On robust and efficient designs for risk estimation in epidemiologic studies

Holger Dette
Ruhr-Universität Bochum
Fakultät für Mathematik
44780 Bochum
Germany
email: holger.dette@ruhr-uni-bochum.de
FAX: +49 2 34 3214 559

June 2, 2003

Abstract

We consider the design problem for the estimation of several scalar measures suggested in the epidemiological literature for comparing the success rate in two samples. The designs considered so far in the literature are local in the sense that they depend on the unknown probabilities of success in the two groups and are not necessarily robust with respect to their misspecification. A maximin approach is proposed to obtain efficient and robust designs for the estimation of the relative risk, attributable risk and odds ratio, whenever a range for the success rates can be specified by the experimenter. It is demonstrated that the designs obtained by this method are usually more efficient than the uniform design, which allocates equal sample sizes to the two groups.

Keywords and Phrases: two by two table, odds ratio, relativ risk, attributable risk, optimal design, efficient design

1 Introduction

The analysis of two by two tables is an important tool in many epidemiological studies [see e.g. Rothman and Greenland (1998)]. For the typical situation of comparing two dichotomous variables analytic methods for planning the sample size have been derived by Haseman (1978).

If the total sample size is fixed a primary objective of experimental design is to determine the sample sizes for the two groups, which increase the efficiency of the statistical analysis. Walter (1977a,b) derived an expression for the optimal sampling ratio in a case-control study by minimizing the asymptotic variance of the estimator for the log of the odds ratio for a fixed total sample size. This author pointed out that the equal allocation to both treatments provides a simple and efficient design for the experiment in many cases. However, if cost considerations have to be taken into account unequal sample sizes may be preferred [Walter (1977b)]. Therefore other authors combine cost and statistical considerations in one optimality criterion to find efficient designs [see Miettinen (1969), Meydrech and Kupper (1978), Morgenstern and Winn (1983) or Moussa (1986) among others]. As pointed out by Kalish and Begg (1987) all of these optimal designs are local in the sense of Chernoff (1953), because they depend on unknown model parameters and the implementation in practice requires prior parameter estimates or some form of sequential design. However, there are many situations, where neither preliminary information regarding the unknown parameters is available, nor sequential designs are applicable.
Morgenstern and Winn (1986) mentioned that a design with equal allocation to both exposures is not robust, if cost considerations have to be taken into account and the parameters have been misspecified. In such cases some care is necessary with the application of locally optimal designs, because these can be rather inefficient under misspecification of the initial parameters. Recently Matthews (1999) considered a Bayesian approach to find efficient and robust designs for the estimation of the odds ratio in a two by two table. For a normal distributed prior this author determined explicit formulas for the optimal allocation of the subjects to the two groups. The locally optimal design problems appear as a special case by using one point priors and the equal allocation rule is not necessarily efficient if there is uncertainty for the estimation of the log-odds ratio.

The present paper has two goals. On the one hand we are interested in the construction of efficient and robust designs for risk estimation in situations, where only very vague information is available, which can not be used for the specification of a prior distribution for a Bayesian approach. On the other hand we want to combine statistical and cost considerations in the construction of optimality criteria, which do not require specific preliminary information about the unknown parameters. We adopt a minimax approach to determine robust and efficient designs for the estimation of the odds ratio, the relative and attributable risk. It is demonstrated that the new minimax designs are usually preferable to the designs which use equal sample sizes in both groups. While this superiority is moderate (but still visible) if cost considerations have not to be taken into account, the improvement is substantial if different costs of sampling within the comparison groups are experienced. In Section 2 we introduce the necessary notation and demonstrate that all estimation problems yield to the same type of optimal design problem. We find the locally optimal designs and investigate the efficiency of the equal allocation design. In Section 3 the minimax optimality criterion is proposed and robust and efficient designs are determined. The new designs are compared with the equal allocation rule in two examples and its superiority is demonstrated. Finally, some technical details are discussed in Section 4.

2 Locally optimal designs for two by two tables

Suppose that X_1, X_2 are two independent responses with $X_i \sim B(n_i, p_i)$, where n_i is a known number of trials and $p_i \in (0,1)$ is an unknown success probability ($i = 1, 2$). Among the many scalar measures suggested in the epidemiological literature [see e.g. Walter (1976)] we consider three important measures. The attributable risk is defined as

$$\Delta = \Delta(p_1, p_2) = p_1 - p_2 \tag{2.1}$$

and varies in the interval $(-1, 1)$, while the relative risk

$$\rho = \rho(p_1, p_2) = \frac{p_1}{p_2} \tag{2.2}$$

and the odds ratio

$$\psi = \psi(p_1, p_2) = \frac{p_1(1-p_2)}{p_2(1-p_1)} \tag{2.3}$$

range over the interval $(0, \infty)$. The basis for the determination of optimal designs is the approximate normal distribution (if $n_1, n_2 \to \infty$) of the common estimate $(\hat{p}_1, \hat{p}_2) = (X_1/n_1, X_2/n_2)$, that is

$$\sqrt{n}\Big\{\begin{pmatrix}\hat{p}_1\\ \hat{p}_2\end{pmatrix} - \begin{pmatrix}p_1\\ p_2\end{pmatrix}\Big\} \xrightarrow{\mathcal{D}} \mathcal{N}\Big(0, \begin{pmatrix}\frac{p_1(1-p_1)}{w} & 0\\ 0 & \frac{p_2(1-p_2)}{1-w}\end{pmatrix}\Big),$$

