How to analyze data on multiple events in the case-crossover study

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May 2008

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for a Doctor of Philosophy degree

ABSTRACT

In the conventional data analysis of most medical research we assume that all observations are mutually independent. However, this assumption is questionable in many applications where the data can be grouped into clusters with responses in the same clusters tending to be more alike than responses in the different clusters. In epidemiology, the 'first event' approach is often used to investigate the risk of drug utilization; i.e., all the subsequent events are ignored. This can be wasteful. Our concern is how the estimate in terms of bias and precision of the odds ratio would differ if an alternative approach 'multiple events' is used. We addressed this question in the context of a case-crossover study design.

The estimates from three different statistical methods were compared; these were based on three-level data analysis units ('overall crude', 'subject-level', and 'event-level'): the Mantel-Haenszel 2×2 table estimator; the conditional logistic regression model where matching is taken into consideration; and the generalized estimating equations technique involving different working correlation structures as well as matching factors.

A simulation study with various combinations of the design parameters (sample size, correlation coefficient, hazard ratio and intensities of exposure and outcome) was conducted. The mean squared error (MSE) was employed to evaluate the performance of these three different methods when the data is correlated. We compared these three different methods with data on the study of the association between benzodiazepine use and repeated motor vehicle crashes (MVCs).

In the simulation study, we concluded that the Mantel-Haenszel method and the conditional logistic regression method with the *event-level* data analyses are the best in analysis of data with repeated outcome events in the same subject. The model-based variances from these two estimators are accurate. In the MVCs real data study, the alternative approach using 'multiple events' at the subject-level and at the event-level data analyses produces practically identical point estimates of the odds ratios as those from the 'first event' approach; however, the estimates from the 'multiple events' approach are more efficient (lower standard error, i.e., smaller confidence interval). Furthermore, if multiple levels of clusters have occurred in the research data, the data analysis needs to be conducted at the finest level of the cluster in order to obtain an unbiased point estimate of the odds ratio.

The major contribution of this study is to provide insights into under what circumstances the multiple events should be chosen to produce better estimates, or whether the use of the 'first event' approach is sufficient to reach our goal in epidemiological studies.

SOMMAIRE

Lors de l'analyse conventionnelle des données dans la plupart des recherches médicales, nous présumons que toutes les observations sont mutuellement indépendantes. Toutefois, cette supposition est discutable dans bien des cas où les données peuvent être groupées en grappes et les réponses dans une même grappe ont tendance à être plus semblables que les réponses dans les autres grappes. En épidémiologie, l'approche du « premier événement » est souvent utilisée pour enquêter sur les risques liés à l'utilisation de médicaments; c'est-à-dire que tous les événements subséquents sont ignorés. Cette approche peut être peu rentable. Nous nous demandons comment l'estimation du rapport de cotes serait différente, en ce qui a trait au biais et à la précision, si une autre approche tenant compte d'événements multiples était utilisée. Nous avons abordé cette question dans le contexte de la conception d'une étude de cas croisés.

Les estimations obtenues à l'aide de trois méthodes statistiques différentes ont été comparées; elles étaient fondées sur l'analyse de données à trois niveaux (brut global, sujet et évènement) : l'estimateur de Mantel-Haenszel (tableau à deux entrées); le modèle de régression logistique conditionnelle où on tient compte de l'appariement; et la méthode statistique d'équations d'estimations généralisées comprenant diverses structures de corrélation de travail de même que des facteurs d'appariement.

Une étude de simulation utilisant diverses combinaisons des paramètres de conception (taille de l'échantillon, coefficient de corrélation, taux de défaillance et degré d'exposition et résultats) a été menée. L'erreur quadratique moyenne (EQM) a été utilisée pour évaluer le rendement de ces trois différentes méthodes lorsque les données sont corrélées. Nous avons comparé les trois différentes méthodes avec les données sur

l'étude de l'association entre l'usage de benzodiazépine et le nombre répété d'accidents de véhicule à moteur (AVM).

Dans l'étude de simulation, nous avons conclus que la méthode Mantel-Haenszel et la régression logistique avec l'analyse des données en 'event-level' étaient les meilleures méthodes d'analyses lorsque les données sont répétées pour le même sujet. Les modèles de base des variances pour ces deux estimateurs sont corrects. L'autre approche utilisant des événements multiples donne des estimations ponctuelles des rapports de cotes pratiquement identiques aux estimations ponctuelles obtenues avec l'approche utilisant le premier événement; toutefois, les estimations de la première approche sont plus efficaces (l'erreur-type est plus petite, c'est-à-dire que l'intervalle de confiance est plus étroit). En outre, si plusieurs niveaux de grappes sont présents dans les données de recherche, l'analyse des données doit être menée au niveau le plus détaillé afin d'obtenir une estimation ponctuelle non biaisée du rapport de cotes.

La principale contribution de cette étude est d'offrir des lignes directrices indiquant dans quelles circonstances il faudrait choisir l'approche utilisant des événements multiples pour obtenir de meilleures estimations ou si l'utilisation de l'approche utilisant le premier événement est suffisante pour atteindre notre but dans la réalisation d'études épidémiologiques.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

ACKNOWLEDGEMENTS

The completion of this thesis would not have been possible without the contribution and help of my supervisor, Dr. Samy Suissa and my co-supervisor, Dr. James A. Hanley. I wish to express my deepest thanks to Dr. Suissa, who provided enormous encouragement, guidance, and has had a constant interest in my thesis work. I would also like to thank Dr. Hanley for his expertise in the methodology and his guidance in all of the practical aspects of this study; his contribution substantially improved my research. In addition, I offer my sincere gratitude to my thesis committee member Dr. Robert Platt, for sharing his time and energy to provide guidance in many theoretical and practical methodology issues.

A special note of gratitude is extended to Dr. TongZhang Zheng, who first introduced me to epidemiology and has constantly encouraged me to undertake this degree, and his wife, Dr. Anne Gilbert, whose encouragement has always been deeply appreciated.

Furthermore, I would like to thank Dr. Barhdadi Amina for her assistance with the MVCs real research dataset, Diane Gaudreau, who graciously helped in coordinating the completion of this thesis, and Dr. SaiBei Zhao, to whom I am extremely grateful.

I would also like to thank the Fonds de la recherche en santé du Québec (FRSQ) for granting a scholarship for my doctoral studies, and so making it possible for me to undertake and finish this study.

Finally, I offer special thanks to my parents, ChangHong Zhang and TongXiu Zheng, who continue to provide me with support and encouragement in all my endeavors.

STATEMENT OF ORIGINALITY

This study is the first to use the case-crossover design in the longitudinal setting as a means of investigating the performance (in terms of bias and precision of the odds ratio) of three different statistical methods (the Mantel-Haenszel method, the conditional logistic regression method, and the GEE method). The investigation is conducted in accordance with three different levels of data analysis units (the 'overall crude', the 'subject-level', and the 'event-level'). In particular, the bias and precision of the estimates of the odds ratio are addressed by comparing the 'first event' to the alternative 'multiple event' approaches. Moreover, this study is the first to extend the case-crossover study from a study of a single outcome event to a study of multiple events of interest. It is also the first study to show that the data analysis needs to be implemented at the finest level of the cluster, to obtain an unbiased estimate of the odds ratio, if multiple levels of clusters have occurred in the research data.

CHAPTER 1

INTRODUCTION

Overview

In this chapter, we will first illustrate some unique advantages of the case-crossover study (Maclure, 1991) in study of the side effects or benefits of medication use over the traditional epidemiological studies (e.g., the cohort study, the case-control study, and the randomized clinical trail). Then, we will discuss some limitations of the conventional statistical methods in analysis of data with repeated events in the same subject. Finally, we will describe the objectives of this thesis and the outlines of each chapter.

1 Study designs for investigating the side effects and benefits of medication use

Epidemiological studies can be roughly divided into non-experimental (or observational) and experimental epidemiological studies (Figure 1). Non-experimental studies can be further classified into descriptive epidemiology and analytical epidemiology. There are two major types of analytical epidemiological studies: the cohort study (or follow-up study) and case-control study.

A cohort study is an epidemiological study in which comparison populations are grouped based on the exposure status of the participants (i.e., either presence or absence of exposure). These subjects who are free of the disease of interest will be followed up over a period of time to let the disease development. Finally, incidence or risk of disease development can be compared between the exposed and the unexposed comparison

populations. A cohort study can be further classified as either prospective cohort study or retrospective cohort study.

Although both prospective and retrospective cohort studies classify study subjects on the basis of presence or absence of exposure, prospective cohort study first ascertains the exposure status of the participants who are at the risk of developing the disease (or outcome of interest), and free of the disease of interest. These subjects will be followed up for a sufficient period of time for disease development. The study will collect all the incident cases produced by both the exposed and nonexposed populations during the study follow-up period, and calculate the incidence ratio or cumulative incidence ratio to estimate the strength of the association between the exposure and the disease of interest. A prospective follow-up study is also called a longitudinal study where the response variable (disease or outcome of interest) for each individual can be repeatedly measured during the study period (Liang and Zeger, 1986; Twisk, 2003).

In a retrospective cohort study, however, both the exposures and outcomes of interest have already occurred at the beginning of the study. The study usually ascertains exposure status for each study subject based on preexisting records (such as hospital records), and assemble exposed and nonexposed comparison groups based on their exposure status. The information on outcome of interest can also be collected from preexisting records, such as cancer registry. Finally, a standardized mortality ratio (SMR) can be calculated by dividing the number of observed deaths by the number of expected deaths. A case-control study is an epidemiological study in which both exposure and disease of interest have already occurred when the study begins. In a case-control study, the investigators first identify cases based on the study case definition and then randomly select a representative sample (or controls) from the population which produced the cases.

Ideally, the control group should represent the population which produced cases for the exposure of interest. The exposure status of the study subjects is retrospectively evaluated through various methods such as interviews, laboratory analyses and/or historical records.

The major difference between a cohort study and a case-control study is that, in a cohort study, investigators first divide the study population into exposed and nonexposed populations at the beginning of the study based on the presence or absence of the exposure of interest, and then longitudinally follow-up with the population over a sufficient period of time to collect the information on the outcome of interest. The main advantages of the cohort study are: 1) the design is less likely being affected by selection bias when the study population is established; 2) generally speaking, the observed association in a prospective cohort study cannot be interpreted as the consequence of the disease because the study subjects are free of disease of interest when the study is initiated; and, 3) a prospective cohort study is particularly useful to study multiple outcomes from a single exposure, especially when the exposure is relatively uncommon. The main disadvantage of a cohort study is that it requires a large sample size to study the relationship between exposure and outcome, especially when the outcome is rare in the study population. Also, a prospective cohort study usually requires a long follow-up period when the disease induction and latent periods are long, and thus, a prospective cohort study can be expensive.

Another potential limitation of a prospective cohort study, as pointed out by Schneeweiss (1997), is that it is difficult to use this type of study to investigate the acute effects of a transient exposure. This is the case because study of acute effects from a transient exposure usually requires constant recording of valid exposure information for

even a very short period of time so that when an event takes place at a time when the event is not anticipated, the exposure information shortly before the event is available, which, in most cases, is not possible.

In a case-control study, on the other hand, the investigators will only need to retrospectively assess the exposure status of the cases and the controls since both the exposure and the disease of interest have already occurred at the beginning of the study. This study design is particularly useful when the disease of interest is rare and when a number of exposures are considered to be the risk factors of the disease. The main challenge of this study design is to avoid selection bias and information bias since both exposure and disease of interest have already occurred when the study starts and selection of study subjects could be affected by their exposure status or ascertainment of exposure status could be affected by their disease status.

In 1991, Maclure proposed a new type of epidemiological study, called case-crossover study, to study the relationship between "transient" exposures and "acute" effects. In a case-crossover study, only subjects who developed the disease of interest will be included in the study (Figure 2). Each selected subject (or "case") will serve as his or her own referent (or "control"). The exposure information collected from the subjects will be used to evaluate the association between exposure and the outcome event by comparing the rates of exposure in the risk period and the control period.

The case-crossover study has several advantages over traditional case-control study which involves selection of controls from a source population: 1) The case will serve as his or her own control, and thus eliminating the potential for selection bias due to the high refusal rate from controls in a typical case-control study; 2) Confounders which remain constant for each subject (e.g., genetic factors) will be effectively controlled through

intra-subject comparisons; and, 3) The study design also increases the cost efficiency by avoiding the expenditure associated with control selection.

Experimental epidemiological study (such as a randomized clinical trial or a randomized chemoprevention trial) is designed to study the effect of treatment on the disease (clinical trial); or the effects of a chemopreventive agent on the prevention of the disease (chemoprevention trial). The unique feature of a randomized clinical trail involves a self-selected population, and the study subject will be randomly assigned to either a treatment group or a control group, and the study subjects will be followed longitudinally for a period of time to collect information on the disease of interest. In an experimental study, the outcome of interest can be measured more than once to assess the effects of intervention on repeated occurrences of a disease (such as beta-agonist use and asthma attacks). Therefore, both the prospective follow-up study and the experimental study are considered to be longitudinal studies because both involve a longitudinal follow-up period of the study subjects to collect the outcome of interest.

Experimental studies, such as a randomized clinical trail (RCT), often face ethical issues, especially in studies which may involve serious side effect from the treatment. For example, RCT is prohibited from recruiting pregnant women as study subjects. The case-crossover study, however, does not have to face ethical issues in assessing exposure and disease relationship since case-crossover study does not involve allocation of study subjects to either the treatment group or the placebo group. For example, a case-crossover study can be used to study the relationship between alcohol intakes and repeated motor vehicle accidents (Vinson, 1995). It would be unethical to conduct an experimental study to assess this relationship.

Since the introduction of the case-crossover study design by Maclure in 1991, the case-crossover study has been applied to the studies of various fields such as occupational and environmental epidemiology, pharmacoepidemiology, and injury epidemiology to study the potential adverse effects of the exposures of interest. For example, the case-crossover study design was used to study the association between acute respiratory-tract infections and risk of first-time acute myocardial infarction (Meier, 1998). It has also been used to study the association between road-traffic accidents and benzodiazepine use (Barbone, 1998). In this thesis, the case-crossover study design will be used to study the relationship between benzodiazepine use and repeated MVCs using the data collected from the Régie de l'assurance maladie du Québec (RAMQ) and the Société de l'assurance automobile du Québec (SAAQ).

2 Limitations with conventional statistical methods for events with multiple occurrences

Longitudinal studies can be used to study the occurrence of an outcome after exposure to a specific treatment to study the change pattern in a disease process of interest over time. A longitudinal study could also be conducted to study the relationship between two or more repeated measurements of an outcome of interest in an individual. For example, a longitudinal study can be conducted to investigate whether previous hospitalization due to asthma could predict the future hospitalization of the same subject due to the same disease. In statistical analysis, if the outcomes of interest are not independent from each other, traditional statistical methods may not be applied to these data because (as described in the following section) the conventional statistical approach has several major

limitations in analyzing data with multiple events which are correlated. Thus, new statistical methods need to be developed to deal with datasets where multiple outcomes are strongly correlated.

In epidemiological studies, there are two ways to analyze outcome event which has repeated measurements from an individual. One way is to take only the first event into consideration and ignore the subsequent events. We term this approach the 'first event' approach (Figures 3 and 4), where Figure 4 shows the common setting of how the case-crossover study design is applied to study the first outcome event of interest. The other way is to divide the study period into multiple small time intervals based on the outcome event of interest, where each interval contains a single event. For example, in studies of medication use and hospitalization due to asthma, many used only the first hospitalization as the outcome of interest (first event approach) in the data analyses. Hospitalization due to asthma, however, could result in further hospitalizations from the disease (Crane et al., 1992; Mitchell et al., 1994; Li et al., 1995). Alison (1999) gave a hypothetical example of estimating a model for birth intervals and a sample of ever-married women who had reproductive histories. He proposed that the data analysis can be started with an analysis for the interval between marriage and the first birth. For all those women who had a first birth, the second analysis can be conducted for the interval between first birth and second birth. Clearly, the data can be analyzed in this way until the number of women becomes too small to reliably estimate a model. However, this approach may increase the probability of false-positive findings due to multiple comparisons, and the more parameters that need to be estimated and interpreted, the more room there is for ambiguity and confusion.

If the purpose of a research is to examine the repeated occurrence of a medical event (for example: tumor recurrences, seizures, and hospitalizations), the consideration of the first event in a longitudinal study may not be sufficient. Consideration of multiple events appears to be a better measurement of disease burden in a population than consideration of the first event only. Moreover, consideration of multiple events may provide more insight into the causes, the patterns and the mechanisms leading to the disease of interest.

However, conventional statistical methods have some limitations in analyzing longitudinal data with multiple events, especially when events are correlated. These limits include: ignoring the positive correlation between the multiple events in the data analysis and treating the outcome events as if they were independent from each other which may result in an underestimation of the standard errors and overestimation of the test statistics, if the predictor variable is fixed within a cluster. However, if the predictor can vary within cluster, then one may achieve lower standard errors and more powerful tests (Burton et al., 1998. See Appendix I). On the other hand, in principle, a conventional approach by excluding data (e.g., 'first event' approach) would produce inefficient coefficient estimates.

Liang and Zeger (1986) introduced a new statistical approach, Generalized Estimating Equations, to overcome the dilemma of using conventional statistical methods in dealing with longitudinal data with multiple events. In this new statistical method, 'multiple events' are used. Figure 5 illustrates multiple events for repeated MVCs in a case-crossover study. The complexity of the correlation among multiple events is also taken into consideration via the working correlation structure. Liang and Zeger demonstrated that GEE provide a consistent estimation of the underlying parameter even

if the working correlation structure is incorrectly specified, although an incorrect specification of the working correlation structure could result in a lack of efficiency in data analyses.

In this thesis, we will evaluate the performance of eight estimators (details will be introduced in Chapter 4) in analyzing longitudinal data with multiple outcome events. The specific example for these eight estimators will be benzodiazepine use and repeated MVCs in Canada. The data on multiple outcome events (car crashes) used in this study came from the Société de l'assurance automobile du Québec (SAAQ). The data on exposure to benzodiazepines were collected from the Régie de l'assurance maladie du Québec (RAMQ). Since only subjects who had the accidents (the cases only) will be used in this study, we will use a case-crossover study design to investigate the relationship. Using this real dataset, we attempt to extend the case-crossover study from a study of a single event to a study of multiple events (Figures 4 and 5).

3 Objectives

The objectives of this thesis are:

1) To evaluate the performance in terms of bias and precision of three different statistical methods for estimating the odds ratio from the case-crossover design with multiple events;

2) To examine which levels of data analysis should be used when there are several levels of clusters;

3) To provide insights into under what circumstances the 'multiple event' approach may be chosen instead of the 'first event' approach; and,

4) To apply the three statistical methods to the study of the association between benzodiazepine use and repeated MVCs.

4 Outline and Summary

This thesis work is described in the following 7 chapters. In Chapter 1, we illustrate some unique advantages of the case-crossover study in investigating the side effects and benefits of medication use over the traditional epidemiological studies. We also discuss the limitations of the conventional statistical methods in analysis of data with multiple events in the same subject and described our study objectives. In Chapter 2, we will briefly review the definition and the design issues in a case-crossover study, including the introduction of a few terms specific to this study design, such as "risk period" and "control period". We will review the two statistical methods which have been used for data generated from the case-crossover study; the Mantel-Haenszel (M-H) method for estimating the odds ratio and the conditional logistic regression (CLR) method for considering matching. In Chapter 3, we will give a detailed review of the generalized estimating equation (GEE) method and the CLR method with m:n (case(s): control(s) ratio) matching. In Chapter 4, we will illustrate three different choices for the unit of data analysis (e.g., 'overall crude', 'subject-level' and 'event-level') and propose eight estimators based on the combinations of three different choices for the unit of data analysis and three different statistical methods. We will then discuss three different criteria (the bias, the variance, and the MSE) used to evaluate the performance of the eight estimators. In Chapter 5, we will summarize the results from the simulation study and reach the conclusion on which estimator(s) is (are) the best in analyzing the data from

a case-crossover study with repeated outcome events. In Chapter 6, we will evaluate the discrepancies in the odds ratio and the corresponding variance estimations by comparing the 'first event' approach with the alternative approach (i.e., 'multiple event'). We will apply the case-crossover study to examine the role of benzodiazepine use on MVCs. Finally, in Chapter 7, we will discuss the possible explanations for different results when three statistical methods are applied to the same dataset and, in this situation, which statistical method should be used when there are multiple clusters in the research data.

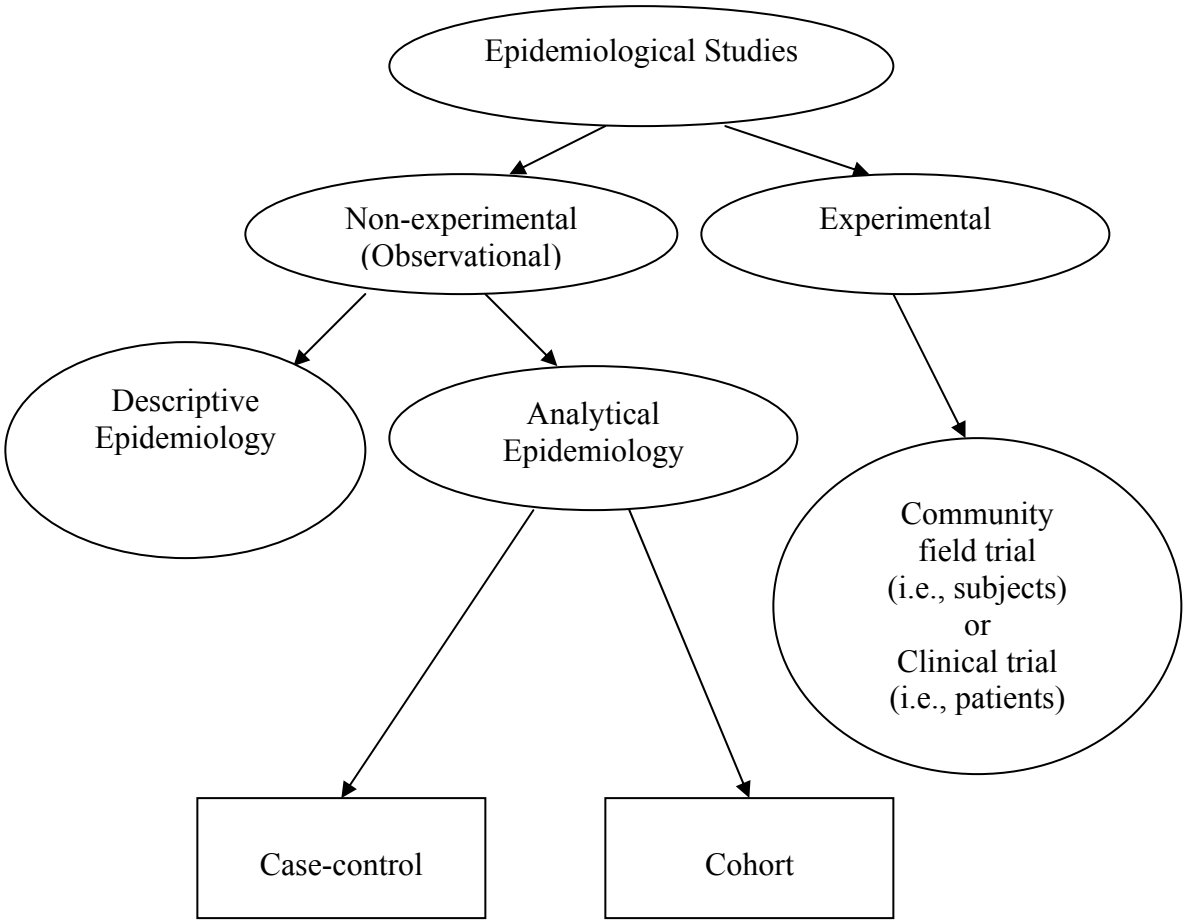


Figure 1: Types of epidemiological studies

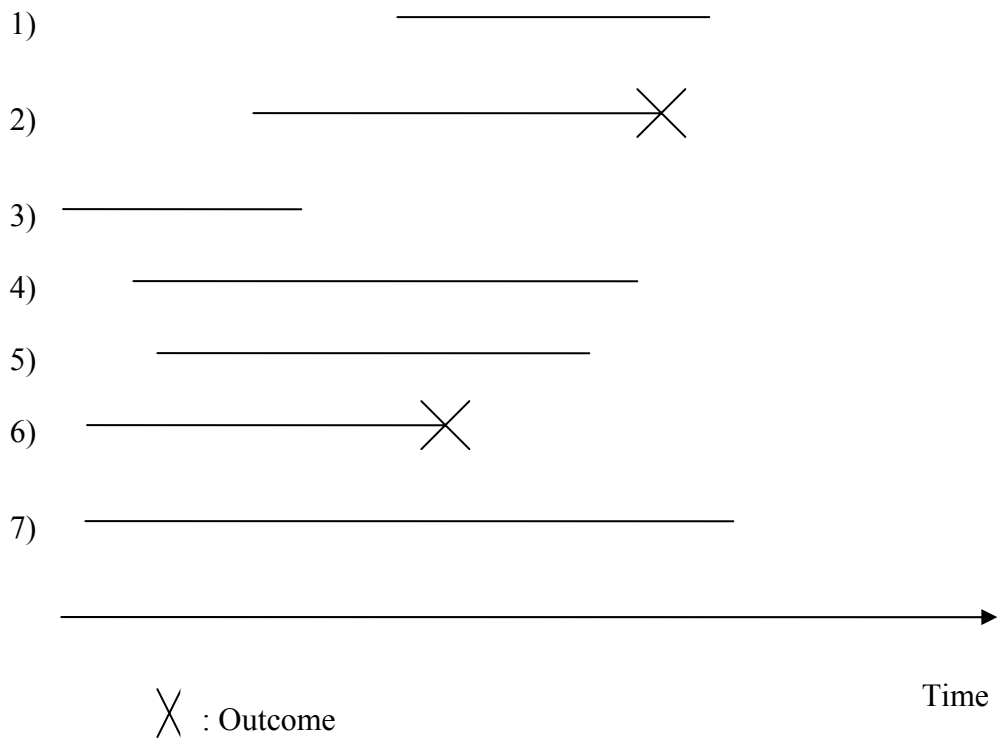
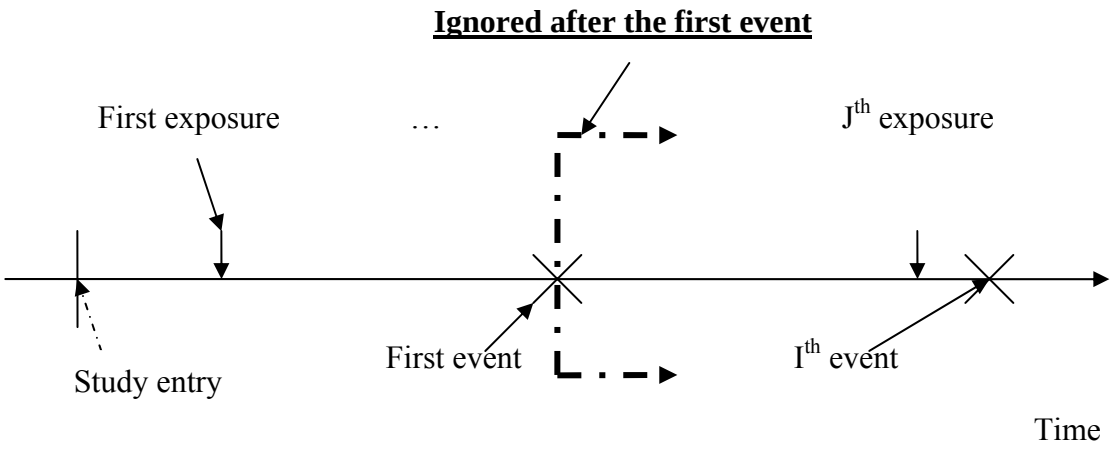


Figure 2: A hypothetical cohort with dynamic population

Subject *i*



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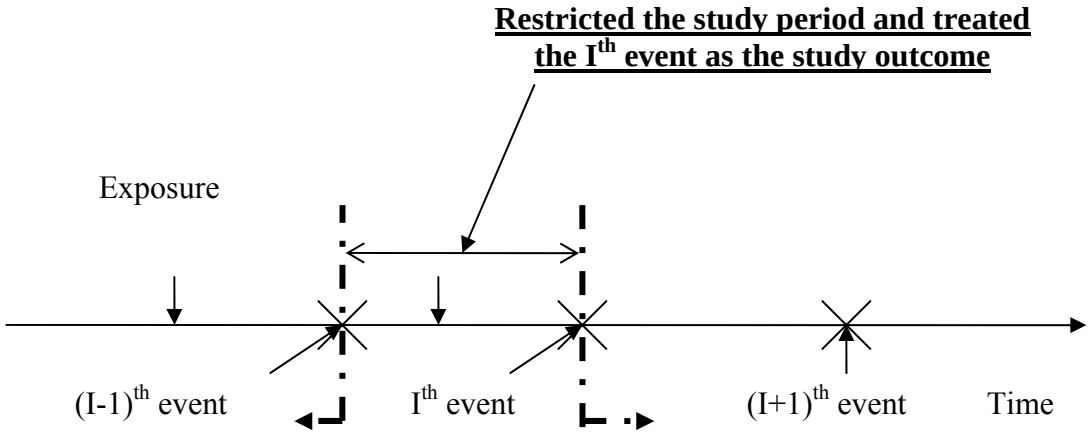
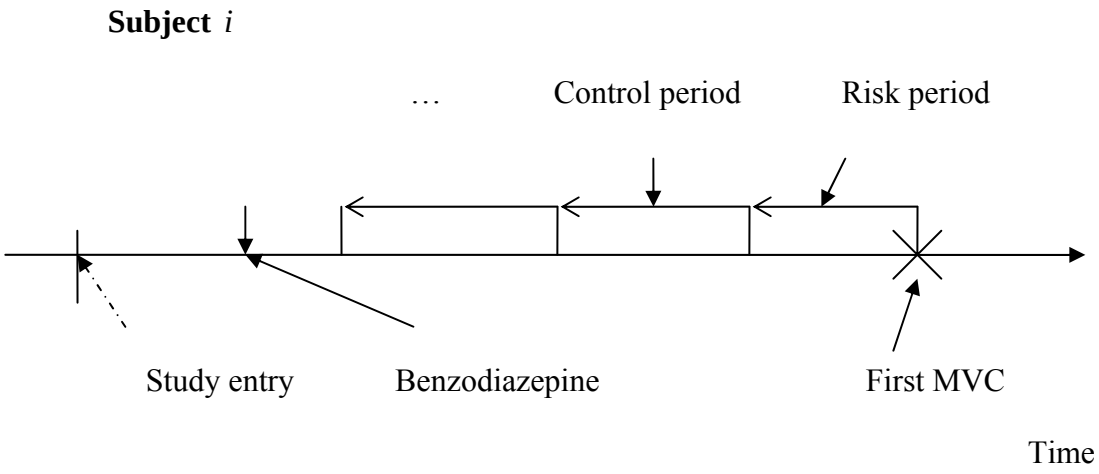


Ignored before (I-1)^th event including this event

Ignored after I^th event

Outcome (event): MVCs
Exposure: Dispensed benzodiazepine

Figure 3: 'First Event' approach for studying the relationship between benzodiazepine use and repeated MVCs

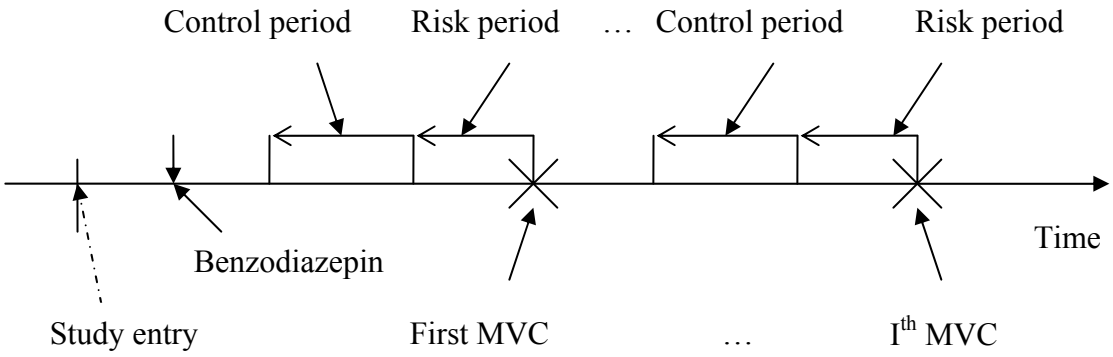


Several control periods can be selected prior to the risk period
in a case-crossover study

First event: First motor vehicle crash (MVC)
Exposure: Dispensed benzodiazepines

Figure 4: Conventional approach using 'First Event' in a case-crossover study

Subject *i*



Several control periods can be selected prior to the risk periods
in a case-crossover study

Multiple events: repeated motor vehicle crashes during the study period
Exposure: Dispensed benzodiazepines

Figure 5: Alternative approach using 'Multiple Event' in a case-crossover study

CHAPTER 2

A BRIEF REVIEW OF THE CASE-CROSSOVER STUDY

Overview

In this chapter, we will first review the definition, study population, and the assumptions of the case-crossover study as proposed by Maclure in 1991. Then, we will discuss the definition of the risk period and possible choices of the control period. In the same section, we will also discuss several ways on how to handle the exposure information in the data analysis. Finally, we will review three available statistical methods (the Mantel-Haenszel, the conditional logistic regression method, and the proportional hazards model for case-only studies) in detail for analyzing the data from a case-crossover study.

2.1 Introduction: Definition, Study population and Assumptions

Definition: Maclure proposed a case-crossover study as a new epidemiological method to study the relationship between transient exposures and acute outcomes (Maclure, 1991). The unique feature of this method is that the study population it uses includes only individuals who have developed the outcome event of interest. A case in a case-crossover study is a subject who has developed the outcome event of interest, and each selected case also serves as his or her own control in this type of study. Thus, the case-crossover study could also be called a self-matched case control study.

To study the relationship between exposure and rates of the outcome event of interest via a case-crossover study, the first step of this study is to retrospectively define a "risk period" for the case (as shown in Figure 2.1.1). A risk period is usually defined as the window of time that immediately precedes the outcome event of interest. The second

step is to retrospectively define a control period for the same subject. A control period is used to estimate the exposure rate if the study subjects did not have the disease or outcome of interest. A more detailed discussion of the selection of the control period is given later in the thesis. Once both the risk period and control period for all the subjects are defined, the next step in the study is to assess the exposure status (both frequency and intensity) of the subjects in the risk and control periods, then use this information to evaluate the association between the exposure and the outcome event of interest.

According to Maclure (1991) and Suissa (1995), several assumptions have to be made to ensure the validity of a case-crossover study. The first assumption proposed by Maclure (1991), is that the underlying risk period (also called the "effect time period") should be longer than the assumed risk period. Maclure defined the "effect time period" of the exposure as the interval between the end of induction time and the maximum carry-over effect time of the exposure (Figure 2.1.2). Maclure also pointed out that the optimal choice of an effect time period is the one that can minimize the non-differential misclassification of exposure and maximize the risk estimation. If the assumption for the duration of effect time period is either too long or too short, it could jeopardize the validity of the study.

Another assumption is that at the population level (aggregated-level) the distribution of the exposure of interest in the risk period and the selected control period should be the same if there is no association between exposure and the outcome of interest. For example, if the risk period and the control period are too long, this assumption may not be valid because the distribution of exposure may change over time. Suissa (1995) first raised this issue using an example of a case-crossover analysis of beta-agonist use and risk of asthma deaths. In that example, Suissa defined the time window

for the risk period as one year because there was a strong seasonal variation for the disease and beta-agonist use. The control period was defined as the year immediately proceeding the 1-year risk period.

Over a period of 2 years, there may be a "natural increase" of drug use over time because of changing medical practice, greater recognition of the drug's benefits, increasing patient reliance on the drug, and aggressive marketing (Suissa, 1995). If that is indeed the case, and if one ignores this time trend in beta-agonist use, one may conclude that beta-agonist use is associated with asthma mortality even though, in reality, there is no such association. To avoid the potential problem caused by a systematic change in the exposure of interest over time, Suissa proposed a case-time-control design to investigate the degree of the effect of time trend of exposure on the outcome event of interest.

The third assumption, noted by Suissa (1995) is that the exposures within a subject during the risk period and control period are conditionally independent and that there is no carryover effect from the control period to the risk period.

2.2 Risk or Control period selection and Exposure assessment

In this section, we will first give the definition of the risk period, then, we will discuss some commonly used methods for the Control period selection and exposure assessment in a case-crossover study.

