A relative power table for nested matched case-control studies

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Abstract

***Objective*—To calculate relative powers for nested case-control studies for different values of both relative risk and numbers of controls per case, given a fixed number of cases available for analysis.**

***Methods*—Algebraic and numerical methods.**

***Results*—In nested case-control studies, statistical power is a function of relative risk, rarity of exposure, number of case-control sets, and the number of controls per case.**

***Conclusion*—The dictum that sufficient power will be obtained in a nested case-control study by selecting only four controls per case cannot be sustained. Appropriate numbers need to be calculated for specific studies.**

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Keywords: relative power; number of controls per case; nested case-control studies

Nested case-control studies are used in many occupational epidemiological studies. For example, in the period January 1994 to July 1996, 11 papers appeared in either the *American Journal of Industrial Medicine* or *Occupational and Environmental Medicine* (formerly *British Journal of Industrial Medicine)* which featured nested matched case-control studies.[1–11] Mantel first showed that case-control studies could be nested within a cohort study by obtaining exposure histories for all cases and a group of randomly selected controls.[12] The nested case-control approach, if used properly, is intended to yield unbiased estimates of the relative risk obtainable from a full cohort analysis[13] with a considerable saving in time and expense. This is useful in occupational epidemiological studies when the abstraction of job history data for the entire cohort may be expensive or time consuming, or it is necessary to contact the next of kin of study subjects for information on other risk factors, such as smoking history. Some methodological issues arise despite these advantages. How many controls per case are necessary to achieve results similar to those given by the entire cohort? The traditional dictum is that four controls per case would be sufficient and all but two of the 11 studies referenced above selected five or fewer controls per case without supplying any power justification; investigators often failed to find any significant association between cancer risk and occupational exposure. Breslow and Day indicated that selecting more than four controls per case was not necessary when the expected relative risk was close to unity, but that more than four controls may be necessary for other values of relative risks.[14] Beaumont *et al* also indicated that “the gain in statistical power diminishes quickly beyond 4 to 20 controls per case”, and that this conclusion depended on “the magnitude of the relative risk and rarity of the exposure”.[15]

It is known that selecting the number of controls required per case without considering the likely magnitude of the relative risk and rarity of exposure (the probability of the control being exposed) is potentially misleading.[14] When a nested case-control study is used, all cases will be selected from the available cohort data. Thus the number of case-control sets is fixed. Researchers need to select sufficient number of controls per case by examining relative powers (absolute power for given number of controls per case/absolute power for infinite number of controls per case). Breslow and Day provided a relevant statistical table (table 7.9).[14] This table showed numbers of case-control sets required to achieve given statistical power for different values of relative risk, rarity of exposure, and numbers of controls per case. The table is most useful for planning traditional case-control studies in which the investigator may have some flexibility in choosing the number of cases to be studied. The table is less useful for nested case-control studies, in that the investigator has little control over the number of case-control sets available for analysis. The purpose of this note is to derive the power function and generate a statistical table which lists values of relative powers for specified numbers of case-control sets.

Implementation

The statistical power function can be expressed in terms of relative risk (R), number of controls per case (M), proportion of controls exposed (p_2), desired significance level (α) and number of case-control sets (N) (appendix). (The relative risk was approximated by the odds ratio.) The results of this procedure were checked with data from Breslow and Day table 7.9.[14] The relative power was then calculated for a given number of controls per case, assuming that 256 controls per case approximates to an infinite number of controls per case. The rationale for this assumption is that the power increased only slightly when more than 128 controls per case were selected. For example, when the relative risk was 2, the proportion of controls exposed was 0.05, and the number of case-control sets was 100, then the powers were 45.70%, 46.17%, 46.40%, 46.52%, and 46.58% for 64, 128, 256, 512, and 1024 controls per case, respectively. It was necessary to make such an

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Relative power for nested matched case-control study design in which the proportion of controls exposed is 0.05*

M†	Relative risk 1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	10.0
Case-control sets (n=10):									
1	13	8	6	5	4	4	4	4	7
2	31	23	21	20	19	20	21	21	38
4	53	46	44	43	44	46	47	49	71
8	72	67	66	66	67	69	70	72	88
16	85	82	82	82	83	84	85	86	94
32	93	91	91	91	92	92	93	93	98
Case-control sets (n=20):									
1	19	13	11	11	11	12	13	15	43
2	39	32	30	31	33	36	40	43	82
4	60	54	54	56	59	62	66	70	95
8	76	73	74	75	78	80	83	85	99
16	87	86	86	87	89	90	92	93	99
32	94	93	93	94	95	95	96	97	100
Case-control sets (n=100):									
1	32	31	39	51	65	77	87	93	100
2	51	54	64	76	86	93	97	99	100
4	70	73	81	89	95	98	99	100	100
8	83	85	91	95	98	99	100	100	100
16	91	93	96	98	99	100	100	100	100
32	96	97	98	99	100	100	100	100	100
Case-control sets (n=500):									
1	47	78	97	100	100	100	100	100	100
2	66	91	99	100	100	100	100	100	100
4	81	96	100	100	100	100	100	100	100
8	90	98	100	100	100	100	100	100	100
16	95	99	100	100	100	100	100	100	100
32	98	100	100	100	100	100	100	100	100

*Relative power is defined as the power of a given number of controls per case to the power for an infinite number of controls per case, as a percentage.
†M=number of controls per case.

