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Commentary

Mantel–Haenszel techniques and logistic regression: always examine one's data first and don't overlook the simpler techniques

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Summary. The authors point out that, in addition to logistic regression, there are other, simpler techniques available for making an adjusted estimate of association between an outcome and a risk factor. Also, the consequence of mismodelling with regression, i.e. of missing the real relationship between an outcome and a risk factor, is illustrated with an example. The need to 'examine one's data' prior to performing multivariable techniques is emphasised.

Introduction

The two excellent expository articles by Brand and Keirse[1,2] on using logistic regression in perinatal epidemiology were very much needed. We would like to make two points.

First, contrary to the impression that the authors' statement[1]

> The 0.75 estimate itself cannot be computed from the table; however it has been obtained by a logistic regression analysis of the data in Figure 10T
>
> (p.33)

may have inadvertently given, logistic regression is not the only method of deriving an adjusted or 'mean' within-stratum estimate of an association between a risk factor and an outcome. In the authors' data set from the first article,[1] the mortality for boys is less than or equal to that of girls at all six gestational ages,

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with odds ratios (OR) ranging from 0.63 to 1.0. However, the crude odds ratio was 1.15 because of confounding by age (Figure 10D).[1] Logistic regression yielded an age-adjusted ratio of the odds of 0.75. In fact, an adjusted estimate can be calculated simply by calculator or spreadsheet, from the age stratified 2 × 2 tables (see Figure 1 and/or their Figure 10T)[1] by several other, simpler approaches.

An obviously oversimplified method would have been to average the six odds ratios over all six gestational age categories to yield an unweighted average odds ratio of 0.765. A more sophisticated approach is to take a weighted mean of the odds ratios. The most commonly used is the Mantel–Haenszel adjusted estimate which averages the odds ratios for the individual 2 × 2 tables using weights which reflect the sample size of each 2 × 2 table.[3,4] The method of Woolf produces similar results but works with weighted calculations carried out in the log odds scale.[3,5]

For example, if the numbers in the four cells of each of the 2 × 2 tables are represented by the traditional letters:

	boys	girls
dead	a	b
alive	c	d

and n = a + b + c + d, the Mantel–Haenszel adjusted estimate is derived from the formula

$$OR = \text{sum}(ad/n)/\text{sum}(bc/n)$$

Using the data from their Figure 10T[1] one can calculate this from Table 1 by dividing the sum of column 6 by the sum of column 7: 16.93/22.60 = 0.7491. This is mathematically equivalent to an average of the 6 odds ratios (ad/bc) using weights of (bc/n)/sum(bc/n) as is illustrated in columns 8, 9 and 10. In this example, the Woolf method yields the same answer to the third decimal. With the Mantel–Haenszel or Woolf method, one can also calculate standard errors to construct confidence intervals and tests.[3–5]

Since this was a follow-up study, one could have measured the association using the relative risk (RR) instead of the OR. A Mantel–Haenszel type weighting procedure, similar to that used for ORs, to average the stratum specific RRs, is available and described in both Kleinbaum *et al.*[4] and Rothman.[5] (Using a regression model to estimate an adjusted RR is also possible but less straightforward.)

Our second point concerns modelling confounding variables when their relationship to outcome is not linear in the log odds scale, as for example in Figure 13 of the second article.[2] In this situation (which Brand and Keirse only mentioned briefly), if the confounder–outcome relationship is mistakenly treated as linear, the resulting adjusted estimate of the odds ratio relating the risk factor and outcome could be very misleading. In fact, the six subtables from Figure 10T of the first article[1] (reproduced in Table 1 here) *do* describe a downward linear

(a) Hypothetical mortality data for boys versus girls, for each of six gestational ages (D = dead, A = alive)

	Gestational age											
	24		25		26		27		28		29	
	D	A	D	A	D	A	D	A	D	A	D	A
Boys	7	20	36	24	15	3	34	11	17	23	2	8
Girls	13	26	28	14	8	1	20	5	30	30	5	20
OR	0.70		0.75		0.63		0.77		0.74		1.00	

(b) Odds of death

(c) Estimates from a logistic regression which incorrectly modelled gestational age as linear

Parameter	Constant	Sex	Gestational age
Coefficient	1.033	0.130	− 0.036
ODDS RATIO	–	1.139	0.965

Figure 1. Adjusted odds ratio (OR) comparing mortality in boys versus girls, estimated via a logistic regression which treats gestational age linearly. The data, shown in tabular form in (a) and graphically in (b), are hypothetical and involve the same numbers as in Table 1. The mortality for boys is less than or equal to that of girls at all gestational ages. As in Table 1, the gestational age-specific ORs range from 0.63 to 1.00 and the Mantel–Haenszel adjusted average is 0.75. The crude OR of 1.15 gives the reverse impression. Modelling age linearly fails to remove the confounding (adjusted OR = 1.139). ■ = boys; □ = girls.