where $n = n_1 + n_2$ denotes the total sample size and

$$w = \lim_{n_1, n_2 \to \infty} \frac{n_1}{n} \in (0,1) \tag{2.4}$$

is the asymptotic proportion of observations in the first sample. In observational studies the problem of an optimal design therefore corresponds to the choice of $w \in (0,1)$ such that one gets most efficient estimates of the risk measures (2.1) - (2.3). If $\hat{\Delta} = \Delta(\hat{p}_1, \hat{p}_2)$, $\hat{\rho} = \rho(\hat{p}_1, \hat{p}_2)$ and $\hat{\psi} = \psi(\hat{p}_1, \hat{p}_2)$ denote the usual estimates of Δ, ρ and ψ, respectively, then an optimal design minimizes the corresponding asymptotic variances. A straightforward application of the Delta-method shows that these are given by (up to the factor $1/n$)

$$\Phi_\Delta^{-1}(p_1, p_2, w) = p_1(1-p_1) \Big\{\frac{1}{w} + \frac{p_2(1-p_2)}{p_1(1-p_1)} \frac{1}{1-w}\Big\}, \tag{2.5}$$

$$\Phi_\rho^{-1}(p_1, p_2, w) = \frac{p_1(1-p_1)}{p_2^2} \Big\{\frac{1}{w} + \frac{p_1(1-p_2)}{p_2(1-p_1)} \frac{1}{1-w}\Big\}, \tag{2.6}$$

$$\Phi_\psi^{-1}(p_1, p_2, w) = \frac{p_1(1-p_2)^2}{(1-p_1)^3 p_2^2} \Big\{\frac{1}{w} + \frac{p_1(1-p_1)}{p_2(1-p_2)} \frac{1}{1-w}\Big\}, \tag{2.7}$$

where the lower index Δ, ρ or ψ of the function Φ corresponds to the different risk measure. We call an allocation rule $w \in (0,1)$ locally optimal design for a specific risk measure if it maximizes the corresponding inverse variance $\Phi_x(p_1, p_2, w)$, where the index $x \in \{\Delta, \rho, \psi\}$ reflects the risk measure under consideration. Usually for risk ratio estimation the logarithmic transformation of the odds ratio is recommended [see e.g. Rothman and Greenland (1998)] but this transformation has no effect on the construction of optimal designs because the corresponding asymptotic variance is obtained by multiplying Φ_ψ^{-1} with a constant, which is independent of w. Therefore, only the odds ratio is considered here and the optimal designs for estimating the log of the odds ratio coincide with the designs maximizing Φ_ψ. Note that all criteria are of the same structure and consequently locally optimal designs can be found by minimizing one function [see the proofs in Section 4]. The following results gives the (locally) optimal designs and is proved in the Appendix.

Lemma 2.1. *The locally optimal design for estimating the risk Δ, ρ and ψ allocates $w_x^* \cdot 100\%$ of the observations to the first exposure, where*

$$
\begin{aligned}
w_\Delta^* &= \frac{\sqrt{p_1(1-p_1)}}{\sqrt{p_2(1-p_2)} + \sqrt{p_1(1-p_1)}} && \text{(attributable risk)} \\
w_\rho^* &= \frac{\sqrt{p_2(1-p_1)}}{\sqrt{p_1(1-p_2)} + \sqrt{p_2(1-p_1)}} && \text{(relative risk)} \\
w_\psi^* &= \frac{\sqrt{p_2(1-p_2)}}{\sqrt{p_1(1-p_1)} + \sqrt{p_2(1-p_2)}} && \text{(odds ratio)}
\end{aligned}
$$

It is interesting to note the optimal allocation for estimating the relative risk depends on the (unknown) odds ratio, i.e. $w_\rho^* = (1+\sqrt{\psi})^{-1}$. Moreover, the optimal allocations for estimating the attributable risk and the odds ratio satisfy $w_\Delta^* = 1 - w_\psi^*$, and we expect that the optimal designs for estimating these risk measures are quite different. For example if $p_1 = 0.1, p_2 = 0.4$ we obtain for the optimal allocation for estimating the attributable risk $w_\Delta^* \approx 37.9\%$ while this quantity is $w_\psi^* \approx 62.1\%$ for the estimation of the odds ratio.
For a given design $w \in (0,1)$ define

$$
\text{eff}_x(p_1, p_2, w) = \frac{\Phi_x(p_1, p_2, w)}{\max_{\eta \in (0,1)} \Phi_x(p_1, p_2, \eta)} = \frac{\Phi_x(p_1, p_2, w)}{\Phi_x(p_1, p_2, w_x^*)} \tag{2.8}
$$

as the efficiency for estimating the risk $x \in \{\Delta, \rho, \psi\}$. Note that $\text{eff}_x(p_1, p_2, w) \in [0,1]$ measures the performance of the allocation of $w \cdot 100\%$ of the observations to the first exposure, if p_1 and p_2 would be the "true" parameters. Our next result shows that the commonly used equal allocation rule $w = 1/2$ has at least efficiency 50%, independent of the particular risk measure.