Selection of Risk or Control Period: A risk period is usually defined as the time window that immediately precedes the outcome event. Valid selection of a control period is vital for the validity of a case-crossover study to evaluate the relationship between exposure and the outcome of interest.

There are several common approaches for control period selection, including 1) Pair-matched interval approach; 2) Multiple intervals approach; 3) Usual frequency approach; 4) Bidirectional case-crossover design; 5) Symmetric bidirectional case-crossover design; and, 6) Semi-symmetric bidirectional case-crossover design.

Mittleman et al. (1995) proposed several control sampling strategies for case-crossover studies. One of the methods for control period selection is called the "pair-matched interval" approach. In the "pair-matched interval" approach, the rates of exposure in the risk period and the control period are compared. One can consider this approach as a type of one-to-one matched (pair-matched) case control study. For example, in a study of heavy physical exertion and risk of acute myocardial infarction onset (Onset Study), Mittleman et al. (1995) defined the risk period as the 1-hour period immediately preceding myocardial infarction onset, and defined the control period as the 1-hour period at the same time of the day preceding the infarction.

Mittleman (1995) also proposed several different methods for the control period selection, including the so called "multiple interval" approach and the "usual frequency" approach. In the "multiple interval" approach, the rates of exposure in the risk period (e.g., 1-hour period immediately preceding myocardial infarction onset) and a number of control periods (1-hour each) preceding myocardial infarction onset are compared. This model is analogous to a M-to-one matched case control study in which a number of controls are matched to each case. In the "usual frequency" approach method, the exposure status in the risk period is compared with the "expected" exposure status based on each individual's usual exposure frequency over the year preceding myocardial infarction. The amount of person-time considered exposed can be estimated by multiplying the reported usual frequency of exposure by its reported usual duration.

Unexposed person-time can then be calculated by subtracting the exposed person-time in hours from the total number of hours in a year.

Mittleman concluded there was no difference in terms of bias in estimation between the methods while the "pair-matched interval" approach, with the least information being used, had the lowest relative efficiency. The "usual frequency" approach had the highest efficiency. The study efficiency increases as the number of control periods sampled increases in the "multiple intervals" approach.

There are also several other modifications of the control period selection proposed for a case-crossover study. One of them, called the "bidirectional case-crossover design", was proposed by Navidi (1998). In this type of case-crossover study, a series of control periods are selected before and after the risk period (Figure 2.2.1). It is considered that bidirectional sampling of control periods will be valid only if the study subjects are still at risk after the first outcome occurrence, an assumption that is certainly invalid when the outcome of interest is death. Lumley and Levy (1999), however, showed that in a rare event other than death, the bias due to sampling of the control periods after the risk period should be small.

Bateson et al. (1999) suggested a symmetric bidirectional case-crossover approach (SBI). In this type of case-crossover study design, two control periods are selected. These are required to be equally spaced immediately before or immediately after the risk period, so that the closely spaced control periods will be roughly matched with the risk period on time itself. In their simulation study they observed that symmetric case-crossover controls for trend and seasonality in unmeasured confounding variables. That is, symmetric bidirectional control sampling approaches with short intervals between the outcome event of interest and the control periods could facilitate to control for temporal

confounding by design. For example, an exposure which may have a seasonal variation could be controlled by sampling the two control periods on each side of the risk period. In their subsequent simulation study, Bateson et al. (2001) reported that symmetric case-crossover may introduce bias due to asymmetric selection of control period (subjects at the beginning or end of the series have fewer control periods) or due to confounding (where exposure and effect share the same short-term temporal pattern), however, both biases are minimized.

Based on Bateson and Schwartz's symmetric bidirectional case-crossover design, Navidi et al. (2001) suggested a "semi-symmetric bidirectional case-crossover design", in which a single control period is randomly chosen from a series of balanced and spaced control periods before or after the outcome event of interest. Thus, in a semi-symmetric bidirectional case-crossover study, each risk set contains one risk period and one control period. In their subsequent simulation study, Navidi et al (2001) reported that the "semi-symmetric bidirectional case-crossover design" affords good control of unobserved confounding variables and for exposure which have a temporal trend.

In conclusion, selection of control period(s) is a crucial step in a case-crossover study. It is central for valid assessment of exposure and the subsequent evaluation of the relationship between the exposure and the outcome event of interest.

Exposure assessment: In a case-crossover study, the exposure information will be collected for subjects who have developed an outcome event of interest. The exposure information collected from the subjects will be used to evaluate the association between exposure and the outcome event by comparing the rates of exposure in the exposed and unexposed periods. For example, hypothetically, in a study of the association between

talking on the cellular phone and inadvertently crossing the solid line when driving, the rate ratio of interest can be calculated as: (number of crossing line on phone ÷ person time on phone) ÷ (number of crossing line off phone ÷ person time off phone).

When the case-crossover study design was first proposed, the exposure of interest in the data analysis was dichotomized into a binary variable (i.e., exposed or unexposed) for the risk period and similarly for the selected control period (Figure 2.2.2). This approach may be suitable for a variable which is not a continuous variable. For example, in occupational injury studies, the "use of protective equipment" was defined as either having or not having used the protective equipment or tools (such as wearing gloves or helmets during sporting events). However, when dose-response is an important issue to be addressed, the exposure of interest has to be measured as a continuous variable instead of as a binary variable. For example, in a study of alcohol intakes and risk of motor vehicle accidents, the alcohol levels at the time of a motor vehicle crash should be evaluated.

Marshall (1993) described an approach to estimate relative risk for exposures which can be measured as quantitative variables. In this approach, which is based on the maximum likelihood method, a continuous variable can be directly included in the logistic regression model or included in the model after being transformed into a categorical variable. For example, in the study of beta-agonists use and asthma death, Suissa (1994) first treated beta-agonists use as a continuous variable by entering the (actual) quantity of beta-agonists use into the logistic regression model, then, by entering the trichotomized quantity of beta-agonists used into the logistic model. In a study of the association between strenuous physical exercises and sudden death from cardiac causes, Muller et al. (1996) divided the frequency of habitual vigorous exercises into 3 categories

(<1, 1-4 and 5 times/week), and a dose-response relationship between exercise activity and cardiac sudden death was evaluated.

In the following, we review three different statistical methods (the M-H method, the CLR method, and the proportional hazards model for case-only studies) which were proposed to analyze data from a case-crossover study.

2.3 Available statistical methods for analyzing data from a case-crossover study

In a case-crossover study, only the exposure information regarding the subjects who have developed the outcome of interest (the cases) will be collected. A case-crossover study can be considered as a highly stratified cohort or case control study (i.e., self-matched case control study) where each subject consists of a stratum (Maclure, 1991). The incidence rate ratio could be estimated from the case-crossover data by using the M-H method or the CLR method. In 1999, Greenland proposed to use the proportional hazards model method to analyze the data from studies based on cases-only, including the case-crossover study. In the following, we will discuss how these statistical methods will be applied to the data analysis in a case-crossover study.

2.3.1 Mantel-Haenszel method: The M-H method can be used to analyze data from a case-crossover study. In using this method, we can consider a case-crossover study to be a type of cohort study or a type of pair-matched case control study as described below.

1) Rate Ratio Estimation by Viewing Case-Crossover Study as a Type of Cohort Study

If the data from a case-crossover study are collected from each subject, then (as shown in Table 2.3.1) the data can be considered to be a series of stratified 2×2 tables. In each stratum, however, there is only one subject (but with many potential person moments). Depending on whether the event occurs concurrently with the exposure, we can assign (1, 0) or (0, 1) to the first row of the 2×2 table to indicate whether the subject developed the outcome of interest. According to the history of exposure before the event took place, the person-time data can be filled in the second row of the 2×2 table. The person time data are the number of time windows that the subject is exposed and the number of time windows that the subject is not exposed. Strata with no outcome event of interest will not contribute information to the relative risk estimate, which means that the cohort is reduced to a case-only study. In this way, the analysis of a case-crossover study with n cases may be viewed as a pooled analysis of n retrospective cohort studies, each with a sample size of one. The data generated from a case-crossover study can be analyzed with standard M-H methods for follow-up studies with sparse data in each stratum.

2) Rate Ratio Estimation by Viewing Case-Crossover Study as a Type of Case Control Study

A case-crossover study can also be considered as a matched case-control study, where each risk period and its matched control periods constitute a stratum. In this special type of case-control study, the risk period and the control period came from the same person and the exposure status were ascertained for the selected risk and the control periods. Thus, in a case-crossover study, the matched control is not a "person", but a "control period" ("person moments"). As in the traditional case-control study, we can apply different strategies of sampling such as 1:1 matching, m :1 matching, or a variable

number of controls matched to each case. For example, if the risk period is defined as the 1-hour period immediately preceding myocardial infarction onset, the control can be chosen as the comparable 1-hour period at the same time of the day, on the day preceding the infarction. The M-H method can be used to estimate the odds ratio in a case-crossover study as is usually done in a pair matched case-control study, which is algebraically equivalent to the McNemar estimate-the number of discordant pairs with exposed cases divided by the number of discordant pairs with nonexposed cases (Rothman, 1986).

2.3.2 Conditional logistic regression method: As stated previously, the case-crossover study can be considered a special type of pair-matched case-control study. In this special type of case-control study, the risk period and its matched control periods form a risk set. It is recommended that the CLR method can be used to estimate the relative risk for a case-control study, especially when incorporation of a separate parameter for each stratum is impractical, and when the size of the dataset is too small relative to the number of parameters to be estimated in the model (Breslow and Day, 1980). For example, in a one-to-one matched study design with n case control pairs, we have only two subjects per stratum. In a fully stratified analysis with p covariates, we need to estimate n + p parameters consisting of the constant term, the p slope coefficients for the covariates and the n-1 coefficients for the stratum-specific design variables using a sample of size 2n. The optimality properties of the method of maximum likelihood, derived by letting the sample size become large, will hold only if the number of parameters remains fixed. This is not the case in a one to M matched case-control study

(Breslow and Day, 1980; Hosmer and Lemeshow, 2000). A brief discussion of the likelihood function of the CLR method will be given below.

2.3.3 Conditional Maximum Likelihood Estimation: As shown by Breslow and Day (1980), it is more appropriate to consider CLR for a matched case-control dataset; if we ignore the matching fact and directly apply the unconditional logistic regression method to a pair-matched case-control study with one intercept per stratum, the estimated odds ratio will have expected value equal to the square of the odds ratio originated from the analyses via CLR method.

For a single 2×2 table, given all the marginal totals n_1, n_0, m_1 and m_0 fixed, the conditional distribution of the frequency in the 'a' cell, developed by Birch (1964), is the non-central hypergeometric distribution ($\Pr(a \mid n_1, n_0, m_1, m_0; \psi) = \dfrac{\binom{n_1}{a}\binom{n_0}{m_1 - a}\psi^a}{\sum_y \binom{n_1}{y}\binom{n_0}{m_1 - y}\psi^y}$, Figure 2.3.2). The summation in the denominator ranges over all the possible values y for the number of exposed cases a, $m_1 - n_0 <= y <= m_1, n_1$. ψ is the theoretical odds ratio measuring the association between exposure and the outcome of interest. In general, the estimated odds ratio from the conditional maximum likelihood is closer to null than that from the unconditional approach (empirical odds ratio, ad/bc). However, the estimate of the odds ratio from the former is close to the latter when the sample size in each cell is large (Breslow and Day, 1980). In the next section, we are going to review the derivation of the conditional likelihood function from a matched case-control study (Collett, 2003).

Let's consider a $1:M$ matched case-control study, where the jth matched set contains one case and M controls, for $j=1, 2,\ldots, n$. Let the vector of values of explanatory variables measured on each of these individuals be $x_{0j},\ x_{1j},\ \ldots,\ x_{Mj},$ where x_{0j} is the vector of values of the explanatory variables $X_1,\ X_2,\ \ldots,\ X_k$ for the case, and x_{ij}, $i \geq 1,$ is the vector of the values of $X_1,\ X_2,\ \ldots,\ X_k$ for the ith control, $i = 1, 2, \ldots, M$, in the jth matched set. Let $P(x_{ij} \mid d)$ be the probability that a diseased person in the jth matched set has explanatory variables x_{ij}, for $i = 0, 1, 2, \ldots, M$, and let $P(x_{ij} \mid \bar{d})$ be the probability that a diseased-free individual has explanatory variable x_{ij}. If x_{0j} is the vector of values of explanatory variables for the case in the study, that individual must have the disease that is being studied. The joint probability that x_{0j} corresponds to the case, and x_{ij} to the controls is

$$P(x_{0j} \mid d)\prod_{i=1}^{M} P(x_{ij} \mid \bar{d}). \qquad (2.3.1)$$

The probability that one of the M +1 individuals in the jth matched set is the case, and the reminder are controls, is the union of the probability that the person with explanatory variables x_{0j} is diseased and the rest disease-free, and the probability that the individual with explanatory variables x_{1j} is diseased and the rest are disease-free, that is,

$$P(x_{0j} \mid d)\prod_{i=1}^{M} P(x_{ij} \mid \bar{d}) + P(x_{1j} \mid d)\prod_{i\neq 1} P(x_{ij} \mid \bar{d}) + \ldots + P(x_{Mj} \mid d)\prod_{i\neq M} P(x_{ij} \mid \bar{d}).$$

This can be written as

$$\sum_{i=0}^{M} P(x_{ij} \mid d)\prod_{r\neq i} P(x_{rj} \mid \bar{d}). \qquad (2.3.2)$$

It then follows that the required conditional probability is the ratio of the probabilities given by (2.3.1) and (2.3.2), namely,

$$\frac{P\left(x_{0j} \mid d\right)\prod_{i=1}^{M} P\left(x_{ij} \mid \bar{d}\right)}{\sum_{i=0}^{M} P\left(x_{ij} \mid d\right)\prod_{r\neq i} P\left(x_{rj} \mid \bar{d}\right)} \tag{2.3.3}$$

Based on Bayes theorem (P(A|B)=P(B|A)P(A)/P(B)) and applying this result to each of the conditional probabilities in (2.3.3), the terms $P(d)$, $P(\bar{d})$ and $P(x_{ij})$ cancel out, and we have

$$\frac{P\left(d \mid x_{0j}\right)\prod_{i=1}^{M} P\left(\bar{d} \mid x_{ij}\right)}{\sum_{i=0}^{M} P\left(d \mid x_{ij}\right)\prod_{r\neq i} P\left(\bar{d} \mid x_{rj}\right)}$$

$$=\left\{1+\frac{\sum_{i=1}^{M} P\left(d \mid x_{ij}\right)\prod_{r\neq i} P\left(\bar{d} \mid x_{rj}\right)}{P\left(d \mid x_{0j}\right)\prod_{i=1}^{M} P\left(\bar{d} \mid x_{ij}\right)}\right\}^{-1}$$

$$=\left\{1+\sum_{i=1}^{M}\frac{P\left(d \mid x_{ij}\right)P\left(\bar{d} \mid x_{0j}\right)}{P\left(d \mid x_{0j}\right)P\left(\bar{d} \mid x_{ij}\right)}\right\}^{-1}. \tag{2.3.4}$$

Now suppose that the probability that a person in the jth matched set, with explanatory variables whose values are x_{ij}, is diseased, $P\left(d \mid x_{ij}\right)$, is described by a linear logistic model, where

$$\text{logit}\left\{P\left(d \mid x_{ij}\right)\right\} = \alpha_j + \beta_1 x_{1ij} + \ldots + \beta_k x_{kij}$$

and where α_j is an effect due to the jth matched set. Then,

$$\frac{P\left(d \mid x_{ij}\right)}{P\left(\bar{d} \mid x_{ij}\right)} = \exp\left(\alpha_j + \beta_1 x_{1ij} + \ldots + \beta_k x_{kij}\right) \text{ for } i = 1, 2, \ldots M \text{ , and}$$

$$\frac{P(d \mid x_{0j})}{P(\bar{d} \mid x_{0j})} = \exp(\alpha_j + \beta_1 x_{10j} + \ldots + \beta_k x_{k0j})$$

Then the conditional probability L_j^* (for the jth matched set) given by expression (2.3.4) becomes:

$$\left\{1 + \sum_{i=1}^{M} \exp\{\beta_1(x_{1ij} - x_{10j}) + \ldots + \beta_k(x_{kij} - x_{k0j})\}\right\}^{-1} \qquad (2.3.5)$$

From the above equation, we can see that the set of nuisance intercept parameters α_j has been eliminated from the likelihood function.

The conditional likelihood for the full data is the product over the J sets:

$$L(\underset{-}{\beta}) = \prod_{j=1}^{J} L_j^*(\underset{-}{\beta}) = \prod_{j=1}^{J} \left\{1 + \sum_{i=1}^{M} \exp\{\beta_1(x_{1ij} - x_{10j}) + \ldots + \beta_k(x_{kij} - x_{k0j})\}\right\}^{-1} \qquad (2.3.6)$$

For 1 case and 1 control in the jth matched set, if we assume that a single explanatory variable needs to be considered, the likelihood for this matched set is:

$\left\{1 + \sum_{i=1}^{1} \exp\{\beta_1(x_{1ij} - x_{10j})\}\right\}^{-1}$. Thus, the conditional likelihood for the j^{th} stratum can be described as follows:

Case	Control	L_j^*	
exposed	**exposed**	$OR/(OR+OR)$ **=1/2**	**concordant pair**
exposed	**unexposed**	$OR/(OR+1)$	**disconcordant pair**
unexposed	**exposed**	$1/(1+OR)$	**disconcordant pair**
unexposed	**unexposed**	$1/(1+1)$=**1/2**	**concordant pair**

The conditional likelihood for the full data can be expressed as:

$$L\left(\underset{\sim}{\beta}\right)=\prod_{j=1}^{J=2}L_j^*\left(\underset{\sim}{\beta}\right)=\frac{OR}{1+OR}\times\frac{1}{1+OR}=\frac{OR}{(1+OR)^2} \quad (2.3.7)$$

This is a 'regular' Binominal likelihood (note that if 2 controls and 1 case, L^* is no longer Binomial). Given that the concordant pairs are not informative with respect to OR (see the above table), in a pair-matched case-control study, only the discordant pairs (pairs with case exposed but control unexposed or case unexposed but control exposed) will contribute to the estimation of the odds ratio. The concordant pairs (both the case and control either exposed or unexposed) will not contribute to the conditional likelihood estimation.

In summary, the estimated regression coefficients and the corresponding standard errors from the CLR method can be used to test hypotheses and to obtain the confidence intervals for the odds ratio. The only difference that we should be aware of, if applying the CLR method to a case-crossover study, is that $\underset{\sim}{X}$ s in case-crossover study represent different periods for the same study subject instead of different subjects as they represent in a traditional matched case-control study.

Now, we turn to the other possibility, proportional hazards model, for analyzing the case-only studies including the case-crossover study.

2.3.4 Proportional hazards model method: Greenland (1999) suggested that the proportional hazards model can be used to estimate the rate ratio for studies involving cases only (e.g., the case-crossover study). A conditional likelihood-based approach can be used to analyze the data from such studies, where exposure information was collected only from cases.

The following is a brief review of the conditional likelihood approach for analyzing data from a case-crossover study as proposed by Greenland. Figure 2.3.3 shows the corresponding parameters and structures of the study setting.

Let $\lambda_i(t)$ denote the hazard for case i at time t, let z be a vector of fixed covariates, let $x(t)$ denote an exposure history up to time t and let $u(t)$ be some function of $x(t)$ and products of $x(t)$ with z (for example, $u(t)$ could be exposure at time $t - t_0$, where t_0 is some fixed known lag period). Suppose that the hazard $\lambda_i(t)$ follows a proportional hazards model, i.e.,

$$\lambda_i(t) = \exp[u(t)\beta + z\gamma]\lambda_{0i}(t) \qquad (2.3.8)$$

where β and γ indicate the effect of dynamic exposure and fixed covariates, respectively. $\lambda_{0i}(t)$ denotes the baseline hazard for subject i at time t.

Let U represent the set of K possible exposure levels $\{u_1, u_2, ..., u_K\}$ for the case, let $t_1, t_2, ..., t_K$ denote the amounts of time the case spent at these values, let T denote the set of these times, and let $t_+ = \sum_k t_k$ be the occurrence time of the case, and let u_c denote

the exposure level of the case at its occurrence time. The multinomial probability that $u(t_+) = u_c$, given U and T, is:

$$p[u(t_+) = u_c \mid U, T] = \frac{p[t_+ \mid u(t_+) = u_c, U, T]\, p[u(t_+) = u_c \mid U, T]}{\sum_k p[t_+ \mid u(t_+) = u_k, U, T]\, p[u(t_+) = u_k \mid U, T]}$$

Assume the baseline hazard is constant and define $p_k(t) = p[u(t) = u_k \mid U, T]$, under the proportional hazards model (2.3.8), the above equation can be simplified into:

$$p[u(t_+) = u_c \mid U, T] = \frac{\exp(u_c\beta) \times p_c(t_+)}{\sum_k \exp(u_k\beta) \times p_k(t_+)} \qquad (2.3.9)$$

Without constraints on the p_k, β is not identified by the likelihood obtained from (2.3.9). If the exposure process $u(t)$ was stationary across all the time intervals, the probability of exposure at any specific time interval is proportional to the width of the interval, i.e., $p_k(t_+) = t_k / t_+$.

Then, the formula (2.3.9) can be written as:

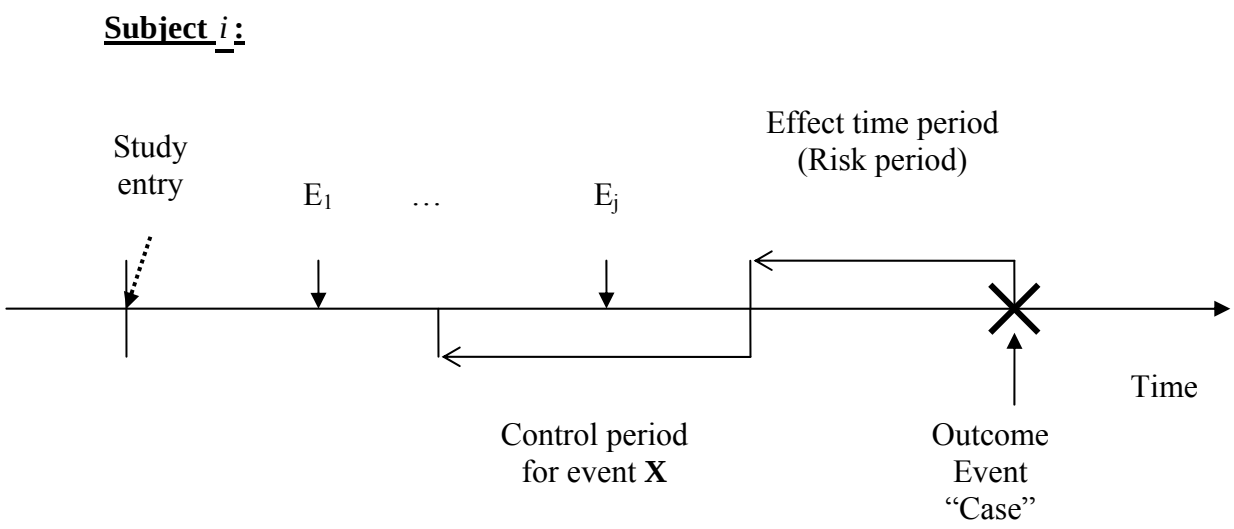
$$p[u(t_+) = u_c \mid U, T] = \frac{\exp(u_c\beta) \times t_c}{\sum_k \exp(u_k\beta) \times t_k} \qquad (2.3.10)$$

Greenland emphasized that the formula above has the form of a conditional logistic likelihood from a case control matched set that has one case with exposure u_c and offset $\ln(t_c)$, and K-1 controls with exposures u_k and offsets $\ln(t_k)$, $k \neq c$. Note that, t_c, t_k are nuisance and rescaled parameters in the above equation.

2.4 Final remarks

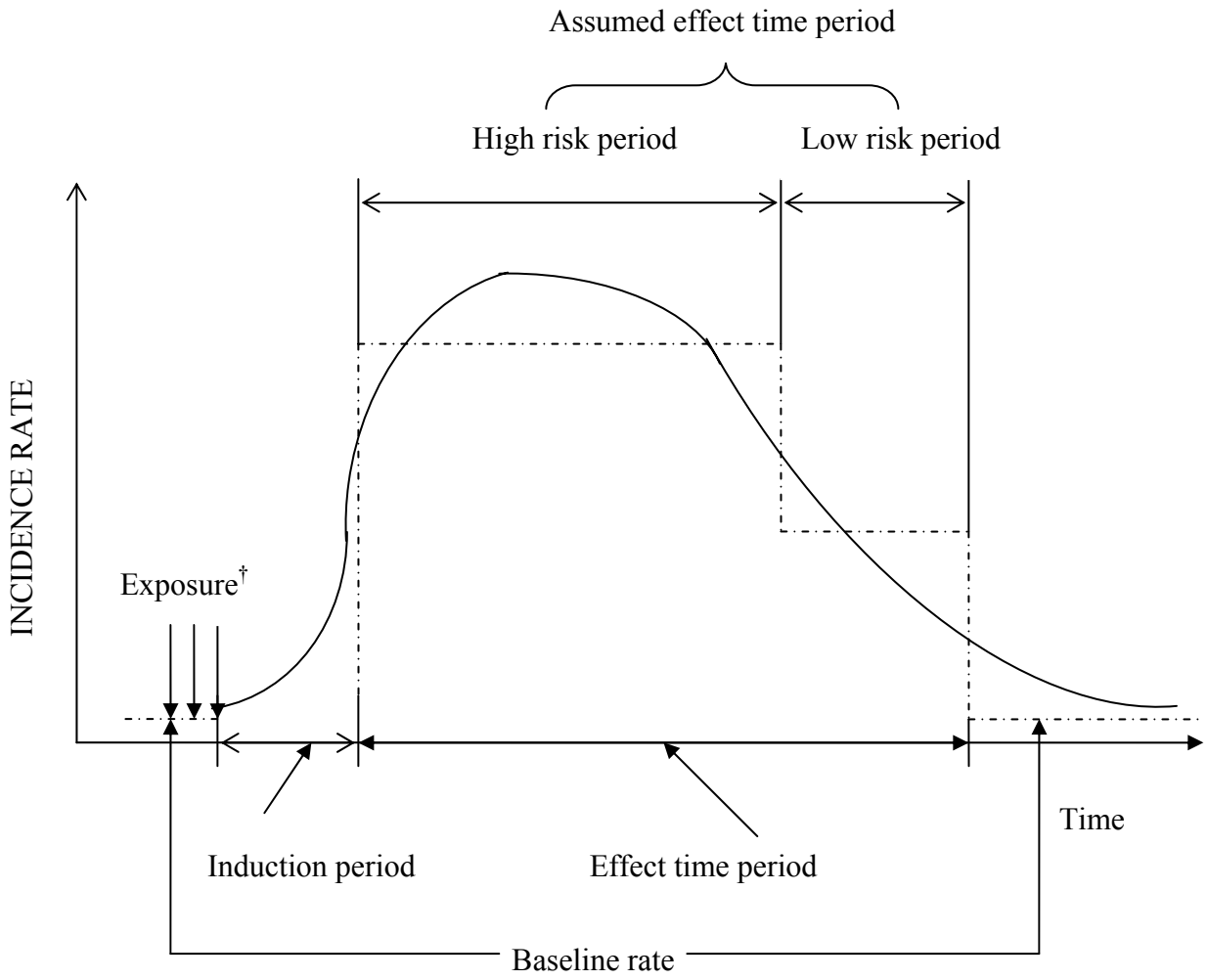
As described in the Introduction section, the classical case-crossover study (Maclure, 1991) in our study will be extended from a study of a single event to a study of multiple events in the same subject. Two available statistical methods (the M-H method and the CLR method), as standard tools, will be used to analyze the data from a case-crossover with repeated measurements in the same subject. Detailed information on how to apply these two available statistical methods based on the different choices of units of data analyses (the *overall crude*, the *subject-level*, and the *event-level* data analyses) will be introduced in Chapters 3 and 4. A hand calculation illustrating how to obtain the estimates of the odds ratio and the corresponding 95% confidence interval at the '*event-level*' data analysis (details will be introduced in Chapter 4, Figure 4.2.2) is given in Appendix II.

In summary, the case-crossover study has provided epidemiologists with a new epidemiological tool to study the relationship between transient exposures and acute outcomes of interest. In this thesis, we will compare the performance of eight estimators (details will be given in Chapter 4) with respect to bias and precision for estimating the odds ratio from a case-crossover design with multiple events in the same subject.



E_1: first exposure; E_2: second exposure;
E_j: jth exposure

Figure 2.1.1: Classical case-crossover study design with a single outcome event



Adapted from
Maclure M. American Journal of Epidemiology, 133, 144-153 (1991)
†: point exposure or multiple exposures of interest. If multiple exposures have occurred, e.g., taking medications every day for 3 days, the last one will be used in this thesis.

Figure 2.1.2: Hazard function after the exposure of interest

Subject *i* :

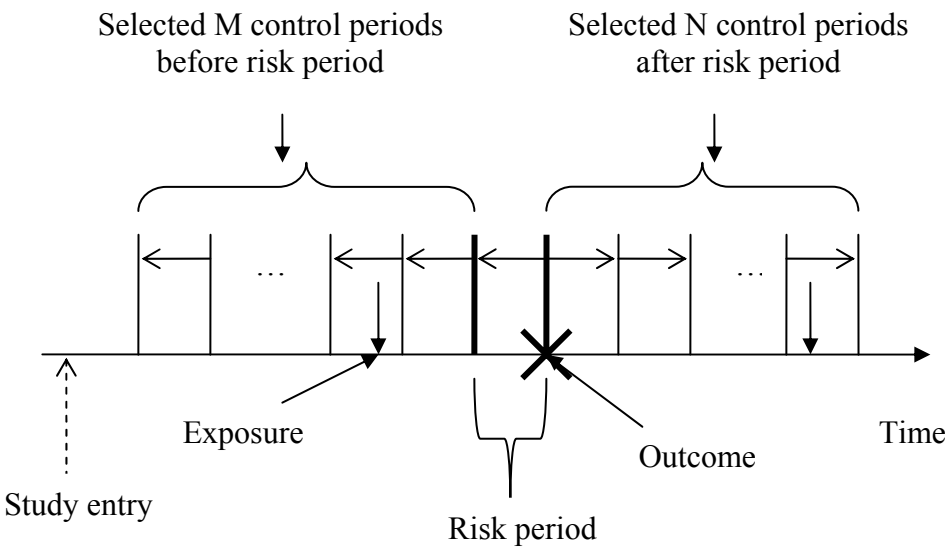


Figure 2.2.1: Bidirectional case-crossover study

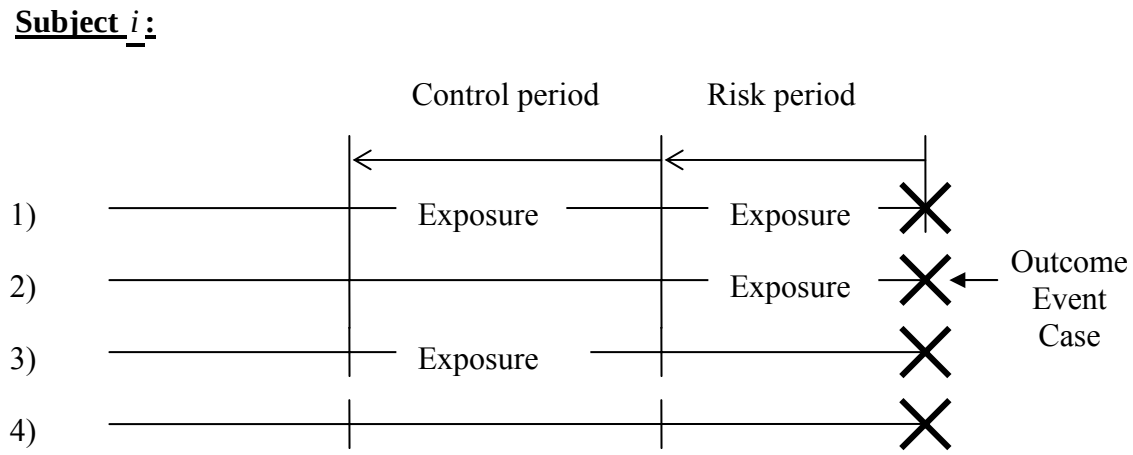


Figure 2.2.2: Retrospective assessment of four different potential exposure statuses for an outcome of interest

Subject *i* :

First scenario:

	Exposed	Not exposed
Outcome (event)	**C_1 (C_1=1)**	**C_0 (C_0=0)**
Person-moment contributed	**N_1**	**N_0**
Rate of event‡	**C_1/ N_1**	**C_0/ N_0**
Incidence rate ratio	**(C_1× N_0)/(C_0× N_1)=(1× N_0)/(0× N_1)=infinity**	

Second scenario:

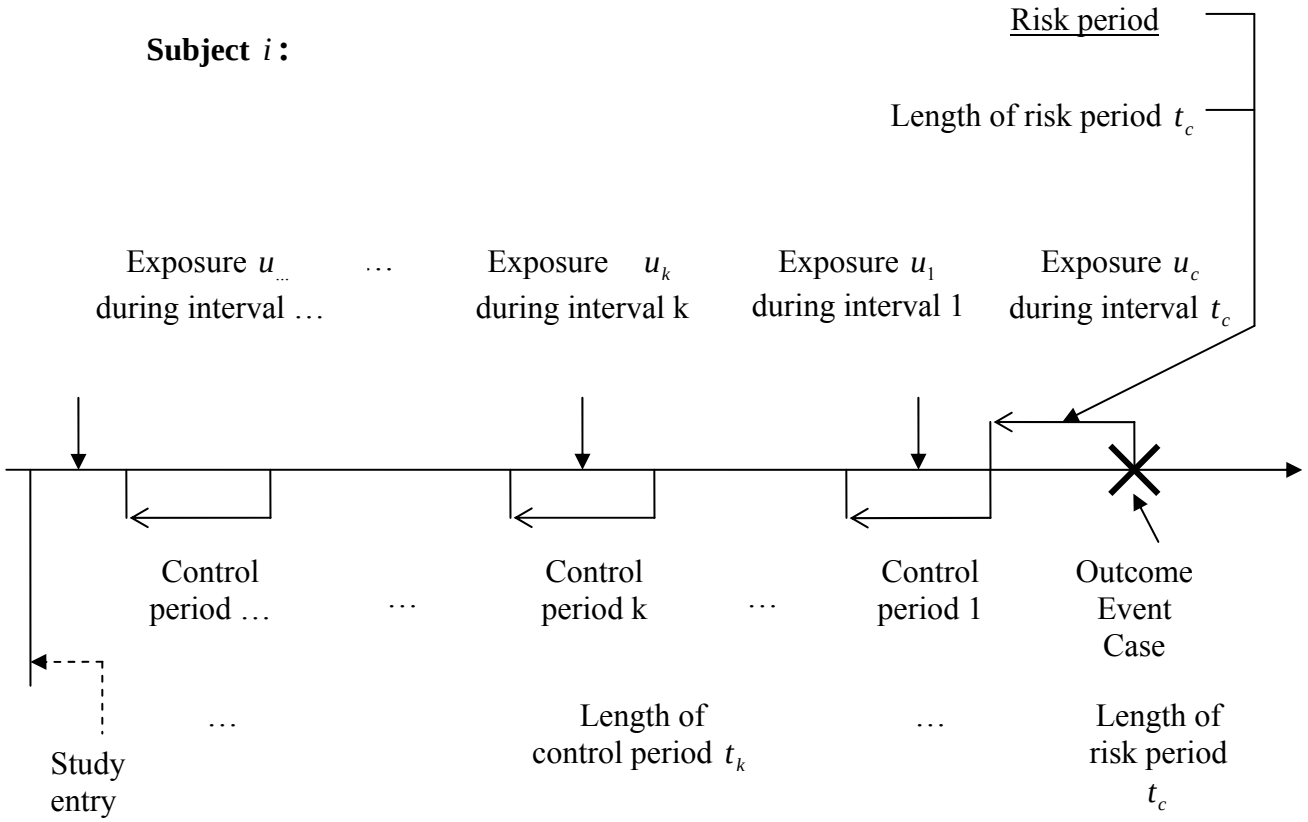
Outcome (event)	**C_1 (C_1=0)**	**C_0 (C_0=1)**
Person-moment contributed	**N_1**	**N_0**
Rate of event‡	**C_1/ N_1**	**C_0/ N_0**
Incidence rate ratio	**(C_1× N_0)/(C_0× N_1)=(0× N_0)/(1× N_1)=0**	

C_0: unexposed cases; C_1: exposed cases, where C_0+ C_1=1.
N_0: unexposed person-moments; N_1: exposed person-moments.
N: total person-moments (N= N_0+ N_1).
‡: rates of event are unstable, however, $\frac{\sum C_1 N_0 / N}{\sum C_0 N_1 / N}$ is stable.

