Calculating the "number needed to be exposed" with adjustment for confounding variables in epidemiological studies

Ralf Bender*, Maria Blettner

Department of Epidemiology and Medical Statistics, School of Public Health, University of Bielefeld, Bielefeld, Germany

Received 28 February 2001; received in revised form 26 October 2001; accepted 4 November 2001

Abstract

The number needed to treat (NNT) is a popular summary statistic to describe the absolute effect of a new treatment compared with a standard treatment or control concerning the risk of an adverse event. The NNT concept can be applied whenever the risk of an adverse event is compared between two groups; for the comparison of exposed with unexposed subjects in epidemiological studies, we propose the term "number needed to be exposed" (NNE). Whereas in randomized clinical trials NNT can be calculated on the basis of a simple 2×2 table, in epidemiological studies methods to adjust for confounders are required in most applications. We derive a method based upon multiple logistic regression analysis to perform point and interval estimation of NNE with adjustment for confounding variables. The adjusted NNE can be calculated from the adjusted odds ratio (OR) and the unexposed event rate (UER) estimated by means of an appropriate multiple logistic regression model. As UER is dependent on the confounders, the adjusted NNEs also vary with the values of the confounding variables. Two methods are proposed to take the dependence of NNE on the values of the confounders into account. The adjusted number needed to be exposed can be a useful complement to the commonly presented results in epidemiological studies, such as ORs and attributable risks.   © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Confounding; Confidence intervals; Epidemiology; Logistic regression; Number needed to treat; Odds ratio; Statistics

1. Introduction

The number needed to treat (NNT) is a popular summary statistic to describe the absolute effect of a new treatment compared with a standard treatment or control concerning the risk of an adverse event [1]. It was first introduced for use in randomized placebo-controlled clinical trials [2] and then proposed as summary measure for systematic reviews [3]; it was extended to the measure "number needed to screen" to compare strategies for disease screening [4] and was recently also applied in case-control studies to express the magnitude of adverse effects [5]. Although NNTs may be misleading when the compared treatments have their effects over different periods of time [6] or when NNTs are pooled in meta-analyses with varying baseline risks [7], the careful and cautious application of NNTs represents a useful way of presenting results. In epidemiological studies, the goal is frequently to compare exposed versus unexposed persons rather than a comparison of a new with a standard treatment or placebo. Hence, the NNT concept can be used in epidemiology as "number needed to be exposed" (NNE). Due to the lack of randomization, an important task in epidemiological studies is the consideration of confounding variables. In this paper, it is shown that NNEs adjusted for confounding variables can be calculated within the framework of multiple logistic regression analysis.

2. The "number needed to be exposed"

The NNT concept can be applied in any trial in which two groups are compared concerning a binary response variable. However, if the two groups are not defined by treatment versus control, the term "number needed to treat" makes no sense. Therefore, Feinstein proposed the term "number needed for one extra effect" to define a measure that is not dependent on the type of agent or the direction of the effect [8]. However, we find this terminology too general and vague. In epidemiology, a common situation is the comparison of exposed versus unexposed persons regarding an adverse event such as death or cancer. To apply the NNT concept in epidemiological studies we propose the term "number needed to be exposed" (NNE), which is the analogous definition of the NNT measure when the considered agent is exposure rather than treatment. This definition makes it pos-

———
* Corresponding author. Department of Epidemiology and Medical Statistics, School of Public Health, University of Bielefeld, P.O. Box 100131, D-33501 Bielefeld, Germany. Tel.: +49 521 106-3803; fax: +49 521 106-6465.

E-mail address: Ralf.Bender@uni-bielefeld.de (R. Bender).

sible to adopt the terminology suggested by Altman to distinguish between harmful and beneficial agents [9]. Thus, we use the abbreviations number needed to be exposed for one additional person to be harmed (NNEH) or benefit (NNEB) when it is necessary to indicate the direction of the effect.