Lemma 2.2. *The equal allocation design with $w = 1/2$ satisfies*

$$
\mathit{eff}_x(p_1, p_2, \tfrac{1}{2}) = \frac{(1+\sqrt{\tilde{x}})^2}{2(1+\tilde{x})} \geq \frac{1}{2}
$$

for all $p_1, p_2 \in (0,1)$ independently of the risk measure $x \in \{\Delta, \rho, \psi\}$, where $\tilde{x}$ is defined by

$$\tilde{x}(p_1,p_2) = \begin{cases} \dfrac{p_2(1-p_2)}{p_1(1-p_1)} & \text{if } x = \Delta \text{ (attributable risk)} \\ \dfrac{p_1(1-p_2)}{p_2(1-p_1)} & \text{if } x = \rho \text{ (relative risk)} \\ \dfrac{p_1(1-p_1)}{p_2(1-p_2)} & \text{if } x = \psi \text{ (odds ratio).} \end{cases} \tag{2.9}$$

Moreover,

$$\mathrm{eff}_\Delta(p_1,p_2,\tfrac{1}{2}) = \mathrm{eff}_\psi(p_1,p_2,\tfrac{1}{2}).$$

Walter (1977a) recommends the equal allocation design for the estimation of the odds ratio because he argued that there is little loss in precision with use of an equal number of cases or non-cases. Lemma 2.2 partially confirms these findings. Moreover, it follows from the proof of Lemma 2.2 that in the case of estimating the odds ratio and the attributable risk the lower bound is only attained if the quantity $p_2(1-p_2)/p_1(1-p_1)$ is very small or very large. A similar observation can be made for the quantity $p_1(1-p_2)/p_2(1-p_1)$ for the problem of estimating the relative risk. Consider for example this problem and assume that the true but unknown success probabilities are $p_1 = 0.1$ and $p_2 = 0.3$, which gives for the odds ratio $\psi = 7/27 \approx 0.259$. In this case the equal allocation of subjects to both groups has efficiency 90.43 % for estimating the relative risk. On the other hand in the more extreme case $p_1 = 0.05, p_2 = 0.5$ we have $\psi = 1/19 \approx 0.052$ and the efficiency of this design would be about 71.79 %. Thus the use of equal allocation of subjects to the different groups can be recommended in many but not all cases. In general the performance of the design depends sensitively on the probabilities of success, which are not known before experiments have been carried out. Moreover, it was pointed out by Walter (1977b) and Morgenstern and Winn (1983) that unequal sampling sizes should be preferred when different costs of sampling within the different comparison groups are experienced. Optimality criteria which incorporate cost considerations were considered by Miettinen (1969), Morgenstern and Winn (1983) among others. Following the lastnamed authors we consider the function

$$\alpha_x(p_1,p_2,\gamma,w) = \frac{\Phi_x(p_1,p_2,w)}{w+\gamma(1-w)} \tag{2.10}$$

as optimality criterion, where $x \in \{\Delta, \psi, \rho\}$ corresponds to the particular risk measure, the function Φ_x is defined in (2.5) - (2.7) and γ is the unit cost ratio comparing exposed with unexposed subjects. An (locally) optimal design for the risk measure x now maximizes the function $\alpha_x(p_1,p_2,\gamma,w)$ with respect to $w \in [0,1]$. The following result is the analogue of Lemma 2.1 and Lemma 2.2 and specifies the locally optimal designs if cost considerations have to be taken into account.

Lemma 2.3. *The locally optimal design maximizing the function α_x allocates $w_x^* \cdot 100\%$ of the subjects to the first exposure, where*

$$\begin{aligned} w_\Delta^* &= \frac{\sqrt{\gamma p_1(1-p_1)}}{\sqrt{\gamma p_1(1-p_1)} + \sqrt{p_2(1-p_2)}} && \textit{(attributable risk)} \\ w_\rho^* &= \frac{\sqrt{\gamma p_2(1-p_1)}}{\sqrt{\gamma p_2(1-p_1)} + \sqrt{p_1(1-p_2)}} && \textit{(relative risk)} \\ w_\psi^* &= \frac{\sqrt{\gamma p_2(1-p_2)}}{\sqrt{\gamma p_2(1-p_2)} + \sqrt{p_1(1-p_1)}} && \textit{(odds ratio).} \end{aligned}$$

Moreover, the efficiency

$$\text{(2.11)} \qquad \mathit{eff}_x(p_1, p_2, \gamma, w) = \frac{\alpha_x(p_1, p_2, \gamma, w)}{\max_{\eta \in (0,1)} \alpha_x(p_1, p_2, \gamma, \eta)} = \frac{\alpha_x(p_1, p_2, \gamma, w)}{\alpha_x(p_1, p_2, \gamma, w_x^*)}$$

of the equal allocation design $w = 1/2$ satisfies

$$\mathit{eff}_x(p_1, p_2, \gamma, \frac{1}{2}) = \frac{(1 + \sqrt{\gamma \tilde{x}})^2}{(1+\gamma)(1+\tilde{x})} \geq \begin{cases} \frac{1}{1+\gamma} & \textit{if } \gamma \geq 1 \\ \frac{\gamma}{1+\gamma} & \textit{if } \gamma \leq 1 \end{cases},$$

where $\tilde{x}$ is defined in (2.9).