Table 1. Calculation of gestational age-adjusted odds ratio using the method of Mantel–Haenszel

age	a [1]	b [2]	c [3]	d [4]	n=a+b+c+d [5]	ad ÷ n [6]	bc ÷ n [7]	OR = ad ÷ bc [8]	W = 7 ÷ Σ[7] [9]	W × OR [10]
24	15	8	3	1	27	0.556	0.889	0.625	0.039	0.025
25	34	20	11	5	70	2.429	3.143	0.773	0.139	0.107
26	36	28	24	14	102	4.941	6.588	0.750	0.291	0.219
27	17	30	23	30	100	5.100	6.900	0.739	0.305	0.226
28	7	13	20	26	66	2.758	3.939	0.700	0.174	0.122
29	2	5	8	20	35	1.143	1.143	1.000	0.051	0.051
Σ	111	104	89	96		16.926	22.602		1.000	0.749

OR (crude) = $\Sigma a \Sigma d \div \Sigma b \Sigma c = (111 \times 96) \div (104 \times 89) = 1.151$
OR (stratified) = $\{\Sigma ad/n\} \div \{\Sigma bc/n\} = \Sigma[6] \div \Sigma[7] = 16.926 \div 22.602 = \{\Sigma(bc/n)OR\} \div \{\Sigma(bc/n)\} = \Sigma[10] = 0.749$

a=number of boys who died; b=girls who died; c=boys who lived; d=girls who lived [from Figure 10T].

relationship between the odds of death (on the log scale) and age. Suppose, however, that exactly the same data and odds ratios were obtained in a study, but at different gestational ages, in such a way that the relationship is an inverted U-shape rather than linear; such a pattern is depicted in Figure 1.

Figure 1 also provides the parameter estimates which are produced if, for this data pattern, age is treated as linear. The apparent estimate for the association between gender and outcome, adjusting for gestational age, is $OR = e^{0.13} = 1.14$, even though within each gestational age stratum the odds ratio is approximately 0.75. Since the 1.14 is so close to the crude odds ratio of 1.15, one might falsely conclude that age does not confound the sex–outcome relationship. Thus, unless the nature of the relationship between outcome and gestational age is examined closely and correctly accounted for in the logistic modelling, the regression estimate will not reflect the real relationship between sex and outcome. The failure in this example is not in the logistic regression methodology *per se*, but in blindly modelling the relationship between a variable and outcome as linear rather than quadratic (which might better reflect the U-shaped relationship).

Alternatively, one might want to treat gestational age as a categorical variable, in which case the adjusted OR will coincide with the Mantel–Haenszel OR. In this example, logistic regression, in which age is modelled as a categorical variable, produced an OR estimate of 0.75. However, using several dummy variables to represent the categorical variable may waste degrees of freedom if the quadratic equation does just as well.

Whether one uses the tabular or modelling approach, it always pays to examine one's data closely first and to understand the nature of the confounding variables (and also to check heterogeneity of odds ratios (effect modification)) through tables. Obviously, with many covariates and/or when data become sparse, the preferred approach for making an adjusted estimate is logistic regression, making assumptions which are reflected in the data.

References

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4 Kleinbaum, D.G., Kupper, L.L., Morgenstern, H. *Epidemiologic Research. Principles and Quantitative Methods*. New York: Van Nostrand Reinhold, 1982; pp. 320–363.

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From our own correspondents

Fumes from the spleen

> I think informed consent is a farce . . . The information [given parents] is what I want it to be.
>
> *an American neonatologist*

Until fairly recently, patients who appeared on the doctor's doorstep were seen as self-directed supplicants. The sick arrived, seemingly, as the result of their own free will. Many patients expressed their need in the form of a plea: 'Please do everything possible, Doctor!' For countless ages, healers interpreted such voluntary submission as clear evidence of unrestricted consent for any and all treatments, including untried experimental interventions. Practitioners responded with enthusiasm and with imagination.

The requirement of formal and specific consent for a medical action, particularly the notion of patients' *informed* consent for previously unevaluated treatment and for medical exploration to improve understanding, is a relatively recent development.[1] The new stipulation has been put in place to restrict the time-honoured paternalistic predilections of the medical profession. The beginning of a change in prevailing attitudes can be traced to a startling incident that took place in America in 1963[2] – the appalling episode called attention to the need for critical examination of long-standing informal arrangements for the conduct of bedside research.

The incident began when a young resident physician at a chronic disease hospital in New York was approached by the director of the department of medicine who asked whether the houseman would be interested in participating in a clinical project conducted by two experienced and highly regarded cancer researchers. The study, funded by the US Public Health Service and already under way at two other institutions, involved the subcutaneous injection of live cancer cells in order to measure the rate of rejection of the foreign cells by weak, debilitated, chronically ill patients. The rate was to be compared with the findings after similar injections already given to cancer patients in a famous American cancer institute and to healthy 'volunteers' in a state prison.

In July 1963, each of 22 patients in the chronic disease hospital received a test injection – it was completely unrelated to their usual care. The helpless patients were not told they had been selected by the houseman to be participants in a clinical experiment. The soon-to-be-infamous episode precipitated stormy debates among the hospital's doctors and these led to investigations by the