In the simple case of a 2×2 table of frequencies, NNEs are calculated as follows. If the exposed event rate (EER) is higher than the unexposed event rate (UER), the absolute risk increase (ARI) is ARI = EER − UER. In the case of a beneficial exposure effect, the absolute risk reduction (ARR) is ARR = UER − EER. The measures NNEH and NNEB are given by the reciprocals of ARI and ARR, respectively. In the case of a harmful exposure, NNEH is the estimated average number of persons needed to be exposed for one additional case of disease or death compared with the unexposed persons. Note that in epidemiology, the difference of two risks usually is called excess risk rather than ARI or ARR [10].

3. NNEs derived from cohort studies

If the design of a study allows an unbiased comparison of the observed crude event rates, the NNT concept of randomized clinical trials can be easily transferred to NNEs for use in epidemiological studies simply by changing the name. However, in observational studies, the specification and calculation of appropriate event rates is more difficult than in experimental randomized studies. In randomized clinical trials, all calculations concerning NNT can be based on a simple 2×2 table because systematic differences between the groups are avoided due to random allocation [11]. In observational studies of classical epidemiology, randomization is usually not possible, so that confounding factors have to be taken into account to minimize bias. Whereas this is generally accepted for the estimation of odds ratios (ORs) and hazard ratios, at present NNTs are usually estimated from crude risk differences without adjustment for confounding factors due to the lack of methods to calculate adjusted NNTs. In epidemiology, an adjustment for confounding factors is frequently performed by means of multiple logistic regression leading to an adjusted OR as relative effect measure [12]. Within the framework of logistic regression, the adjusted OR is constant over the distribution of the considered confounding factors; on the other hand, the event rates and their differences are dependent on the values of the confounders. Thus, NNEs also vary with the values of the confounding variables, which has to be taken into account when NNEs are estimated.

An adjusted NNE can be calculated by means of the relationship

$$NNEH = \frac{1}{(OR-1) \times UER} + \frac{OR}{(OR-1) \times (1-UER)} \quad (1)$$

where OR > 1 (harmful exposure) is the adjusted OR, and UER is the unexposed event rate (see Appendix for derivation). If OR < 1 (beneficial exposure), the corresponding NNEB is

given by NNEB = −NNEH. A similar formula was recently proposed to express the magnitude of adverse effects by means of NNTs in case-control studies [5]. However, the second term of the sum in equation (1) was left out. The resulting simpler equation can be used only to approximate equation (1) in situations where the considered disease is rare, such as case-control studies. In general, however, equation (1) represents the correct relationship between NNT measures and the OR and should be used at least in all situations where the rare disease assumption does not hold [13]. Whereas in case-control studies an external source is required to estimate UER [5], in prospective cohort studies UER can be calculated from the logistic regression model. However, the event rates are dependent on the values of the confounding factors leading to different possible NNE values. Hence, methods are required that take the dependence of the adjusted NNEs on the values of the confounding factors into account. Two alternative methods are described below with a further discussion of this issue.

4. Confidence intervals for adjusted NNEs

The distribution of estimated NNEs can frequently not be approximated by the normal distribution [14]. Hence, confidence intervals (CIs) for NNEs are calculated indirectly via CIs for ARI or ARR [15]. Within the framework of logistic regression analysis applied to prospective cohort data, risk differences between the exposed and unexposed persons can be expressed as functions of the logistic regression coefficients. Thus, standard errors and CIs for risk differences can be calculated by means of the multivariate delta method [16] (see Appendix for a description of the method). A SAS/IML [17] program to calculate adjusted NNEs with CIs is available on the internet (http://www.uni-bielefeld.de/~rbender/SOFTWARE/nne_logistic.sas) or can be obtained from the first author. This method takes the estimation uncertainties of both OR and UER into account. This is not possible in case-control studies, where an external estimate of UER is required. The uncertainty of the estimation of UER is disregarded in the calculation of CIs for the number needed to treat in case-control studies [5].

5. Examples

The proposed method of calculating adjusted NNEs in epidemiological studies is illustrated by means of two examples. In the first example generated data with a known true OR are used to demonstrate the bias with regard to NNE due to confounding by comparison of the crude and adjusted NNE estimates. Moreover, it is shown clearly that adjusted NNEs vary with the values of the confounding factors. Two alternative ways to deal with this issue are presented and explained. In the second example, observed data are used to explain the meaning of adjusted NNEs in a real situation.