Lemma 2.3 indicates that the equal allocation design is more sensitive with respect to misspecification of the unknown success probabilities if cost considerations have to be taken into account. Consider for example the situation of the previous paragraph, where $p_1 = 0.1, p_2 = 0.3$, if the relative costs are given by $\gamma = 9$, then the locally optimal designs is given by $w_\rho^* \approx 85.5\%$ and the efficiency of the equal allocation design (locally optimal for $p_1 = 0.5$ and $p_2 = 0.1$) for both groups is 50.7% for the estimation of the relative risk.

3 Robust designs

As pointed out in the previous sections the locally optimal designs depend on the unknown parameters p_1, p_2, which are not known before any experiments have been performed. In many cases these designs are not robust with respect to misspecification of the probabilities of success. For example the design which uses equal sample sizes for both groups is locally optimal for estimating Δ, ρ and ψ if $p_1 = p_2$ and no cost considerations have to be taken into account (i.e. $\gamma = 1$). However, if the probabilities of success are of different size or if different costs of sampling with different groups are experienced this design is not necessarily efficient any more.

For these reasons we propose a maximin approach for the construction of robust and efficient designs, which determines the proportion of total observations w in the first sample such that

$$\text{(3.1)} \qquad \min\{\mathrm{eff}_x(p_1, p_2, \gamma, w) \mid (p_1, p_2) \in \mathcal{P}\}$$

is maximal. Here $\mathcal{P} \subset [0,1] \times [0,1]$ is a certain region for the unknown success probabilities, which has to be specified by the experimenter (the locally optimal designs are obtained by using one point sets). The problem of maximizing a minimum of efficiencies has been considered by several authors in different contexts [see e.g. Dette (1997) or Imhof (2001) among others]. A design maximizing the function in (3.1) will be called maximin optimal design. Because maximizing the function (3.1) considers the worst scenario over the set $\mathcal{P}$, this approach yields efficient estimates, whenever the unknown success probabilities satisfy $(p_1, p_2) \in \mathcal{P}$. The following result specifies the maximin optimal designs.

Theorem 3.1. *Assume that $\mathcal{P}$ is compact and define*

$$\begin{aligned} \underline{x} &= \min\{\tilde{x}(p_1, p_2) \mid (p_1, p_2) \in \mathcal{P}\} \\ \bar{x} &= \max\{\tilde{x}(p_1, p_2) \mid (p_1, p_2) \in \mathcal{P}\}, \end{aligned}$$

where $\tilde{x}$ corresponds to the particular risk measure under consideration and is defined in (2.9). The maximin optimal design for estimating the risk measure x allocates $w^*_{\underline{x},\bar{x}} \cdot 100\%$ of the subjects to the first exposure, where

$$w^*_{\underline{x},\bar{x}} = \frac{\sqrt{\gamma}(2 + \sqrt{\underline{x}\gamma} + \sqrt{\bar{x}\gamma})}{(\sqrt{\underline{x}} + \sqrt{\bar{x}})(1+\gamma) + 2\sqrt{\gamma}(1 + \sqrt{\underline{x}\bar{x}})} . \qquad (3.2)$$

Moreover, for all $(p_1, p_2) \in \mathcal{P}$ the efficiency of the maximin optimal design satisfies

$$\mathrm{eff}_x(p_1, p_2, \gamma, w^*_{\underline{x},\bar{x}}) \geq \left\{1 - \frac{2}{2 + \sqrt{\gamma\underline{x}} + \sqrt{\gamma\bar{x}}} + \frac{\sqrt{\underline{x}} + \sqrt{\bar{x}}}{\sqrt{\underline{x}} + \sqrt{\bar{x}} + 2\sqrt{\underline{x}\bar{x}\gamma}}\right\}^{-1} .$$

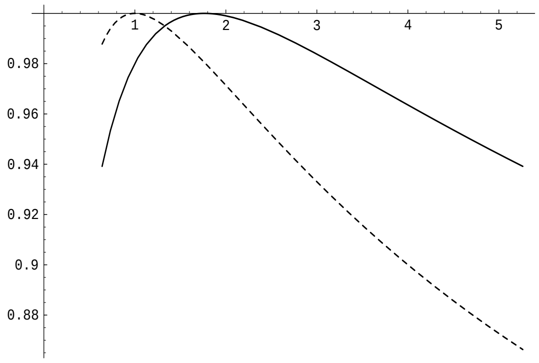
The optimal designs can easily be found by a hand calculator as soon as $\underline{x}$ and $\bar{x}$ have been specified. Some designs are given in Table 3.1 and 3.2 for various values of $\underline{x}$ and $\bar{x}$ for the sake of quick reference. Note that the function $\tilde{x}$ in (2.9) is different for the three risk measures, and consequently for a fixed set $\mathcal{P} \subset [0,1] \times [0,1]$ the quantities $\underline{x}$ and $\bar{x}$ are changing with the different problems of estimating the attributable, relative risk and the odds ratio. Nevertheless, the tables can be used for all three risk measures. In the following discussion we illustrate the application of Theorem 3.1. We study two typical examples to demonstrate that maximin optimal designs should usually be preferred to the uniform allocation rule.