Table 2.3.1: Hypothetically consider a case-crossover study as a highly stratified cohort study (Each subject consists of a stratum)

	Exposure^{+}	Exposure^{-}	
Diseased^{+}	**a**	**b**	n_1
Diseased^{-}	**c**	**d**	n_0
	m_1	m_0	

Figure 2.3.2: Conditional maximum likelihood for a single 2 × 2 table



Assumptions: 1) the hazard $\lambda_i(t)$ for subject i follows a proportional hazards model; 2) the baseline hazard $\lambda_{0i}(t)$ for subject i is constant; and, 3) exposure process $x(t)$ are stationary over time

Figure 2.3.3: Greendland's derivation of the likelihood function for the case-only studies including the case-crossover study design

CHAPTER 3

AVAILABLE STATISTICAL METHODS FOR ANALYZING REPEATED MEASUREMENTS IN THE SAME SUBJECT

Overview

In this chapter, we will review two available statistical methods, generalized estimating equations and conditional logistic regression for m:n matching, that are commonly used to analyze data with repeated measurements in the same person / unit.

GENERALIZED ESTIMATING EQUATION METHOD

In this section, we will first introduce the GEE method, as a tool, to analyze data when there are repeated outcome measurements in the same subject. In particular, we will explain its use of the quasi-likelihood, working correlation structure, and fitting algorithm, and the properties of the estimator. In the end of this section, we will then briefly discuss the alternating logistic regression (ALR), which could be used in two or more levels of clusters where the outcome variable within a cluster is binary.

3.1 Introduction

In epidemiological studies, we often encounter a "response" (an outcome) variable that has been repeatedly measured over time in the same individual. For example, in a study of the association between dietary fat intake and overweight among school children, body weight can be repeatedly measured during the study period. Such data are often called "longitudinal" data.

In general, the traditional statistical methods do not apply to longitudinal data because the repeated measurements in the same subject are correlated. Therefore, it requires special statistical methods to handle the correlation in the data analysis. As an example, the standard error of the estimated parameter will be underestimated if one treats the repeated measurements of the body weight of the same individual as if they were independent, when, in fact, they were positively correlated (Allison, 1999).

The GEE method, developed by Liang and Zeger (1986), can be used to handle the complexities of correlation among the repeated measurements in the same individual, particularly when the outcome variable is binary. Their method is based on the quasi-likelihood theory. Many attractive features (e.g., the working correlation structure and the properties of the estimator) of the GEE method will be discussed later.

In the GEE approach, only the likelihood for the marginal distributions and a working correlation matrix for the vector of repeated measurements from each subject are specified. The joint distribution of a subject's observations is not fully specified, and so we cannot specify the full likelihood. Liang and Zeger (1986) adopted a quasi-likelihood approach by specifying only the mean-covariance structure to develop the GEE statistical technique. Since the GEE method uses quasi-likelihood rather than maximum likelihood, we will briefly review the quasi-likelihood method below.

3.2 Quasi-likelihood

The following description of the quasi-likelihood is adapted from the book *generalized linear models* (McCullagh and Nelder, 1989).

Quasi-likelihood, developed by Wedderburn (1974) and McCullagh (1991), is a method for statistical inference when it is difficult to construct a full likelihood function. For simplicity, we are going to review the quasi-likelihood in the regression framework.

Let $Y = (Y_{1,},...,Y_n)'$ be a vector of independent random variables with mean vector $\mu = (\mu_1,...,\mu_n)'$. Let $\beta = (\beta_1,...\beta_p)'$ be a vector of unknown parameters with $p \le n$. Here, we suppose that for each observation $\mu_i\ (i = 1,...,n)$ is some known functions for a set of parameters $\beta_1,...,\beta_p$. For each observation, the quasi-likelihood function $Q(\mu_i; Y_i)$ was defined by the relation:

$$\frac{\partial Q(\mu_i; Y_i)}{\partial \mu_i} = \frac{Y_i - \mu_i}{\phi V(\mu_i)}$$

or equivalently: $$Q(\mu_i; Y_i) = \int^{\mu_i} \frac{Y_i - t}{\phi V(t)} dt + \text{function of } Y_i \qquad (3.2.1)$$

Based on the *generalized linear model* (*GLM*) theory, the variance of Y_i can be expressed as: $Var(Y_i) = \phi\, V(\mu_i)$, where $V(.)$ is a known function, ϕ is a unknown scale parameter. Thus,

$$Var(Y) = \phi V(\mu)$$

where $V(\mu)$ is a matrix (the variance function) with diagonal elements $dv(\mu_1),..., dv(\mu_n)$ and off-diagonal elements of zeroes. Note that ϕ is a dispersion parameter, it is assumed to be constant for all subjects and does not depend on β or $Var(Y_i)$.

Based on the equation 3.2.1, the quasi-likelihood function for U_i based on the data Y_i can be written:

$$Q(\mu_i; Y_i) = \int_{y_i}^{\mu_i} \frac{Y_i - t}{\phi\, V(t)} dt$$

Because the components of Y are independent, the quasi-likelihood for the full data is:

$$Q(\boldsymbol{\mu}, Y) = \sum_{i=1}^{n} Q(\mu_i; Y_i)$$

Quasi-likelihood and log likelihood function has many properties in common. In fact, quasi-likelihood is the log likelihood function if Y comes from a one parameter exponential family. For example, suppose that $Y \propto Poisson(\mu)$, then $V(\mu) = \mu$, $\phi = 1$, and the random variable is:

$$U = \frac{Y - \mu}{\mu}$$

The quasi-likelihood function is: $Q(\mu, y) = \int_{y}^{\mu} \frac{y - t}{t} dt$

$$= \left[y \log(t) - t \right]_{y}^{\mu}$$

$$= y \log(\mu) - \mu - y \log(y) + y \qquad (3.2.2)$$

As known, the log-likelihood for the $Poisson(\mu)$ distribution is:

$$y \log(\mu) - \mu - \log(y!) \qquad (3.2.3)$$

When comparing the equation (3.2.2) to (3.2.3), the only difference between these two equations is the terms which do not involve the parameter μ. If we regard the quasi-likelihood function as if it were a "true" log-likelihood, the estimate of β_j satisfies the equation (McCullagh and Nelder, 1989):

$$0 = \frac{\partial Q(\mu, y)}{\partial \beta_j} = \sum_{i=1}^{n} \frac{\partial Q(\mu_i; y_i)}{\partial \beta_j} = \sum_{i=1}^{n} \frac{\partial Q(\mu_i; y_i)}{\partial \mu_i} \left(\frac{\partial \mu_i}{\partial \beta_j} \right) = \sum_{i=1}^{n} \frac{y_i - \mu_i}{\phi\, V(\mu_i)} \left(\frac{\partial \mu_i}{\partial \beta_j} \right)$$

Where:

$$Y_{(n\times 1)} = (y_1,...,y_n)' ; \qquad U_{(n\times 1)} = (\mu_1,...,\mu_n)' ;$$

$$V_{(n\times n)} = \begin{bmatrix} dv(\mu_1) & 0 & . & 0 & 0 \\ 0 & dv(\mu_2) & . & . & . \\ . & . & . & . & . \\ . & . & . & dv(\mu_{n-1}) & . \\ 0 & 0 & . & . & dv(\mu_n) \end{bmatrix}; \quad D_{(n\times p)} = \left(\frac{\partial \underline{\mu}}{\partial \underline{\beta}}\right)$$

The quasi-likelihood estimating equation is (McCullagh and Nelder):

$$W(\underline{\beta}) = D'V^{-1}(\underline{Y} - \underline{\mu})/\phi = \underline{0} \qquad (3.2.4)$$

where $W(\underline{\beta})$ is called the quasi-score function.

In summary, compared with the *GLM* (McCullagh and Nelder, 1989), quasi-likelihood is a methodology for regression that requires fewer assumptions about the distribution of the response variable. What is required in quasi-likelihood method is to specify the relationship between the mean and the variance.

3.3 Generalized estimating equations

By adopting a quasi-likelihood approach and specifying only the mean-covariance structure, Liang and Zeger (1986) developed the GEE method to analyze data with repeated measurements in the same subject. In the following, we will give a brief overview of the GEE method.

Let Y_{ij}, $j = 1,...,n_i, i = 1,...,K$ represent the $j\,th$ measurement on the $i\,th$ subject. Here, many repeated measurements on Y in the same individual are considered as a "cluster". For correlated data, besides the variance function, the covariance structure

must also be modelled. Let the vector of measurements on the ith subject be: $Y_i = \left[Y_{i1}, Y_{i2,}..., Y_{in_i}\right]'$ with the corresponding vector of means $\boldsymbol{\mu}_i = \left[\mu_{i1}, \mu_{i2},..., \mu_{in_i}\right]'$ and let V_i be an estimator of the covariance matrix of Y_i. Here, assume that the repeated measurements in the same individual are correlated, but that the repeated measurements for different individuals are mutually independent. Therefore, the covariance matrix of Y_i. has the form $\sigma^2 V_i$, where:

$$V_i = \left\{diag\left[V(\mu_{i1}),..., V(\mu_{in_i})\right]\right\}^{\frac{1}{2}} \times R_i \times \left\{diag\left[V(\mu_{i1}),..., V(\mu_{in_i})\right]\right\}^{\frac{1}{2}} \qquad (3.3.1)$$

and R_i is a correlation matrix among the repeated observations measured at different time points within the same person. The generalized estimating equation for estimating β is an extension from the independent case to correlated data and is given by:

$$\sum_{i=1}^{K} \frac{\partial \underline{\mu_i}'}{\partial \underline{\beta}} V_i^{-1}\left(\underline{Y_i} - \underline{\mu_i}\right) = \underline{0} \qquad (3.3.2)$$

The GEEs have the same form as the quasi-score function, except that the matrix V now contains nonzero off diagonal terms. The solution to the GEEs (3.3.2) provides a consistent estimate of $\underline{\beta}$ that is asymptotically multivariate normal with covariance matrix (Liang and Zeger):

$$\sigma^2\left[D'V^{-1}D\right]^{-1} = \sigma^2\left\{\sum_{i=1}^{K}\left[D_i'V_i^{-1}D_i\right]\right\}^{-1}. \qquad (3.3.3)$$

In order to solve the GEEs, the correlation terms in each R_i must be known in advance. Unfortunately, the true correlation structure is almost always unknown. Liang and Zeger used a "working" estimate of the correlation structure to approximate equation (3.3.1). Thus, the estimating equations are given by:

$$\sum_{i=1}^{K} \frac{\partial \underline{\mu}_i^{'}}{\partial \underline{\beta}} \hat{V}_i^{-1} \left(\underline{Y}_i - \underline{\mu}_i \right) = \underline{0} \qquad (3.3.4)$$

where $\hat{V}_i$ is an estimator based on the pre-assumed working correlation structure $\hat{R}_i$. The solution to the GEEs (3.3.4) gives a consistent estimate of $\underline{\beta}$ that is asymptotically multivariate normal with the covariance matrix given by (Liang and Zeger):

$$\operatorname{cov}\left(\hat{\underline{\beta}}\right) = \sigma^2 \left[\sum_{i=1}^{K} D_i^{'} \hat{V}_i^{-1} D_i \right]^{-1} \left[\sum_{i=1}^{K} D_i^{'} \hat{V}_i^{-1} V_i \hat{V}_i^{-1} D_i \right] \left[\sum_{i=1}^{K} D_i^{-1} \hat{V}_i^{-1} D_i \right]^{-1} \qquad (3.3.5)$$

If $\hat{V}_i = V_i$, which means the assumed working correlation structure is exactly identical to the true correlation structure, then (3.3.5) reduces to (3.3.3). The most commonly used working correlation structures will be discussed in the "working correlation structures" section.

In the GEE approach, similar to the *GLM* (McCullagh and Nelder), we can have a model link function based on the nature of the outcome variables, i.e., the link can be either logistic, log-linear or other. By specifying a link function for the marginal expectation of the response variable and assuming the variance is a known function of the mean, the GEE method can provide consistent estimation of the regression coefficients and the corresponding variances (Liang and Zeger). The parameters of interest are estimated by iteratively solving a series of quasi-likelihood score equations.

3.4 Working correlation structures

The following is a brief review of two commonly used working correlation structures in the GEE method. The others (e.g., *unstructured*, *auto-regression* and *stationary m-dependent*) can be found in Liang and Zeger's article (Liang and Zeger, 1986).

Let $R_i(\alpha)$ be a $n_i \times n_i$ "working" correlation matrix that is fully specified by the vector of parameters α. The covariance matrix of Y_i is modelled as:

$$V_i = \Phi A^{\frac{1}{2}} R_i(\alpha) A^{\frac{1}{2}}$$

where A is an $n_i \times n_i$ diagonal matrix with $v(u_{ij})$ as the jth diagonal element. Here, $v(u_{ij})$ is the variance evaluated at μ_{ij}. If $R_i(\alpha)$ is the true correlation matrix of Y_i, then V_i is the true covariance matrix of Y_i.

The following two working correlation structures are widely used in the GEE framework (Liang and Zeger).

1) ***Independent:*** Let $R_i(\alpha) = I$, the identity matrix. That is:

$$\begin{array}{l} Corr(Y_{ij,}\, Y_{ik}) = 1 \;\; if \;\; j = k \\ or \quad Corr(Y_{ij,}\, Y_{ik}) = 0 \;\; if \;\; j \neq k \end{array};$$

2) ***Exchangeable:*** that is:

$$\begin{array}{l} Corr(Y_{ij,}\, Y_{ik}) = 1 \;\; if \;\; j = k \\ or \quad Corr(Y_{ij,}\, Y_{ik}) = \alpha \;\; if \;\; j \neq k \end{array};$$

In this case, only 1 correlation α needs to be estimated;

Wang et al. (2003) evaluated the performance of the working correlation structure and reported that the asymptotic relative efficiency of the estimate depends on four main features of the analysis of a correlated data set: 1) how close the working correlation structure is to the underlying correlation structure existing in the data set; 2) the decision in choosing which type of working correlation structure (it is likely that the decision will be affected by how well one understands the data set); 3) the magnitude of the underlying

correlation and the correlation structure within an individual; and, 4) the number of repeated measurements per subject (cluster).

3.5 Fitting algorithm

The following is a brief review of an algorithm for fitting any specific model using the GEE method:

1) Compute an initial estimate of β (ignoring the correlation among the repeated measurements within a cluster, e.g., the maximum likelihood estimate of β from the GLM or by the Least Squares method);

2) Compute an estimate of the covariance $V_i = \Phi A^{\frac{1}{2}} \hat{R}_i(\alpha) A^{\frac{1}{2}}$ based on the assumed working correlation $\hat{R}_i(\alpha)$; and,

3) Update β: $\hat{\beta}^{(r+1)} = \hat{\beta}^{(r)} - \left[\sum_{i=1}^{K} \frac{\partial u_i'}{\partial \beta} V_i^{-1} \frac{\partial u_i}{\partial \beta}\right]^{-1} \left[\sum_{i=1}^{K} \frac{\partial u_i'}{\partial \beta} V_i^{-1} (Y_i - u_i)\right]$ until the convergence condition is satisfied.

3.6 Properties of the estimated variance

The GEE method in terms of the estimated parameters has some desirable statistical properties that make it an appealing method for handling correlated data. The estimated regression parameters from the GEE method are consistent and normally distributed. That is, $\sqrt{K}\left(\hat{\beta} - \beta\right) \rightarrow N(0, M(\Phi))$, if the mean model is correct even if V_i is

incorrectly specified (Liang and Zeger, 1986), where $M(\Phi) = I_0^{-1} I_1 I_0^{-1}$,

$I_0 = \sum_{i=1}^{K} \frac{\partial u_i^{'}}{\partial \beta} V_i^{-1} \frac{\partial u_i}{\partial \beta}$ and $I_1 = \sum_{i=1}^{K} \frac{\partial u_i^{'}}{\partial \beta} V_i^{-1} Cov(Y_i) V_i^{-1} \frac{\partial u_i}{\partial \beta}$.

The model-based estimator of $Cov(\hat{\beta})$ is given by $Cov_M(\hat{\beta}) = I_0^{-1}$. This is the inverse of the Fisher information matrix that is often used in the *GLM* as an estimator of the covariance estimate of the maximum likelihood estimator of β. The model-based estimator is a consistent and robust estimator (of the covariance matrix of $\hat{\beta}$) only if the mean model and the working correlation matrix are correctly specified. Liang and Zeger proposed another estimator, $M = I_0^{-1} I_1 I_0^{-1}$, called an empirical estimator of the covariance matrix of $\hat{\beta}$, which has the property of being a consistent estimator of the covariance matrix of $\hat{\beta}$, even if the working correlation matrix is incorrectly specified, for instance, if $Cov(Y_i) \neq V_i$.

An important issue one needs to realize is that if the mean model and the working correlation structure are correctly specified, the model-based estimator of the covariance matrix of $\hat{\beta}$ is more efficient than the empirical one; otherwise, the empirical estimator of the covariance matrix of $\hat{\beta}$ is likely to be more trustworthy. Agreement between the empirical and model-based variances indicates that the assumed working correlation structure is reasonable (Hanley et al., 2003). The dispersion parameter Φ is estimated by the following equation: $\hat{\Phi} = \frac{1}{N-p} \sum_{i=1}^{K} \sum_{j=1}^{n_i} e_{ij}^2$, where $N = \sum_{i=1}^{K} n_i$ is the total number of

measurements, p is the number of regression parameters that need to be estimated in the model and e_{ij} is the standardized Pearson residual (defined as $e_{ij} = \frac{y_{ij} - \hat{\mu}_{ij}}{\sqrt{V(\hat{\mu}_{ij})}}$).

3.7 Two or more levels of clusters

In reality, we often encounter a situation where two or more levels of clusters are present in the longitudinal studies. For example, in a study of the association between medication use and school performance among the students, the schools were sampled as the first level of cluster and the classes within the selected schools were selected as the second level of clusters. The data structure *(two levels of clusters*) in this case is different from the one we discussed in the GEE section, where the repeated outcome events are measured over time in the same subject.

In the following, we will briefly review the alternating logistic regression (ALR), which can be used to analyze longitudinal studies via the odds ratio as the measure of associations instead of correlations between the repeated measurements, particularly when the outcome variable is binary.

As stated previously, the GEE method can be used to handle the complexities of longitudinal studies, particularly when the outcome events are binary variables. If the outcome variable is a continuous variable and if its values, conditional on the random effects and on fixed covariates, can be safely assumed to have a Gaussian distribution, a class of different linear models (e.g., hierarchical linear models) can be used to analyze this type of data. On the other hand, if the outcome of interest is a categorical variable,

there are only a number of limited statistical methods that can be used to analyze this type of data.

The alternating logistic regression (ALR), developed by Carey et al. (1993), could be used in longitudinal studies where the outcome events within a cluster are binary. It models the association between pairs of outcome events with log odds ratios. As a tool, the ALR provides us an opportunity to investigate two levels of clustering by defining subgroups of interest within clusters. As an example, if the clusters are schools and subclusters are classes within schools, then students within the same class have one log odds ratio parameter while students from different classes have another parameter. The subcluster effect can be estimated by directly modeling the association between the log odds ratios and the explanatory variables defined at the subcluster levels. Upon convergence, the ALR produces estimates of the regression parameters for the log odds ratios, standard errors as well as the covariances.

3.8 Final remarks

In summary, the GEE method seems to be a good approach to carry out the data analysis based on the structure of our case-crossover data, where repeated measurements in the same subject are aggregated at the *subject-level* (detail will be introduced in Chapter 4, Figure 4.2.2). In particular, an *independent* and an *exchangeable* working correlation structures will be implemented while applying the GEE method. A hand calculation illustrating how to apply the GEE method to the '*subject-level data analysis*' is given in Appendix II, where two subjects (clusters) with 4 and 6 repeated events are investigated.

Now, we turn to the other possibility, conditional logistic regression, for analyzing the repeated measurements in the same subject.

CONDITIONAL LOGISTIC REGRESSION (CLR) METHOD

Overview

In this section, we will first discuss the CLR method when the matching ratio is extended from 1:1 (as discussed in Chapter 2) to m:n per matched set. Next, we will use a hypothetical data to illustrate how to construct the likelihood for a variable number of cases and controls in a matched set.

Conditional logistic regression for m:n [case(s): control(s) ratio] matching

3.9 Introduction

Logistic regression analysis is often used to investigate the relationship between discrete response variables (e.g., binary, ordinal or nominal) and a set of explanatory variables. In a matched study, it is generally suggested that data analysis must account for the matching variable(s) that was (were) used for the selection of the controls. The probability of the response variable Y (=1) is conditional on the explanatory variable X and the matched set.

As described in Chapter 2, CLR is commonly used to investigate the association between an outcome and a set of explanatory variables in matched studies. For example, in a matched case-control study, if there is only one case and one control, then, the

matching is one to one (case : control ratio). The m:n matching refers to the situation in which there is a varying number of cases and controls in the matched set.

In the next section, we will use a hypothetical data to illustrate how to construct the likelihood for m:n matching ratio in a matched set.

3.10 Likelihood for m:n matching ratio in a matched set

3.10 Data

In order to illustrate the likelihood for the CLR with m:n matching ratio in a matched set, we begin with an excerpt of some records from the data shown in Figure 4.2.3. For simplification, we use the first 4 observations from Stratum 1 and 3 observations from Stratum 2. The data are listed as follows:

Observation	**Stratum (Risk set)**	outcome	exposure
1	1	1	x_1
2	1	0	x_2
3	1	1	x_3
4	1	0	x_4
5	2	1	x_5
6	2	0	x_6
7	2	1	x_7

Obviously, there are two events in stratum 1 (observations 1 and 3) and two events in stratum 2 (observations 5 and 7). Since there are 2 distinct matched sets in this dataset, the likelihood function of β based on the CLR model will take the following form:

$$L(\beta) = L_1(\beta) \times L_2(\beta)$$

where $L_j(\beta)$ ($j = 1, 2$) is the component in the full likelihood corresponding to the j^{th} stratum. The probability, $L_1(\beta)$, can be interpreted as: $L_1(\beta) = P$ [events occurred to observations 1 and 3 | there are 2 events out of 4 observations in stratum 1]. Since the rationale of constructing $L_1(\beta)$ and $L_2(\beta)$ is the same, we will focus on producing $L_1(\beta)$.

Given that 2 events occurred in stratum 1, the probability that they occurred to these particular two observations (1 and 3) rather than some different set of 2 events from the 4 observations at risk is ψ_1 and the likelihood for the stratum 1 is $\psi_1 / (\psi_1 + \psi_2 + ... + \psi_6)$, where the subscript 6 ($= \frac{4!}{2! \times 2!}$) indicates the total different ways of selecting those 2 events from a set of 4 observations. Here, ψ is defined as the product of the odds for all the events in stratum 1, i.e., $\psi_1 = \prod_{i=1}^{2} (P_{i1} / (1 - P_{i1}))$. Thus, the conditional likelihood for the stratum 1 is:

$$L_1(\beta) = \frac{e^{(x_1 + x_3)\beta}}{\sum all\ 6\ possible\ combinations\ of\ \ pairs\ of\ e^{x\beta}}.$$

Likewise, for stratum 2, we can obtain the conditional likelihood as that in stratum 1.

Once the full likelihood $L(\beta)$ is constructed, we can maximize it with respect to β just like an ordinary likelihood function. As usual, it is convenient to maximize the logarithm of the full likelihood.

Most statistical softwares have their special ways to fit the CLR model. In SAS 8.2, it was suggested to use "Proc Phreg" procedure with "Discrete" method in the model statement to fit the CLR model, because, in this case, the likelihood for the CLR with m

cases : n controls per matched set is the same as the partial likelihood for fitting Cox's proportional hazards model (Cox, 1972). A new procedure for fitting the CLR model has been released in SAS 9.1.

This procedure is computationally quite intensive. Substantial numbers of terms could be added into the denominator if large data sets with many events happened at the same time. A recursive algorithm, however, makes it practical even with large numbers of ties (Gail et al., 1977).

3.11 Final remarks

In summary, the CLR method with m:n matching ratio can be used to analyze data with a variable number of cases and controls per matched set. This method seems to fit the structure of our case-crossover data, where the repeated measurements in the same subject are collapsed at the *subject-level* (detail will be introduced in Chapter 4). However, we should be aware that, when applying the CLR method to a case-crossover study, the cases and the matched controls are the different periods for the same study subject rather than different subjects as they commonly represent in a traditional matched case-control study.

CHAPTER 4

METHODS TO EVALUATE THE PROPOSED ESTIMATORS

Overview

In this chapter, we will first introduce an excerpt of a real data set used in a study of the association between benzodiazepine use and MVCs. Second, we will introduce eight estimators based on a combination of three different choices for the unit of analysis (e.g., the overall crude, the subject-level, and the event-level) and three different choices for the statistical methods (the M-H method, the CLR method, and the GEE method). We will then illustrate the three choices of the unit of data analysis via the real data, and, the three statistical methods which can be applied with the chosen unit of data analysis. Finally, we will describe a simulation study we carried out to evaluate the bias, the variance, and the mean squared error of these eight estimators.

4.1 Real data

In order to illustrate the three different units of data analyses and these eight estimators, we begin with an excerpt of some records from a study of MVCs. The data, shown in Figure 4.2.1, were obtained from the SAAQ and RAMQ databases. This figure shows information on two study subjects with multiple MVCs. Individual one in Figure 4.2.1 (**id= '4699'**, who filled a prescription for benzodiazepine on 21 January, 1984) had a first Motor Vehicle Crash on 27 January, 1984; the same individual filled another benzodiazepine on 17 January, 1986 and had the second MVC on 29 January, 1986 and so on. In total, nine repeated MVCs were identified for this individual. Likewise, for individual two (id **= '9364'**), three repeated MVCs were observed in the study period.

In the next section, we illustrate three different units of data analyses using the data and introduce the eight estimators based on the combinations of three different units of data analyses and three different statistical methods.

4.2 Proposed estimators

4.2.1 Choice of unit of data analysis

We will use the data in Figure 4.2.1 to illustrate two different levels of clusters (the 'event-level cluster' and the 'subject-level cluster') and thus three different ways to regroup or aggregate case-crossover data for statistical analysis.

There are two levels of clusters in such a case-crossover data set: the event-level cluster and the subject-level cluster (Figure 4.2.2). For the event-level cluster (labeled as **(1)**), each case and its pair-matched "control" (the matched control period) are formed as the first level of clustering, i.e., each event within each study subject is regarded as a separate entity. For the subject-level cluster (**(2)**), the repeated events are aggregated within the subject level, and the subject per se is treated as the second level of clustering, i.e., there is only one data summary per subject. If the data analysis is implemented at the event-level, we call it the 'event-level data analysis'. Likewise, if the data analysis is conducted at the subject-level, we call it the 'subject-level data analysis'. Obviously, the event-level cluster is nested within the subject-level cluster.

There are three different ways to group or aggregate such data for statistical analyses: First, the researcher can ignore the event-level clusters and the subject-level clusters (as shown in Figure 4.2.2 across subject i and subject i+1), and directly classify all the cases and all the "controls" into a single 2×2 table based on their exposure status

with cell frequencies a, b, c and d (**(3)** in Figure 4.2.2). We will call this type of analysis, in which all matching is ignored, the '*overall crude 2×2 table data analysis*' (**(3)**).

Second, one can conduct the data analysis at the *subject-level* instead of simply ignoring it as was done in the 'overall crude 2×2 table data analysis'. We call this type of analysis the '*subject-level data analysis*' or '*time-unmatched data analysis*' because the time sequence of the events within an individual is not taken into consideration. In the 'subject-level data analysis', the repeated events are aggregated at the individual level rather than aggregated across all the subjects, i.e., there is one 2×2 frequency table per subject. An advantage of data analysis at this subject level is that it will help control the confounding effect from fixed-in-time inter-personal factors (e.g., genetic factors) which do not vary during the study period. For example, when we evaluate the relationship between the use of a specific medication and the subsequent repeated occurrence of a particular outcome, if the data analysis is conducted at the subject-level, the risk profile of an individual prior to taking the very first medication will be controlled as a baseline factor.

Third, we can conduct the data analysis at the *event-level* or at the *pair-matched level*. We call this type of analysis the '*event-level data analysis*' or '*time-matched data analysis*'. Unlike the analysis which is conducted at the subject-level, the event-level analysis also takes time into consideration by ordering the times of the individual events and by keeping the matched "control" (control period), in the risk set linked to its corresponding case (risk period), i.e., it deals with intrapersonal confounding.

In the 'event-level data analysis', we need an identification number to indicate each individual, and a sub-identification number to identify which event generated the pair-matched case and control "risk set". Figure 4.2.3 uses a theoretical example to illustrate how to indicate the pair-matched case and control in the event-level data analysis. As shown in Figure 4.2.3, patients 1 and 2 have unique identification numbers (ID) 1 or 2. Patient 1 has 5 repeated hospitalizations for COPD, and patient 2 has 3 repeated hospitalizations; the corresponding sub-IDs for patient 1 will be 1.01, 1.02, 1.03, 1.04, and 1.05 at the 'event-level data analysis'. Likewise, the corresponding sub-IDs for patient 2 will be 2.01, 2.02, and 2.03. Figure 4.2.4 shows the two pair-matched individuals and their corresponding cluster levels with the Motor Vehicle Crash dataset (Figure 4.2.1).

Figure 4.2.5 displays a series of 2×2 tables according to the three different levels of data analyses, i.e., the overall crude 2×2 table data analysis, the subject-level data analysis, and the event-level data analysis using raw data shown in Figure 4.2.1.

As shown in Figure 4.2.6 we can apply the M-H estimator to the three different units of data analyses to produce three different summary estimators. That is, we can calculate an odds ratio from a single 2×2 table at the 'overall crude 2×2 table data analysis', or from the two 2×2 tables in the 'subject-level data analysis', or from the nine 'event-level data analysis' tables.

So far, we have applied the same *method* (the M-H method) no matter which level of the data analysis is used; however, other available statistical methods can be used to analyze such data.

4.2.2 All possible estimators (combinations of unit and method of analysis)

In Chapter 3, we described other two statistical methods, conditional logistic regression and generalized estimating equations, which can also be used to analyze a case-crossover dataset with multiple events per person. The different combinations of the three units of data analyses and three statistical methods result in eight estimators; these are shown in the following diagram (Table 4.2.2.D):

Unit of Data Analysis	Statistical Method			
	M-H[¶]	***CLR***[§]	***GEE***[&]	
			Independent W.C.S.[#]	**Exchangeable W.C.S.**
Overall crude	√	–[*]	–	–
Subject-level	√	√	√	√
Event-level	√	√	√	–

¶: M-H: Mantel Haenszel method. §: Conditional Logistic Regression. &: Generalized Estimating Equations. *: Not studied. #: Independent W.C.S.: independent **w**orking **c**orrelation **s**tructure.

Table 4.2.2.D: Eight proposed estimators based on the combinations of three different units of data analyses and three different statistical methods

Before we apply these eight estimators to a real case-crossover dataset with repeated events, we will first conduct a simulation study to evaluate and compare their performance in situations where we know the true value of the parameter being estimated. The results from this simulation study will guide users on which estimator should be used to obtain the least biased and most precise estimate of the odds ratio of interest.

4.3 Methods for simulation study

Overview

We will simulate datasets with repeated exposures and repeated outcome events. In the following, we will explicitly describe the assumptions, design parameters, structure of the simulation study and the simulation steps used to generate the repeated exposures and the outcomes.

4.3.1 Assumptions for the simulation study

We will subdivide the study population into four subpopulations according to (a) the subject's propensity of being exposed and (b) the subject's propensity of developing the outcome of interest, i.e., into the four combinations of "more or less likely to be exposed", and "more or less likely to develop the outcome of interest". The rationale for generating these four subpopulations is based on the following:

1) Part of the population has more frequent exposures than others. For example, some people take a certain medication (e.g., Benzodiazepine) more frequently than others.

2) Part of the population has a higher tendency to develop an adverse event (e.g., Motor vehicle crash) than others, even if not taking the medication.

3) Part of the population is less likely to develop adverse events even in the presence of exposure.

4) A person taking a medication may have an increased risk of developing an adverse event (Hazard Ratio > 1) in the subsequent risk period (such as the upcoming 2 days).

In addition, the following two assumptions need to be made for the validity of the simulation study:

1. Separate subpopulations have different propensities of exposure (I_e) and propensities of outcome (I_o). The intensity of exposure (I_e) determines the daily probability (P) of being exposed. Conditional on the daily probability (P), daily exposure E is Bernoulli (P). Conditional on E, whether an individual develops the outcome of interest will follow another Bernoulli distribution. Table 4.3.1.D describes four subpopulations with different propensities of exposure and different propensities of outcome.

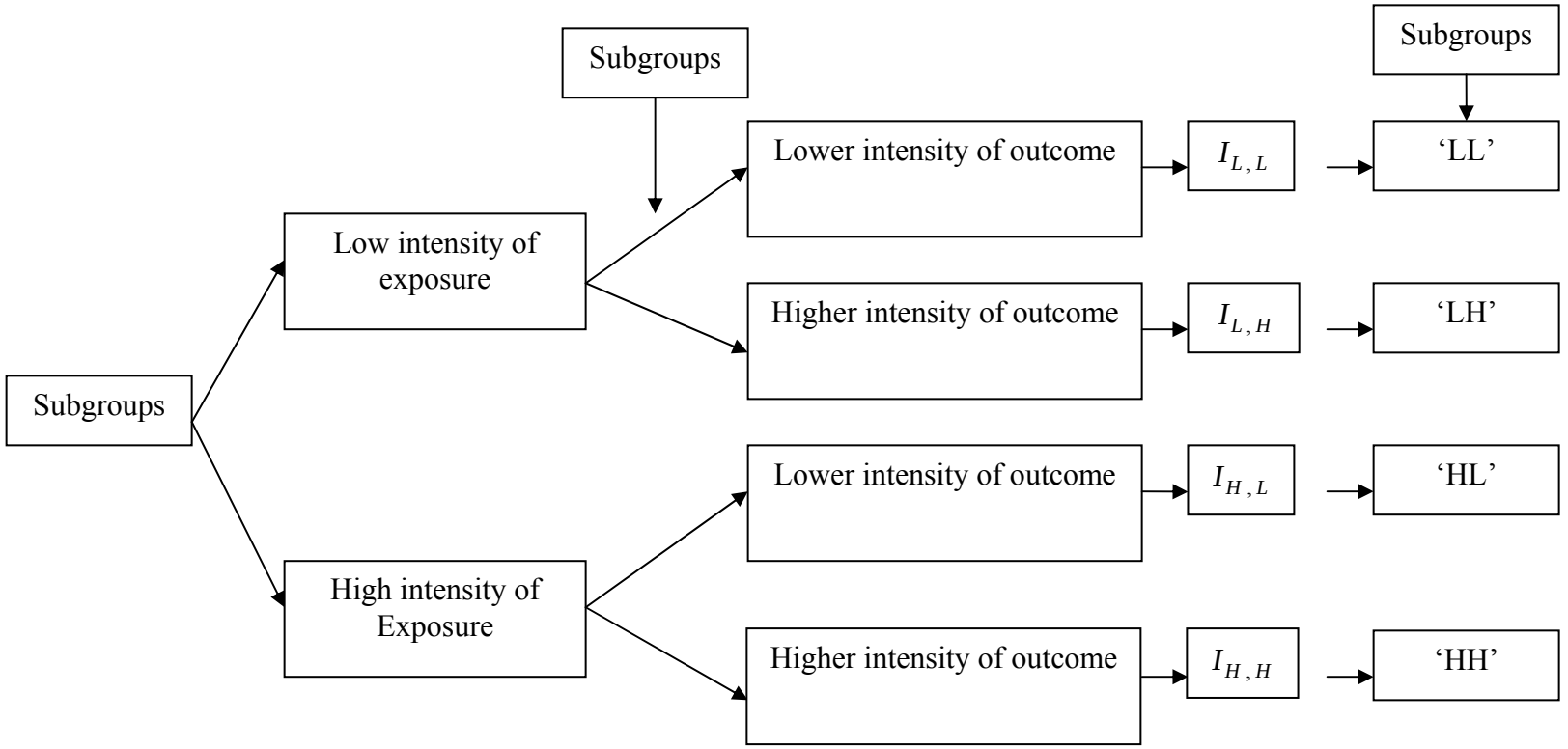


Table 4.3.1.D: Four subpopulations based on subjects' different propensities of exposure and different propensities of outcome

2. We assume that the duration of each risk period (i.e., the duration when the hazard is elevated) following exposure is reasonably long in relation to the "effect time period" of exposure of interest. Here, we assume the length of the risk period is 12 days following an exposure (Figure 4.3.1.1). In addition, we also assume that there will be no exposure to the risk factor of interest within 30 days following the occurrence of an outcome of interest.