5.1. Generated data: Effect of exposure adjusted for age

Suppose in a cohort study 1,000 persons are followed for the same time, say 5 years. Let Y be a binary response of an

Table 1
Simple 2×2 table of exposure and response of artificial cohort data

	Adverse event		
	Yes	No	Total
Exposure			
Yes	130 (26.3%)	365 (73.4%)	495
No	149 (29.5%)	356 (70.5%)	505
Total	279	721	1,000

adverse event, Z a binary exposure variable, and X a continuous confounding variable, say age. Values for these variables were generated as follows. The exposure Z has values 1 and 0 each with probability 0.5; X is normally distributed with standard deviation (SD) 5 and mean 41 for the exposed and mean 45 for the unexposed persons. Hence, if X is interpreted as age, the unexposed persons are on average 4 years older than the exposed persons. The probability of an adverse event was modeled following the logistic regression model

$$p = \frac{exp(\alpha + \gamma z + \beta x)}{1 + exp(\alpha + \gamma z + \beta x)}$$

with $\alpha = -10$, $\gamma = 0.693$, and $\beta = 0.2$, which means that the true OR for the comparison of the exposed versus unexposed persons is $exp(0.693) = 2$. The response variable was generated by assigning the value 1 (event) with probability p and the value 0 (no event) with probability $1 - p$.

In the following the analysis of one arbitrary set of generated data is shown. If only the simple 2×2 table of these data (Table 1) is considered, the exposure has a nonsignificant beneficial effect (crude OR, 0.85; 95% CI, 0.65–1.12; P = 0.253). The crude NNEB is 31 (95% CI, NNEB 11 to $\pm\infty$ to NNEH 43). However, this result is seriously biased because the confounding factor X is not taken into account. By using multiple logistic regression (Table 2), the estimated adjusted OR is 2.005 (95% CI, 1.43–2.81; P = 0.0001), which is close to the true OR of 2 due to the large sample size of $n = 1,000$. By means of equation (1), using the adjusted OR (2.005) and the event rate over the age distribution among the unexposed persons (UER 0.295), the adjusted NNE is NNEH = 6.2 (95% CI, 4-12). Thus, on average, six persons from a population with an age distribution equal to that of the unexposed persons are needed to be exposed for one extra event.

These results are illustrated in Fig. 1. It is required to specify age values for which NNEH should be calculated. One possibility is to take the mean of the risks of the unex-

Table 2
Results of the multiple logistic regression model applied to the artificial cohort data

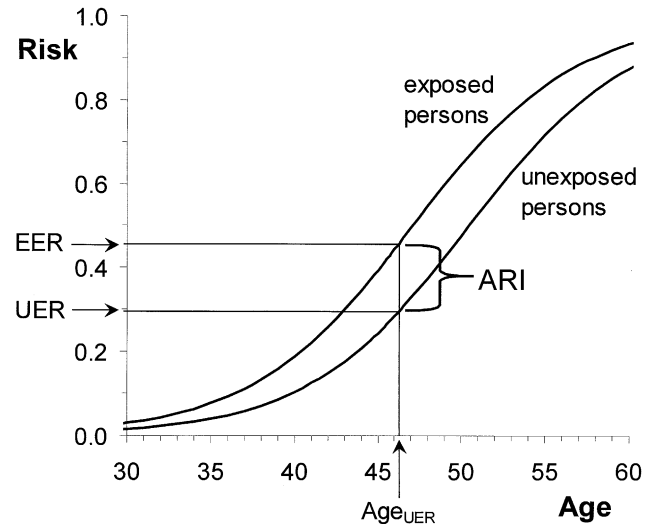|	Logistic coefficient	Standard error	P value	Odds ratio	95% confidence interval
Intercept	−10.3727	0.8646	0.0001		
Z (exposure)	0.6955	0.1718	0.0001	2.005	1.43–2.81
X (age)	0.2054	0.0182	0.0001	1.228	1.18–1.27

Hosmer-Lemeshow goodness-of fit test: P = 0.761.

