Chapter 1

Introduction

In the past two decades, multicenter studies experience increased popularity when compared to single center studies. The main reason for conducting a multicenter study is to recruit an adequate number of patients within a reasonable duration of time [21, 30]. The centers are often a clinical, medical or public health institution in which the clinical trial takes place.

A special problem of multicenter studies is the heterogeneity of treatment effect. The estimation of an average treatment effect from a multicenter study may not be appropriate when heterogeneity is present [1, 11, 18, 35]. Recently, methods have been suggested to incorporate modelling of covariate information to investigate the reasons for heterogeneity and to estimate the treatment effect based upon that model. However, there has been discussion on the choice of appropriate statistical methods to address this issue [3, 32, 36, 38].

The purpose of this study is to develop the modelling of covariate information in multicenter studies with binary outcome using the profile likelihood method. A binary outcome frequently occurs in medical research, for example, improvement of health status (yes/no), renal failure (yes/no), patient status (death/alive) etc. In this study focus is on the measurement of treatment effect by means of the relative risk, relative risk can be definded as the risk of an event in the treatment arm divided by the risk of an event in the control arm [41].

In the following some background and some of the special problems of multicenter studies are provided. These are the rationale, the typical setting, and the special problems of multicenter studies.

1.1 Rationale for Multicenter Studies

There are several reasons for conducting a multicenter study. The first reason is to recruit an adequate number of patients within a reasonable duration of time in order to enhance the precision to estimate the treatment effect. This circumstance occurs when the disease under investigation is rare, the outcome of therapy uncommon, or when the anticipated treatment effect is small [18, 21, 22, 42].

The second reason is to examine generalization of the treatment efficacy. In a multicenter study, several factors naturally tend to vary from center to center, for example, patient characteristics, the geographic or cultural setting, the time and duration of the treatment, and the manner in which the treatment is implemented. Such factors can rarely be examined in the context of a single study because these factors seldom vary within a single study [22, 29, 35].

1.2 Typical Setting of Multicenter Studies

This study focuses on the comparison of two treatments with a binary outcome when observations occur for several centers. The centers are often a clinical, medical or public health institution in which the clinical trial takes place. Additionally, they may be different studies of the same sort evaluated in a meta-analysis. The binary outcome frequently occurs in medical research, for example, improvement of health status (yes/no), renal failure (yes/no), patient status (death/alive) etc. Other examples of binary outcome include diagnostic procedures that result frequently in continuous measures. However, the outcome is almost uniquely represented in terms of test positive or test negative. The comparison of two treatments, is denoted here as treatment and control arm.

A typical setting of multicenter studies is provided in Table 1.1. The data set consists of 22 trials performed to investigate the effect of beta-blocker for reducing mortality after myocardial infarction [44]. In this setting, x_i^T is the number of deaths in the treatment arm of the i-th center and n_i^T is patients at risk in the treatment arm of the i-th center. Also x_i^C is the number of deaths in the control arm of the i-th center and n_i^C is patients at risk in the control arm of the i-th center.

Table 1.1: Data Illustration for a Multicenter Study of Effect of Beta-Blocker for Reducing Mortality after Myocardial Infarction

Study i	Deaths x_i^T	At risk n_i^T	Deaths x_i^C	At risk n_i^C	Relative risk
1	3	38	3	39	1.03
2	7	114	14	116	0.51
3	5	69	11	93	0.61
4	102	1533	127	1520	0.80
5	28	355	27	365	1.07
6	4	59	6	52	0.59
7	98	945	152	939	0.64
8	60	632	48	471	0.93
9	25	278	37	282	0.69
10	138	1916	188	1921	0.74
11	64	873	52	583	0.82
12	45	263	47	266	0.97
13	9	291	16	293	0.57
14	57	858	45	883	1.30
15	25	154	31	147	0.77
16	33	207	38	213	0.89
17	28	251	12	122	1.13
18	8	151	6	154	1.36
19	6	174	3	134	1.54
20	32	209	40	218	0.83
21	27	391	43	364	0.58
22	22	680	39	674	0.56

1.3 Special Problems of Multicenter Studies

1.3.1 Heterogeneity

In standard analyses of multicenter studies, the primary analysis involves pooling the treatment effect estimates across centers. It is suggested to use the traditional method, the fixed effects model, to estimate an average treatment effect from a multicenter study. This model assumes that the true treatment effects from each center are homogeneous. However, heterogeneity of treatment effects commonly occur in multicenter studies. Table 1.1 exhibits a potential heterogeneity that most centers show a beneficial effect of beta-blocker, while some centers (14, 17, 18 and 19) show a markedly harmful effect. Figure 1.1 shows the risk ratio for beta-blocker in reducing mortality after myocardial infarction of 22 centers. Other controversial examples and discussion on heterogeneity of treatment effects are given in Colditz, Horwitz and Thompson [11, 18, 35].