4.3.2 Design parameters and confounding

For simplicity, we will only consider 2 levels for the exposure intensity and 2 levels for the outcome intensity. Table 4.3.2.1 shows the frequency distribution of the exposure and the outcome propensities of the study participants.

4.3.2.1 Design parameters

Table 4.3.2.2 lists/describes the eight design factors considered based on the objectives of the simulation study. The values for each of the design parameters were assigned as follows:

1) The entire study period was 3,650 days (10 years).
2) The elevated risk lasted for 12 days following the exposure.
3) The sample size of study subject (n) in each simulated dataset was assigned a value of 30 (small), 50(medium) and 100(large).
4) The hazard ratio was assigned as 1, 2, 5 and 10.

4.3.2.2 Correlation

To generate a correlation between the propensity of exposure and the propensity of the outcome of interest, we assume that some individuals in the population who have higher propensities of becoming exposed also have higher probabilities of developing the outcome of interest and vice versa. As shown in (5)-(8) below, we can increase/decrease the amount of correlation by altering the percentages in the four cells in Table 4.3.2.1. The more the populations are concentrated in the 'a' and 'd' cells, the greater the potential for correlation.

5) The correlation coefficient was set to 0, 0.5 and 0.9.
6) "Lower propensity of exposure, lower propensity of outcome" individuals, had, on average, 2 instances of exposure per year and in the absence of exposure developed the outcome of interest on average twice per year.
7) "Moderate propensity of exposure, moderate propensity of outcome" individuals, had, on average, 10 instances of exposure per year and in the absence of exposure developed the outcome of interest on average 10 times per year.
8) "Highest propensity of exposure, highest propensity of outcome" individuals, had, on average, 20 instances of exposure per year and in the absence of exposure developed the outcome of interest on average 20 times per year.

4.3.3 Structure of the simulation

In all, 108 different configurations are formed; for each configuration, 500 data sets are randomly generated according to a series of random seeds. Each of the eight estimators was applied to each dataset. The mean of the 500 estimates yielded by a given estimator was used to assess bias, and the variance of the 500 estimates was used to evaluate the

precision (or real sampling variance). Those various configurations are shown in Figure 4.3.3.1.

4.3.4 Simulation Steps

The steps used in this simulation study are detailed as follows:

1) Set up the initial values of the propensities of exposure and outcome for the four types of people, true hazard ratio, random starting values, and the number of subjects of each type that need to be generated.

The following procedures were used to assign subjects into the 4 subtypes based on their propensities for both the exposure and the outcome of interest (see SAS programs in Appendix III):

2) For each person:

Generate the person's (exposure propensity, outcome propensity) combination as a multinomial random variable with probabilities 15%, 25%, 5% and 55%. Detailed steps are presented in Appendix III.

To generate the exposures and the outcomes of interest over the 3650 days for a specific subject, we used the following procedures (conditional on the realization for the exposure propensity, outcome propensity category):

3) Set up the initial values for the following variables in day 0: two count variables (counting the number of repeated exposures and outcomes); a clock, which is used to count how many times the exposure and outcome occur; a daily probability of becoming exposed and a daily probability of developing the outcome when unexposed. The counting process goes from day 1 to the end of the study (3650 days).

4) For a given day for one person:

a) Determine whether the subject is currently exposed;
b) If the subject is newly exposed, then use the hazard ratio to change risk of outcome from that of an unexposed day;
c) If the subject is not exposed or exposed more than 12 days ago, then change the risk back to where the individual is not exposed;
d) Use a Bernoulli random variable with appropriate probability to determine whether the outcome of interest occurred.

5) Use the same procedure to generate the exposure for the next day before repeating for next day.
6) Repeat for next subject.

Figure 4.3.4.1 shows an example of the realizations for 4 simulated subjects with different (propensity of exposure, propensity of outcome of interest) combinations.

4.4 Procedures for constructing a pair-matched case-crossover dataset

The exact dates of exposure and outcome were retained from the simulated data. In order to construct each risk period and the corresponding matched "control" (matched control period, 1:1 ratio) for an individual, we did the following:

First, we created an 'exposure' data set consisting of the date of each of the exposures and the unique subject's identification number. We then transposed the data set from a vertical to a horizontal format in order to manipulate it in the next steps.

Second, we created an 'outcome' data set consisting of the outcome dates, in the same way as was done for the exposure dataset.

Finally, we merged the two datasets in such a way that the dates of exposure were systematically matched with all of the dates of events (Figure 4.4.1). The dates of the exposures and outcomes were compared in order to guarantee that exposure always occurred before the corresponding outcome.

We used the last exposure that occurred immediately preceding the event to decide the case's exposure status, on the premise that the most recent exposure is most relevant to the closest event. The same procedure for defining exposure status was also applied to the corresponding "controls" (control periods).

The ending dates of the control periods were defined by using the event dates minus the length of the risk period in order to keep the same length of period for both the risk period and the control period (Figure 4.4.1). We made separate records for the case period and control periods. Each record contained a binary variable indicating the case's exposure status. If the latest exposure occurred in the risk period, then this case (risk period) was exposed, otherwise, the case (risk period) was not exposed (Figure 4.4.1).

All the cases were included in the data analysis. However, a number of the "controls" (control periods) had to be omitted, since they had missing exposure information, because of how the ending point of the control period was defined. For example, the beginning of the control period may have antedated the beginning of the study (Figure 4.4.1). There are two possible solutions which can be used to handle this problem: one can simply delete the "controls" and the corresponding cases, or one can keep the matched pairs in the data analysis by classifying the "controls" into the unexposed category.

At this point a pair-matched case control dataset was created (Figure 4.4.2) and the dataset was analyzed with each of the eight different estimators.

4.5 Quantifying the performance of each estimator

In the following, we will introduce three different criteria (the Bias, the Variance and the MSE) which will be used to evaluate the performance of each of the eight estimators. In the 'Bias' section, we will provide the definition and the formula for the bias calculation. In the 'Variance' section, we will also provide the formula for the variance calculation and discuss the reliability of the empirical variance of the estimated odds ratio. Finally, we will give the definition of the MSE and the formula for the calculation.

4.5 1. Bias of Estimator

In our simulation study, the bias of the empirical odds ratio is estimated as the mean of 500 estimates of the common odds ratio minus the true hazard ratio, i.e.,

$Bias = \left(\overline{\hat{HR}} - HR \right)$, and expressed as a percentage of the true HR.

4.5.2 Variance of Estimator

The empirical variance of the estimated *log* odds ratio is obtained as:

$\frac{1}{499} \times \sum_{i=1}^{500} \left(\ln \hat{HR}_i - \overline{\ln \hat{HR}_i} \right)^2$. Here, we use the *log* transformation in the calculation of the empirical variance to avoid the skewness of the estimated odds ratio. Moreover, we compare the magnitude of the empirical variance of the estimated odds ratio with the mean of the model-based variances from those 500 simulated datasets. If the value of the empirical variance is substantially different from the model-based variance, then the accuracy of the model-based variance is questionable.

We based our choice of the number of datasets (500) on the desired reliability of the estimated coefficient of variation (CV), we calculated the C.V. as follows:

Assume that $Z_1, \ldots, Z_n$ are n i.i.d. estimates that follow $N(\mu, \sigma^2)$ distribution; where, σ is unknown. S^2 is the sample variance based on the chosen sample size n. From mathematical statistics, we know that:

$$\frac{(n-1)S^2}{\sigma^2} \sim X^2_{n-1}$$

$$\Rightarrow S^2 \sim \frac{X^2_{n-1}}{n-1} \times \sigma^2$$

$$\Rightarrow Var(S^2) \sim Var(\frac{X^2_{n-1}}{n-1}) \times \sigma^4$$

Where $Var(X^2_{n-1}) = 2(n-1)$, in our case $n = 500$.

By the delta method:

$$Var(S) = Var(S^2) \times \left[\frac{1}{2 \times S}\right]^2_{S^2=\sigma^2}$$

$$= \frac{2(n-1)}{(n-1)^2} \times \sigma^4 \times \frac{1}{4 \times \sigma^2}$$

$$= \frac{1}{2(n-1)} \times \sigma^2$$

$$\Rightarrow \quad SD(S) = \frac{1}{\sqrt{2(n-1)}} \times \sigma$$

$$CV(S) = \frac{SD(S)}{E(S)} \times 100\%$$

Then,

$$= \frac{\frac{1}{\sqrt{2(n-1)}} \times \sigma}{\sigma} = \frac{1}{\sqrt{2(n-1)}} \times 100\%$$

Where: $E(S) = \sigma$ (approximate). Now, based on the above formula one sees that the coefficient of variation is a function of the number of the simulated datasets. For example, if the number of the simulated datasets is equal to 500, then the value of the

coefficient of variation is equal to 3%, which means the estimated standard deviation of the empirical odds ratio is unlikely to be more than 6% different from the true value.

4.5.3 Mean squared error (MSE)

The mean squared error (MSE), which combines both the bias and variance of the empirical *log* odds ratio, will be utilized as a gold standard to evaluate the performance of the eight estimators. The smaller the MSE, the better the estimator performs.

The MSE is defined as: **MSE**= (mean of the squares of the 500 $\left(\overline{\ln \hat{HR}} - \ln HR\right)$ values. In our simulations, we use the following formula for the MSE calculation, i.e., $MSE = \left(\overline{\ln \hat{HR}} - \ln HR\right)^2 + \frac{1}{499} \times \sum_{i=1}^{500} \left(\ln \hat{HR}_i - \overline{\ln \hat{HR}_i}\right)^2$, where i represents each randomly simulated dataset.

4.6 Illustration of the data frame and units of data analysis based on one simulated dataset

In order to illustrate each estimator, we randomly generated one dataset with 10 individuals based on a certain combination of the design parameters ($HR = 1, n = 10, \rho = 0.9$). The corresponding point estimates of the HR and their associated 95% confidence intervals (CIs) are reported in Table 4.6.1.

From the first three rows of Table 4.6.1, we can see that the simulated dataset gives us a total of 17 events over 10 years for individual 1, a total of 116 events for individual 2, etc. In addition, we can also see that the cell frequencies in the single overall 2×2

table at the 'overall crude-level' can be directly calculated by adding the corresponding cell frequencies from the ten smaller 2×2 tables at the 'subject-level'; likewise, the 'subject-level' 2×2 tables can be further divided into a series of the mini 2×2 tables at the 'event-level', where one mini 2×2 table consists of one "case" (risk period) and its matched "control" (control period). There are four different configurations of exposure for those matched pairs, neither exposed nor unexposed (concordant pairs) and one exposed one unexposed (disconcordant pairs). The GEE method is not studied at the 'overall crude-level' analysis since, in this case, all the events are aggregated into the four cells of a single 2×2 table. That is, there is no repeated events involved after regrouping all of the events into a single 2×2 table. Although the conditional MLE for a single 2×2 table (Breslow and Day, 1980) is available, we exclude this more complex conditional approach (when all of the frequencies in each cell in a single 2×2 table at the 'overall crude-level' data analysis are large, the estimate of the odds ratio from the conditional MLE is close to that from the unconditional MLE). The other problematic issue is in the context of the GEEs: the estimated working residual correlation becomes negative one (-1) with an exchangeable working correlation structure when the data analysis is conducted at the event-level. Therefore, it is impossible to obtain a summary statistic based on this approach, and thus we excluded this model in the data analysis.

Now, from randomly generated 500 datasets, we will obtain 500 point estimates for each statistical method, such as the one simulated dataset. The mean of the 500 point estimates in our study is our primary concern.

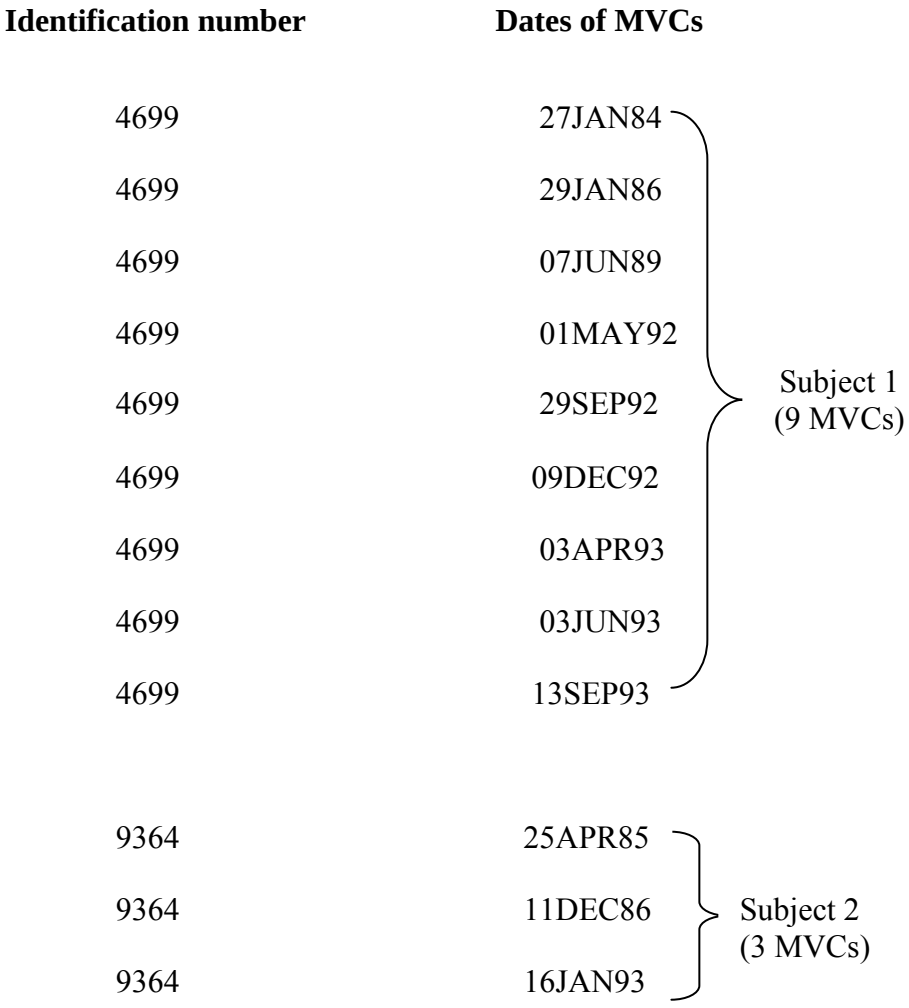


Figure 4.2.1: A real example of repeated MVCs in two subjects

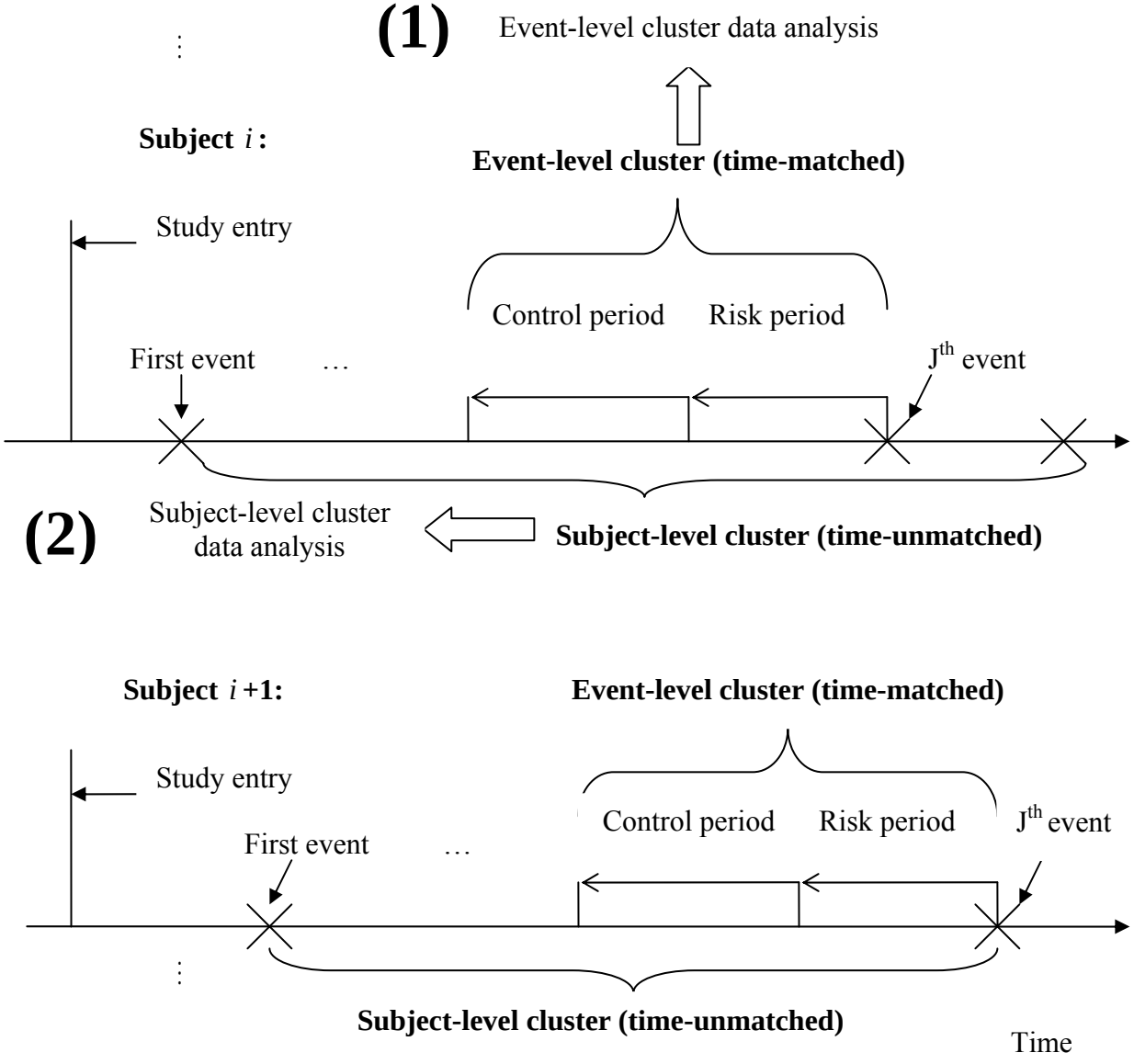


Figure 4.2.2: Illustration of the three possible units of data analyses

Subject	Sub_ID	Outcome	Exposure
1	1.01	1(case)	0
1	1.01	0(control)	1
1	1.02	1(case)	1
1	1.02	0(control)	0
1	1.03	1(case)	0
1	1.03	0(control)	0
1	1.04	1(case)	1
1	1.04	0(control)	1
1	1.05	1(case)	0
1	1.05	0(control)	0
2	2.01	1(case)	0
2	2.01	0(control)	1
2	2.02	1(case)	1
2	2.02	0(control)	0
2	2.03	1(case)	0
2	2.03	0(control)	1

Figure 4.2.3: A hypothetical example of the levels of identification required for the 'event-level data analysis'

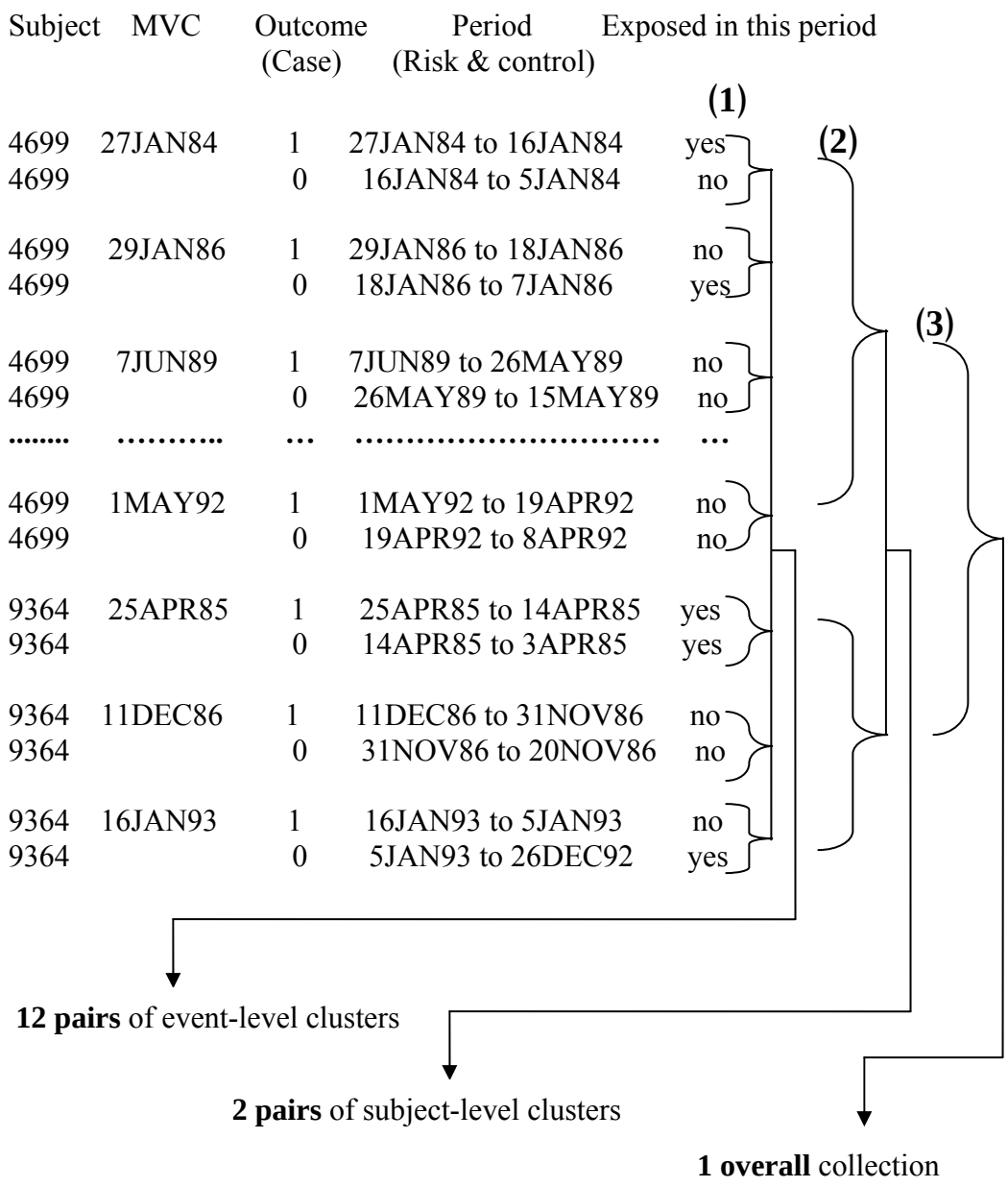
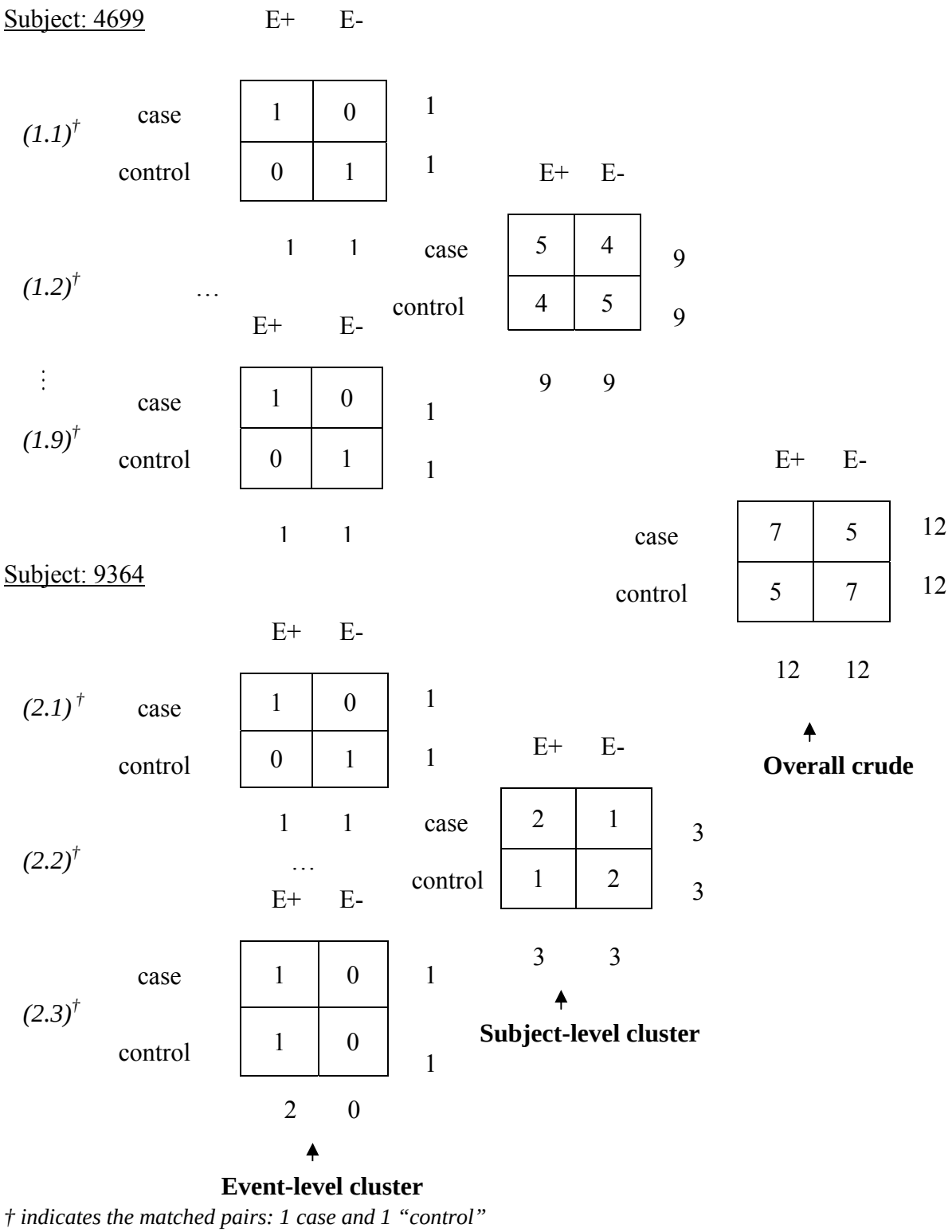


Figure 4.2.4: Illustration of three possible levels of aggregation of data from case-crossover study with multiple events (data from Figure 4.2.1)



† indicates the matched pairs: 1 case and 1 "control"

Figure 4.2.5: 2 ×2 tables at three different levels of data analyses (data from Figure 4.2.1)

For the overall crude level (empirical odds ratio):

$$\hat{\psi}_{overall} = \frac{ad}{bc} = \frac{7 \times 7}{5 \times 5} = 1.96$$

For the subject-level cluster:

$$\hat{\psi}_{M-H-subject} = \frac{\sum_i \frac{a_i d_i}{n_i}}{\sum_i \frac{b_i c_i}{n_i}} = \frac{\frac{25}{18} + \frac{4}{6}}{\frac{16}{18} + \frac{1}{6}} = \frac{37}{19} = 1.95$$

For the event-level cluster:

$$\hat{\psi}_{M-H-event} = \frac{\sum_i \sum_j \frac{a_{ij} d_{ij}}{n_{ij}}}{\sum_i \sum_j \frac{b_{ij} c_{ij}}{n_{ij}}} = \frac{\frac{1}{2} + \frac{0}{2} + \frac{0}{2} + \frac{0}{2} + \frac{0}{2} + \frac{0}{2} + \frac{1}{2} + \frac{0}{2} + \frac{1}{2}}{\frac{0}{2} + \frac{0}{2} + \frac{1}{2} + \frac{0}{2} + \frac{0}{2} + \frac{0}{2} + \frac{1}{2} + \frac{0}{2} + \frac{0}{2}}$$

$$\frac{+\frac{1}{2} + \frac{0}{2} + \frac{0}{2}}{+\frac{0}{2} + \frac{0}{2} + \frac{0}{2}} = \frac{4 \times \frac{1}{2}}{2 \times \frac{1}{2}} = 2$$

Figure 4.2.6: Mantel-Haenszel summary estimates according to three different levels of data analyses (data from Figure 4.2.1)

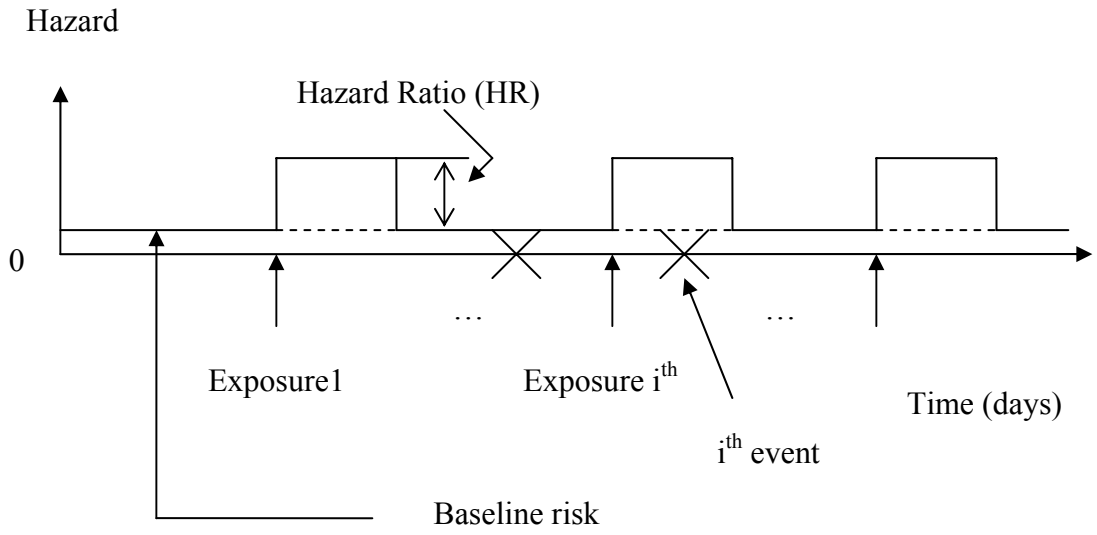


Figure 4.3.1.1: Risk elevated after any exposure

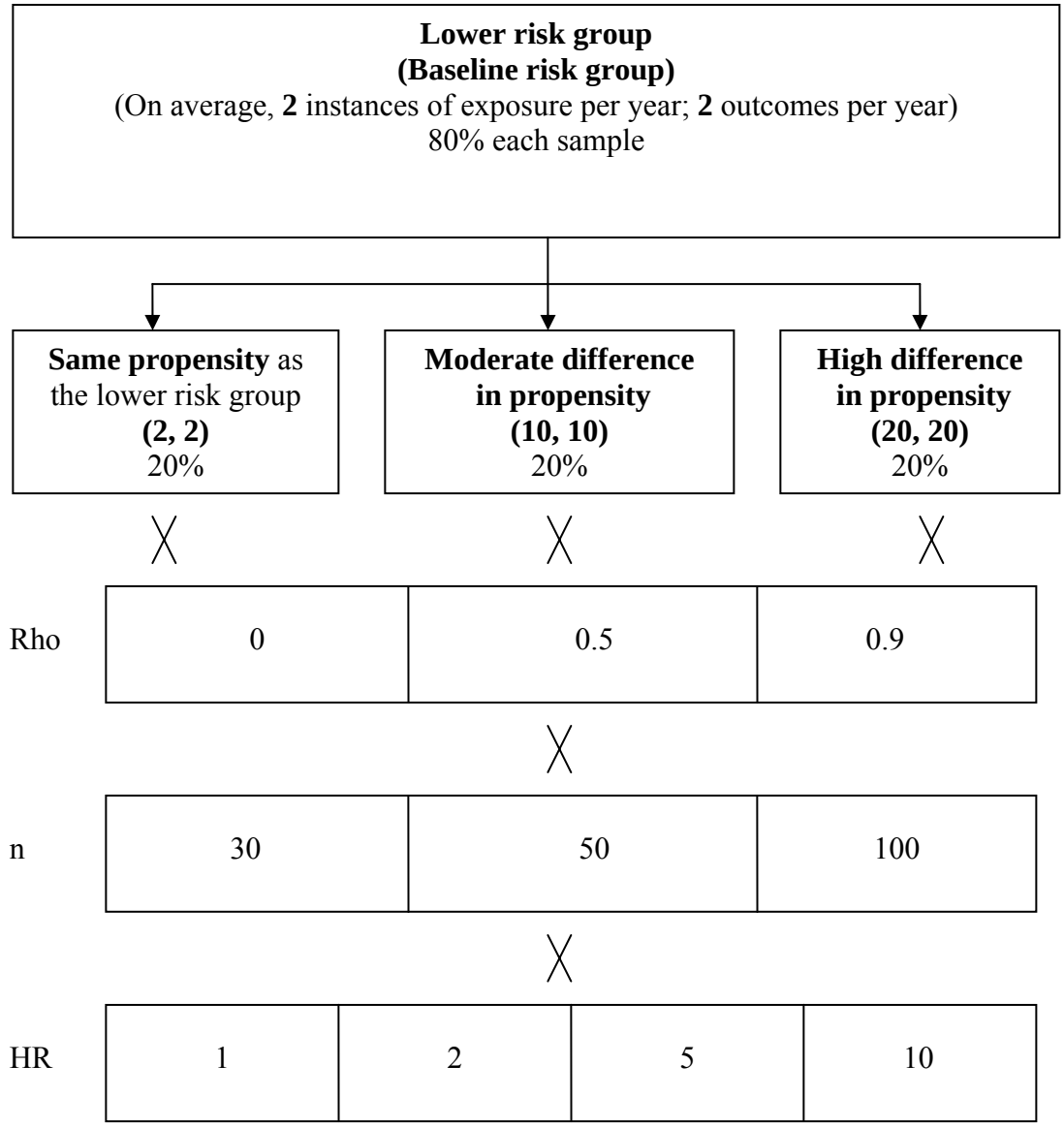
		Outcome Propensity		
		Oi_hi (**higher rate**) (e.g., 10 events/year on average)	Oi_low (**lower rate**) (e.g., 2 events/year on average)	
Exposure Propensity	Ei_hi (**more often exposed**) (**higher rate**) (e.g., 10 instances/year on average)	a% (15%)	b% (25%)	m% (40%)
	Ei_low (**less often exposed**) (**lower rate**) (e.g., 2 instances/year on average)	c% (5%)	d% (55%)	n% (60%)
		p% * (20%)	q% (80%)	1

* The entries in the cell and marginal are the percentages of such type of persons in the population, e.g., 25% of the subjects have a higher propensity of being exposed, but a lower propensity of developing the outcome.

Table 4.3.2.1: Frequency distribution of four subpopulations with different propensities of exposure and different propensities of outcome

	Design Factors	Effect
1	Difference in propensity of exposure between two groups	Key elements in introducing correlation between the propensity of exposure and the propensity of outcome of interest within an individual
2	Difference in propensity of outcome between two groups	
3	Frequency distribution of types of persons with different exposure and outcome propensities	
4	Correlation coefficient	
5	Effect of exposure (hazard ratio)	
6	Sample size	Precision
7	Random seed	Random variation
8	Three statistical methods (total 8 estimators): 3 (the overall crude M-H, the subject-level M-H, and the event-level M-H method) 2 (the subject-level CLR and the event-level CLR methods) 3 (the subject-level GEE method with an independent or an exchangeable w.c.s. and the event-level GEE method with an independent w.c.s.)	

Table 4.3.2.2: List of eight design factors in the simulation study



Where, Rho: the correlation coefficient; n: sample size in each simulated dataset; and HR: hazard ratio.

Figure 4.3.3.1: The structure of the simulation study
108 configurations, 500 datasets per configuration

	DAY														Total New
	1	2	3	4	5	6	7	8	9	10	11	. . . .	3649	3650	
Subject 1															
E	0	0	1	0	0	1	0	0	0	1	0	. . . .	0	0	27
o	0	1	0	0	0	0	0	0	0	0	0	. . . .	0	0	7
Subject 2															
E	0	0	0	0	0	0	1	0	1	1	0	. . . .	0	0	33
o	0	0	1	0	0	1	0	0	1	0	1	. . . .	0	0	39
Subject 3															
E	0	0	0	0	0	0	0	0	0	0	1	. . . .	0	0	5
o	0	0	1	0	0	0	0	0	0	0	0	. . . .	0	0	9
Subject 4															
E	0	0	0	0	0	0	1	0	0	0	0	. . . .	0	0	9
o	0	0	0	1	0	0	0	0	0	0	0	. . . .	0	0	37

E=0: no exposure; E=1: exposure exists on that day
O=0: no event; O=1: event exists on that day.