Fig. 1. Estimation of the absolute risk increase (ARI) for the risk comparison of exposed versus unexposed persons adjusted for age based upon logistic regression (artificial data). EER, exposed event rate; UER, unexposed event rate; Age$_{UER}$, value of age corresponding to UER.

posed persons and calculate NNEH for the corresponding age value (age$_{UER}$; Fig. 1). This leads to the event rate over the age distribution among the unexposed persons. Then the event rate of the exposed persons is calculated for the same age by means of the logistic regression model. The difference of these risks represents the adjusted ARI (Fig. 1), and the reciprocal of ARI is the adjusted NNEH of 6.2 calculated above.

Another possibility is to calculate NNEH for some fixed age values (Table 3). NNEH varies from 70 for age 30 to 6 for age 50 to 17 for age 60 years. These results give an impression about different absolute effects of the exposure in cohorts with varying age distributions. Note, however, that the considered low- and high-age values are located at the extreme tails of the age distribution of the unexposed persons, which was normal with mean 45 $\pm$ 5 years (mean $\pm$ SD). Within the range of say, mean $\pm$ SD (40–50 years), the differences of the NNEH values are quite smaller than for the whole age distribution (Table 3). The NNEH value for the mean age of 45 years (6.7) is approximately the

Table 3
Event rates, RR, OR, ARI, and NNEH for different age values estimated from the artificial cohort data

Age (years)	EER	UER	RR	OR	ARI	NNEH
30	0.0289	0.0146	1.976	2.005	0.0143	70.1
35	0.0767	0.0398	1.928	2.005	0.0369	27.1
40	0.1883	0.1037	1.816	2.005	0.0846	11.8
45	0.3931	0.2442	1.610	2.005	0.1489	6.7
50	0.6440	0.4743	1.358	2.005	0.1697	5.9
55	0.8348	0.7159	1.166	2.005	0.1189	8.4
60	0.9338	0.8756	1.066	2.005	0.0582	17.2

Abbreviations: RR, risk ratio; OR, odds ratio; ARI, absolute risk increase; NNEH, number needed to be exposed for one additional person to be harmed; EER, exposed event rate; UER, unexposed event rate.

Table 4
Descriptive statistics for retinopathy status and risk factors of type 1 diabetic patients

| Variable | Label | Retinopathy at follow-up | | Total |
		No ($n = 388$)	Yes ($n = 225$)	($n = 613$)
Z	Smoking during follow-up (yes/no)	197 (50%)	128 (57%)	325 (53%)
X_1	Diabetes duration, y	12.7 (6.7)	19.0 (6.8)	15.0 (7.4)
X_2	Squared diabetes duration, y^2	204 (236.5)	408 (269.5)	279 (267.6)
X_3	Glycosylated hemoglobin, %	7.5 (1.2)	8.2 (1.3)	7.8 (1.3)
X_4	Diastolic blood pressure, mm Hg	78.6 (6.6)	82.6 (7.2)	80.1 (7.1)

Data are given as means (SD) or numbers (%).

same as the NNEH value corresponding to the event rate over the age distribution among the unexposed persons (6.2).

5.2. Real data: smoking and diabetic retinopathy

Mühlhauser et al. analyzed the association of several risk factors with the development of diabetic retinopathy [18]. In short, 613 type 1 diabetic patients were followed for 6 years to investigate the effect of smoking (Z) on the response retinopathy (Y), adjusted for the risk factors diabetes duration (X_1), quadratic term of diabetes duration (X_2), glycosylated hemoglobin (X_3), and diastolic blood pressure (X_4). The quadratic effect of diabetes duration has to be taken into account because the risk of retinopathy increases until 25 years of diabetes duration and decreases thereafter [19]. In Table 4 a descriptive overview of the data is given.