$\underline{x} \backslash \bar{x}$	0.01	0.2	0.4	0.6	0.8	1.0	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0
0.01	.909	.800	.761	.736	.718	.705	.679	.662	.648	.638	.629	.621	.609	.599
0.2		.691	.652	.627	.609	.595	.570	.553	.539	.528	.520	.512	.500	.490
0.4			.613	.588	.570	.566	.531	.513	.500	.489	.480	.473	.460	.451
0.6				.563	.546	.532	.506	.488	.475	.465	.456	.448	.436	.427
0.8					.528	.514	.489	.471	.458	.447	.438	.431	.418	.409
1.0						.500	.474	.457	.443	.433	.424	.417	.405	.395
1.5							.449	.432	.418	.408	.399	.391	.379	.369
2.0								.414	.401	.390	.381	.374	.362	.352
2.5									.387	.377	.368	.354	.348	.339
3.0										.366	.357	.350	.337	.328
3.5											.348	.341	.329	.319
4.0												.333	.321	.311
5.0													.309	.299
6.0														.289

Table 3.1. *Maximin optimal designs for various ranges $[\underline{x}, \bar{x}]$ and cost efficiency $\gamma = 1$. The value $w^*_{\underline{x},\bar{x}}$ in the table gives the relative proportion of total observations to the first exposure.*

$\underline{x} \backslash \bar{x}$	0.01	0.2	0.4	0.6	0.8	1.0	1.5	2.0	2.5	3.0	3.5	4.0	5.0	6.0
0.01	.876	.734	.684	.653	.630	.613	.581	.559	.542	.529	.518	.508	.493	.481
0.2		.613	.569	.541	.522	.506	.479	.460	.445	.433	.424	.415	.402	.392
0.4			.528	.502	.483	.469	.442	.424	.410	.399	.390	.382	.369	.359
0.6				.477	.459	.445	.419	.402	.388	.377	.368	.361	.348	.339
0.8					.442	.428	.403	.385	.372	.362	.353	.345	.333	.324
1.0						.414	.390	.372	.360	.349	.341	.333	.321	.312
1.5							.366	.349	.337	.327	.319	.312	.300	.291
2.0								.333	.321	.311	.303	.296	.285	.276
2.5									.309	.299	.291	.285	.274	.265
3.0										.290	.282	.275	.270	.256
3.5											.274	.268	.257	.249
4.0												.261	.250	.242
5.0													.240	.232
6.0														.224

Table 3.2. *Maximin optimal designs for various ranges $[\underline{x}, \bar{x}]$ and cost efficiency $\gamma = 0.5$. The value $w^*_{\underline{x},\bar{x}}$ in the table gives the relative proportion of total observations to the first exposure.*



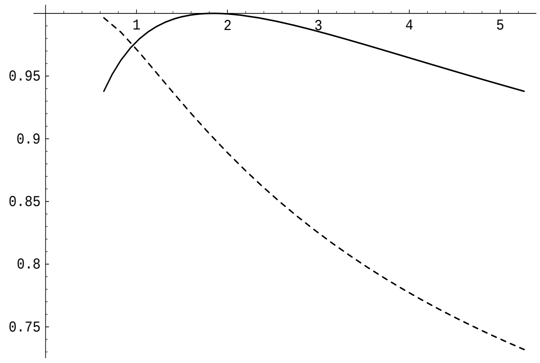


Figure 3.1: *Efficiencies of the equal allocation design (dotted line) and the maximin optimal optimal design for estimating the odds ratio. The maximin optimal design is calculated under the assumption that $p_1 \in [0.2, 0.7]; p_2 \in [0.05, 0.55]$, which yields $\tilde{x}(p_1, p_2) \in [0.64, 5.26]$. Left panel: cost efficiency $\gamma = 1$, right panel: $\gamma = 0.5$.*

Example 3.3. Consider the problem of estimating the odds ratio and assume that the experimenter has some preliminary knowledge about the unknown probabilities of success, that is

$$(p_1, p_2) \in \mathcal{P}_1 := [0.2, 0.7] \times [0.05, 0.55]. \tag{3.3}$$

For the calculation of the maximin optimal designs for the estimation of the odds ratio we note (2.9) and determine

$$\begin{aligned} \underline{x} &= \min\Big\{\frac{p_1(1-p_1)}{p_2(1-p_2)} \mid (p_1, p_2) \in \mathcal{P}_1\Big\} = 0.64, \\ \bar{x} &= \max\Big\{\frac{p_1(1-p_1)}{p_2(1-p_2)} \mid (p_1, p_2) \in \mathcal{P}_1\Big\} = 5.26, \end{aligned}$$