Figure 4.3.4.1: Simulated four persons with different propensities of exposure and different propensities of outcome

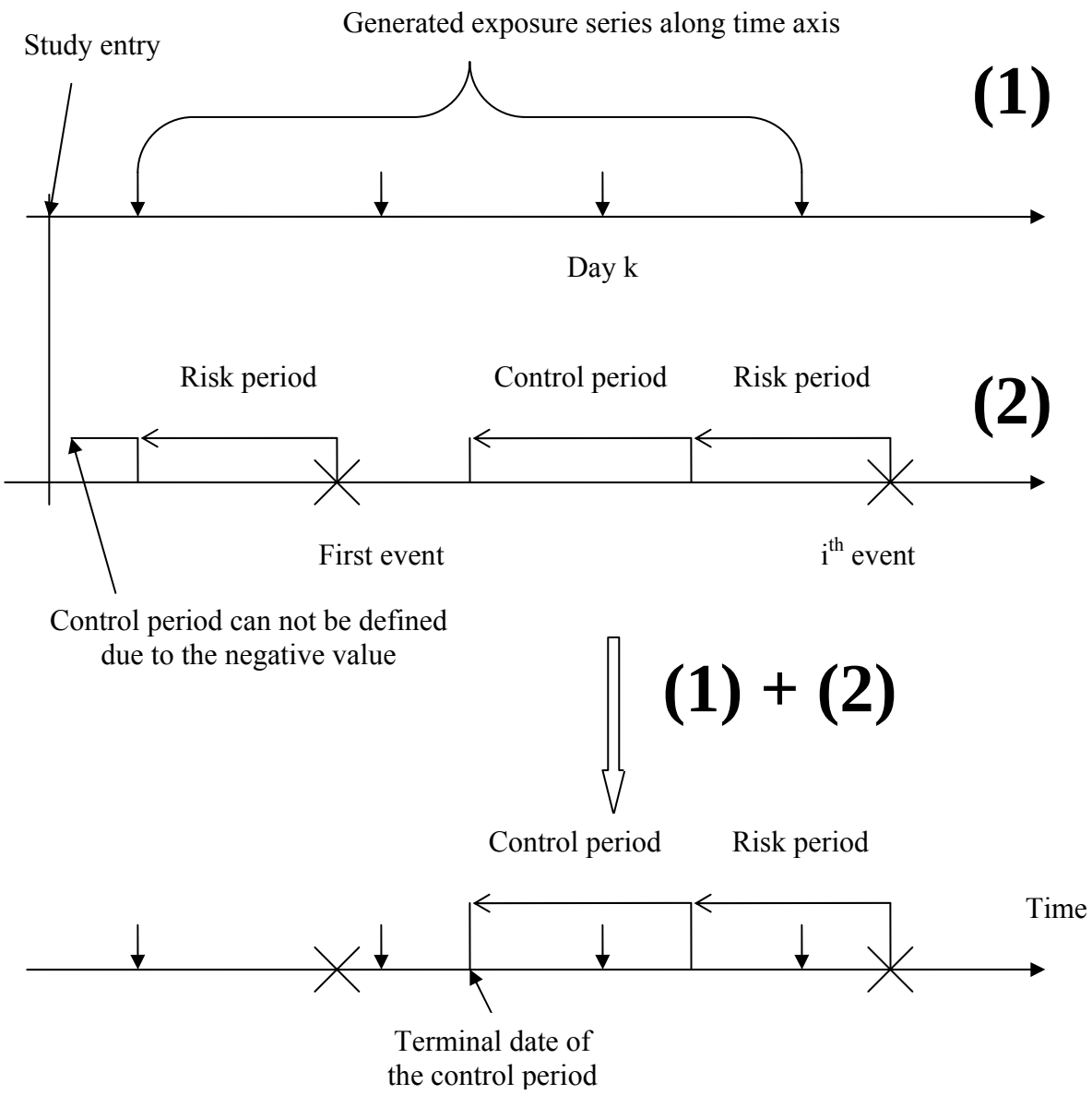


Figure 4.4.1: Illustration of merging the simulated exposure and outcome two series for an individual

Obs	subj	outcome	exposure	status
1	1	1	0	case1
2	1	0	1	ctl1
3	1	1	0	case2
4	1	0	1	ctl2
5	1	1	0	case3
6	1	0	0	ctl3
7	1	1	1	case4
8	1	0	1	ctl4
9	1	1	0	case5
10	1	0	0	ctl5
11	2	1	0	case1
12	2	0	1	ctl1
13	2	1	1	case2
14	2	0	0	ctl2
15	2	1	0	case3
16	2	0	1	ctl3
17	2	1	0	case4
18	2	0	0	ctl4

Subject 1 and subject 2 (i.e., cluster 1 and cluster 2);
Outcome: 1: event (case), 0: no event ("control");
Exposure: 1: exposed, 0: unexposed; and,
Status: risk or control period.

Figure 4.4.2: A pair-matched case control dataset created from the simulated exposure and outcome series

Table 4.6.1: Illustration of the eight estimators based on one simulated dataset

($HR = 1$, $n = 10$, $\rho = 0.9$)

	Subgroup1	Subgroup2
Average exposures per year:	10	2
Average events per year:	10	2

Methods		Unit of analysis		
		Event-Level (Time-Matched)	Subject-Level (Time-Unmatched)	Overall Crude
subject propensities¶ number of events		1 2 … 10 2 10 10 (17) (116) … (91)	1 2 … 10 2 10 10 (17) (116) … (91)	
2 ×2 table Case Control		*(1.1†)* $\begin{bmatrix}0 & 1\\1 & 0\end{bmatrix}$ *(2.1†)* $\begin{bmatrix}0 & 1\\1 & 0\end{bmatrix}$ … *(10.1†)* $\begin{bmatrix}1 & 0\\1 & 0\end{bmatrix}$ *(1.2†)* $\begin{bmatrix}1 & 0\\1 & 0\end{bmatrix}$ *(2.2†)* $\begin{bmatrix}1 & 0\\0 & 1\end{bmatrix}$ … *(10.2†)* $\begin{bmatrix}1 & 0\\1 & 0\end{bmatrix}$ .. .. *(1.17†)* $\begin{bmatrix}0 & 1\\1 & 0\end{bmatrix}$ *(2.116†)* $\begin{bmatrix}1 & 0\\0 & 1\end{bmatrix}$ … *(10.91†)* $\begin{bmatrix}1 & 0\\1 & 0\end{bmatrix}$	$\begin{bmatrix}6 & 11\\5 & 12\end{bmatrix}\begin{bmatrix}13 & 103\\10 & 106\end{bmatrix}$ … $\begin{bmatrix}4 & 87\\4 & 87\end{bmatrix}$	73 434 65 442
2 ×2 table M-H OR (95%CI)		**1.19** (0.79, 1.78)	**1.17** (0.79, 1.73)	**1.14** (0.80, 1.64)
Conditional logistic regression OR (95%CI)		**1.19** (0.79, 1.78)	**1.17** (0.79, 1.72)	Not studied‡
GEEs* OR (95%CI)	IND§	**1.14** (0.83, 1.57)	**1.14** (0.80, 1.64)	Not studied
	EXCH#		**1.13** (0.90, 1.43)	

¶: Shown for illustration only, in practice, these are not observable. †: Representing the number of matched pairs.
‡: The odds ratio for a single 2 ×2 table based on the conditional approach can be obtained. *: Generalized estimating equations; §: Independent working correlation structure; and, #: Exchangeable working correlation structure.

CHAPTER 5

RESULTS FROM THE SIMULATION STUDY

Overview

In this chapter, we will first introduce the numbering system for all the tables and figures used to present the results from the simulation study. Then, we will summarize the performance of the eight estimators with respect to the bias in the estimates of odds ratio, the MSE and the ratio of the empirical variance to model-based variance, as described in Sections 5.2, 5.3 and 5.4. The conclusion on which estimator(s) should be used to analyze a case-crossover data with multiple outcome events of interest will be reached. A more detailed presentation of the results from each individual table and a cross examination of multiple tables (e.g., Table 5.2.1(a), Table 5.2.2(a) and Table 5.2.3(a)) will be given in Appendix IV.

5.1 Orientation and numbering systems for tables and figures

In all, 7 design parameter factors and their effects on 3 measures (percentage of bias ($\Delta\%$), mean squared error and ratio of the empirical variance to the model-based variance) are studied. As explained in orientation **Table 5.1T,** the 3 effect measures are reported in a series of Tables 5.2.X(X) (Percentage of bias), 5.3.X(X) (Mean squared error) to 5.4.X(X) (Ratio of the empirical variance to the model-based variance), while 4 design parameters (the sample size, the hazard ratio, the correlation coefficient and the propensities of exposure and outcome) are varied within each table. Within each set, such as Table 5.2.X(X), the two other factors are varied to give ending **.1a** to ending **.3c**. Here, **.1**, **.2** and **.3** refer to relative propensities for exposure and outcome (from low (2/2

instances per year on average) to high (20/2 instances per year on average)), while **.a**, **.b** and **.c** refer to the degree of correlation (in same person) between propensities of becoming exposed and of developing the outcome of interest.

Table 5.1F (2 consecutive tables) refers to the sequencing and numbering of the figures. The performances of the eight different estimators are compared within each figure, but only for fixed values of the propensities of exposure and the outcome of interest; and the correlation coefficient. Since we cannot show as many dimensions in the figures as what we did in the tables, we will separately report the effects from the hazard ratio and the sample size as described below.

The propensity and the effect of the exposure are varied across tables, from Figure 5.3.4.1 to Figure 5.3.6.7, with the last digits 1-4 referring to the hazard ratio, the last digits 5-7 referring to the sample size, and the second last digits 4-6 referring to the three different propensities of exposure and the outcome of interest (from low (2/2 instances per year on average) to high (20/2 instances per year)). The second digit 5.3 still refers to the measure of the MSE from each statistical method as discussed in the earlier section of this chapter.

In the next section, we are going to summarize the results across the 27 tables (9 tables (Table 5.2.1(a) to Table 5.2.3(c)) for the percentage of bias; 9 tables (Table 5.3.1(a) to Table 5.3.3(c)) for the MSE; and 9 tables (Table 5.4.1(a) to Table 5.4.3(c)) for the ratio between the empirical variance and the model-based variance). In comparing the performance of these three statistical methods (the M-H method, the CLR method, and the GEE method), we will first compare the 500 estimated empirical odds ratios with the true hazard ratio to determine the bias from each statistical method. Next, we will examine the MSE of the estimated log odds ratio to evaluate the performance of each

statistical method. Finally, we will analyze the empirical variance of the log odds ratio and the ratio of those two variances (empirical and model-based) to assess the ability of the model-based variance to reflect real sampling variation of each statistical method.

The results presented in Table 5.2.1(a) to Table 5.4.3(c) (27 tables) are based on 500 randomly simulated datasets. As stated previously, the tables were arranged into three groups based on the propensities of becoming exposed and of developing the outcome of interest. The results presented in Table 5.3.1(a) to Table 5.3.3(c) (9 tables) will be used to evaluate the performance of each of the three statistical methods in analyzing data with repeated outcome events.

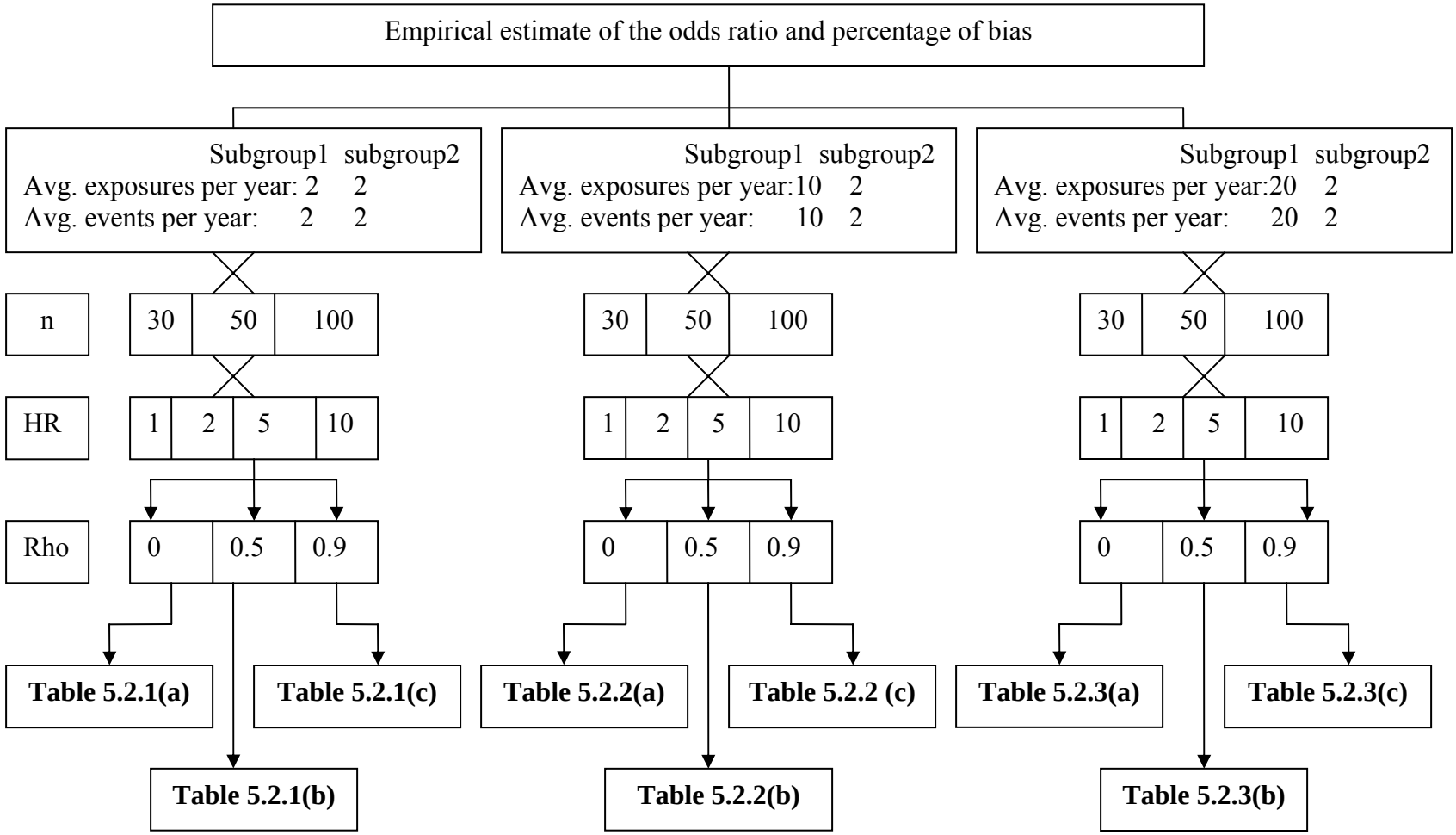


Table 5.1.T: Orientation to sequencing and numbering of tables for percentage of bias [5.2.1-3.a-c]. 9 Tables for other measures follow same sequence.5.3=MSE; 5.4=Empirical variance vs. model-based variance
Abbreviation: n=# of study subjects, HR=hazard ratio, and Rho=correlation coefficient.

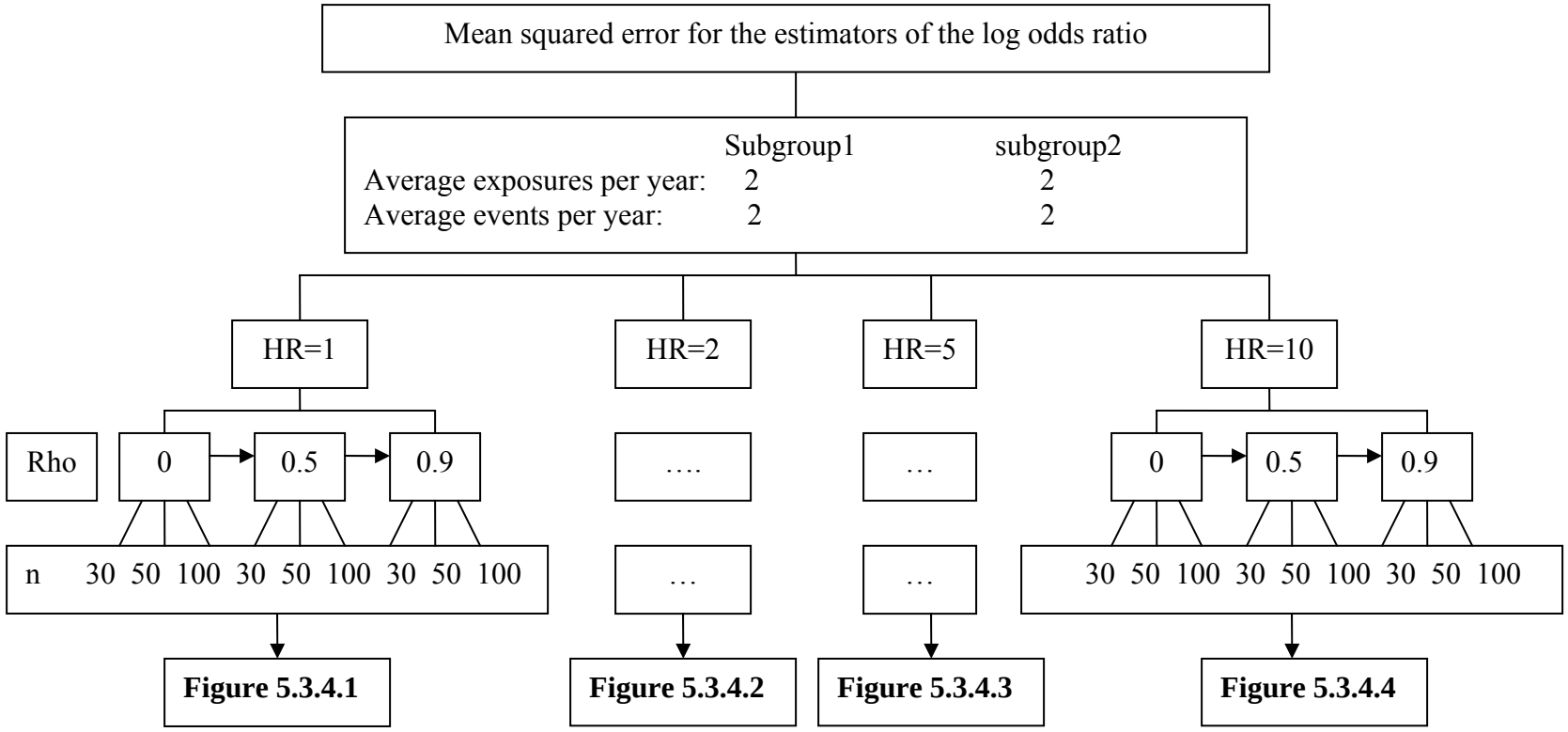


Table 5.1.F: Orientation to sequencing and numbering of Figures on various indices of performance, in relation to the hazard ratio

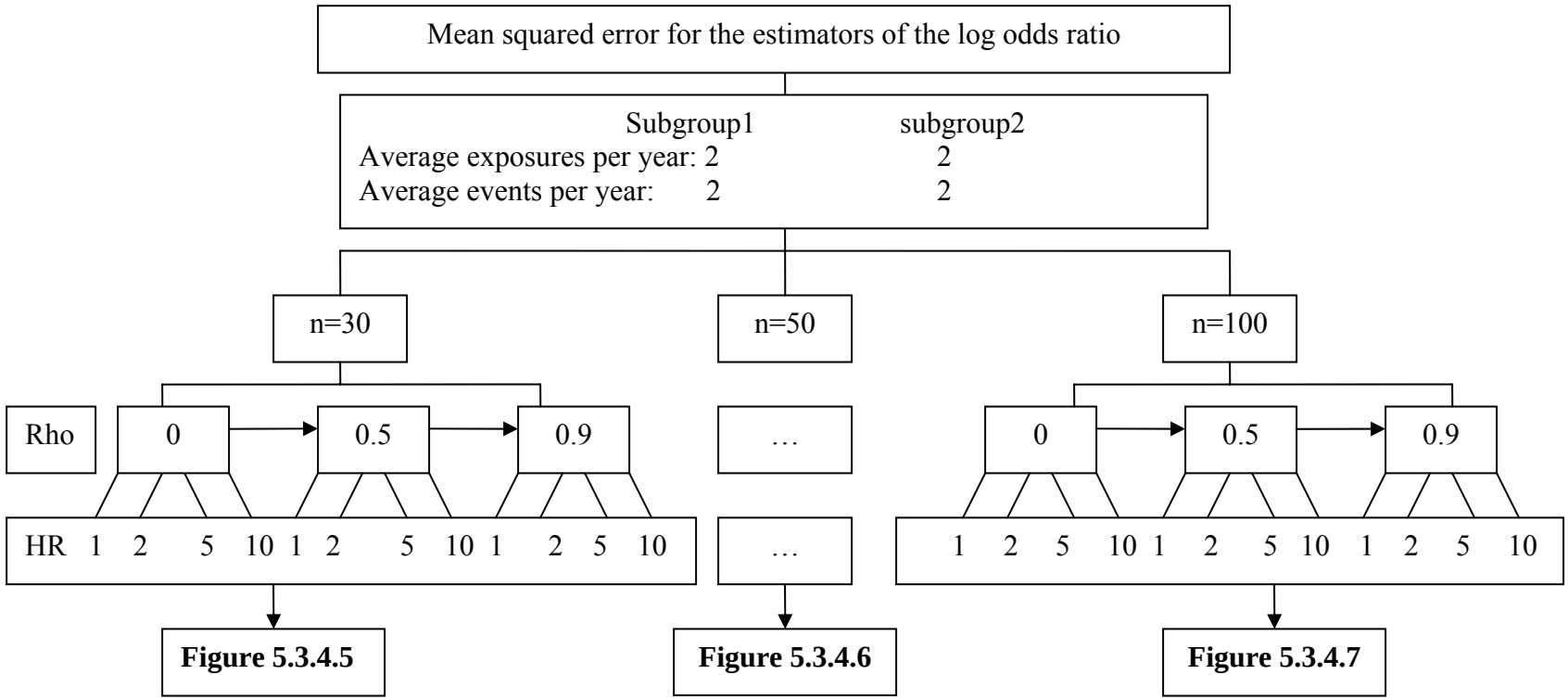


Table 5.1.F: Orientation to sequencing and numbering of Figures on various indices of performance, in relation to the sample size

5.2 Magnitude of bias in odds ratio from the eight estimators

In the following, we will first introduce the symbols / abbreviations to represent the eight estimators based on three different statistical methods with three different units of data analyses; then, we will summarize the overall results regarding the performance of each individual estimator from all of the 9 tables (Tables 5.2.1(a), (b) and (c); Tables 5.2.2(a), (b) and (c); Tables 5.2.3(a), (b) and (c)).

- INTRODUCTION OF THE SYMBOLS / ABBREVIATIONS FOR EIGHT ESTIMATORS

For simplicity, we will use a symbol / abbreviation, as shown in **Table 5.2.T**, to represent each of the eight estimators. Each symbol stands for the combination of one statistical method and the corresponding unit of data analysis in our presentation.

Estimator	Symbol
Overall crude MH 2 × 2 table	$MH_{overallcrude}$
Subject-level MH 2 × 2 table	$MH_{subject}$
Subject-level CLR	$CLR_{subject}$
Subject-level GEE with an independent working correlation structure	$GEE^{ind}_{subject}$
Subject-level GEE with an exchangeable working correlation structure	$GEE^{exch}_{subject}$
Event-level GEE with an independent working correlation structure	GEE^{ind}_{event}
Event-level MH 2 × 2 table	MH_{event}
Event-level CLR	CLR_{event}

Table 5.2.T: The symbols used for the eight estimators

➢ BIAS IN EACH OF THE EIGHT ESTIMATORS OF ODDS RATIO---**Summary of the results from Tables 5.2.1 (a, b, and c), Tables 5.2.2 (a, b and c) and Tables 5.2.3(a, b and c) (9 Tables)**

As shown in **Table 5.2.D**, we rank the eight estimators with respect to the magnitude of bias in the estimates of odds ratio, while the design parameters vary from a lower value to a higher one (e.g., $\rho: 0 \rightarrow 0.5 \rightarrow 0.9$; $N: 30 \rightarrow 50 \rightarrow 100$; $HR: 1 \rightarrow 10$ and intensities of exposure and the outcome of interest between subgroup1 and subgroup2: $2/2 \rightarrow 10/2 \rightarrow 20/2$). The major findings can be described as below:

1) The M-H method and the CLR method with the *event-level* data analyses are the best when using the bias to evaluate the performance of each individual estimator. These two estimators produce the smallest bias in the empirical estimates of odds ratio.

2) The estimators in the same box indicate that they have approximately the same magnitude of bias. For example, on the left hand side of **Table 5.2.D**, when the hazard ratio is set to unity the bias for the eight estimators is approximately the same: none of the statistical methods is superior to the others. On the right hand side of **Table 5.2.D**, two different scenarios are presented to show how the bias varies as the hazard ratio increases. For instance, the magnitudes of bias from the M-H and the CLR methods with the *event-level* data analyses do not show any material changes as the hazard ratio varies from a lower value (2) to a higher value (10); however, the bias from the other six estimators such as the *subject-level* GEE method with an exchangeable working correlation structure have substantial increases (moving from the solid boxes to the dashed ones). In other words, these six estimators produce higher bias in the estimates of odds ratio compared with the *event-level* M-H and the CLR methods.

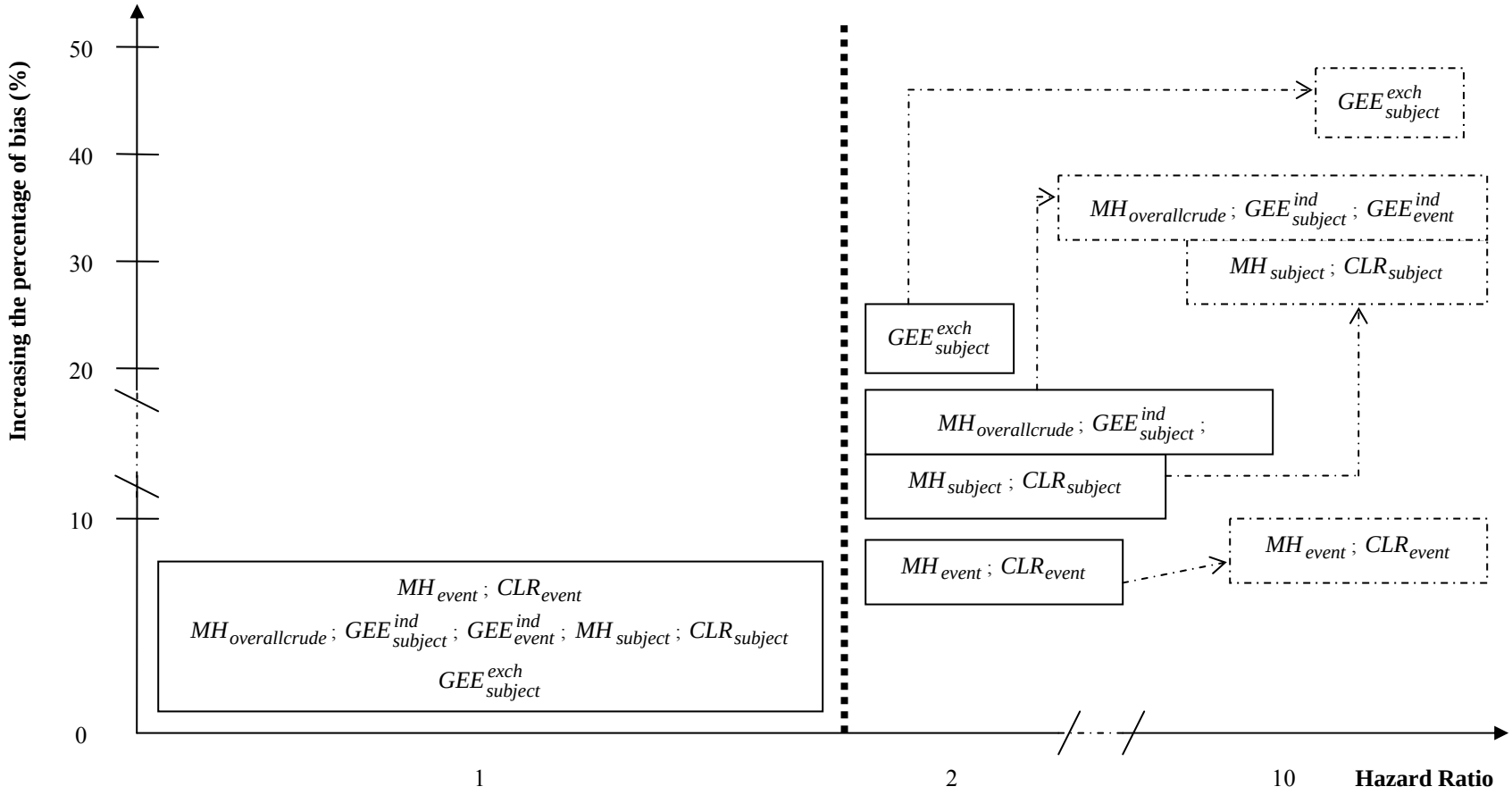
3) The results presented in Tables 5.2.1(a) to 5.2.3(c) also demonstrate that the bias of the parameter of interest decreases as the number of the outcome events increase. In our simulation, there are two comparison groups with one group having a higher propensity of developing the outcome of interest while the other having a lower propensity of developing the outcome of interest. For the group with higher propensity, each individual has a likelihood of developing 10 or 20 events per year, while in the lower propensity group each individual has a likelihood of developing 2 events per year.

a) When the propensity of developing the outcome of interest between the two comparison groups is the same ($I_1 = I_2 = 2$, i.e., each individual in these two groups has the same likelihood of developing 2 events per year, on average), and when $n = 100$, $\rho = 0$, and $OR = 10$, then as shown in Table 5.2.1(a), the percentage of bias from the conditional logistic regression method at the event-level data analysis is 12.1%;

b) When the difference in the propensity of developing the outcome of interest between the two comparison groups increases ($I_1 = 10$ vs. $I_2 = 2$), while the other parameters remain the same ($n = 100$, $\rho = 0$, and $OR = 10$), then the percentage of bias from the conditional logistic regression method at the event-level data analysis decreases from 12.1 to 7.7% as shown in Table 5.2.2(a); and,

c) When the difference in the propensity of developing the outcome of interest between the two comparison groups becomes even larger ($I_1 = 20$ vs. $I_2 = 2$), while the other parameters remain the same ($n = 100$, $\rho = 0$, and $OR = 10$), the percentage of bias from the conditional logistic regression method at the event-level data analysis is further reduced from 7.7% to 5.8% (Table 5.2.3(a)).

In summary, these results presented above show that, as the propensity of developing the outcome of interest in the higher risk group increases, and therefore, as the number of events is increased, the bias decreases. These results are also presented in the tables of the thesis: Tables 5.2.1(b) $\rightarrow$ 5.2.2(b) $\rightarrow$ 5.2.3(b) and Tables 5.2.1(c) $\rightarrow$ 5.2.2(c) $\rightarrow$ 5.2.3(c).



Methods in the same box have approximately the same percentages of bias in the empirical estimates of odds ratio. Design parameters: ρ : 0 $\longrightarrow$ 0.5 $\longrightarrow$ 0.9; N : 30 $\longrightarrow$ 50 $\longrightarrow$ 100; HR : 1 $\longrightarrow$ 10 and intensities of exposure and the outcome of interest between subgroup1 and subgroup2: 2/2 $\longrightarrow$ 10/2 $\longrightarrow$ 20/2.

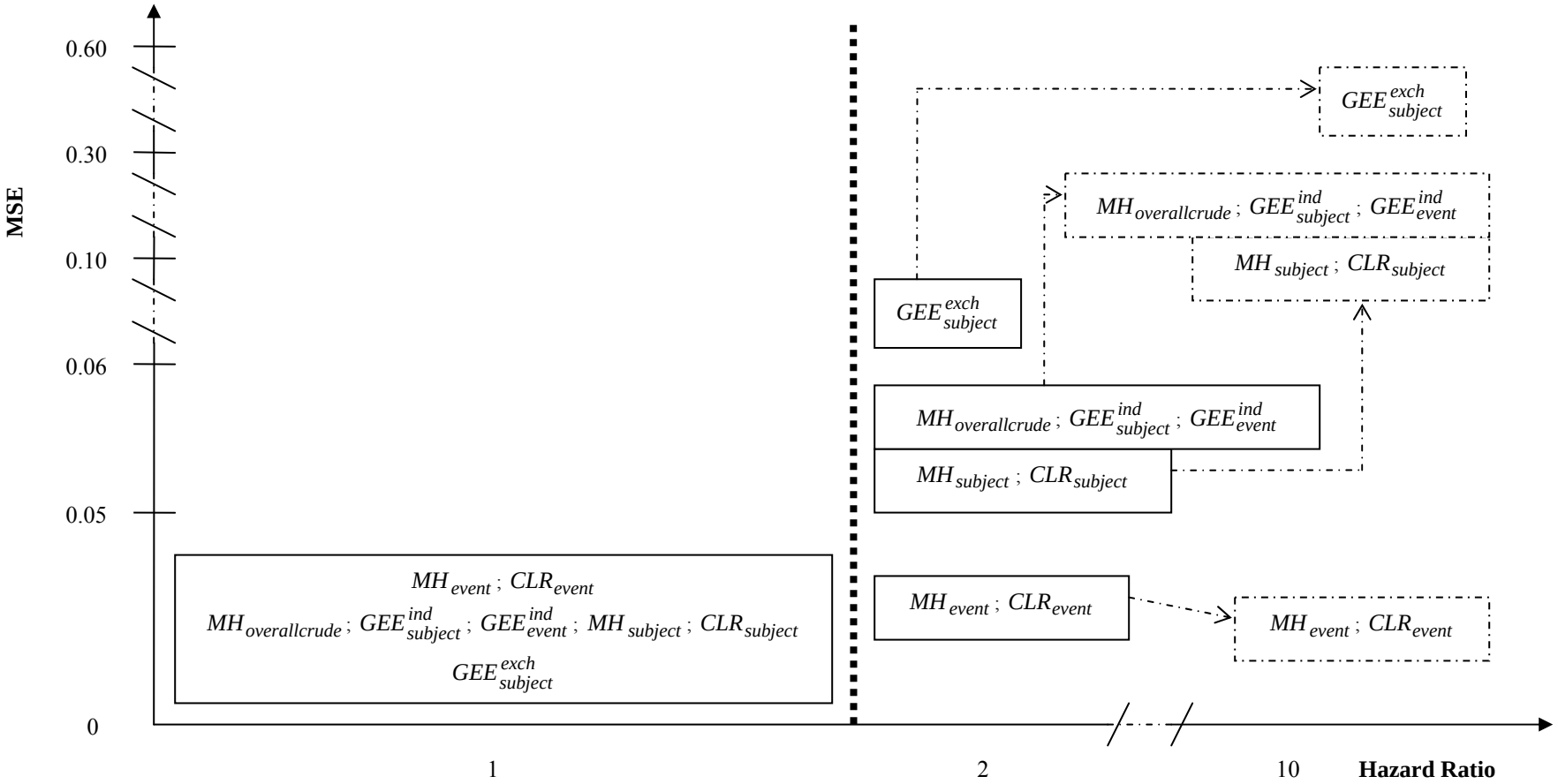
Table 5.2.D: Ranking of eight estimators with respect to the percentage of bias

5.3 Mean squared error of the eight estimators of the log odds ratio

- **Summary of the results from Tables 5.3.1(a, b and c), Tables 5.3.2(a, b and c) and Tables 5.3.3(a, b and c) (9 Tables)**

As justified in Chapter 4, the MSE with respect to the *log* odds ratio will be used to evaluate the performance of each individual estimator in analyzing data with multiple outcome events. The effects of the design parameters on the MSEs of these eight estimators are summarized in 9 Tables (Table 5.3.1(a) $\rightarrow$ Table 5.3.3(c)) and displayed in 21 Figures (Figure 5.3.4.1 $\rightarrow$ Figure 5.3.6.7) to visualize the differences.