assumption because the equation could only be solved by numerical methods; α was set to be 0.05 (two sided). Given values for the number of case-control sets (N) and the proportion of controls exposed (p_2), this procedure created a relative power table (rows refer to number of controls per case and columns refer to relative risk). The relative risk was assigned to be in the range of 1.5 to 10. The number of controls per case was assigned to be in the range of 1 to 32. Tabulations were then produced, showing relative power for all combinations of 13 different values for the number of case-control sets (N) and five different values for the proportion of controls exposed (p_2). All intermediate calculations maintained 20 significant digits. All programming was written in Maple scripts.[16 17]

Results and discussion

Relative powers are shown in the table for a number of nested case-control studies (four different values of N, p_2 is always 0.05). The relative power increased with the number of controls per case. For example, when the relative risk was 1.5 and the number of case-control sets was 20, relative powers for 1, 2, 4, 8, 16, and 32 controls per case were 19%, 39%, 60%, 76%, 87%, and 94%, respectively.

The relative power increased more with the number of controls per case for small numbers of case-control sets than for large numbers of case-control sets. For example, for 20 case-control sets and a relative risk of 1.5, the relative power increased by 26.7% ((76−60)/60) as the number of controls per case increased from 4 to 8. However, a smaller increase of 11.1% ((90–81)/81) in the corresponding relative power was found for 500 case-control sets.

The table also shows that relative power always increased with relative risk for risks in the range 3.5–10. However this was not always the case when the relative risk was in the range 1.5–3.5. For example, when the number of case-control sets was 20 and the number of controls per case was 4, relative power decreased from 60%–54% as relative risk increased from 1.5–2. Other tabulations for other values of p_2 (0.1, 0.3, 0.5, and 0.7) were also produced and similar results were found.

The present study shows that selecting a sufficient number of controls per case will play an important part in minimising power loss when a nested case-control study is carried out, in particular, for studies with few case-control sets and a small relative risk. The conventional dictum, "it is not worth choosing more than four controls per case", does not apply to small studies (small number of risk sets). It would be more appropriate to select the number of controls per case on the basis of desired relative power, available number of risk sets, likely relative risk, and rarity of exposure. The conventional dictum which attempts to give a summary in a single number—for example, four controls per case can lead to 80% efficiency is known to be oversimplistic.[14] The new tables provide a basis for more appropriate nested case-control studies to be carried out. A fuller set of tables may be obtained from me. A stand alone executable computer program written in Maple Scripts is also available for researchers wishing to produce their own tables.

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Statistical appendix: Derivation of power function

For simplicity, we consider studies with 1:M matching.

The layout for nested case-control studies with M controls per case was specified by Breslow and Day[14] as follows.

	Controls exposed (n) 0	1	2	…	m−1	…	M
Cases:							
Exposed	$n_{1,0}$	$n_{1,1}$	$n_{1,2}$	…	$n_{1,m-1}$	…	$n_{1,M}$
Not exposed	$n_{0,0}$	$n_{0,1}$	$n_{0,2}$	…	$n_{0,m-1}$	…	$n_{0,M}$

where n_{1j} is the number of sets with a case exposed and j controls exposed;. $n_{0,j}$ is the number of sets with a case unexposed and j controls exposed. M is the number of controls per case and m=1,2,..., M.

The mean and variance of $n_{1,m-1}$ were estimated by Breslow and Day[14] from the conditional likelihood using the maximum likelihood method as follows:

$$E_R(n_{1,m-1}) = (T_m mR)/(mR+M-m+1) \qquad (1)$$

$$Var_R(n_{1,m-1}) = T_m(MR(M-m+1))/(mR+M-m+1)^2 \qquad (2)$$

where T_m is the number of discordant sets and R is the relative risk.

T_m and R were approximated as follows:

$$T_m = NP_m = N\left[C_M^m (1-p_1)p_2^m (1-p_2)^{M-m} + C_M^{m-1} p_1 p_2^{(m-1)} (1-p_2)^{(M-m+1)}\right] \quad (3)$$

$$R = p_1(1-p_2)/p_2(1-p_1) \quad (4)$$

where P_m is the probability of T_m discordant sets; p_1 and p_2 are the proportion of cases exposed and the proportion of controls exposed, respectively.

Power $(1-\beta)$ is the probability (%) of obtaining a result significant at the α level (two sided) assuming no excess risk (R=l). The power is then determined from the following equation (continuity corrected)

$$\sum_{m=1}^{M}\{E_R(n_{l,m-1}) - E_{R=1}(n_{l,m-1})\} - 0.5$$

$$= Z_{\alpha/2}\sum_{m=1}^{M}\{\mathrm{Var}_{R=1}(n_{l,m-1})\}^{1/2}\} + Z_\beta\sum_{m=1}^{M}\{\mathrm{Var}_R(n_{l,m-1})\}^{1/2}\} \quad (5)$$

where $Z_{\alpha/2}$ and Z_β are the $\alpha/2$ and β points of the standard normal distribution, respectively.

Z_β was solved by substituting equations (1), (2), (3) and (4) into equation (5). Then the statistical power function $(1-\beta)$ was obtained given Z_β. The relative power was calculated as the power with a given number of controls per case divided by the power with infinite number of controls per case, expressed as a percentage. In the present note, the power for 256 controls per case is used as approximation for the power for an infinite number of controls per case.

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