and an application of Theorem 3.1 yields $w^*_{0.64,5.26} = 34.23\%$ in the case $\gamma = 0.5$ and $w^*_{0.64,5.26} = 42.95\%$ in the case $\gamma = 1$. These numbers have been directly obtained from formula (3.2). If Table 3.2 and 3.1 are used we get the estimates 34.8 % and 43.6 % for these proportions. The efficiencies of the equal allocation rule and the maximin optimal design are depicted in Figure 3.1 for the cost efficiencies $\gamma = 1$ and $\gamma = 0.5$, where the $\tilde{x}(p_1, p_2) = \frac{p_1(1-p_1)}{p_2(1-p_2)}$ varies between $\underline{x}$ and $\bar{x}$. Note that the equal allocations design is locally optimal for $\tilde{x} = 1$ in the case $\gamma = 1$ and for $\tilde{x} = 0.707$ in the case $\gamma = 0.5$. If $\gamma = 1$, the equal allocation design has a slightly better performance if $\tilde{x} = \tilde{x}(p_1, p_2) = p_1(1 - p_1)/p_2(1 - p_2)$ varies between 0.64 and 1.0 (approximately 4 %), but is substantially less efficient for large values of $\tilde{x}(p_1, p_2) > 1.3$. The situation for the case $\gamma = 0.5$ is quite similar, where we observe even stronger advantages for the maximin optimal design [see the right panel in Figure 3.1]. If $\tilde{x} < 0.8$ the maximin optimal design is at most 5 % less efficient, in the region $\tilde{x} \in [0.8, 1.1]$ the designs are comparable while for $\tilde{x} > 1.1$ the application of the maximin optimal design would yield substantial advantages. Thus in these cases the equal allocation rule can only be recommended if $x(p_1, p_2) < 1.1$. However, with this additional information the performance of the maximin optimal design can even be improved using a smaller set $\mathcal{P}_1$ for the construction of the maximin optimal design. Consider for example the case $\tilde{x} \in [0.64, 1.1]$ and the maximin optimal design $w^*_{0.64,1.1} = 43.51\%(\gamma = 1)$ and $w^*_{0.64,1.1} = 52.18\%(\gamma = 0.5)$. The corresponding efficiencies of the maximin and uniform design are shown in Figure 3.2. In the case $\gamma = 1$ there are no essential differences, while in the case $\gamma = 0.5$ the maximin optimal design is nearly uniformly more efficient than the equal allocation rule.

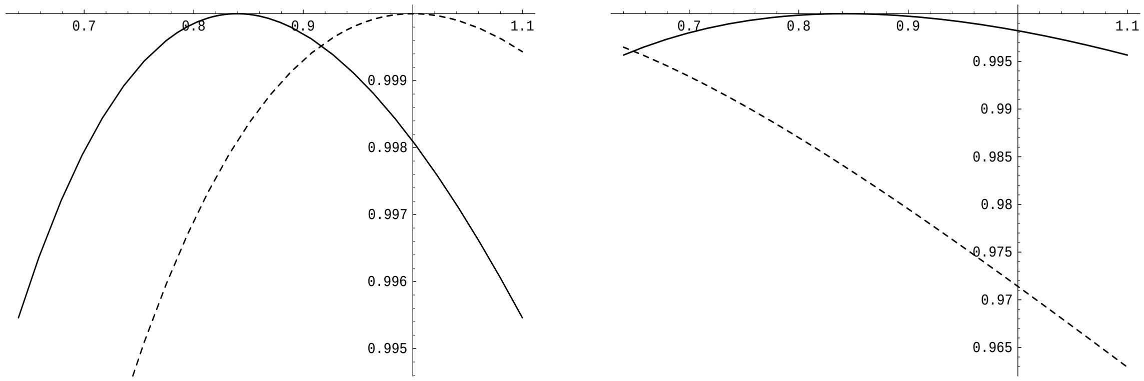


Figure 3.2: *Efficiencies of the equal allocation design (dotted line) and the maximin optimal design for estimating the odds ratio. The maximin optimal design is calculated under the assumption that* $\tilde{x}(p_1, p_2) \in [0.64, 1.1]$. *Left panel: cost efficiency* $\gamma = 1$, *right panel:* $\gamma = 0.5$.

Example 3.4. We have investigated several other examples, where we observed a similar superiority of the maximin optimal designs. Examplarily, we discuss the problem of estimating the relative risk with cost efficiency $\gamma = 1$ and $\gamma = 0.5$. Assume that the range

$$\mathcal{P}_2 = [0.6, 0.9] \times [0.2, 0.4]$$

could be specified by the experimenter for the unknown success probabilities (p_1, p_2). In this case we obtain $\underline{x} = 0.17$ und $\bar{x} = 36$ and for equal cost efficiencies the maximin optimal design allocates 42.26% of the observations to the exposure. The corresponding efficiencies are depicted in the left panel of Figure 3.3. The loss of efficiency of the equal allocation rule can be substantial, if $x(p_1, p_2) = p_1(1 - p_2)/p_2(1 - p_1)$ is large. On the other hand the minimal efficiency of the maximin optimal design is approximately 80% if $\tilde{x} \in [0.17, 36]$ and therefore this design yields efficient estimates over the whole range $\mathcal{P}_2$. If the cost efficiency is $\gamma = 0.5$ we obtain $w^*_{0.17,36} = 31.87\%$, the superiority of the maximin optimal design is even more visible and illustrated in the right panel of Figure 3.3.

Acknowledgements. The author is grateful to Stefanie Biedermann for some help with the references and to Isolde Gottschlich who typed this paper with considerable technical expertise. The support of the Deutsche Forschungsgemeinschaft (SFB 475, Komplexitätsreduktion in multivariaten Datenstrukturen) is gratefully acknowledged.