The data analysis based upon the simple 2×2 table (Table 5) leads to nonsignificant results. The crude OR is 1.28 (95% CI, 0.92–1.78; P = 0.144), and the crude number needed to be exposed is NNEH = 17.5 (95% CI, NNEH 8 to $\pm\infty$ to NNEB 52). However, these results are biased because the confounding variables are not taken into account. The adjusted results of the multiple logistic regression model are given in Table 6. The Hosmer-Lemeshow test [12] (P = 0.581) as well as graphical checks indicated that this model has an adequate goodness of fit [19]. The adjusted estimated effect measures for smoking are OR 1.52 (95% CI, 1.004–2.285; P = 0.048) and NNEH = 10.2 (95% CI, 5–4,169). On average, among 10 smoking diabetic patients, one additional patient will develop retinopathy after 6 years compared with nonsmoking patients. This result holds for a population of diabetic patients with distributions of the covariables equal to the nonsmoking patients of the cohort. However, the uncertainty of this estimation is huge because the upper confidence limit for NNEH is 4,169. This large

upper limit reflects that the P value is very close to the significance level of 0.05. Note that the lower confidence limit (1.004) of the adjusted OR is also very close to 1. Nevertheless, the adjusted NNEH based on logistic regression shows a significant harmful effect of smoking, which could not be demonstrated by means of the crude number needed to be exposed (NNEH = 17.5) obtained on the basis of the simple 2×2 table.

6. Discussion

The use of NNT as effect measure for the comparison of risks between two groups has been advocated in medical journals for several years [1–3,5,20,21] but was recently criticized [6,7,22,23] or even rejected [24]. As pointed out by Walter, a clear distinction should be made between data analysis and subsequent risk communication [25]. In the framework of logistic regression, which is one of the most frequently used statistical methods in epidemiology and public health [26,27], the OR is the leading measure for purposes of data analysis. On the other hand, the number needed to treat is frequently a useful way of presenting results and plays a role in risk communication to clinicians, patients, and the public [28]. However, the effects of presenting study results in terms of absolute effect measures such as NNT on actual clinical practice are still unknown [29].

In the common situation of the comparison of risks between exposed and unexposed persons in epidemiology, the NNT concept can be used as NNE to present results. However, to apply this measure adequately in epidemiologic studies, methods to adjust for confounding variables are required. In this paper, we have derived a method based on logistic re-

Table 5
Simple 2×2 table of exposure and response of the retinopathy data

| | Retinopathy | | |
	Yes	No	Total
Smoking			
Yes	128 (39.4%)	197 (60.6%)	325
No	97 (33.7%)	191 (66.3%)	288
Total	225	388	613

Table 6
Results of the multiple logistic regression model applied to the retinopathy data

	Logistic coefficient	Standard error	P value	Odds ratio	95% confidence interval
Intercept	−13.3203	1.5111	0.0001		
Smoking	0.4154	0.2097	0.0476	1.515	1.004–2.285
X_1	0.4083	0.0655	0.0001		
X_2	−0.0075	0.0016	0.0001		
X_3	0.4292	0.0835	0.0001		
X_4	0.0614	0.0152	0.0001		

Hosmer-Lemeshow goodness-of fit test: P = 0.581.

gression analysis to estimate adjusted NNEs with CIs. Two alternative methods are proposed to take the dependence of the adjusted NNEs on the values of the confounding variables into account. A SAS/IML [17] program is available to perform the corresponding calculations.

The proposed method is applicable in prospective cohort studies with fixed follow-up time. Other application situations are controlled clinical trials in which randomization is impossible and randomized trials in which an adjustment for confounding factors seems to be appropriate despite randomization. The method is not applicable in studies with varying follow-up times, which require methods for survival data [30].

The adequacy of the proposed method depends heavily on the goodness-of-fit of the logistic regression model. If the model used is not a good description of the considered data, the results are questionable. Hence, before adjusted ORs and adjusted NNEs are calculated on the basis of logistic regression, the goodness-of-fit of the model should be investigated carefully [31].

The NNEH answers the question how many people are needed to be exposed for one additional person to be harmed. Hence, we also know how many people must be protected against the exposure for one additional person to benefit. Thus, NNEH is a useful measure especially if the exposure is modifiable (e.g., stopping smoking or rehabilitating houses with high radon load). In the context of public health, it may be useful to incorporate the prevalence of exposure like the population attributable risk. This is possible by applying the generalizations of NNT proposed by Heller and Dobson [32] to the adjusted NNE.