The same pattern (as shown in **Table 5.2.D**) of the ranking of these eight estimators with respect to the MSE is observed in **Table 5.3.D**. For example, when the hazard ratio is set to unity, the MSEs from all eight estimators do not show any material difference; however, when the hazard ratio is fixed at a value greater than 1, again, the M-H method and the CLR method with the *event-level* data analyses yield the smallest MSEs. Moreover, the MSEs of these two estimators appear to decrease as the hazard ratio increases. On the other hand, the other six estimators produce higher MSEs compared with the above two. Based on the MSE criterion, the smaller the MSE, the better the estimator performs. We can conclude that the M-H method and the CLR method with the *event-level* data analyses are the best in the various settings.



Methods in the same box have approximately the same MSEs. Design parameters: ρ : 0 $\rightarrow$ 0.5 $\rightarrow$ 0.9; N : 30 $\rightarrow$ 50 $\rightarrow$ 100; HR : 1 $\rightarrow$ 10 and intensities of exposure and the outcome of interest between subgroup1 and subgroup2: 2/2 $\rightarrow$ 10/2 $\rightarrow$ 20/2.

Table 5.3.D: Ranking of eight estimators with respect to the MSE

5.4 Empirical variance and model-based variance

- **Summary of the results from Tables 5.4.1(a, b and c), Tables 5.4.2(a, b and c) and Tables 5.4.3(a, b and c) (9 Tables)**

In order to better understand the results presented in Tables 5.4.1(a) $\rightarrow$ 5.4.3(c), we will first briefly explain how the empirical and model-based variances were calculated and, then, briefly describe how the ratios of the empirical and model-based variances were calculated:

1. Calculation of the empirical and model-based variances of the *log* odds ratio

1) *The empirical variance of the estimated log odds ratio*

As described in Chapter 4, the empirical variance of the estimated *log* odds ratio is calculated from 500 simulated datasets as the following: $\frac{1}{499} \times \sum_{i=1}^{500} \left(\ln \hat{HR}_i - \overline{\ln \hat{HR}_i} \right)^2$.

2) *The model-based variance of the estimated log odds ratio*

The model-based variance of the *log* odds ratio is defined as the mean of 500 variances of the estimated *log* odds ratio from each individual model.

2. Calculation of the variance ratios

1) For the overall crude M-H method and the CLR method

The variance ratios for the overall crude M-H method and the CLR method presented in Tables 5.4.1(a) $\rightarrow$ 5.4.3(c) are calculated as the empirical variance divided by the model-based variance. As an example, as shown in Table 5.4.1(a), with $n = 100$, the empirical variance of 500 estimated *log* odds ratios from the overall crude M-H method is 0.0147, while the model-based variance (mean of the 500 variances of the

estimated *log* odds ratio from each individual model) is 0.0161. Thus the variance ratio for this estimator is 0.91 (0.0147 / 0.0161).

2) For the GEE method

The variance ratios for the GEE method presented in Tables 5.4.1(a) $\rightarrow$ 5.4.3(c) are calculated as the empirical variance (variance of the 500 estimated *log* odds ratio) divided by the mean of 500 variances of the parameter of interest obtained from each individual model. For the latter the empirical "Robust" variance was used rather than the model-based one.

If we compare the variance ratios from the two GEE methods (that is, the subject-level GEE method with an independent w.c.s., and the event-level GEE method with an independent w.c.s.) with those obtained from the overall crude M-H method, we will find that the variance ratios from the M-H method are different from those obtained from the two GEE methods as shown in Tables 5.4.1(a) $\rightarrow$ 5.4.3(c). This is because of the different ways to calculate the variance ratios as described previously. That is, for the overall crude M-H method, variance ratios were calculated by the empirical variance (variance of the 500 estimated *log* odds ratio) divided by the model-based variance (the mean of 500 model-based variances of the parameter of interest obtained from each individual model), while the variance ratios for the two GEE methods were calculated by the variance of the 500 estimated *log* odds ratio divided by the mean of 500 robust variances of the parameter of interest obtained from each individual model. The variance ratios from these three different statistical methods (the overall crude M-H method, the subject-level GEE method with an independent w.c.s., and the event-level GEE method with an independent w.c.s.), however, are identical when the two GEE methods also uses

model-based variances (rather than the robust variances) to calculate the variance ratios (the data are not presented in the thesis).

From the above nine tables, we can see that the empirical variance appears to be a function of the sample size, the correlation coefficient, the hazard ratio, and the propensities of exposure and the outcome of interest. It is very difficult to independently differentiate each individual design effect from the others in a single table or figure, as presented for the bias and MSE. However, a few common conclusions can be drawn from these 9 tables as below:

1) With the same size of the hazard ratio, as expected, the empirical variance of each individual estimator decreases as the sample size increases from 30 to 100. Moreover, the empirical variance is approximately proportional to the inverse of the sample size. Likewise, with the same size of the sample size, the empirical variance from each estimator increases as the hazard ratio increases from 1 to 10.

2) The empirical variances of the M-H method and the CLR method with the *event-leve*l data analyses are slightly larger than those from the *overall crude* M-H method and all three statistical methods (the M-H method, the CLR method, and the GEE method) with the *subject-level* data analyses. This may be due to the fact that many concordant pairs were eliminated at the *event-level* data analysis by using the CLR method. In other words, the M-H method and the CLR method with the *event-level* data analysis can produce much less bias in the odds ratio estimation with a slight increase in the empirical variance. There is a trade-off between bias and precision; however, it is important to keep in mind that the validity of epidemiological study should be the primary objective, not precision. Detailed discussion on this issue will be given in Chapter 7 "Conclusions and Discussions".

3) The ratios of the empirical variance to model-based variance from the M-H method and from the CLR method with the *event-level* data analyses are close to 1, i.e., the model-based variances from these two methods are accurate. This is not the case, however, for the other six estimators where the ratios of those two variances appear to be a function of the hazard ratio, the sample size, the correlation coefficient, and the propensities of exposure and of the outcome of interest.

4) The subject-level GEE method with an exchangeable working correlation structure produces the smallest empirical variance when the hazard ratio is assigned a value between 1 and 2. However, this estimator produces the largest empirical variance when the hazard ratio is fixed at a value between 5 and 10. This lack of uniform performance for the different values of hazard ratio may deter people from using it.

In summary, as described above, the M-H method and the CLR method with the *event-level* data analysis produces less bias in the odds ratio estimation with a slight increase in the empirical variance. In addition, the model-based variances from these two statistical methods with the *event-level* unit of data analyses are accurate and valid. On the other hand, the model-based variances from the *overall crude* M-H method and all of three different statistical methods (the M-H method, the CLR method and the GEE method) with the *subject-level* data analyses and the GEE method with the *event-level* data analyses lack the abilities to reflect real sampling variance.

5.5 Summary of the results from the simulation study

In Sections 5.2, 5.3 and 5.4, we examined the performance of the eight estimators in analyzing a case-crossover data with multiple outcome events of interest via the bias, the

ratio of the empirical to model-based variances and the MSE of the estimator. The overall performance of these eight estimators can be described as below:

The *event-level* M-H method and the CLR method can provide less biased estimates of the underlying odds ratios with a slight increase in the empirical variance, while compared with the other six estimators. As long as the *event-level* data analysis is used, the M-H method and the CLR method can produce numerically better estimates of the underlying odds ratios. On the other hand, the other six estimators are not sufficient enough to control for the bias. The model-based variances from these six estimators are inaccurate and appear to be more likely affected by the correlation among the repeated outcome events of interest.

Table 5.2.1(a): Percentage Bias in the Empirical Estimates of Odds Ratio

Entire Population

Average exposures per year: 2

Average events per year: 2

Rho=0

n	Unit of analysis	Statistical Method	Est.	*OR*							
				1		2		5		10	
				Emp.	Δ%	Emp.	Δ%	Emp.	Δ%	Emp.	Δ%
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.966	**3.4**	1.729	**13.6**	3.631	**27.4**	6.191	**38.1**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.965	**3.4**	1.738	**13.1**	3.684	**26.3**	6.331	**36.7**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.966	**3.4**	1.734	**13.3**	3.667	**26.7**	6.316	**36.8**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.966	**3.4**	1.729	**13.6**	3.631	**27.4**	6.191	**38.1**
			$\hat{\psi}_{GEE-ex}$	.971	**2.9**	1.593	**20.4**	3.025	**39.5**	4.969	**50.3**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.966	**3.4**	1.729	**13.6**	3.631	**27.4**	6.191	**38.1**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.962	**3.8**	1.841	**7.9**	4.488	**10.2**	8.946	**10.5**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.962	**3.8**	1.841	**7.9**	4.488	**10.2**	8.946	**10.5**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.939	**6.1**	1.714	**14.3**	3.621	**27.6**	6.137	**38.6**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.939	**6.1**	1.723	**13.8**	3.676	**26.5**	6.278	**37.2**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.939	**6.1**	1.720	**14.0**	3.660	**26.8**	6.264	**37.4**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.939	**6.1**	1.714	**14.3**	3.621	**27.6**	6.137	**38.6**
			$\hat{\psi}_{GEE-ex}$	.946	**5.4**	1.598	**20.1**	3.070	**38.6**	5.016	**49.8**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.939	**6.1**	1.714	**14.3**	3.621	**27.6**	6.137	**38.6**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.934	**6.6**	1.828	**8.6**	4.482	**10.4**	8.719	**12.8**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.934	**6.6**	1.828	**8.6**	4.482	**10.4**	8.719	**12.8**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.952	**4.8**	1.706	**14.7**	3.604	**27.9**	6.156	**38.4**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.951	**4.9**	1.715	**14.3**	3.662	**26.8**	6.295	**37.1**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.951	**4.9**	1.712	**14.4**	3.646	**27.1**	6.281	**37.2**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.952	**4.8**	1.706	**14.7**	3.604	**27.9**	6.156	**38.4**
			$\hat{\psi}_{GEE-ex}$	.956	**4.4**	1.616	**19.2**	3.130	**37.4**	5.229	**47.7**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.952	**4.8**	1.706	**14.7**	3.604	**27.9**	6.156	**38.4**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.948	**5.2**	1.811	**9.4**	4.439	**11.2**	8.795	**12.1**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.948	**5.2**	1.811	**9.4**	4.439	**11.2**	8.795	**12.1**

Table 5.2.1(b): Percentage Bias in the Empirical Estimates of Odds Ratio

Entire Population

Average exposures per year: 2

Average events per year: 2

Rho=0.5

n	Unit of analysis	Statistical Method	Est.	*OR*							
				1		2		5		10	
				Emp.	Δ%	Emp.	Δ%	Emp.	Δ%	Emp.	Δ%
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.940	**5.9**	1.732	**13.4**	3.637	**27.3**	6.234	**37.7**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.939	**6.0**	1.741	**12.9**	3.692	**26.2**	6.382	**36.2**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.940	**5.9**	1.738	**13.1**	3.673	**26.5**	6.366	**36.3**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.940	**5.9**	1.732	**13.4**	3.637	**27.3**	6.234	**37.7**
			$\hat{\psi}_{GEE-ex}$	.948	**5.1**	1.598	**20.1**	3.021	**39.6**	4.959	**50.4**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.940	**5.9**	1.732	**13.4**	3.637	**27.3**	6.234	**37.7**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.936	**6.4**	1.846	**7.7**	4.502	**9.9**	9.066	**9.3**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.936	**6.4**	1.846	**7.7**	4.502	**9.9**	9.066	**9.3**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.938	**6.2**	1.700	**15.0**	3.631	**27.4**	6.163	**38.4**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.937	**6.3**	1.708	**14.6**	3.686	**26.3**	6.305	**36.9**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.938	**6.2**	1.705	**14.7**	3.670	**26.6**	6.291	**37.1**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.938	**6.2**	1.700	**15.0**	3.631	**27.4**	6.163	**38.4**
			$\hat{\psi}_{GEE-ex}$	.946	**5.4**	1.587	**20.7**	3.075	**38.5**	5.035	**49.7**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.938	**6.2**	1.700	**15.0**	3.631	**27.4**	6.163	**38.4**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.933	**6.7**	1.807	**9.7**	4.468	**10.6**	8.834	**11.7**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.933	**6.7**	1.807	**9.7**	4.468	**10.6**	8.834	**11.7**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.951	**4.9**	1.716	**14.2**	3.597	**28.1**	6.183	**38.2**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.951	**4.9**	1.725	**13.8**	3.653	**26.9**	6.324	**36.8**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.951	**4.9**	1.723	**13.9**	3.639	**27.2**	6.311	**36.9**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.951	**4.9**	1.716	**14.2**	3.597	**28.1**	6.183	**38.2**
			$\hat{\psi}_{GEE-ex}$	.956	**4.4**	1.624	**18.8**	3.151	**36.9**	5.226	**47.7**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.951	**4.9**	1.716	**14.2**	3.597	**28.1**	6.183	**38.2**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.947	**5.3**	1.823	**8.9**	4.422	**11.6**	8.854	**11.4**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.947	**5.3**	1.823	**8.9**	4.422	**11.6**	8.854	**11.4**

Table 5.2.1(c): Percentage Bias in the Empirical Estimates of Odds Ratio

Entire Population

Average exposures per year: 2

Average events per year: 2

Rho=0.9

n	Unit of analysis	Statistical Method	Est.	*OR*							
				1		2		5		10	
				Emp.	Δ%	Emp.	Δ%	Emp.	Δ%	Emp.	Δ%
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.955	**4.5**	1.735	**13.2**	3.613	**27.7**	6.114	**38.9**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.954	**4.6**	1.744	**12.8**	3.671	**26.6**	6.249	**37.5**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.955	**4.5**	1.741	**13.0**	3.655	**26.9**	6.234	**37.7**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.955	**4.5**	1.735	**13.2**	3.613	**27.7**	6.114	**38.9**
			$\hat{\psi}_{GEE-ex}$	.959	**4.1**	1.593	**20.3**	2.973	**40.5**	4.932	**50.7**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.955	**4.5**	1.735	**13.2**	3.613	**27.7**	6.114	**38.9**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.951	**4.9**	1.848	**7.6**	4.459	**10.8**	8.786	**12.1**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.951	**4.9**	1.848	**7.6**	4.459	**10.8**	8.786	**12.1**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.946	**5.4**	1.731	**13.4**	3.613	**27.7**	6.153	**38.4**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.945	**5.5**	1.741	**13.0**	3.667	**26.7**	6.293	**37.1**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.945	**5.5**	1.738	**13.1**	3.651	**27.0**	6.278	**37.2**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.946	**5.4**	1.731	**13.4**	3.613	**27.7**	6.153	**38.4**
			$\hat{\psi}_{GEE-ex}$	.952	**4.8**	1.610	**19.5**	3.086	**38.3**	5.063	**49.4**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.946	**5.4**	1.731	**13.4**	3.613	**27.7**	6.153	**38.4**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.941	**5.9**	1.844	**7.8**	4.455	**10.9**	8.769	**12.3**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.941	**5.9**	1.844	**7.8**	4.455	**10.9**	8.769	**12.3**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.964	**3.6**	1.706	**14.7**	3.632	**27.4**	6.158	**38.4**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.963	**3.7**	1.715	**14.3**	3.690	**26.2**	6.302	**36.9**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.963	**3.7**	1.712	**14.4**	3.674	**26.5**	6.287	**37.1**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.964	**3.6**	1.706	**14.7**	3.632	**27.4**	6.158	**38.4**
			$\hat{\psi}_{GEE-ex}$	.967	**3.3**	1.616	**19.2**	3.178	**36.4**	5.210	**47.9**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.964	**3.6**	1.706	**14.7**	3.632	**27.4**	6.158	**38.4**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.960	**3.9**	1.812	**9.4**	4.460	**10.8**	8.852	**11.5**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.960	**3.9**	1.812	**9.4**	4.460	**10.8**	8.852	**11.5**

Table 5.2.2(a): Percentage Bias in the Empirical Estimates of Odds Ratio

	subgroup1	*subgroup2*
Average exposures per year:	***10***	***2***
Average events per year:	***10***	***2***

Rho=0

n	Unit of analysis	Statistical Method	Est.	*OR* = 1		*OR* = 2		*OR* = 5		*OR* = 10	
				Emp.	Δ%	Emp.	Δ%	Emp.	Δ%	Emp.	Δ%
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.985	**1.5**	1.762	**11.9**	3.815	**23.7**	7.018	**29.8**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.984	**1.6**	1.819	**9.0**	4.144	**17.1**	7.803	**21.9**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.984	**1.6**	1.818	**9.1**	4.147	**17.0**	7.805	**21.9**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.985	**1.5**	1.762	**11.9**	3.815	**23.7**	7.018	**29.8**
			$\hat{\psi}_{GEE-ex}$	.988	**1.2**	1.622	**18.9**	3.924	**21.5**	7.431	**25.7**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.985	**1.5**	1.762	**11.9**	3.815	**23.7**	7.018	**29.8**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.983	**1.7**	1.905	**4.7**	4.670	**6.6**	9.204	**7.9**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.983	**1.7**	1.905	**4.7**	4.670	**6.6**	9.204	**7.9**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.986	**1.3**	1.760	**12.0**	3.809	**23.8**	7.025	**29.7**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.985	**1.4**	1.818	**9.1**	4.125	**17.5**	7.820	**21.8**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.986	**1.3**	1.818	**9.1**	4.128	**17.4**	7.822	**21.8**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.986	**1.3**	1.760	**12.0**	3.809	**23.8**	7.025	**29.7**
			$\hat{\psi}_{GEE-ex}$	.989	**1.1**	1.623	**18.8**	3.906	**21.9**	7.425	**25.8**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.986	**1.3**	1.760	**12.0**	3.809	**23.8**	7.025	**29.7**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.984	**1.5**	1.903	**4.9**	4.635	**7.3**	9.220	**7.8**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.984	**1.5**	1.903	**4.9**	4.635	**7.3**	9.220	**7.8**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.985	**1.4**	1.758	**12.1**	3.801	**23.9**	7.001	**30.0**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.984	**1.5**	1.816	**9.2**	4.124	**17.5**	7.812	**21.9**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.984	**1.5**	1.816	**9.2**	4.127	**17.4**	7.815	**21.9**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.985	**1.4**	1.758	**12.1**	3.801	**23.9**	7.001	**30.0**
			$\hat{\psi}_{GEE-ex}$	.988	**1.2**	1.634	**18.3**	3.902	**21.9**	7.425	**25.8**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.985	**1.4**	1.758	**12.1**	3.801	**23.9**	7.001	**30.0**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.983	**1.6**	1.902	**4.9**	4.640	**7.2**	9.229	**7.7**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.983	**1.6**	1.902	**4.9**	4.640	**7.2**	9.229	**7.7**

Table 5.2.2(b): Percentage Bias in the Empirical Estimates of Odds Ratio

subgroup1 ***subgroup2***

Average exposures per year: ***10*** ***2***

Average events per year: ***10*** ***2***

Rho=0.5

n	Unit of analysis	Statistical Method	Est.	*OR*							
				1		2		5		10	
				Emp.	Δ%	Emp.	Δ%	Emp.	Δ%	Emp.	Δ%
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.989	**1.1**	1.725	**13.8**	3.653	**26.9**	6.632	**33.7**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.988	**1.2**	1.803	**9.8**	4.107	**17.8**	7.753	**22.5**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.988	**1.2**	1.802	**9.9**	4.111	**17.7**	7.757	**22.4**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.989	**1.1**	1.725	**13.8**	3.653	**26.9**	6.632	**33.7**
			$\hat{\psi}_{GEE-ex}$	.992	**.8**	1.536	**23.2**	3.861	**22.8**	7.146	**28.5**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.989	**1.1**	1.725	**13.8**	3.653	**26.9**	6.632	**33.7**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.987	**1.3**	1.888	**5.6**	4.648	**7.0**	9.217	**7.8**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.987	**1.3**	1.888	**5.6**	4.648	**7.0**	9.217	**7.8**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.988	**1.2**	1.729	**13.5**	3.654	**26.9**	6.610	**33.9**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.987	**1.3**	1.808	**9.6**	4.101	**17.9**	7.746	**22.5**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.987	**1.3**	1.808	**9.6**	4.105	**17.9**	7.749	**22.5**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.988	**1.2**	1.729	**13.5**	3.654	**26.9**	6.610	**33.9**
			$\hat{\psi}_{GEE-ex}$	.991	**.9**	1.553	**22.3**	3.856	**22.8**	7.146	**28.5**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.988	**1.2**	1.729	**13.5**	3.654	**26.9**	6.610	**33.9**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.986	**1.4**	1.895	**5.3**	4.634	**7.3**	9.238	**7.6**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.986	**1.4**	1.895	**5.3**	4.634	**7.3**	9.238	**7.6**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.985	**1.5**	1.728	**13.6**	3.645	**27.0**	6.599	**34.0**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.984	**1.6**	1.811	**9.5**	4.093	**18.1**	7.716	**22.8**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.984	**1.6**	1.810	**9.6**	4.097	**18.0**	7.720	**22.7**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.985	**1.5**	1.728	**13.6**	3.645	**27.0**	6.599	**34.0**
			$\hat{\psi}_{GEE-ex}$	.989	**1.0**	1.561	**21.9**	3.849	**23.0**	7.092	**29.1**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.985	**1.5**	1.728	**13.6**	3.645	**27.0**	6.599	**34.0**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.983	**1.7**	1.895	**5.2**	4.624	**7.5**	9.212	**7.9**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.983	**1.7**	1.895	**5.2**	4.624	**7.5**	9.212	**7.9**

Table 5.2.2(c): Percentage Bias in the Empirical Estimates of Odds Ratio

subgroup1 ***subgroup2***

Average exposures per year: ***10*** ***2***

Average events per year: ***10*** ***2***

Rho=0.9

n	Unit of analysis	Statistical Method	Est.	*OR*							
				1		2		5		10	
				Emp.	Δ%	Emp.	Δ%	Emp.	Δ%	Emp.	Δ%
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.983	**1.7**	1.693	**15.4**	3.452	**30.9**	6.211	**37.9**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.981	**1.9**	1.798	**10.0**	4.053	**18.9**	6.353	**36.5**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.981	**1.9**	1.797	**10.1**	4.058	**18.8**	6.357	**36.4**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.983	**1.7**	1.693	**15.4**	3.452	**30.9**	6.211	**37.9**
			$\hat{\psi}_{GEE-ex}$	.988	**1.2**	1.448	**27.6**	3.772	**24.5**	4.997	**50.0**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.983	**1.7**	1.693	**15.4**	3.452	**30.9**	6.211	**37.9**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.980	**2.0**	1.884	**5.8**	4.631	**7.4**	8.974	**10.3**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.980	**2.0**	1.884	**5.8**	4.631	**7.4**	8.974	**10.3**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.979	**2.1**	1.697	**15.2**	3.445	**31.1**	6.192	**38.1**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.977	**2.3**	1.804	**9.8**	4.054	**18.9**	6.284	**37.2**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.977	**2.3**	1.803	**9.8**	4.059	**18.8**	6.289	**37.1**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.979	**2.1**	1.697	**15.2**	3.445	**31.1**	6.192	**38.1**
			$\hat{\psi}_{GEE-ex}$	.985	**1.5**	1.459	**27.0**	3.774	**24.5**	5.157	**48.5**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.979	**2.1**	1.697	**15.2**	3.445	**31.1**	6.192	**38.1**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.975	**2.5**	1.894	**5.3**	4.626	**7.5**	8.931	**10.7**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.975	**2.5**	1.894	**5.3**	4.626	**7.5**	8.931	**10.7**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.981	**1.9**	1.692	**15.4**	3.440	**31.2**	6.199	**38.0**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.979	**2.1**	1.802	**9.9**	4.053	**18.9**	6.345	**36.5**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.979	**2.1**	1.801	**9.9**	4.059	**18.8**	6.349	**36.4**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.981	**1.9**	1.692	**15.4**	3.440	**31.2**	6.199	**38.0**
			$\hat{\psi}_{GEE-ex}$	.986	**1.4**	1.478	**26.1**	3.773	**24.5**	5.240	**47.6**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.981	**1.9**	1.692	**15.4**	3.440	**31.2**	6.199	**38.0**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.978	**2.2**	1.890	**5.5**	4.616	**7.7**	8.869	**11.3**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.978	**2.2**	1.890	**5.5**	4.616	**7.7**	8.869	**11.3**

Table 5.2.3(a): Percentage Bias in the Empirical Estimates of Odds Ratio

	subgroup1	*subgroup2*
Average exposures per year:	***20***	***2***
Average events per year:	***20***	***2***

Rho=0

n	Unit of analysis	Statistical Method	Est.	*OR* = 1		*OR* = 2		*OR* = 5		*OR* = 10	
				Emp.	Δ%	Emp.	Δ%	Emp.	Δ%	Emp.	Δ%
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.994	**.6**	1.716	**14.2**	3.668	**26.6**	6.722	**32.8**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.994	**.6**	1.859	**7.0**	4.368	**12.6**	8.472	**15.3**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.994	**.6**	1.862	**6.9**	4.375	**12.5**	8.478	**15.2**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.994	**.6**	1.716	**14.2**	3.668	**26.6**	6.722	**32.8**
			$\hat{\psi}_{GEE-ex}$	.996	**.4**	1.720	**14.0**	4.132	**17.4**	7.729	**22.7**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.994	**.6**	1.716	**14.2**	3.668	**26.6**	6.722	**32.8**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.993	**.7**	1.923	**3.8**	4.707	**5.9**	9.398	**6.0**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.993	**.7**	1.923	**3.8**	4.707	**5.9**	9.398	**6.0**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.993	**.7**	1.716	**14.2**	3.680	**26.4**	6.729	**32.7**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.992	**.8**	1.860	**7.0**	4.361	**12.8**	8.476	**15.2**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.992	**.8**	1.862	**6.9**	4.365	**12.7**	8.479	**15.1**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.993	**.7**	1.716	**14.2**	3.680	**26.4**	6.729	**32.7**
			$\hat{\psi}_{GEE-ex}$	.996	**.4**	1.718	**14.1**	4.126	**17.5**	7.721	**22.8**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.993	**.7**	1.716	**14.2**	3.680	**26.4**	6.729	**32.7**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.992	**.8**	1.925	**3.8**	4.707	**5.9**	9.409	**5.9**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.992	**.8**	1.925	**3.8**	4.706	**5.9**	9.409	**5.9**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.993	**.7**	1.710	**14.5**	3.677	**26.5**	6.693	**33.1**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.992	**.8**	1.855	**7.3**	4.370	**12.6**	8.472	**15.3**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.992	**.8**	1.856	**7.2**	4.375	**12.5**	8.476	**15.2**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.993	**.7**	1.710	**14.5**	3.677	**26.5**	6.693	**33.1**
			$\hat{\psi}_{GEE-ex}$	.995	**.5**	1.712	**14.4**	4.132	**17.4**	7.729	**22.7**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.993	**.7**	1.710	**14.5**	3.677	**26.5**	6.693	**33.1**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.991	**.9**	1.919	**4.1**	4.711	**5.7**	9.417	**5.8**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.991	**.9**	1.919	**4.1**	4.711	**5.7**	9.417	**5.8**

Table 5.2.3(b): Percentage Bias in the Empirical Estimates of Odds Ratio

	subgroup1	*subgroup2*
Average exposures per year:	***20***	***2***
Average events per year:	***20***	***2***

Rho=0.5

n	Unit of analysis	Statistical Method	Est.	*OR* = 1		*OR* = 2		*OR* = 5		*OR* = 10	
				Emp.	Δ%	Emp.	Δ%	Emp.	Δ%	Emp.	Δ%
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.992	**.8**	1.645	**17.8**	3.297	**34.1**	5.768	**42.3**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.990	**1.0**	1.852	**7.4**	4.314	**13.7**	8.257	**17.4**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.990	**1.0**	1.849	**7.5**	4.320	**13.6**	8.261	**17.3**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.992	**.8**	1.645	**17.8**	3.297	**34.1**	5.768	**42.3**
			$\hat{\psi}_{GEE-ex}$	.996	**.4**	1.684	**15.8**	4.037	**19.3**	7.407	**25.9**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.992	**.8**	1.645	**17.8**	3.297	**34.1**	5.768	**42.3**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.989	**1.1**	1.920	**3.9**	4.691	**6.2**	9.344	**6.6**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.989	**1.1**	1.920	**3.9**	4.691	**6.2**	9.344	**6.6**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.990	**1.0**	1.640	**18.0**	3.317	**33.7**	5.822	**41.8**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.987	**1.3**	1.849	**7.5**	4.311	**13.8**	8.277	**17.2**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.987	**1.3**	1.849	**7.5**	4.310	**13.8**	8.276	**17.2**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.990	**1.0**	1.640	**18.0**	3.317	**33.7**	5.822	**41.8**
			$\hat{\psi}_{GEE-ex}$	.995	**.5**	1.685	**15.8**	4.036	**19.3**	7.429	**25.7**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.990	**1.0**	1.640	**18.0**	3.317	**33.7**	5.822	**41.8**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.986	**1.4**	1.917	**4.2**	4.693	**6.1**	9.349	**6.5**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.986	**1.4**	1.917	**4.2**	4.693	**6.1**	9.349	**6.5**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.991	**.9**	1.641	**17.9**	2.813	**43.7**	5.800	**42.0**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.989	**1.1**	1.850	**7.5**	4.196	**16.1**	8.256	**17.4**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.989	**1.1**	1.850	**7.5**	4.200	**16.0**	8.261	**17.3**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.991	**.9**	1.641	**17.9**	2.813	**43.7**	5.800	**42.0**
			$\hat{\psi}_{GEE-ex}$	.995	**.5**	1.686	**15.7**	3.889	**22.2**	7.421	**25.8**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.991	**.9**	1.641	**17.9**	2.813	**43.7**	5.800	**42.0**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.988	**1.2**	1.915	**4.2**	4.661	**6.8**	9.326	**6.7**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.988	**1.2**	1.915	**4.2**	4.661	**6.8**	9.326	**6.7**

Table 5.2.3(c): Percentage Bias in the Empirical Estimates of Odds Ratio

subgroup1 ***subgroup2***

Average exposures per year: ***20*** ***2***

Average events per year: ***20*** ***2***

Rho=0.9

n	Unit of analysis	Statistical Method	Est.	*OR* = 1		*OR* = 2		*OR* = 5		*OR* = 10	
				Emp.	Δ%	Emp.	Δ%	Emp.	Δ%	Emp.	Δ%
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.987	**1.3**	1.550	**22.5**	2.847	**43.1**	4.700	**53.0**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.983	**1.7**	1.820	**9.0**	4.184	**16.3**	7.851	**21.5**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.983	**1.7**	1.819	**9.1**	4.190	**16.2**	7.856	**21.4**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.987	**1.3**	1.550	**22.5**	2.847	**43.1**	4.700	**53.0**
			$\hat{\psi}_{GEE-ex}$	.993	**.7**	1.482	**25.9**	3.885	**22.3**	6.965	**30.3**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.987	**1.3**	1.550	**22.5**	2.847	**43.1**	4.700	**53.0**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.982	**1.8**	1.892	**5.4**	4.652	**6.9**	9.275	**7.3**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.982	**1.8**	1.892	**5.4**	4.652	**6.9**	9.275	**7.3**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.989	**1.1**	1.552	**22.4**	2.815	**43.7**	4.668	**53.3**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.986	**1.4**	1.833	**8.4**	4.181	**16.4**	7.863	**21.4**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.986	**1.4**	1.833	**8.4**	4.185	**16.3**	7.867	**21.3**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.989	**1.1**	1.552	**22.4**	2.815	**43.7**	4.668	**53.3**
			$\hat{\psi}_{GEE-ex}$	.995	**.5**	1.500	**25.0**	3.877	**22.5**	6.964	**30.4**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.989	**1.1**	1.552	**22.4**	2.815	**43.7**	4.668	**53.3**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.985	**1.5**	1.908	**4.6**	4.651	**6.9**	9.243	**7.57**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.985	**1.5**	1.908	**4.6**	4.651	**6.9**	9.243	**7.57**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.988	**1.2**	1.541	**23.0**	2.813	**43.7**	4.652	**53.5**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.984	**1.6**	1.821	**9.0**	4.196	**16.1**	7.873	**21.3**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.984	**1.6**	1.821	**9.0**	4.200	**16.0**	7.878	**21.2**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.988	**1.2**	1.541	**23.0**	2.813	**43.7**	4.652	**53.5**
			$\hat{\psi}_{GEE-ex}$	.994	**.6**	1.503	**24.8**	3.889	**22.2**	6.964	**30.3**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.988	**1.2**	1.541	**23.0**	2.813	**43.7**	4.652	**53.5**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.983	**1.7**	1.894	**5.3**	4.661	**6.8**	9.252	**7.5**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.983	**1.7**	1.894	**5.3**	4.661	**6.8**	9.252	**7.5**

Table 5.3.1(a): Mean squared error of estimate of the logarithm of Odds Ratio

Entire Population

Average exposures per year: 2

Average events per year: 2

Rho=0

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.035	**.049**	-.145	**.056**	-.320	**.124**	-.480	**.248**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.035	**.050**	-.140	**.055**	-.306	**.115**	-.457	**.228**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.035	**.050**	-.142	**.055**	-.310	**.118**	-.459	**.229**
		G.E.E	$\hat{\psi}_{GEE-ind}$	-.035	**.049**	-.145	**.056**	-.320	**.124**	-.480	**.248**
			$\hat{\psi}_{GEE-ex}$	-.030	**.037**	-.228	**.081**	-.502	**.285**	-.700	**.523**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	-.035	**.049**	-.145	**.056**	-.320	**.124**	-.480	**.248**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.039	**.059**	-.083	**.051**	-.108	**.046**	-.112	**.048**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.039	**.059**	-.083	**.051**	-.108	**.046**	-.112	**.048**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.062	**.034**	-.154	**.044**	-.323	**.118**	-.489	**.246**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.063	**.035**	-.149	**.043**	-.308	**.109**	-.466	**.225**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.063	**.034**	-.150	**.043**	-.312	**.112**	-.469	**.226**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.062	**.034**	-.154	**.044**	-.323	**.118**	-.489	**.246**
			$\hat{\psi}_{GEE-ex}$	-.055	**.027**	-.224	**.067**	-.488	**.257**	-.690	**.495**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.062	**.034**	-.154	**.044**	-.323	**.118**	-.489	**.246**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.068	**.040**	-.090	**.034**	-.109	**.038**	-.138	**.035**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.068	**.040**	-.090	**.034**	-.109	**.038**	-.138	**.035**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.050	**.017**	-.159	**.036**	-.327	**.114**	-.486	**.240**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.050	**.017**	-.154	**.034**	-.312	**.104**	-.463	**.219**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.050	**.017**	-.155	**.035**	-.316	**.106**	-.465	**.220**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.050	**.017**	-.159	**.036**	-.327	**.114**	-.486	**.240**
			$\hat{\psi}_{GEE-ex}$	-.045	**.014**	-.213	**.055**	-.468	**.228**	-.649	**.430**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.050	**.017**	-.159	**.036**	-.327	**.114**	-.486	**.240**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.053	**.020**	-.099	**.023**	-.119	**.024**	-.129	**.026**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.053	**.020**	-.099	**.023**	-.119	**.024**	-.129	**.026**

Table 5.3.1(b): Mean squared error of estimate of the logarithm of Odds Ratio

Entire Population

Average exposures per year: 2

Average events per year: 2

Rho=0.5

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.062	**.054**	-.144	**.060**	-.318	**.125**	-.473	**.237**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.062	**.055**	-.138	**.060**	-.303	**.117**	-.449	**.216**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.062	**.055**	-.141	**.060**	-.308	**.120**	-.452	**.217**
		G.E.E	$\hat{\psi}_{GEE-ind}$	-.062	**.054**	-.144	**.060**	-.318	**.125**	-.473	**.237**
			$\hat{\psi}_{GEE-ex}$	-.053	**.039**	-.224	**.084**	-.504	**.284**	-.702	**.520**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	-.062	**.054**	-.144	**.060**	-.318	**.125**	-.473	**.237**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.066	**.063**	-.080	**.056**	-.105	**.049**	-.098	**.042**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.066	**.063**	-.080	**.056**	-.105	**.049**	-.098	**.042**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.064	**.034**	-.163	**.047**	-.320	**.117**	-.484	**.243**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.065	**.034**	-.158	**.046**	-.305	**.108**	-.462	**.221**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.065	**.034**	-.159	**.046**	-.309	**.110**	-.465	**.223**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.064	**.034**	-.163	**.047**	-.320	**.117**	-.484	**.243**
			$\hat{\psi}_{GEE-ex}$	-.055	**.026**	-.231	**.072**	-.486	**.258**	-.687	**.489**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.064	**.034**	-.163	**.047**	-.320	**.117**	-.484	**.243**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.069	**.040**	-.102	**.037**	-.112	**.034**	-.124	**.034**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.069	**.040**	-.102	**.037**	-.113	**.034**	-.124	**.034**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.050	**.018**	-.153	**.034**	-.329	**.116**	-.481	**.236**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.050	**.018**	-.148	**.033**	-.314	**.106**	-.459	**.215**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.050	**.018**	-.149	**.033**	-.318	**.108**	-.462	**.216**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.050	**.018**	-.153	**.034**	-.329	**.116**	-.481	**.236**
			$\hat{\psi}_{GEE-ex}$	-.045	**.015**	-.208	**.053**	-.462	**.223**	-.649	**.431**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.050	**.018**	-.153	**.034**	-.329	**.116**	-.481	**.236**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.055	**.021**	-.093	**.022**	-.123	**.026**	-.122	**.024**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.055	**.021**	-.093	**.022**	-.123	**.026**	-.122	**.024**

