clin Trials* 1990;11:116–28).

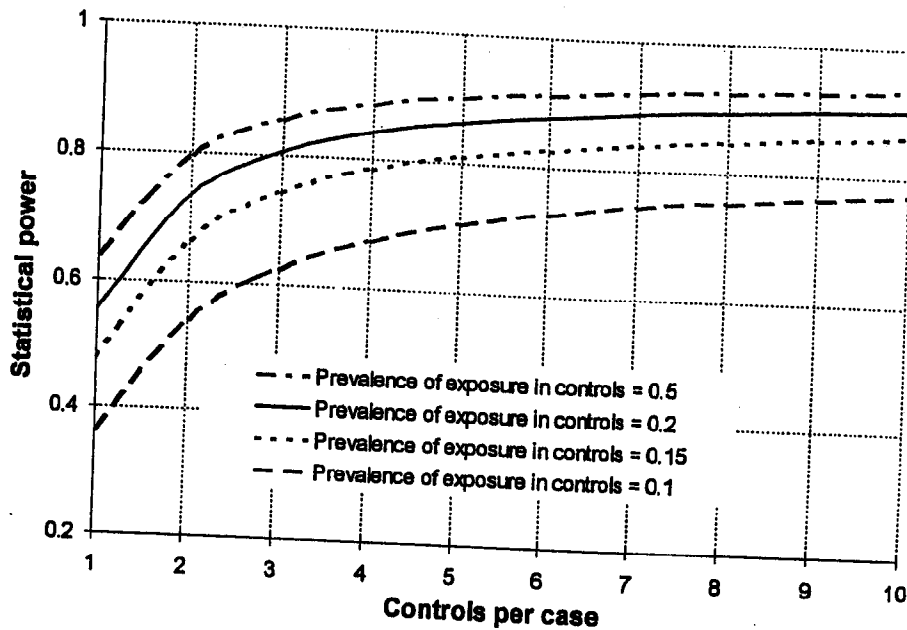


FIGURE 2. Estimated statistical power for a hypothetical matched case-control study with $\alpha = 0.05$, correlation coefficient for exposure between cases and matched controls (ϕ) = 0.2, and odds ratio = 3 (produced using software described in *Control Clin Trials* 1990;11:116-28).

gain in statistical power would be worth the added costs. In contrast, if ϕ is 0.5, the estimated statistical power increases from 68 percent to 77 percent (an absolute increase of 9 percentage points) for the same increase in the control-to-case ratio. Under these circumstances, it might well be worth the expense to enroll 10 or more controls per case. As an extreme example, if one desires 80 percent statistical power when ϕ is 0.5, 18 controls per case are necessary. In terms of a rough rule-of-thumb, it appears as though one should consider increasing the control-to-case ratio beyond 5 when ϕ is expected to be greater than about 0.2.

P_0 also has a very dramatic effect on statistical power (figure 2). While there is an effect of P_0 on the relation between statistical power and the control-to-case ratio (figure 2), this effect is more subtle than the effect of ϕ . In particular, the value of increasing the control-to-case ratio beyond 5 increases as P_0 falls. A rough rule-of-thumb would be to consider increasing the control-to-case ratio beyond 5 when P_0 is expected to be less than about 0.15.

It should be noted that the calculations presented here assume that the matching factor is the only variable that will be used for stratification. As noted by Rothman (1), analyses that are also stratified on other factors will have less statistical power than is estimated by standard formulas. In these situations, it may be even more advantageous than is suggested here to include more

than five controls per case, particularly when there is a strict limit to the number of cases available.

In summary, meaningful increases in statistical power can be obtained by increasing the control-to-case ratio above 5 in matched case-control studies when there is a high (but plausible) correlation in exposure status between cases and matched controls, or when there is a low prevalence of exposure among controls. Therefore, investigators conducting a matched case-control study in which the number of possible cases is limited should consider using a control-to-case ratio of greater than 5 when either ϕ is expected to be greater than about 0.2 or P_0 is expected to be less than about 0.15.

REFERENCES

1. Rothman KJ. *Modern epidemiology*. Boston: Little, Brown and Company, 1986.
2. Hennekens CH, Buring JE. *Epidemiology in medicine*. Boston: Little, Brown and Company, 1987.
3. Dupont WD. Power calculations for matched case-control studies. *Biometrics* 1988;44:1157-68.
4. Fleiss JL. *Statistical methods for rates and proportions*. 2nd ed. New York: John Wiley & Sons, Inc, 1981.
5. Hennessy S, Liu Z, Tsai TF, et al. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study. *Lancet* 1996;347:1583-6.
6. Dupont WD, Plummer WD Jr. Power and sample size calculations. A review and computer program. *Control Clin Trials* 1990;11:116-28.