In conclusion, the NNE is a useful complement to the commonly presented results in epidemiological studies, such as ORs and attributable risks. Adjusted NNEs with CI can be calculated within the framework of logistic regression analysis.

Appendix 1

Derivation of the formula for NNEH

Let EER be the event rate among the exposed and UER the event rate among the unexposed persons, then conceptually

$$NNEH = \frac{1}{ARI} = \frac{1}{EER - UER},$$

$$RR = \frac{EER}{UER},$$

$$OR = \frac{EER \times (1 - UER)}{UER \times (1 - EER)}$$

The following relation between RR and OR is valid [33,34]

$$RR = \frac{OR}{1 - UER + OR \times UER}$$

Thus,

$$NNEH = \frac{1}{EER - UER} = \frac{1}{\frac{EER}{UER} \times UER - UER}$$

$$= \frac{1}{RR \times UER - UER}$$

$$= \frac{1}{\frac{OR}{1 - UER + OR \times UER} \times UER - UER}$$

$$= \frac{1}{\frac{OR \times UER - UER \times (1 - UER + OR \times UER)}{1 - UER + OR \times UER}}$$

$$= \frac{1 - UER + OR \times UER}{OR \times UER \times (1 - UER) - UER \times (1 - UER)}$$

$$= \frac{1 - UER + OR \times UER}{(OR - 1) \times UER \times (1 - UER)}$$

$$= \frac{1 - UER}{(OR - 1) \times UER \times (1 - UER)}$$

$$+ \frac{OR \times UER}{(OR - 1) \times UER \times (1 - UER)}$$

$$= \frac{1}{(OR - 1) \times UER} + \frac{OR}{(OR - 1) \times (1 - UER)}$$

Calculating CIs for ARI

The absolute risk increase can be calculated by

$$RI = \frac{1}{NNEH} = \frac{(OR - 1) \times UER \times (1 - UER)}{1 - UER + OR \times UER}$$

$$= \frac{UER \times (1 - UER) \times (OR - 1)}{1 + UER \times (OR - 1)}$$

(i.e., ARI is a function of OR and UER). In logistic regression applied to prospective cohort data, the probability of an event is a function of the exposure and all considered covariables. Let p be the probability of an event, Z the binary exposure ($Z = 1$ if a person is exposed and $Z = 0$ if a person is unexposed), and $X_1, \ldots, X_k$ are k additional continuous or binary covariables for which the effect of the exposure should be adjusted. By using logistic regression the risk p can be written as

$$p = \frac{exp(\alpha + \gamma z + \beta_1 x_1 + \ldots + \beta_k x_k)}{1 + exp(\alpha + \gamma z + \beta_1 x_1 + \ldots + \beta_k x_k)}$$

where $\alpha, \gamma, \beta_1, \ldots, \beta_k$ are the logistic regression coefficients. Let n_u be the number of unexposed persons in the sample and p_i the risk of the ith unexposed person for $i = 1, \ldots, n_u$. The adjusted OR for the comparison of the exposed versus unexposed persons as well as the UER over the distribution

of $X_1,...,X_k$ among the unexposed persons can be expressed as functions of the logistic regression coefficients, namely

$$OR = exp(\gamma) \text{ and}$$

$$UER = \frac{1}{n_u}\sum_{i=1}^{n_u} p_i$$

Thus, the absolute risk increase itself is a function of the logistic regression coefficients. Statistical software for logistic regression usually provides the covariance matrix for the estimated logistic regression coefficients, so it is possible to calculate the standard error (SE) of the estimated ARI by means of the multivariate delta method [16]. For these calculations matrix operations are required.

Let B be the covariance matrix of the estimated logistic regression coefficients and Δ be the row vector of the partial derivatives of ARI expressed as function of the logistic regression coefficients. The SE of the estimated ARI can be calculated by

$$SE(ARI) = \sqrt{\Delta B\Delta'}$$

and an approximate 95% CI for ARI can be calculated by

$$ARI \pm 1.96 \times SE(ARI)$$

References

[1] Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ 1995;310:452–4.

[2] Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988;318:1728–33.

[3] McQuay HJ, Moore A. Using numerical results from systematic reviews in clinical practice. Ann Intern Med 1997;126:712–20.