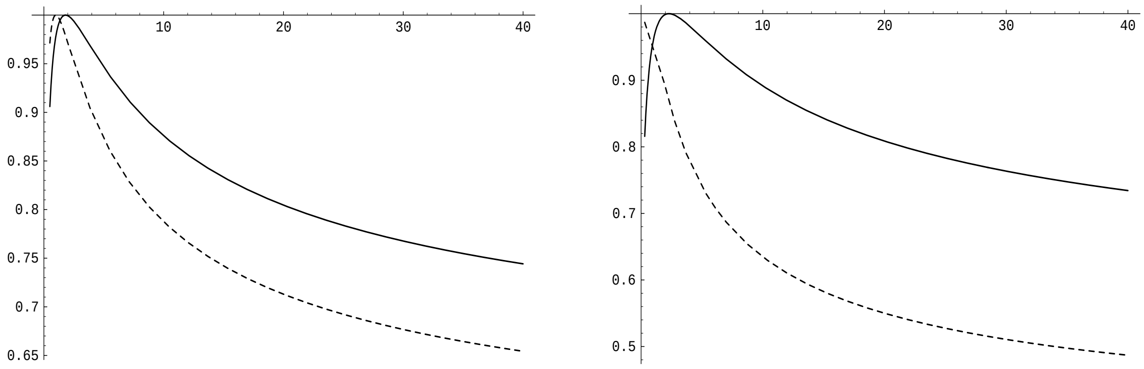


Figure 3.3: *Efficiencies of the equal allocation design (dotted line) and the maximin optimal design for estimating the relative risk. The maximin optimal design is calculated under the assumption that* $p_1 \in [0.6, 0.9]; p_2 \in [0.2, 0.4]$*, which yields* $\tilde{x}(p_1, p_2) \in [0.17, 36]$*. Left panel: cost efficiency* $\gamma = 1$*, right panel:* $\gamma = 0.5$*.*

4 Appendix: proofs

Note first that all results can be obtained by maximizing the function

$$h(\tilde{x}, \gamma, w) = \Big\{ \Big(w + \gamma(1-w)\Big)\Big(\frac{1}{w} + \frac{\tilde{x}}{1-w}\Big)\Big\}^{-1}, \tag{4.1}$$

where the parameter $\tilde{x} = \tilde{x}(p_1, p_2)$ is defined in (2.9) and corresponds to the specific risk measure under consideration and γ is the cost efficiency.

Proof of Lemma 2.1, 2.2 and 2.3. Lemma 2.1 and 2.2 are obtained from Lemma 2.3 for the special choice $\gamma = 1$. For the proof of Lemma 2.3 we maximize the function $h(\tilde{x}, \gamma, w)$ with respect to w and obtain

$$w^*_{\tilde{x}} = \frac{\sqrt{\gamma}}{\sqrt{\gamma} + \sqrt{\tilde{x}}},$$

which gives the locally optimal designs in Lemma 2.1 ($\gamma = 1$) and Lemma 2.3. The cost efficiency defined by (2.11) is then given by

$$\mathrm{eff}(\tilde{x}, \gamma, w) := \frac{h(\tilde{x}, \gamma, w)}{h(\tilde{x}, \gamma, w^*_{\tilde{x}})} = \frac{(1 + \sqrt{\gamma \tilde{x}})^2}{\Big(w + \gamma(1-w)\Big)\Big(\frac{1}{w} + \frac{\tilde{x}}{1-w}\Big)}. \tag{4.2}$$

For the equal allocation design $w = 1/2$ we obtain

$$\mathrm{eff}(\tilde{x}, \gamma, \frac{1}{2}) = \frac{(1 + \sqrt{\gamma \tilde{x}})^2}{(1+\gamma)(1+\tilde{x})},$$

which has minimal value $1/(1+\gamma)$ if $\gamma \geq 1$ ($\tilde{x} \to \infty$) and minimal value $\gamma/(1+\gamma)$ if $\gamma \leq 1$ ($\tilde{x} \to 0$).
$\square$

Proof of Theorem 3.1. Recalling the definition of the maximin criterion in (3.1), (4.1) and (4.2) it follows that

$$\min\{\mathrm{eff}_x(p_1, p_2, \gamma, w) \mid (p_1, p_2) \in \mathcal{P}\} = \min_{\tilde{x} \in [\underline{x}, \bar{x}]} \mathrm{eff}(\tilde{x}, \gamma, w), \tag{4.3}$$

where $\mathrm{eff}(\tilde{x}, \gamma, w)$ is defined in (4.2). Therefore the maximin optimal design can be found by maximizing the right hand side of (4.3) with respect to w. A straightforward calculation shows that

$$\frac{\partial}{\partial \tilde{x}}\Big(\log(\mathrm{eff}(\tilde{x}^2, \gamma, w)\Big) = 2\frac{(\tilde{x} + \sqrt{\gamma})w - \sqrt{\gamma}}{(1 + \sqrt{\gamma}\tilde{x})(w - 1 - w\tilde{x})},$$

which vanishes only at the point $\tilde{x} = \sqrt{\gamma}(1 - w)/w$. A similar calculation of the second derivative yields

$$\frac{\partial^2}{\partial^2 \tilde{x}} \log(\mathrm{eff}(\tilde{x}^2, \gamma, w))\Big|_{\tilde{x}=\frac{\sqrt{\gamma}(1-w)}{w}} = \frac{2w^3}{(w-1)(w + \gamma(1-w))^2} < 0.$$