In a situation where heterogeneity is present, it is suggested to use the random effects model to incorporate a component of between-study variance into the overall estimate of the treatment effect; the between-study variance represents the excess variation in observed treatment effects over the expected variation from the imprecision of results within each study [36]. This model assumes that true treatment effects vary randomly between centers.

In standard statistical practice, tests for heterogeneity were used to decide which method, the fixed effects or the random effects, is more appropriate for a particular multicenter study. In many multicenter studies, the tests for heterogeneity will be non-significant. This cannot be interpreted as evidence of homogeneity of the treatment effects. This is not only because a non-significant test can never be interpreted as direct evidence in favour of the null hypothesis (homogeneity or total consistency), but in particular because such tests for heterogeneity have low power and may fail to detect a statistical significance, even when there is a moderate degree of heterogeneity [16, 18, 35, 40]. However, several authors [3, 4, 6, 16] suggest the routine use of the random effects model, since similar results to the fixed effects model will be obtained when the between-study variance equals zero. Although the random effects model may be useful when heterogeneity of treatment effects is present, it cannot obviously unmask the possible reasons for heterogeneity between study results. In particular, understanding the possible reasons for any heterogeneity is more important than the evidence for its existence.

More recent approaches [4, 11, 17, 29, 32, 36, 38] have been proposed to investigate the possible sources of heterogeneity between studies. These approaches allow the inclusion of covariates that may explain any heterogeneity of treatment effects.

In this study, first, the classical methods for investigating heterogeneity by covariate information are described, and then some potential problems related to these methods are pointed out. Next we have developed the alternative model for this situation, modelling covariate information using the profile likelihood approach. Some detailed examples are given, and possible extensions of this idea are discussed.

1.3.2 Sparsity

Sparsity of the observed data often occurs in multicenter studies. The data is considered sparse if the observed event counts are close to zero, or identical to zero. This can occur when the event risks are very small. Even with a large trial, sparsity has to be expected. Likewise, in a small trial with large event risks, the occurences of low frequency counts, including zero counts, are likely to occur. An example of this nature is provided in Table 1.2. The data set consists of 21 institutions from a Cancer and Leukemia Group (CALGB) randomized trial which compares two chemotherapy treatments with respect to survival in patients with multiple myeloma [8].

In multicenter sparsity trials, the fixed effects approach has insufficient information to estimate the treatment effect. Moreover, it is difficult to detect heterogeneity of the treatment effects between centers, especially in the case of risk ratio, since center-specific risk ratios cannot be estimated when event counts equal zero. In addition, the construction of a risk ratio estimator under homogeneity needs to be done with careful consideration [1]. Here, the profile likelihood approach turns out to be benificial.