[4] Rembold CM. Number needed to screen: development of a statistic for disease screening. BMJ 1998;317:307–12.

[5] Bjerre LM, LeLorier L. Expressing the magnitude of adverse effects in case-control studies: "The number of patients needed to be treated for one additional patient to be harmed." BMJ 2000;320:503–6.

[6] Wu LA, Kottke TE. Number needed to treat: caveat emptor. J Clin Epidemiol 2001;54:111–6.

[7] Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses – sometimes informative, usually misleading. BMJ 1999; 318:1548–51.

[8] Feinstein AR. Indexes of contrast and quantitative significance for comparisons of two groups. Stat Med 1999;18:2557–81.

[9] Altman DG. Confidence intervals for the number needed to treat. BMJ 1998;317:1309–12.

[10] Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincott-Raven Publishers; 1998. p. 47–54.

[11] Altman DG, Bland JM. Treatment allocation in controlled trials: why randomise? BMJ 1999;318:1209.

[12] Hosmer DW, Lemeshow S. Applied logistic regression. New York: Wiley; 1989.

[13] Bender R. Expressing the number needed to treat as a function of the odds ratio and the unexposed event rate (rapid response). eBMJ (http://www.bmj.com/cgi/eletters/320/7233/503#EL7).

[14] Lesaffre E, Pledger G. A note on the number needed to treat. Control Clin Trials 1999;20:439–47.

[15] Bender R. Calculating confidence intervals for the number needed to treat. Control Clin Trials 2001;22:102–10.

[16] Bishop YMM, Fienberg SE, Holland PW. Discrete multivariate analysis: theory and methods. Cambridge, MA: MIT Press; 1975.

[17] SAS. SAS/IML® Software: Usage and Reference, Version 6, First Edition. Cary, NC: SAS Institute; 1990.

[18] Mühlhauser I, Bender R, Bott U, Jörgens V, Grüsser M, Wagener W, et al. Cigarette smoking and progression of retinopathy and nephropathy in type 1 diabetes. Diabetic Med 1996;13:536–43.

[19] Bender R, Grouven U. Using binary logistic regression models for ordinal data with non-proportional odds. J Clin Epidemiol 1998;51:809–16.

[20] Sackett DL. On some clinically useful measures of the effects of treatment. Evidence-Based Med 1996;1:37–8.

[21] Chatellier G, Zapletal E, Lemaitre D, Ménard J, Degoulet P. The number needed to treat: a clinically useful nomogram in its proper context. BMJ 1996;312:426–9.

[22] North D. Number needed to treat: absolute risk reduction may be easier for patients to understand. BMJ 1995;310:1269.

[23] Newcombe RG. Confidence intervals for the number needed to treat: absolute risk reduction is less likely to be misunderstood. BMJ 1999;318:1765.

[24] Hutton JL. Number needed to treat: properties and problems. J R Stat Soc A 2000;163:403–15.

[25] Walter SD. Choice of effect measure for epidemiological data. J Clin Epidemiol 2000;53:931–9.

[26] Altman DG. Statistics in medical journals: developments in the 1980s. Stat Med 1991;10:1897–913.

[27] Levy PS, Stolte K. Statistical methods in public health and epidemiology: a look at the recent past and projections for the next decade. Stat Meth Med Res 2000;9:41–55.

[28] Altman DG, Deeks JJ. Comments on the paper by Hutton. J R Stat Soc A 2000;163:415–6.

[29] McGettigan P, Sly K, O'Connell D, Hill S, Henry D. The effects of information framing on the practices of physicians. J Gen Intern Med 1999;14:633–42.

[30] Altman DG, Andersen PK. Calculating the number needed to treat where the outcome is time to an event. BMJ 1999;319:1492–5.

[31] Bender R, Grouven U. Logistic regression models used in medical research are poorly presented. BMJ 1996;313:628.

[32] Heller RF, Dobson A. Disease impact number and population impact number: population perspectives to measures of risk and benefit. BMJ 2000;321:950–2.

[33] Davies HTO, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ 1998;316:989–91.

[34] Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690–1.