Consequently it follows that the function $\mathrm{eff}(\tilde{x}, \gamma, w)$ has at most one local extremum in the interval $[\underline{x}, \bar{x}]$, which is a local maximum. Therefore we have

$$\min_{\tilde{x} \in [\underline{x}, \bar{x}]} \mathrm{eff}(\tilde{x}, \gamma, w) = \min\{\mathrm{eff}(\underline{x}, \gamma, w), \mathrm{eff}(\bar{x}, \gamma, w)\}, \tag{4.4}$$

and we will show in the following that for the maximin optimal design $w^*_{\underline{x},\bar{x}}$, the minimum on the right hand side is attained for $\tilde{x} = \underline{x}$ and $\tilde{x} = \bar{x}$, i.e.

$$\mathrm{eff}(\underline{x}, \gamma, w^*_{\underline{x},\bar{x}}) = \mathrm{eff}(\bar{x}, \gamma, w^*_{\underline{x},\bar{x}}). \tag{4.5}$$

If this fact has been proven the last equation determines the optimal allocation to the first exposure $w^*_{\underline{x},\bar{x}}$ as

$$w^*_{\underline{x},\bar{x}} = \frac{\sqrt{\gamma}(2 + \sqrt{\underline{x}\gamma} + \sqrt{\bar{x}\gamma})}{(\sqrt{\underline{x}} + \sqrt{\bar{x}})(1 + \gamma) + 2\sqrt{\gamma}(1 + \sqrt{\underline{x}\bar{x}})},$$

which completes the first part of the theorem. The assertion regarding the cost efficiency follows by a straightforward calculation.

In order to prove (4.5) we can split the maximization of the right hand side of (4.4) in the maximization over the sets

$$\begin{aligned}
\mathcal{M}_< &= \Big\{w \in [0, 1] \mid \mathrm{eff}(\underline{x}, \gamma, w) < \mathrm{eff}(\bar{x}, \gamma, w)\Big\}, \\
\mathcal{M}_> &= \Big\{w \in [0, 1] \mid \mathrm{eff}(\underline{x}, \gamma, w) > \mathrm{eff}(\bar{x}, \gamma, w)\Big\}, \\
\mathcal{M}_= &= \Big\{w \in [0, 1] \mid \mathrm{eff}(\underline{x}, \gamma, w) = \mathrm{eff}(\bar{x}, \gamma, w)\Big\}.
\end{aligned}$$

Now assume that $w^*_{\underline{x},\bar{x}} \in \mathcal{M}_<$. In this case we obtain $w^*_{\underline{x},\bar{x}} = \sqrt{\gamma}/(\sqrt{\gamma} + \sqrt{\underline{x}})$ and by the definition of $\mathcal{M}_<$ the inequality

$$\mathrm{eff}(\underline{x}, \gamma, \frac{\sqrt{\gamma}}{\sqrt{\gamma} + \sqrt{\underline{x}}}) < \mathrm{eff}(\bar{x}, \gamma, \frac{\sqrt{\gamma}}{\sqrt{\gamma} + \sqrt{\underline{x}}}).$$

But this inequality is equivalent to

$$\sqrt{\gamma}(\sqrt{\underline{x}} - \sqrt{\bar{x}})^2 < 0,$$

which yields a contradiction. A similar argument for the set $\mathcal{M}_>$ shows that the maximum is attained in $\mathcal{M}_=$, which establishes (4.4) and completes the proof.

$\square$

References

Chernoff, H. (1953). Locally optimal designs for estimating parameters. Ann. Math. Statist. 24, 586-602.

Dette, H. (1997). Designing experiments with respect to 'standardized' optimality criteria. J. Roy. Statist. Soc. Ser. B 59, 97-110.

J.K. Haseman (1978). Exact sample sizes for use with the Fisher-Irwin Test for 2×2 tables. Biometrics 34, 106-109.

Imhof, L.A. (2001). Maximin designs for exponential growth models and heteroscedastic polynomial models. Ann. Statist. 29, 561-576.

L.A. Kalish, C.B. Begg (1987). Evaluation of efficient designs for observational epidemiologic studies. Biometrics 43, 143-167.

J.N.S. Matthews (1999). Effect of prior specification for Bayesian design for two sample comparison of binary outcome. Amer. Statist. 53, 254-256.

O.S. Miettinen (1969). Individual matching with multiple controls in the case of all-or-none responses. Biometrics 25, 339-355.

E.F. Meydrich, L.L. Kupper (1978). Cost considerations and sample size requirements in cohort and case control studies. Amer. J. Epidemiology 107, 201-205.

H. Morgenstern, D.M. Winn (1983). A method for determining the sampling ratio in epidemiologic studies. Statistics in Medicine 2, 387-396.

M.A. Moussa (1986). Allocation designs in cohort and case control studies. Statistics in Medicine 5, 319-326.

K.J. Rothman, S. Greenland (1998). Modern Epidemiology. Lipincott-Raven, PA.

S.D. Walter (1976). The estimation and interpretation of attributable risk in health research. Biometrics 32, 829-849.

S.D. Walter (1977a). Determination of significant relative risks and optimal sampling procedures in prospective and retrospective comparitive studies of various sizes. Amer. J. Epidemiology 106, 387-397.

S.D. Walter (1977b). Optimal sampling ratios for prospective studies - the author replies (letter to the Editor). Amer. J. Epidemiology 106, 437-438.