Table 5.3.1(c): Mean squared error of estimate of the logarithm of Odds Ratio

Entire Population

Average exposures per year: 2

Average events per year: 2

Rho=0.9

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.046	**.057**	-.142	**.056**	-.325	**.128**	-.492	**.256**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.047	**.057**	-.137	**.056**	-.309	**.118**	-.471	**.236**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.046	**.057**	-.139	**.056**	-.313	**.121**	-.473	**.237**
		G.E.E	$\hat{\psi}_{GEE-ind}$	-.046	**.057**	-.142	**.056**	-.325	**.128**	-.492	**.256**
			$\hat{\psi}_{GEE-ex}$	-.042	**.043**	-.227	**.081**	-.520	**.303**	-.707	**.527**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	-.046	**.057**	-.142	**.056**	-.325	**.128**	-.492	**.256**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.050	**.065**	-.079	**.052**	-.115	**.049**	-.130	**.049**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.050	**.065**	-.079	**.052**	-.115	**.049**	-.130	**.049**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.056	**.033**	-.144	**.042**	-.325	**.119**	-.486	**.244**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.056	**.033**	-.139	**.041**	-.310	**.110**	-.464	**.223**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.056	**.033**	-.140	**.041**	-.314	**.113**	-.468	**.224**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.056	**.033**	-.144	**.042**	-.325	**.119**	-.486	**.244**
			$\hat{\psi}_{GEE-ex}$	-.049	**.025**	-.217	**.065**	-.483	**.253**	-.681	**.481**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.056	**.033**	-.144	**.042**	-.325	**.119**	-.486	**.244**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.061	**.039**	-.081	**.034**	-.115	**.035**	-.132	**.035**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.061	**.039**	-.081	**.034**	-.116	**.035**	-.132	**.035**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.037	**.016**	-.159	**.036**	-.320	**.109**	-.485	**.239**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.037	**.016**	-.154	**.034**	-.304	**.099**	-.462	**.217**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.037	**.016**	-.155	**.035**	-.308	**.102**	-.465	**.219**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.037	**.016**	-.159	**.036**	-.320	**.109**	-.485	**.239**
			$\hat{\psi}_{GEE-ex}$	-.033	**.013**	-.213	**.055**	-.453	**.215**	-.652	**.435**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.037	**.016**	-.159	**.036**	-.320	**.109**	-.485	**.239**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.040	**.018**	-.099	**.023**	-.114	**.023**	-.122	**.024**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.040	**.018**	-.099	**.023**	-.114	**.023**	-.122	**.024**

Table 5.3.2(a): Mean squared error of estimate of the logarithm of Odds Ratio

	subgroup1	*subgroup2*
Average exposures per year:	***10***	***2***
Average events per year:	***10***	***2***

Rho=0

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.015	**.005**	-.127	**.019**	-.270	**.076**	-.354	**.129**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.016	**.005**	-.095	**.012**	-.188	**.037**	-.248	**.063**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.016	**.005**	-.095	**.012**	-.187	**.037**	-.247	**.063**
		G.E.E	$\hat{\psi}_{GEE-ind}$	-.015	**.005**	-.127	**.019**	-.270	**.076**	-.354	**.129**
			$\hat{\psi}_{GEE-ex}$	-.012	**.003**	-.210	**.047**	-.242	**.061**	-.297	**.090**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	-.015	**.005**	-.127	**.019**	-.270	**.076**	-.354	**.129**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.017	**.006**	-.049	**.006**	-.068	**.008**	-.083	**.009**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.017	**.006**	-.049	**.006**	-.068	**.008**	-.083	**.009**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.014	**.002**	-.128	**.018**	-.272	**.076**	-.353	**.127**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.015	**.003**	-.095	**.011**	-.192	**.038**	-.246	**.061**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.015	**.003**	-.095	**.011**	-.191	**.038**	-.245	**.061**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.014	**.002**	-.128	**.018**	-.272	**.076**	-.353	**.127**
			$\hat{\psi}_{GEE-ex}$	-.011	**.001**	-.208	**.046**	-.247	**.062**	-.298	**.090**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.014	**.002**	-.128	**.018**	-.272	**.076**	-.353	**.127**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.016	**.003**	-.050	**.005**	-.076	**.007**	-.081	**.008**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.016	**.003**	-.050	**.005**	-.076	**.007**	-.081	**.008**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.015	**.001**	-.129	**.018**	-.274	**.076**	-.357	**.128**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.017	**.001**	-.096	**.010**	-.193	**.038**	-.247	**.062**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.016	**.001**	-.097	**.010**	-.192	**.037**	-.246	**.062**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.015	**.001**	-.129	**.018**	-.274	**.076**	-.357	**.128**
			$\hat{\psi}_{GEE-ex}$	-.012	**.001**	-.202	**.042**	-.248	**.062**	-.298	**.089**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.015	**.001**	-.129	**.018**	-.274	**.076**	-.357	**.128**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.017	**.002**	-.050	**.004**	-.075	**.006**	-.080	**.007**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.017	**.002**	-.050	**.004**	-.075	**.006**	-.080	**.007**

Table 5.3.2(b): Mean squared error of estimate of the logarithm of Odds Ratio

	subgroup1	*subgroup2*
Average exposures per year:	***10***	***2***
Average events per year:	***10***	***2***

Rho=0.5

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.011	**.005**	-.148	**.026**	-.314	**.102**	-.411	**.174**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.012	**.006**	-.103	**.015**	-.197	**.042**	-.255	**.067**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.012	**.006**	-.104	**.015**	-.196	**.041**	-.254	**.067**
		G.E.E	$\hat{\psi}_{GEE-ind}$	-.011	**.005**	-.148	**.026**	-.314	**.102**	-.411	**.174**
			$\hat{\psi}_{GEE-ex}$	-.008	**.002**	-.264	**.074**	-.259	**.070**	-.336	**.118**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	-.011	**.005**	-.148	**.026**	-.314	**.102**	-.411	**.174**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.013	**.007**	-.057	**.008**	-.073	**.010**	-.082	**.011**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.013	**.007**	-.057	**.008**	-.073	**.010**	-.082	**.011**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.012	**.003**	-.146	**.024**	-.314	**.101**	-.414	**.175**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.013	**.004**	-.101	**.013**	-.198	**.041**	-.255	**.067**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.013	**.004**	-.101	**.013**	-.197	**.041**	-.254	**.067**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.012	**.003**	-.146	**.024**	-.314	**.101**	-.414	**.175**
			$\hat{\psi}_{GEE-ex}$	-.009	**.002**	-.253	**.068**	-.260	**.101**	-.336	**.116**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.012	**.003**	-.146	**.024**	-.314	**.101**	-.414	**.175**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.014	**.004**	-.054	**.006**	-.076	**.009**	-.079	**.009**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.014	**.004**	-.054	**.006**	-.076	**.009**	-.079	**.009**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.015	**.002**	-.146	**.022**	-.316	**.101**	-.417	**.175**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.016	**.002**	-.099	**.011**	-.200	**.041**	-.259	**.068**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.016	**.002**	-.099	**.011**	-.199	**.041**	-.258	**.068**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.015	**.002**	-.146	**.022**	-.316	**.101**	-.417	**.175**
			$\hat{\psi}_{GEE-ex}$	-.011	**.001**	-.248	**.063**	-.262	**.070**	-.343	**.119**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.015	**.002**	-.146	**.022**	-.316	**.101**	-.416	**.175**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.017	**.002**	-.054	**.005**	-.078	**.007**	-.082	**.008**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.017	**.002**	-.054	**.005**	-.078	**.007**	-.082	**.008**

Table 5.3.2(c): Mean squared error of estimate of the logarithm of Odds Ratio

	subgroup1	*subgroup2*
Average exposures per year:	***10***	***2***
Average events per year:	***10***	***2***

Rho=0.9

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.017	**.010**	-.167	**.034**	-.370	**.142**	-.476	**.243**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.019	**.013**	-.106	**.019**	-.210	**.049**	-.454	**.222**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.019	**.012**	-.107	**.019**	-.209	**.048**	-.453	**.221**
		G.E.E	$\hat{\psi}_{GEE-ind}$	-.017	**.010**	-.167	**.034**	-.370	**.142**	-.476	**.243**
			$\hat{\psi}_{GEE-ex}$	-.012	**.005**	-.323	**.111**	-.282	**.085**	-.694	**.512**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	-.017	**.010**	-.167	**.034**	-.370	**.142**	-.476	**.243**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.021	**.014**	-.059	**.012**	-.077	**.014**	-.108	**.041**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.021	**.014**	-.059	**.012**	-.077	**.014**	-.108	**.041**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.021	**.006**	-.164	**.031**	-.373	**.142**	-.479	**.235**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.024	**.007**	-.103	**.015**	-.210	**.047**	-.465	**.221**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.024	**.007**	-.103	**.015**	-.208	**.047**	-.463	**.221**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.021	**.006**	-.164	**.031**	-.373	**.142**	-.479	**.235**
			$\hat{\psi}_{GEE-ex}$	-.015	**.003**	-.315	**.104**	-.281	**.083**	-.662	**.443**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.021	**.006**	-.164	**.031**	-.373	**.142**	-.479	**.235**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.025	**.008**	-.055	**.008**	-.078	**.010**	-.113	**.032**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.025	**.008**	-.055	**.008**	-.078	**.010**	-.113	**.032**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.019	**.003**	-.167	**.030**	-.374	**.141**	-.478	**.233**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.021	**.003**	-.104	**.013**	-.210	**.046**	-.455	**.212**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.021	**.003**	-.105	**.014**	-.208	**.045**	-.453	**.211**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.019	**.003**	-.167	**.030**	-.374	**.141**	-.478	**.233**
			$\hat{\psi}_{GEE-ex}$	-.014	**.002**	-.302	**.094**	-.282	**.081**	-.646	**.427**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.019	**.003**	-.167	**.030**	-.374	**.141**	-.478	**.233**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.023	**.004**	-.056	**.006**	-.080	**.009**	-.120	**.024**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.022	**.004**	-.056	**.006**	-.080	**.009**	-.120	**.024**

Table 5.3.3(a): Mean squared error of estimate of the logarithm of Odds Ratio

	subgroup1	*subgroup2*
Average exposures per year:	***20***	***2***
Average events per year:	***20***	***2***

Rho=0

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.006	**.001**	-.153	**.025**	-.310	**.101**	-.397	**.167**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.006	**.002**	-.073	**.007**	-.135	**.019**	-.166	**.029**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.006	**.002**	-.071	**.007**	-.134	**.019**	-.165	**.029**
		G.E.E	$\hat{\psi}_{GEE-ind}$	-.006	**.001**	-.153	**.025**	-.310	**.101**	-.397	**.167**
			$\hat{\psi}_{GEE-ex}$	-.004	**.001**	-.151	**.024**	-.191	**.037**	-.258	**.068**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	-.006	**.001**	-.153	**.025**	-.310	**.101**	-.397	**.167**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.007	**.002**	-.039	**.003**	-.060	**.005**	-.062	**.005**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.007	**.002**	-.039	**.003**	-.060	**.005**	-.062	**.005**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.007	**.001**	-.153	**.025**	-.307	**.097**	-.396	**.164**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.008	**.001**	-.073	**.006**	-.137	**.019**	-.165	**.028**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.008	**.001**	-.071	**.006**	-.136	**.019**	-.164	**.028**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.007	**.001**	-.153	**.025**	-.307	**.097**	-.396	**.164**
			$\hat{\psi}_{GEE-ex}$	-.004	**.001**	-.152	**.024**	-.192	**.037**	-.259	**.068**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.007	**.001**	-.153	**.025**	-.307	**.097**	-.396	**.164**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.008	**.001**	-.038	**.002**	-.060	**.004**	-.061	**.005**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.008	**.001**	-.038	**.002**	-.060	**.004**	-.061	**.005**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.007	**.001**	-.156	**.025**	-.307	**.096**	-.402	**.167**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.009	**.001**	-.075	**.006**	-.135	**.018**	-.165	**.029**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.009	**.001**	-.075	**.006**	-.134	**.017**	-.164	**.028**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.007	**.001**	-.156	**.025**	-.307	**.096**	-.402	**.167**
			$\hat{\psi}_{GEE-ex}$	-.005	**.001**	-.156	**.025**	-.191	**.037**	-.258	**.067**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.007	**.001**	-.156	**.025**	-.307	**.096**	-.402	**.167**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.009	**.001**	-.041	**.002**	-.06	**.004**	-.060	**.004**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.009	**.001**	-.041	**.002**	-.06	**.004**	-.060	**.004**

Table 5.3.3(b): Mean squared error of estimate of the logarithm of Odds Ratio

	subgroup1	*subgroup2*
Average exposures per year:	***20***	***2***
Average events per year:	***20***	***2***

Rho=0.5

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.008	**.002**	-.195	**.041**	-.416	**.181**	-.550	**.320**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.010	**.003**	-.077	**.008**	-.148	**.024**	-.192	**.039**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.010	**.003**	-.078	**.008**	-.146	**.023**	-.191	**.038**
		G.E.E	$\hat{\psi}_{GEE-ind}$	-.008	**.002**	-.195	**.041**	-.416	**.181**	-.550	**.320**
			$\hat{\psi}_{GEE-ex}$	-.004	**.001**	-.172	**.033**	-.214	**.048**	-.300	**.093**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	-.008	**.002**	-.195	**.041**	-.416	**.181**	-.550	**.320**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.011	**.004**	-.041	**.004**	-.064	**.006**	-.068	**.007**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.011	**.004**	-.041	**.004**	-.064	**.006**	-.068	**.007**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.010	**.001**	-.198	**.041**	-.410	**.173**	-.541	**.302**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.013	**.002**	-.078	**.007**	-.148	**.023**	-.189	**.037**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.013	**.002**	-.079	**.007**	-.148	**.023**	-.189	**.037**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.010	**.001**	-.198	**.041**	-.410	**.173**	-.541	**.302**
			$\hat{\psi}_{GEE-ex}$	-.005	**.001**	-.172	**.031**	-.214	**.047**	-.297	**.090**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.010	**.001**	-.198	**.041**	-.410	**.173**	-.541	**.302**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.014	**.002**	-.043	**.003**	-.063	**.005**	-.067	**.006**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.014	**.002**	-.043	**.003**	-.063	**.005**	-.067	**.006**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.009	**.001**	-.197	**.040**	-.411	**.172**	-.545	**.303**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.011	**.001**	-.078	**.007**	-.147	**.022**	-.192	**.035**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.011	**.001**	-.078	**.007**	-.147	**.022**	-.192	**.035**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.009	**.001**	-.197	**.040**	-.411	**.172**	-.545	**.303**
			$\hat{\psi}_{GEE-ex}$	-.005	**.000**	-.170	**.030**	-.213	**.046**	-.298	**.090**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.009	**.001**	-.197	**.040**	-.411	**.172**	-.545	**.303**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.012	**.001**	-.043	**.003**	-.062	**.005**	-.069	**.006**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.012	**.001**	-.043	**.003**	-.062	**.005**	-.069	**.006**

Table 5.3.3(c): Mean squared error of estimate of the logarithm of Odds Ratio

	subgroup1	*subgroup2*
Average exposures per year:	***20***	***2***
Average events per year:	***20***	***2***

Rho=0.9

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Bias	MSE	Bias	MSE	Bias	MSE	Bias	MSE
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.013	**.004**	-.255	**.068**	-.563	**.325**	-.755	**.584**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.018	**.007**	-.094	**.014**	-.178	**.036**	-.242	**.063**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.018	**.007**	-.094	**.014**	-.177	**.036**	-.241	**.063**
		G.E.E	$\hat{\psi}_{GEE-ind}$	-.013	**.004**	-.255	**.068**	-.563	**.325**	-.755	**.584**
			$\hat{\psi}_{GEE-ex}$	-.007	**.001**	-.300	**.110**	-.252	**.068**	-.362	**.135**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	-.013	**.004**	-.255	**.068**	-.563	**.325**	-.755	**.584**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.019	**.008**	-.056	**.009**	-.072	**.010**	-.075	**.010**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.019	**.008**	-.056	**.009**	-.072	**.010**	-.075	**.010**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.011	**.002**	-.254	**.066**	-.574	**.334**	-.762	**.589**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.015	**.004**	-.087	**.011**	-.179	**.034**	-.240	**.060**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.015	**.004**	-.087	**.011**	-.178	**.034**	-.239	**.060**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.011	**.002**	-.254	**.066**	-.574	**.334**	-.762	**.589**
			$\hat{\psi}_{GEE-ex}$	-.005	**.001**	-.288	**.100**	-.254	**.067**	-.362	**.134**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.011	**.002**	-.254	**.066**	-.574	**.334**	-.762	**.589**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.015	**.005**	-.047	**.006**	-.072	**.008**	-.079	**.009**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.015	**.005**	-.047	**.006**	-.072	**.008**	-.079	**.009**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	-.012	**.001**	-.261	**.069**	-.575	**.333**	-.765	**.590**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	-.016	**.002**	-.094	**.010**	-.175	**.032**	-.239	**.058**
		C.L.R.	$\hat{\psi}_{CLR-s}$	-.016	**.002**	-.094	**.010**	-.174	**.032**	-.238	**.058**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	-.012	**.001**	-.261	**.069**	-.575	**.333**	-.765	**.590**
			$\hat{\psi}_{GEE-ex}$	-.006	**.000**	-.285	**.093**	-.251	**.064**	-.362	**.132**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	-.012	**.001**	-.261	**.069**	-.575	**.333**	-.765	**.590**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	-.017	**.003**	-.054	**.005**	-.070	**.006**	-.078	**.007**
		C.L.R.	$\hat{\psi}_{CLR-e}$	-.017	**.003**	-.054	**.005**	-.070	**.006**	-.078	**.007**

Table 5.4.1(a): Ratio of the empirical vs. the model-based variances

Entire Population

Average exposures per year: 2

Average events per year: 2

Rho=0

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Var.	Ratio	Var.	Ratio	Var.	Ratio	Var.	Ratio
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0482	**.87**	.0347	**.89**	.0217	**.87**	.0184	**1.08**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0489	**.88**	.0355	**.90**	.0220	**.87**	.0192	**1.10**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0486	**.88**	.0351	**.89**	.0219	**.87**	.0191	**1.10**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.0482	**1.00**	.0347	**1.03**	.0217	**1.02**	.0184	**1.22**
			$\hat{\psi}_{GEE-ex}$	.0358	**.99**	.0291	**1.16**	.0322	**1.78**	.0340	**2.11**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.0482	**.95**	.0347	**.98**	.0217	**.98**	.0184	**1.23**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0575	**.95**	.0438	**.98**	.0340	**.96**	.0351	**1.08**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0575	**.95**	.0437	**.98**	.0340	**.96**	.0351	**1.08**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0301	**.93**	.0204	**.87**	.0142	**.92**	.0077	**.75**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0305	**.93**	.0208	**.88**	.0147	**.93**	.0080	**.77**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0304	**.93**	.0206	**.88**	.0144	**.92**	.0079	**.77**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0301	**1.02**	.0204	**.99**	.0142	**1.04**	.0077	**.84**
			$\hat{\psi}_{GEE-ex}$	.0235	**1.03**	.0171	**1.05**	.0197	**1.60**	.0191	**1.80**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0301	**1.00**	.0204	**.97**	.0142	**1.04**	.0077	**.86**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0350	**.99**	.0262	**.97**	.0257	**1.11**	.0163	**.86**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0349	**.99**	.0262	**.97**	.0257	**1.11**	.0163	**.86**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0147	**.91**	.0105	**.91**	.0064	**.83**	.0046	**.91**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0149	**.92**	.0107	**.92**	.0065	**.84**	.0047	**.91**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0149	**.92**	.0107	**.92**	.0065	**.84**	.0047	**.91**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0147	**1.01**	.0105	**1.02**	.0064	**.93**	.0046	**1.02**
			$\hat{\psi}_{GEE-ex}$	.0120	**1.00**	.0098	**1.14**	.0090	**1.24**	.0091	**1.49**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0147	**.99**	.0105	**1.00**	.0064	**.94**	.0046	**1.04**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0173	**.99**	.0132	**1.00**	.0100	**.93**	.0092	**.98**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0173	**.99**	.0132	**1.00**	.0100	**.93**	.0092	**.98**

Table 5.4.1(b): Ratio of the empirical vs. the model-based variances

Entire Population

Average exposures per year: 2

Average events per year: 2

Rho=0.5

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Var.	Ratio	Var.	Ratio	Var.	Ratio	Var.	Ratio
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0500	**.90**	.0397	**1.02**	.0241	**.96**	.0140	**.82**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0507	**.91**	.0405	**1.03**	.0247	**.97**	.0144	**.82**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0505	**.91**	.0402	**1.02**	.0245	**.97**	.0143	**.82**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.0500	**1.01**	.0397	**1.19**	.0241	**1.16**	.0140	**.93**
			$\hat{\psi}_{GEE-ex}$	.0361	**1.00**	.0332	**1.34**	.0304	**1.66**	.0281	**1.80**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.0500	**.97**	.0397	**1.13**	.0241	**1.09**	.0140	**.93**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0585	**.97**	.0495	**1.11**	.0384	**1.08**	.0319	**.98**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0585	**.97**	.0495	**1.10**	.0384	**1.08**	.0319	**.98**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0295	**.90**	.0207	**.89**	.0144	**.96**	.0084	**.82**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0300	**.91**	.0210	**.89**	.0146	**.96**	.0087	**.83**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0298	**.90**	.0208	**.89**	.0146	**.96**	.0087	**.83**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0295	**1.00**	.0207	**1.02**	.0144	**1.10**	.0084	**.93**
			$\hat{\psi}_{GEE-ex}$	.0229	**1.00**	.0184	**1.16**	.0214	**1.74**	.0178	**1.64**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0295	**.97**	.0207	**.99**	.0144	**1.08**	.0084	**.94**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0347	**.97**	.0263	**.99**	.0217	**1.03**	.0184	**.96**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0347	**.97**	.0263	**.99**	.0216	**1.03**	.0184	**.96**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0155	**.96**	.0106	**.92**	.0072	**.97**	.0046	**.91**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0157	**.97**	.0108	**.93**	.0074	**.98**	.0047	**.89**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0156	**.96**	.0108	**.93**	.0074	**.98**	.0047	**.89**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0155	**1.06**	.0106	**1.04**	.0072	**1.11**	.0046	**1.00**
			$\hat{\psi}_{GEE-ex}$	.0126	**1.05**	.0095	**1.11**	.0096	**1.42**	.0096	**1.49**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0155	**1.04**	.0106	**1.02**	.0072	**1.10**	.0046	**1.03**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0183	**1.04**	.0133	**1.01**	.0113	**1.09**	.0096	**1.01**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0183	**1.04**	.0133	**1.01**	.0113	**1.09**	.0096	**1.01**

Table 5.4.1(c): Ratio of the empirical vs. the model-based variances

Entire Population

Average exposures per year: 2

Average events per year: 2

Rho=0.9

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Var.	Ratio	Var.	Ratio	Var.	Ratio	Var.	Ratio
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0546	**.99**	.0363	**.93**	.0222	**.89**	.0142	**.84**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0553	**1.00**	.0369	**.94**	.0225	**.89**	.0148	**.85**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0550	**1.00**	.0367	**.93**	.0225	**.89**	.0148	**.85**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.0546	**1.12**	.0363	**1.06**	.0222	**1.02**	.0142	**.94**
			$\hat{\psi}_{GEE-ex}$	.0414	**1.14**	.0291	**1.15**	.0332	**1.79**	.0268	**1.66**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.0546	**1.07**	.0363	**1.02**	.0222	**1.00**	.0142	**.96**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0627	**1.05**	.0462	**1.03**	.0356	**1.00**	.0324	**1.01**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0627	**1.05**	.0462	**1.03**	.0356	**1.00**	.0324	**1.01**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0297	**.91**	.0213	**.91**	.0136	**.91**	.0084	**.83**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0301	**.92**	.0217	**.92**	.0139	**.92**	.0087	**.84**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0300	**.91**	.0216	**.92**	.0138	**.92**	.0086	**.84**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0297	**1.00**	.0213	**1.05**	.0136	**1.04**	.0084	**.93**
			$\hat{\psi}_{GEE-ex}$	.0230	**1.00**	.0183	**1.15**	.0200	**1.64**	.0179	**1.69**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0297	**.98**	.0213	**1.01**	.0136	**1.03**	.0084	**.94**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0352	**.99**	.0272	**1.02**	.0214	**1.02**	.0175	**.92**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0352	**.99**	.0272	**1.02**	.0214	**1.02**	.0175	**.92**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0142	**.88**	.0106	**.92**	.0068	**.92**	.0043	**.85**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0144	**.88**	.0108	**.93**	.0070	**.92**	.0043	**.82**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0143	**.88**	.0107	**.92**	.0069	**.92**	.0043	**.82**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0142	**.97**	.0106	**1.03**	.0068	**1.05**	.0043	**.95**
			$\hat{\psi}_{GEE-ex}$	.0116	**.98**	.0093	**1.09**	.0095	**1.40**	.0102	**1.59**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0142	**.95**	.0106	**1.01**	.0068	**1.03**	.0043	**.97**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0166	**.95**	.0135	**1.02**	.0104	**.99**	.0093	**.98**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0166	**.95**	.0135	**1.02**	.0104	**.99**	.0093	**.98**

Table 5.4.2(a): Ratio of the empirical vs. the model-based variances

	subgroup1	*subgroup2*
Average exposures per year:	***10***	***2***
Average events per year:	***10***	***2***

Rho=0

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Var.	Ratio	Var.	Ratio	Var.	Ratio	Var.	Ratio
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0045	**1.07**	.0027	**.88**	.0028	**1.47**	.0036	**2.78**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0050	**1.13**	.0028	**.88**	.0020	**.97**	.0015	**1.06**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0050	**1.12**	.0028	**.87**	.0020	**.98**	.0020	**1.06**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.0045	**1.29**	.0027	**1.05**	.0028	**1.03**	.0036	**1.07**
			$\hat{\psi}_{GEE-ex}$	.0028	**1.28**	.0035	**1.17**	.0021	**.92**	.0017	**.83**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.0045	**1.20**	.0027	**1.00**	.0028	**1.67**	.0036	**3.10**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0056	**1.19**	.0034	**.93**	.0028	**.97**	.0024	**.91**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0056	**1.19**	.0034	**.93**	.0028	**.97**	.0024	**.91**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0021	**.84**	.0016	**.89**	.0017	**1.48**	.0022	**2.79**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0024	**.88**	.0017	**.89**	.0012	**.96**	.0009	**1.09**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0023	**.88**	.0017	**.89**	.0012	**.96**	.0009	**1.09**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0021	**.99**	.0016	**1.02**	.0017	**1.02**	.0022	**1.06**
			$\hat{\psi}_{GEE-ex}$	.0013	**.99**	.0021	**1.15**	.0012	**.89**	.0008	**.80**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0021	**.94**	.0016	**1.02**	.0017	**1.68**	.0022	**3.11**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0027	**.94**	.0021	**.96**	.0015	**.85**	.0015	**.93**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0027	**.94**	.0021	**.96**	.0015	**.85**	.0015	**.93**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0011	**.86**	.0009	**.96**	.0009	**1.52**	.0011	**2.73**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0012	**.90**	.0009	**.94**	.0006	**1.08**	.0005	**1.16**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0012	**.90**	.0009	**.94**	.0007	**1.09**	.0006	**1.17**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0011	**1.00**	.0009	**1.08**	.0009	**1.02**	.0011	**1.06**
			$\hat{\psi}_{GEE-ex}$	.0007	**1.00**	.0011	**1.23**	.0007	**.97**	.0005	**.89**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0011	**.96**	.0009	**1.10**	.0009	**1.73**	.0011	**3.04**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0014	**.96**	.0011	**1.00**	.0008	**.98**	.0008	**.96**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0014	**.96**	.0011	**1.00**	.0008	**.98**	.0008	**.96**

Table 5.4.2(b): Ratio of the empirical vs. the model-based variances

	subgroup1	*subgroup2*
Average exposures per year:	***10***	***2***
Average events per year:	***10***	***2***

Rho=0.5

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Var.	Ratio	Var.	Ratio	Var.	Ratio	Var.	Ratio
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0051	**.79**	.0037	**.80**	.0037	**1.30**	.0054	**2.76**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0058	**.85**	.0041	**.82**	.0030	**.95**	.0027	**1.18**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0059	**.85**	.0041	**.82**	.0030	**.96**	.0027	**1.18**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.0051	**.96**	.0037	**.96**	.0037	**.91**	.0054	**1.07**
			$\hat{\psi}_{GEE-ex}$	.0024	**.93**	.0046	**1.12**	.0031	**.95**	.0049	**1.26**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.0051	**.91**	.0037	**.94**	.0037	**1.52**	.0054	**3.14**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0067	**.90**	.0049	**.88**	.0046	**1.02**	.0039	**.96**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0067	**.90**	.0049	**.88**	.0046	**1.02**	.0039	**.96**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0031	**.81**	.0027	**1.00**	.0026	**1.56**	.0035	**3.02**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0036	**.87**	.0029	**.98**	.0020	**1.03**	.0017	**1.29**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0036	**.87**	.0029	**.98**	.0020	**1.04**	.0017	**1.29**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0031	**.99**	.0027	**1.17**	.0026	**1.08**	.0035	**1.37**
			$\hat{\psi}_{GEE-ex}$	.0016	**.98**	.0036	**1.45**	.0021	**1.03**	.0033	**1.33**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0031	**.93**	.0027	**1.16**	.0026	**1.82**	.0035	**3.45**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0041	**.93**	.0035	**1.04**	.0027	**1.02**	.0027	**1.12**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0041	**.93**	.0035	**1.04**	.0027	**1.02**	.0027	**1.12**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0016	**.82**	.0012	**.85**	.0013	**1.61**	.0018	**3.22**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0018	**.88**	.0013	**.88**	.0010	**1.04**	.0008	**1.24**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0018	**.88**	.0013	**.88**	.0010	**1.04**	.0008	**1.24**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0016	**.99**	.0012	**.99**	.0013	**1.08**	.0018	**1.37**
			$\hat{\psi}_{GEE-ex}$	.0009	**1.00**	.0015	**1.20**	.0010	**1.02**	.0017	**1.24**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0016	**.94**	.0012	**.99**	.0013	**1.87**	.0018	**3.67**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0021	**.93**	.0016	**.98**	.0013	**1.00**	.0011	**.89**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0021	**.93**	.0016	**.98**	.0013	**1.00**	.0011	**.89**

Table 5.4.2(c): Ratio of the empirical vs. the model-based variances

	subgroup1	*subgroup2*
Average exposures per year:	***10***	***2***
Average events per year:	***10***	***2***

Rho=0.9

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Var.	Ratio	Var.	Ratio	Var.	Ratio	Var.	Ratio
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0102	**.92**	.0062	**.82**	.0049	**1.03**	.0162	**.95**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0121	**1.01**	.0074	**.86**	.0048	**.88**	.0167	**.96**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0121	**1.00**	.0074	**.87**	.0049	**.89**	.0167	**.96**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.0102	**1.14**	.0062	**.99**	.0049	**.91**	.0162	**1.07**
			$\hat{\psi}_{GEE-ex}$	.0053	**1.10**	.0072	**1.39**	.0055	**1.09**	.0304	**1.95**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.0102	**1.08**	.0062	**.98**	.0049	**1.24**	.0162	**1.08**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0139	**1.08**	.0089	**.92**	.0081	**1.03**	.0297	**.92**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0139	**1.08**	.0089	**.92**	.0081	**1.03**	.0297	**.92**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0056	**.85**	.0039	**.86**	.0034	**1.19**	.0056	**.95**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0067	**.94**	.0046	**.90**	.0031	**.92**	.0048	**.96**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0067	**.93**	.0046	**.90**	.0031	**.93**	.0048	**.96**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0056	**1.03**	.0039	**1.06**	.0034	**1.02**	.0056	**1.05**
			$\hat{\psi}_{GEE-ex}$	.0029	**1.00**	.0046	**1.40**	.0035	**1.14**	.0057	**1.74**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0056	**1.00**	.0039	**1.04**	.0034	**1.44**	.0056	**1.08**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0077	**1.00**	.0054	**.94**	.0043	**.91**	.0192	**.95**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0077	**1.00**	.0054	**.94**	.0043	**.91**	.0192	**.95**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0024	**.73**	.0021	**.92**	.0017	**1.24**	.0048	**.94**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0029	**.80**	.0026	**1.01**	.0017	**1.04**	.0050	**.95**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0029	**.80**	.0026	**1.01**	.0017	**1.03**	.0050	**.95**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0024	**.88**	.0021	**1.09**	.0017	**1.05**	.0048	**1.05**
			$\hat{\psi}_{GEE-ex}$	.0013	**.87**	.0021	**1.18**	.0019	**1.19**	.0093	**1.53**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0024	**.85**	.0021	**1.10**	.0017	**1.50**	.0048	**1.08**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0033	**.85**	.0031	**1.05**	.0024	**1.04**	.0092	**.96**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0033	**.85**	.0030	**1.05**	.0024	**1.04**	.0092	**.96**

Table 5.4.3(a): Ratio of the empirical vs. the model-based variances

	subgroup1	*subgroup2*
Average exposures per year:	***20***	***2***
Average events per year:	***20***	***2***

Rho=0

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Var.	Ratio	Var.	Ratio	Var.	Ratio	Var.	Ratio
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0014	**.83**	.0017	**1.42**	.0052	**1.65**	.0092	**14.5**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0018	**.94**	.0012	**.86**	.0011	**1.15**	.0011	**1.35**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0018	**.94**	.0012	**.85**	.0011	**1.16**	.0011	**1.35**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.0014	**1.13**	.0017	**1.01**	.0052	**1.05**	.0092	**1.04**
			$\hat{\psi}_{GEE-ex}$	.0005	**1.11**	.0016	**.90**	.0011	**.80**	.0017	**.93**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.0014	**1.00**	.0017	**1.72**	.0052	**1.78**	.0092	**16.3**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0021	**.99**	.0013	**.84**	.0012	**.96**	.0011	**.92**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0021	**.99**	.0013	**.84**	.0012	**.96**	.0011	**.92**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0008	**.75**	.0011	**1.55**	.0030	**6.28**	.0073	**14.3**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0010	**.87**	.0008	**.91**	.0005	**.97**	.0012	**1.34**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0010	**.92**	.0008	**.91**	.0005	**.97**	.0012	**1.34**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0008	**1.00**	.0011	**1.09**	.0030	**.97**	.0073	**1.03**
			$\hat{\psi}_{GEE-ex}$	.0003	**.94**	.0010	**.94**	.0006	**.68**	.0013	**.89**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0008	**.91**	.0011	**1.87**	.0030	**7.31**	.0073	**15.7**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0011	**.92**	.0009	**.93**	.0007	**.90**	.0012	**.93**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0011	**.92**	.0009	**.93**	.0007	**.90**	.0012	**.93**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0004	**.72**	.0006	**1.56**	.0017	**7.44**	.0056	**13.2**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0005	**.82**	.0004	**.96**	.0003	**1.15**	.0023	**1.36**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0005	**.87**	.0004	**.96**	.0003	**1.16**	.0023	**1.36**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0004	**.94**	.0006	**1.06**	.0017	**1.12**	.0056	**1.04**
			$\hat{\psi}_{GEE-ex}$	.0001	**.92**	.0005	**.95**	.0003	**.81**	.0010	**.90**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0004	**.87**	.0006	**1.89**	.0017	**8.68**	.0056	**16.1**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0005	**.87**	.0005	**1.00**	.0004	**1.05**	.0004	**.92**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0005	**.87**	.0005	**1.00**	.0004	**1.05**	.0004	**.92**