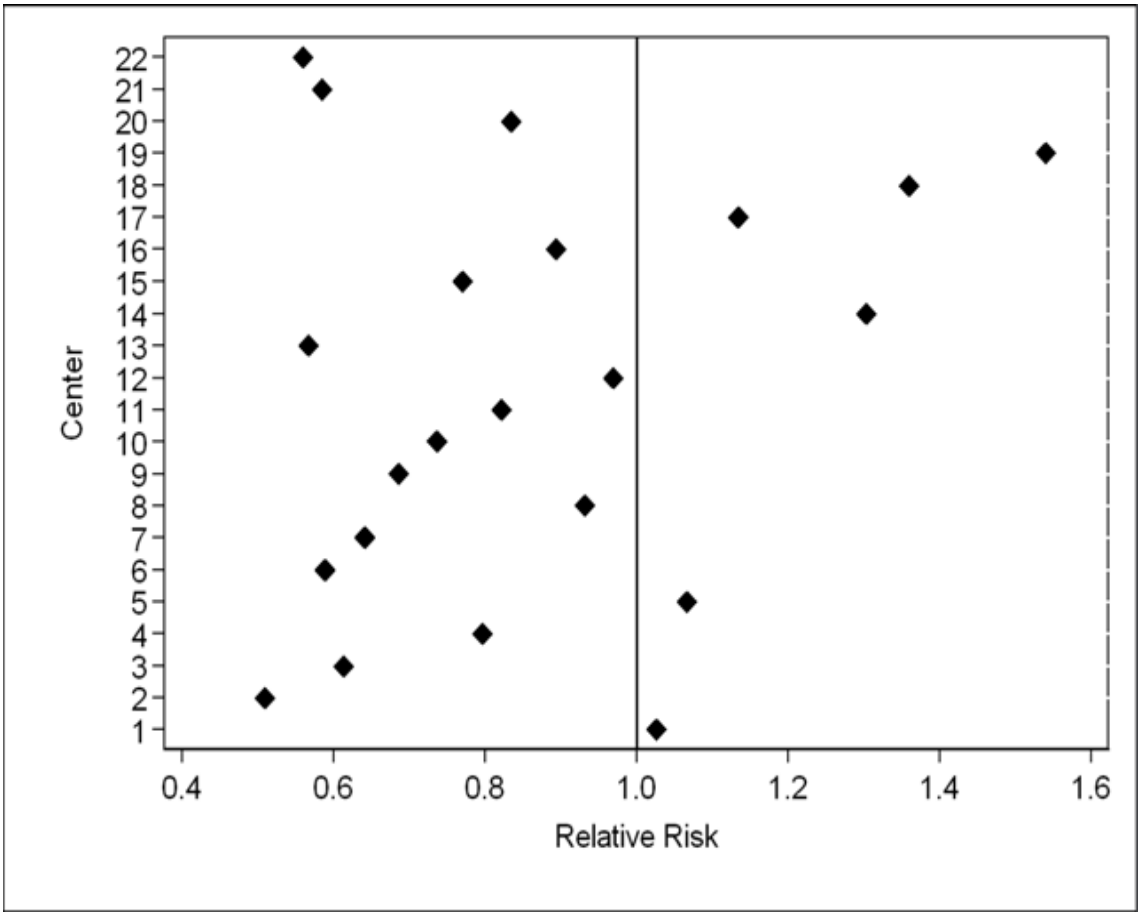

Figure 1.1: Estimated Relative Risks for the Effect of Beta-blocker in Reducing Mortality after Myocardial Infarction of 22 Studies

Table 1.2: Data Illustration for High Sparsity Data from a Cancer and Leukemia Group B (CALGB)

Study i	Deaths x_i^T	Under risk n_i^T	Deaths x_i^C	Under risk n_i^C
1	1	3	3	4
2	8	11	3	4
3	2	3	2	2
4	2	2	2	2
5	0	3	2	2
6	2	3	1	3
7	2	3	2	2
8	4	4	1	5
9	2	3	2	2
10	2	3	0	2
11	3	3	3	3
12	0	2	2	2
13	1	5	1	4
14	2	4	2	3
15	4	6	2	4
16	3	9	4	12
17	2	3	1	2
18	1	4	3	3
19	2	3	1	4
20	0	2	0	3
21	1	5	2	4

1.4 Aims and Objectives

The purpose of this study is to develop the modelling of covariate information using the profile likelihood approach for investigating reasons for heterogeneity of treatment effect in multicenter studies.
In particular, the objectives of this study are as follows:

- to provide a review of classical methods for investigating the reasons for heterogeneity of treatment effects and point out some potential problems related to them.
- to develop a model for incorporating covariate information using the profile likelihood approach to investigate the reasons for heterogeneity of the treatment effects.
- to develop a software tool for estimating the relative risk based upon covariate information.
- to discuss some possible extensions of the profile likelihood model.

This study is outlined as follows. Chapter 2 provides a review of classical methods for investigating the reasons for heterogeneity of the treatment effects and point out some potential problems related to them at the end of the chapter. Chapter 3 presents the basic model for multicenter studies which has been developed by Böhning (2004), and Chapter 4 presents the modelling of covariate information using the profile likelihood approach which has been developed in this study. Additionally, this chapter illustrates the elements of the developed software tool which has been developed for this work to do the analysis of multicenter study with covariate information. Chapter 5 illustrates the applications of the modelling of covariate information using the profile likelihood approach to four examples of multicenter studies. Chapter 6 discusses some theoretical disadvantages of classical approaches and some possible extensions of the profile likelihood model.