Table 5.4.3(b): Ratio of the empirical vs. the model-based variances

	subgroup1	*subgroup2*
Average exposures per year:	***20***	***2***
Average events per year:	***20***	***2***

Rho=0.5

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Var.	Ratio	Var.	Ratio	Var.	Ratio	Var.	Ratio
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0020	**.72**	.0026	**1.33**	.0079	**6.45**	.0170	**17.7**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0031	**.90**	.0022	**.91**	.0018	**1.12**	.0019	**1.43**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0031	**.90**	.0022	**.91**	.0018	**1.13**	.0019	**1.43**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.0020	**1.09**	.0026	**1.06**	.0079	**.92**	.0170	**1.20**
			$\hat{\psi}_{GEE-ex}$	.0005	**1.02**	.0038	**1.59**	.0019	**.85**	.0028	**.91**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.0020	**.94**	.0026	**1.74**	.0079	**8.13**	.0170	**21.4**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0035	**.96**	.0026	**.95**	.0020	**.92**	.0020	**.92**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0035	**.96**	.0026	**.95**	.0020	**.92**	.0020	**.92**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0013	**.78**	.0016	**1.41**	.0048	**6.59**	.0095	**16.9**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0019	**.97**	.0013	**.91**	.0010	**1.03**	.0011	**1.42**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0019	**.97**	.0013	**.91**	.0010	**1.04**	.0011	**1.42**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0013	**1.11**	.0016	**1.08**	.0048	**.99**	.0095	**1.08**
			$\hat{\psi}_{GEE-ex}$	.0003	**1.03**	.0019	**1.35**	.0010	**.78**	.0015	**.82**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0013	**1.02**	.0016	**1.85**	.0048	**8.27**	.0095	**20.3**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0022	**1.03**	.0015	**.96**	.0011	**.88**	.0012	**.96**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0022	**1.03**	.0015	**.96**	.0011	**.88**	.0012	**.96**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0006	**.71**	.0008	**1.45**	.0036	**6.41**	.0060	**17.1**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0009	**.87**	.0007	**.98**	.0012	**1.12**	.0018	**1.41**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0009	**.87**	.0007	**.98**	.0012	**1.12**	.0018	**1.41**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0006	**.99**	.0008	**1.08**	.0036	**.94**	.0060	**1.10**
			$\hat{\psi}_{GEE-ex}$	.0002	**.98**	.0010	**1.37**	.0012	**.81**	.0010	**.80**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0006	**.92**	.0008	**1.89**	.0036	**8.30**	.0060	**20.1**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0010	**.93**	.0007	**.95**	.0010	**.89**	.0012	**.92**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0010	**.93**	.0007	**.95**	.0010	**.89**	.0012	**.92**

Table 5.4.3(c): Ratio of the empirical vs. the model-based variances

	subgroup1	*subgroup2*
Average exposures per year:	***20***	***2***
Average events per year:	***20***	***2***

Rho=0.9

n	Unit of analysis	Statistical Method	Est.	$\log OR$							
				0.0		0.693		1.609		2.303	
				Var.	Ratio	Var.	Ratio	Var.	Ratio	Var.	Ratio
30	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0040	**.70**	.0035	**.91**	.0073	**3.08**	.0142	**8.33**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0071	**.94**	.0049	**.91**	.0042	**1.15**	.0041	**1.49**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0071	**.93**	.0049	**.92**	.0042	**1.16**	.0041	**1.50**
		G.E.E	$\hat{\psi}_{GEE-ind}$	.0040	**1.09**	.0035	**1.15**	.0073	**1.03**	.0142	**1.02**
			$\hat{\psi}_{GEE-ex}$	.0012	**1.00**	.0206	**7.30**	.0043	**1.04**	.0046	**.81**
	E-level	G.E.E	$\hat{\psi}_{GEE-ind}$	.0040	**.99**	.0035	**1.31**	.0073	**4.35**	.0142	**11.1**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0081	**1.00**	.0057	**.95**	.0045	**.93**	.0043	**.94**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0081	**1.00**	.0057	**.95**	.0045	**.93**	.0043	**.94**
50	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0023	**.69**	.0020	**.87**	.0036	**2.63**	.0089	**8.92**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0042	**.93**	.0033	**1.04**	.0023	**1.09**	.0026	**1.62**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0042	**.93**	.0033	**1.04**	.0023	**1.10**	.0026	**1.63**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0023	**1.07**	.0020	**1.06**	.0036	**.86**	.0089	**1.06**
			$\hat{\psi}_{GEE-ex}$	.0006	**1.02**	.0172	**9.08**	.0023	**.89**	.0030	**.85**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0023	**.99**	.0020	**1.27**	.0036	**3.76**	.0089	**11.9**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0047	**.99**	.0039	**1.07**	.0027	**.94**	.0027	**1.00**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0046	**.98**	.0039	**1.07**	.0027	**.94**	.0027	**1.00**
100	Crude	2×2 table	$\hat{\psi}_{MH-c}$	.0012	**.71**	.0009	**.82**	.0018	**2.66**	.0041	**8.31**
	S-level	2×2 table	$\hat{\psi}_{MH-s}$	.0021	**.95**	.0015	**.93**	.0012	**1.12**	.0012	**1.44**
		C.L.R.	$\hat{\psi}_{CLR-s}$	.0021	**.95**	.0015	**.93**	.0012	**1.11**	.0012	**1.44**
		G.E.E.	$\hat{\psi}_{GEE-ind}$	.0012	**1.06**	.0009	**1.02**	.0018	**.88**	.0041	**.95**
			$\hat{\psi}_{GEE-ex}$	.0003	**1.04**	.0111	**11.6**	.0012	**.94**	.0013	**.75**
	E-level	G.E.E.	$\hat{\psi}_{GEE-ind}$	.0012	**1.01**	.0009	**1.21**	.0018	**3.80**	.0041	**11.2**
	E-level	2×2 table	$\hat{\psi}_{MH-e}$	.0024	**1.01**	.0017	**.97**	.0014	**1.02**	.0012	**.92**
		C.L.R.	$\hat{\psi}_{CLR-e}$	.0024	**1.01**	.0017	**.97**	.0014	**1.02**	.0012	**.92**

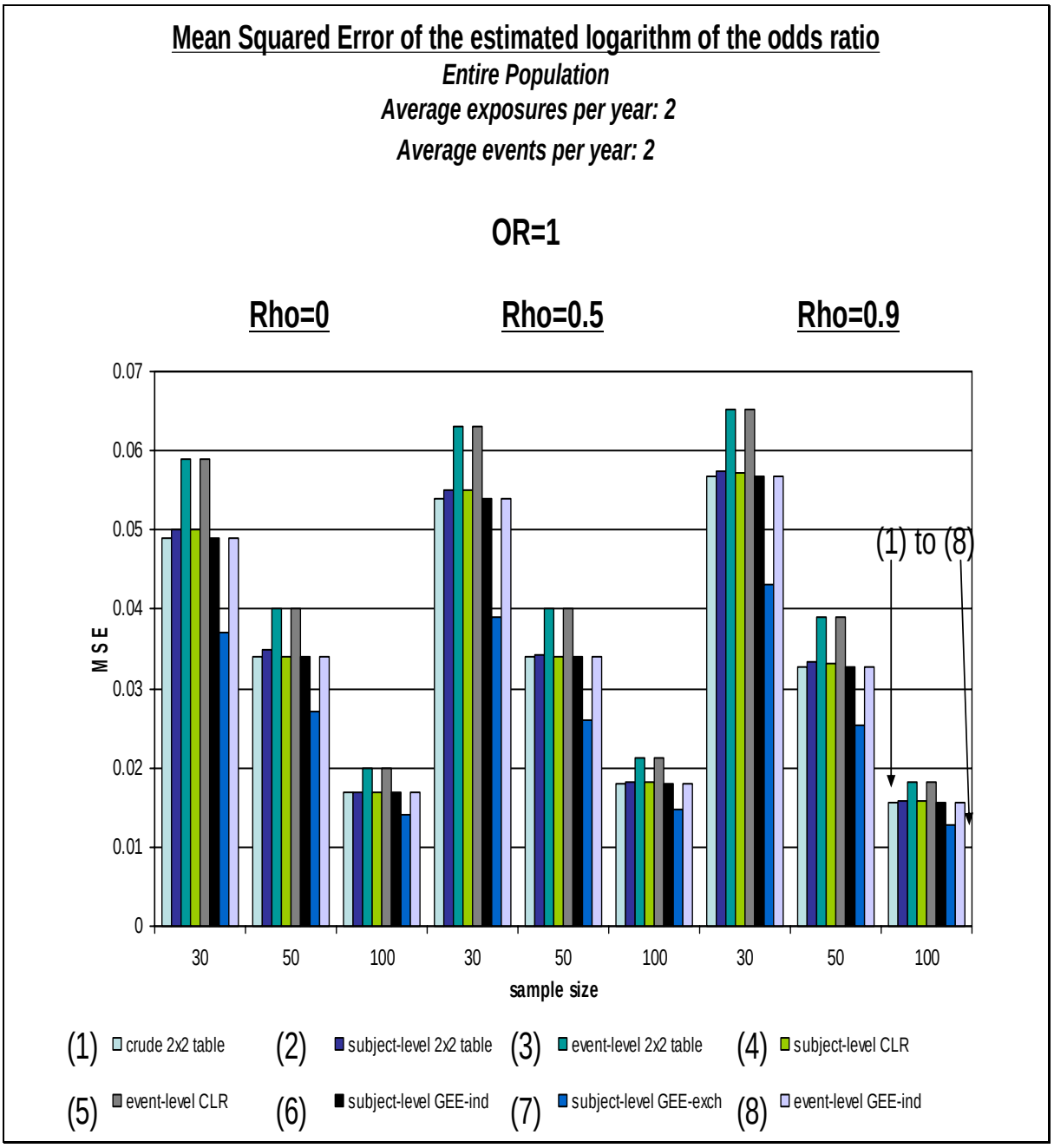


Figure 5.3.4.1: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

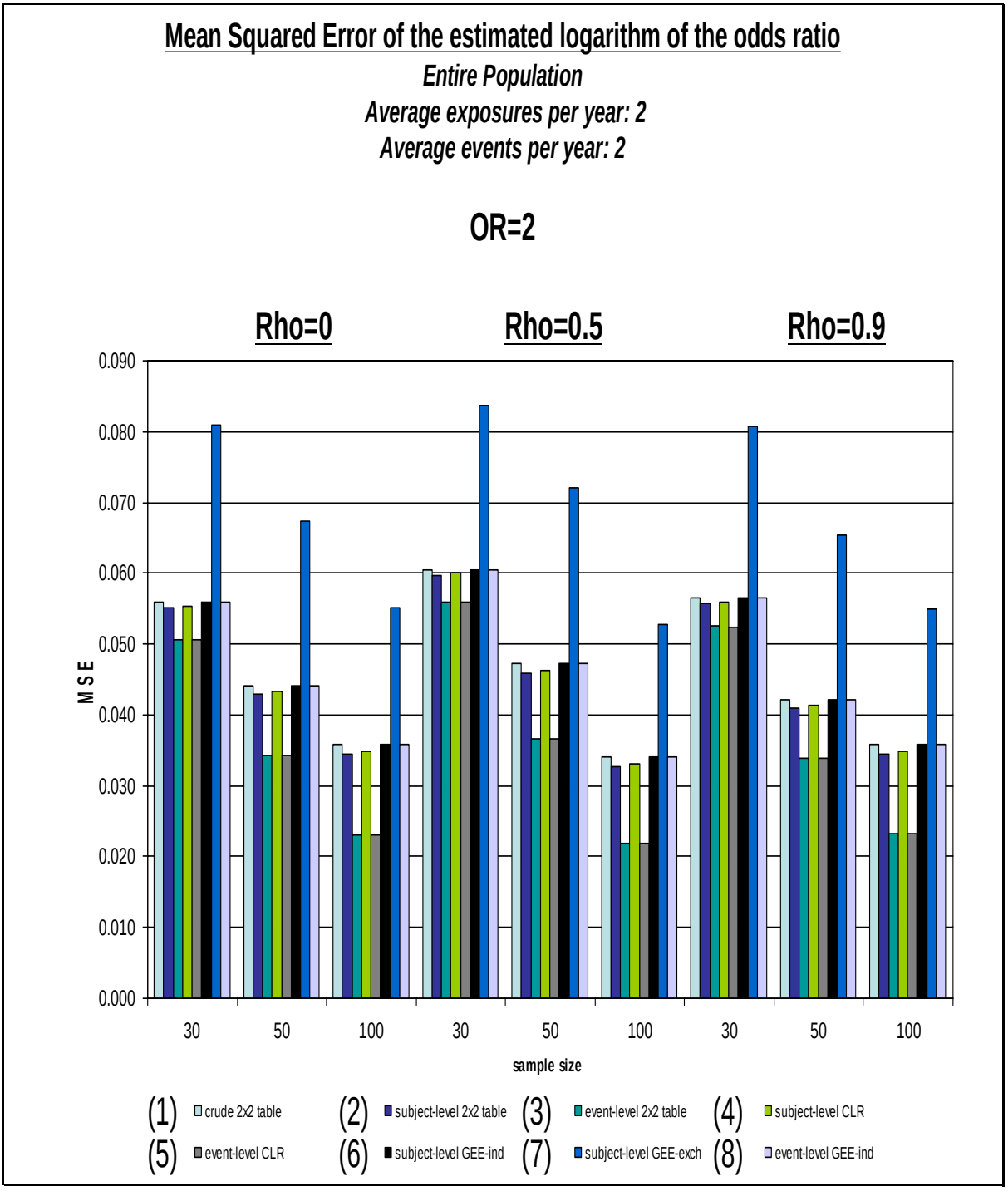


Figure 5.3.4.2: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

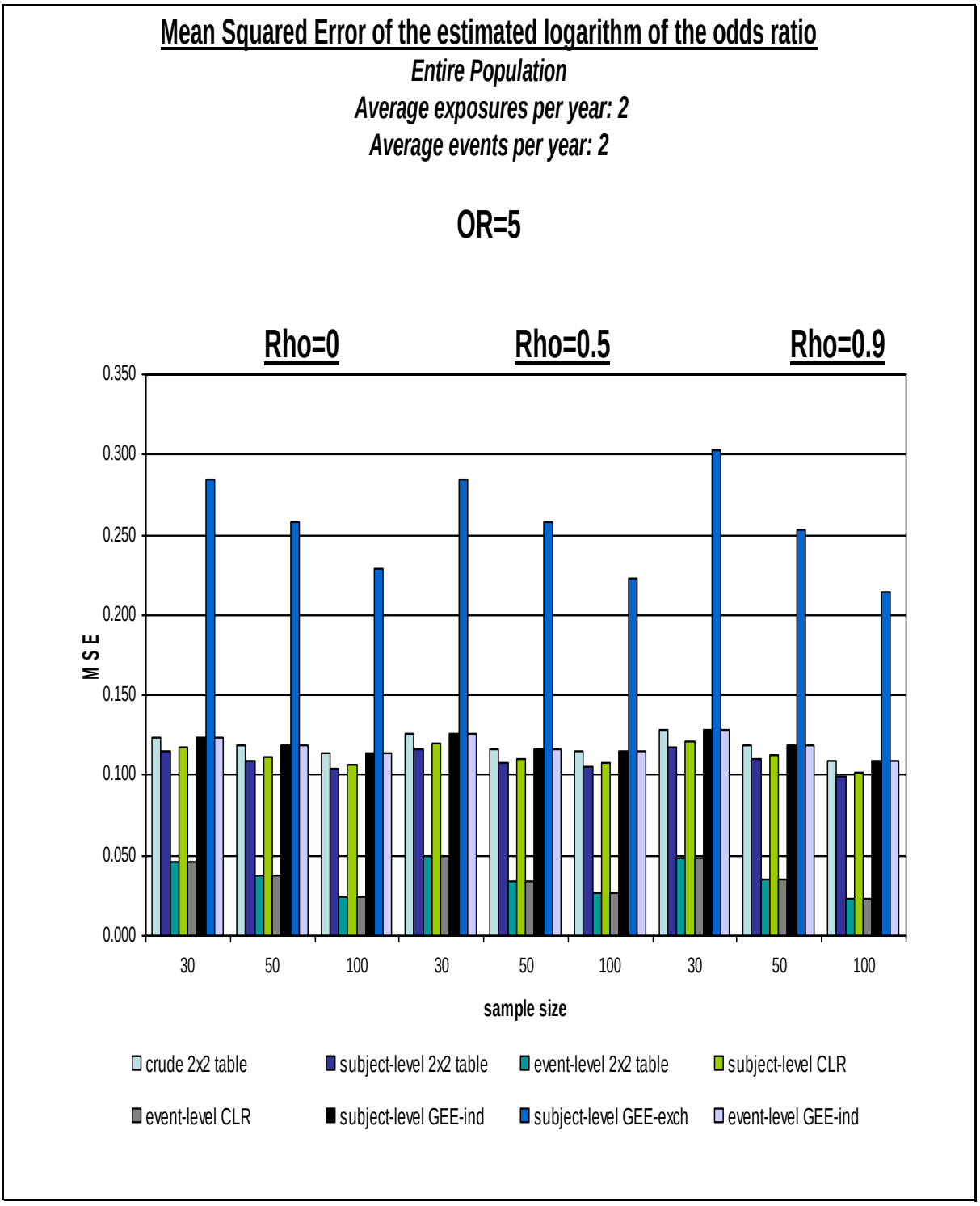


Figure 5.3.4.3: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

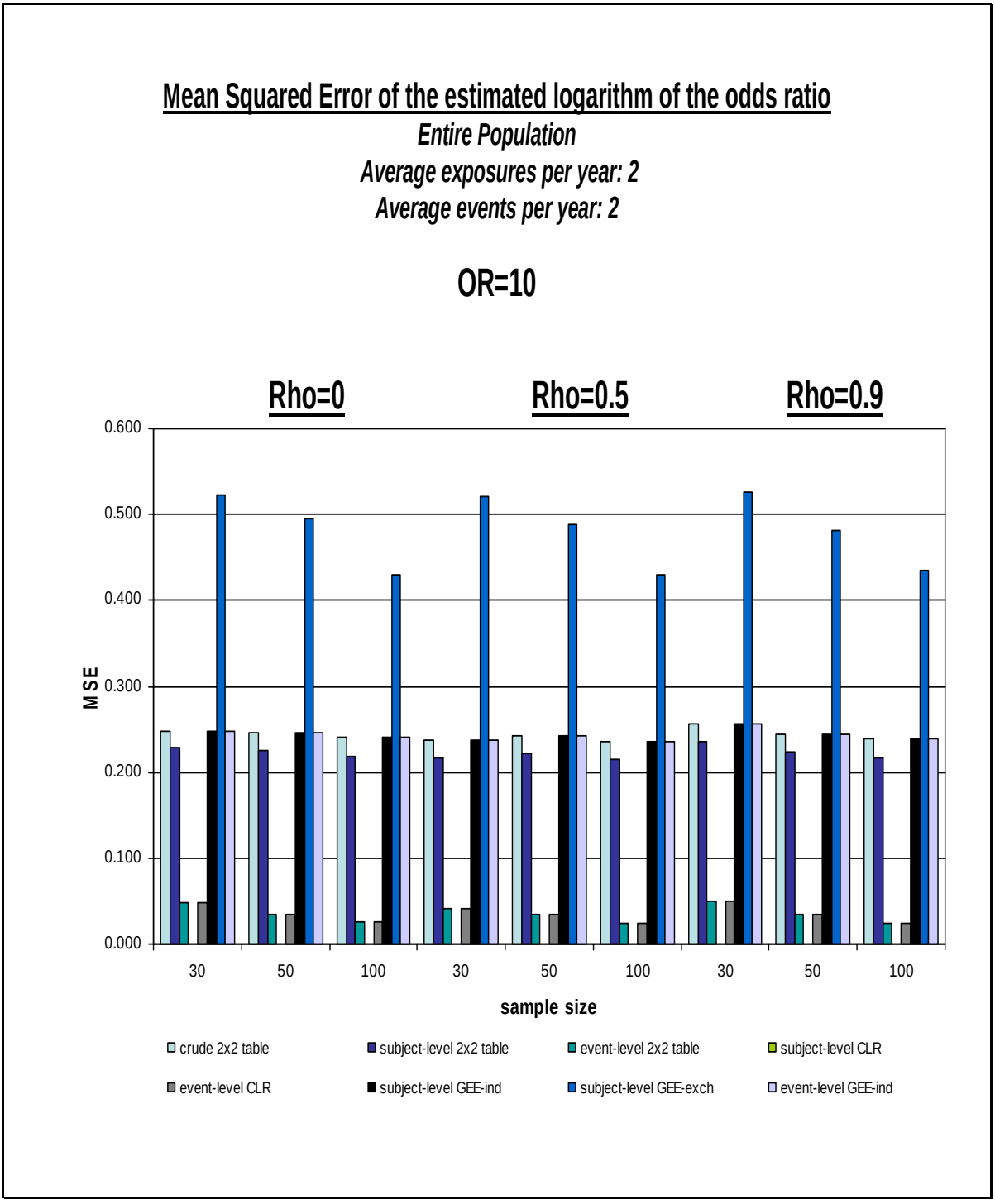


Figure 5.3.4.4: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

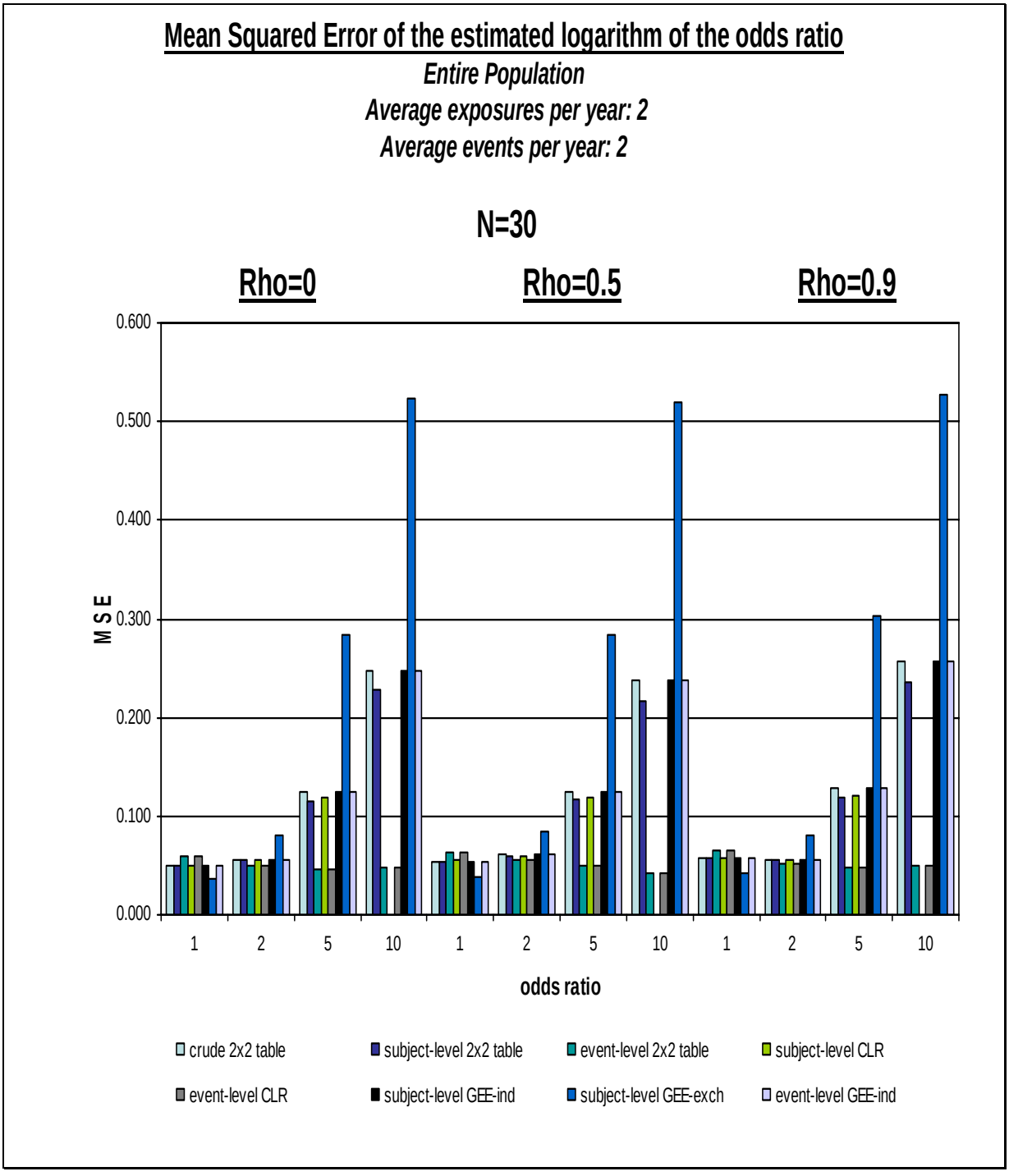


Figure 5.3.4.5: Relationship among the mean squared error, odds ratio and correlation coefficient with respect to different statistical models

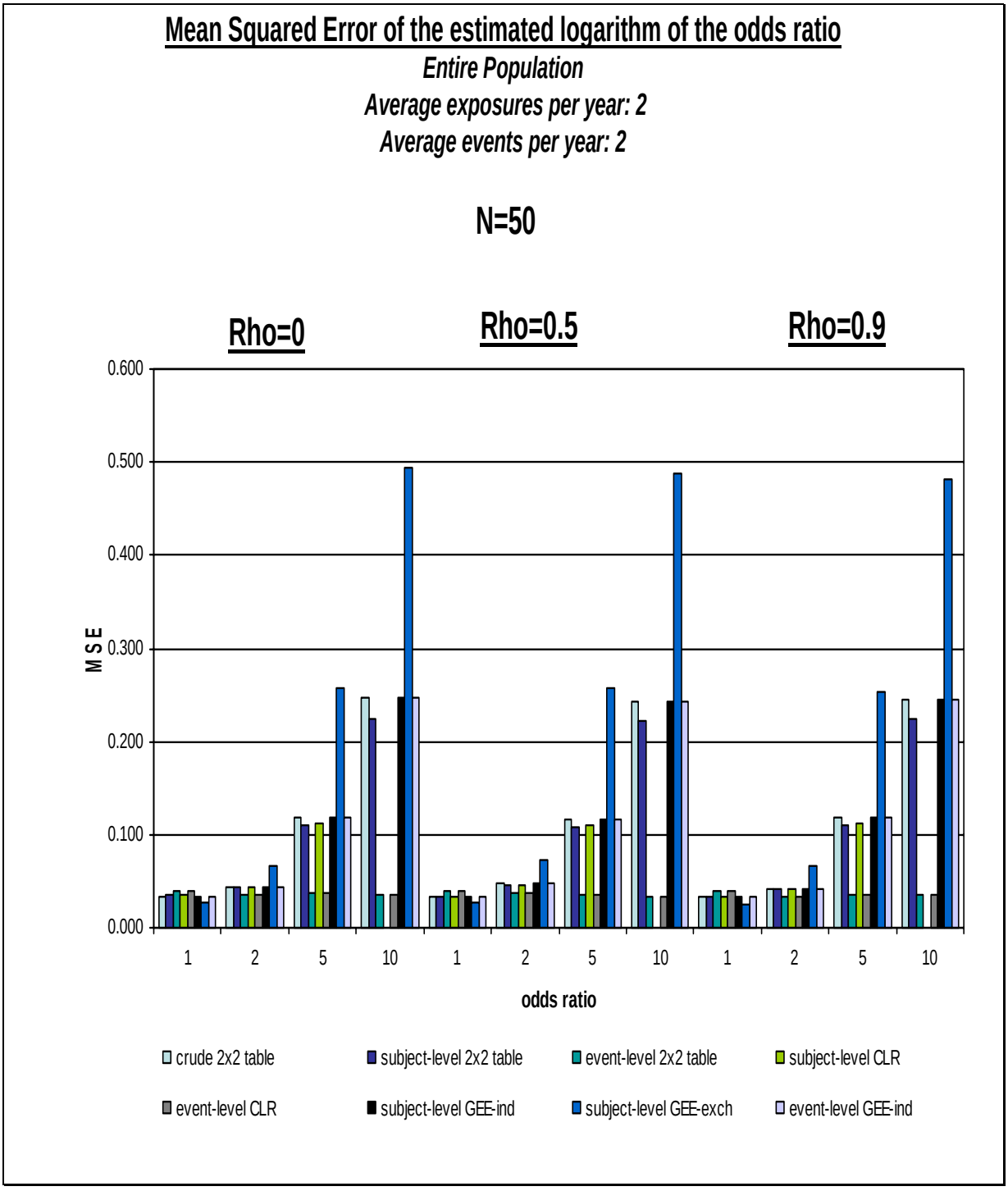


Figure 5.3.4.6: Relationship among the mean squared error, odds ratio and correlation coefficient with respect to different statistical models

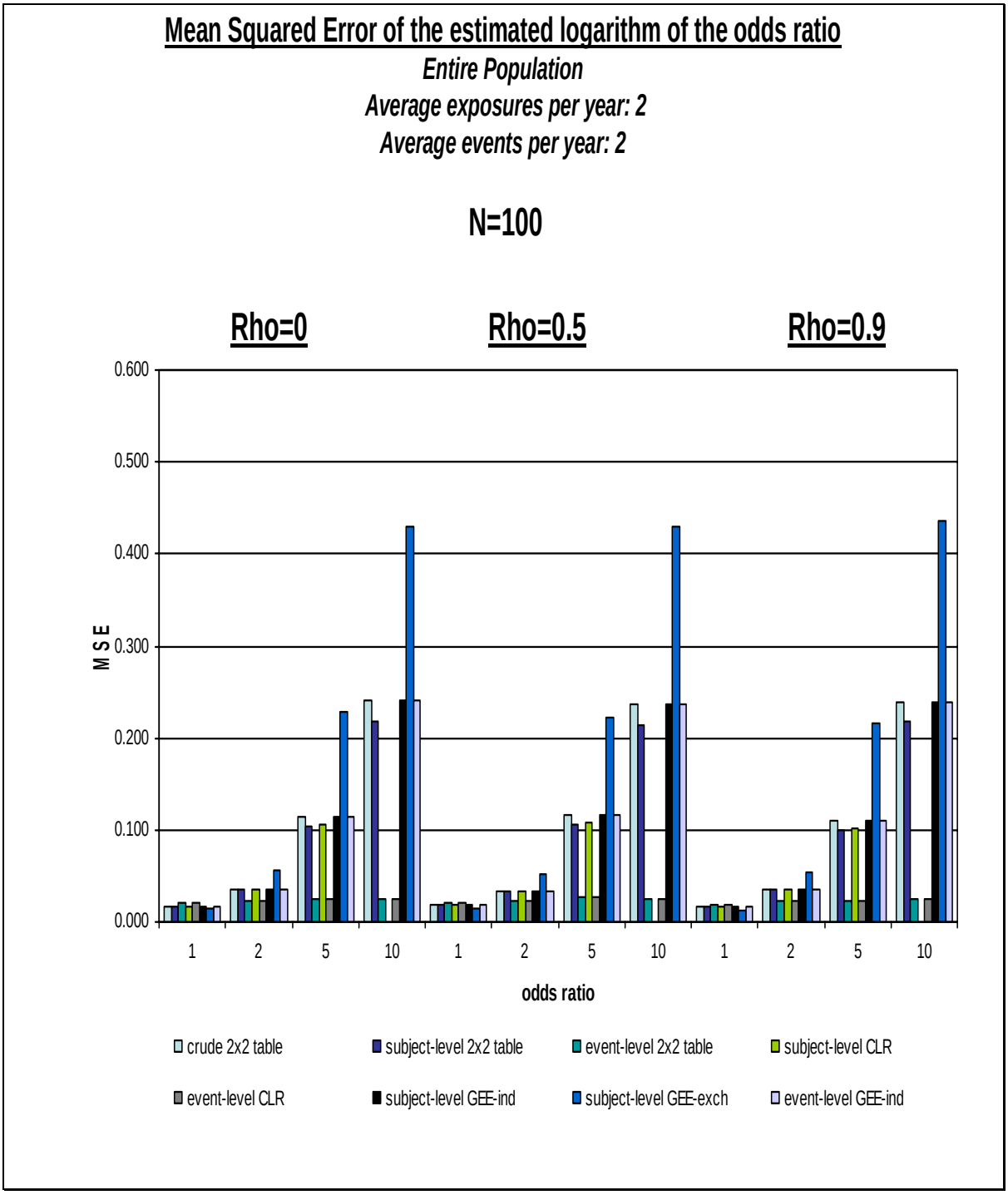


Figure 5.3.4.7: Relationship among the mean squared error, odds ratio and correlation coefficient with respect to different statistical models

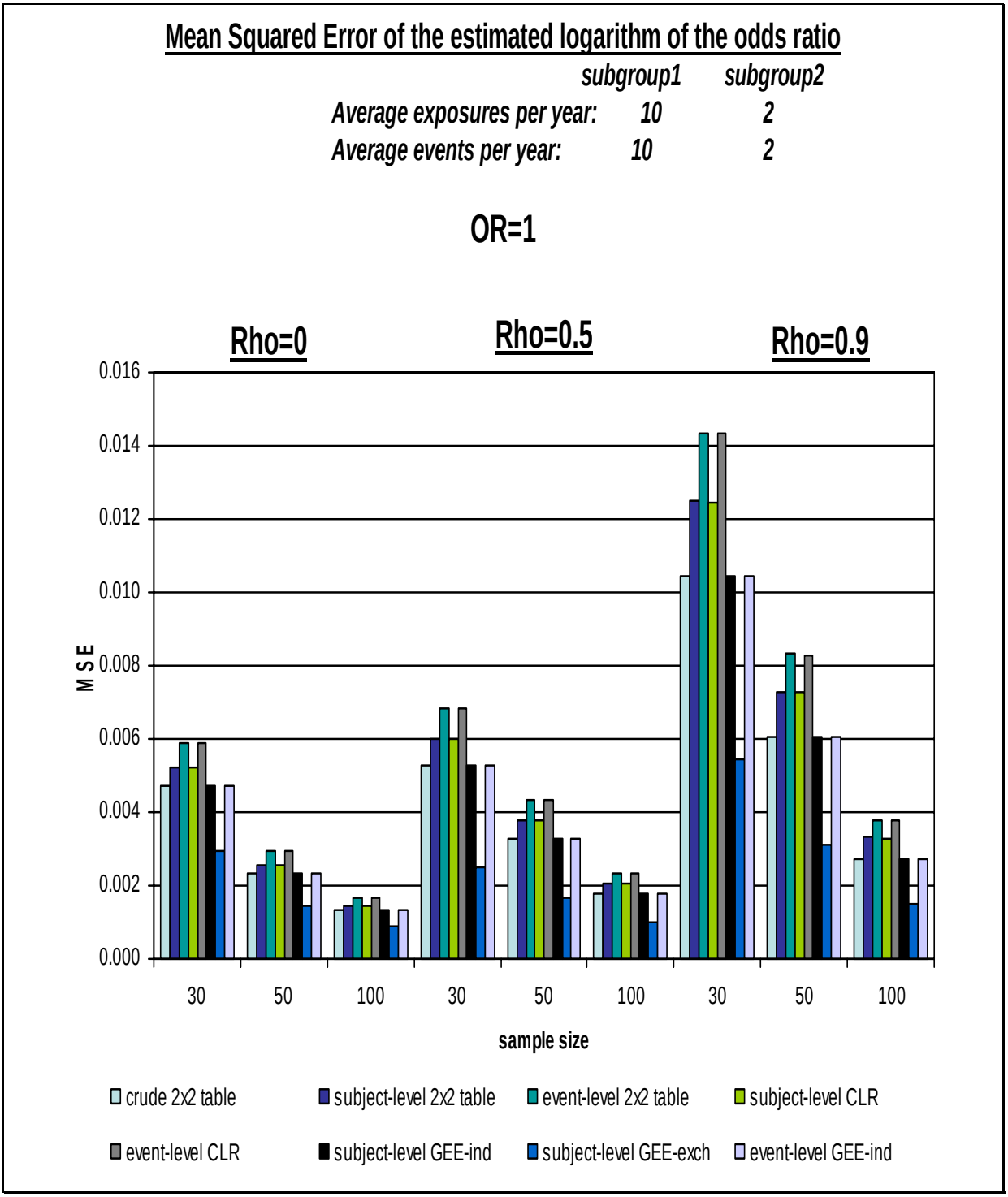


Figure 5.3.5.1: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

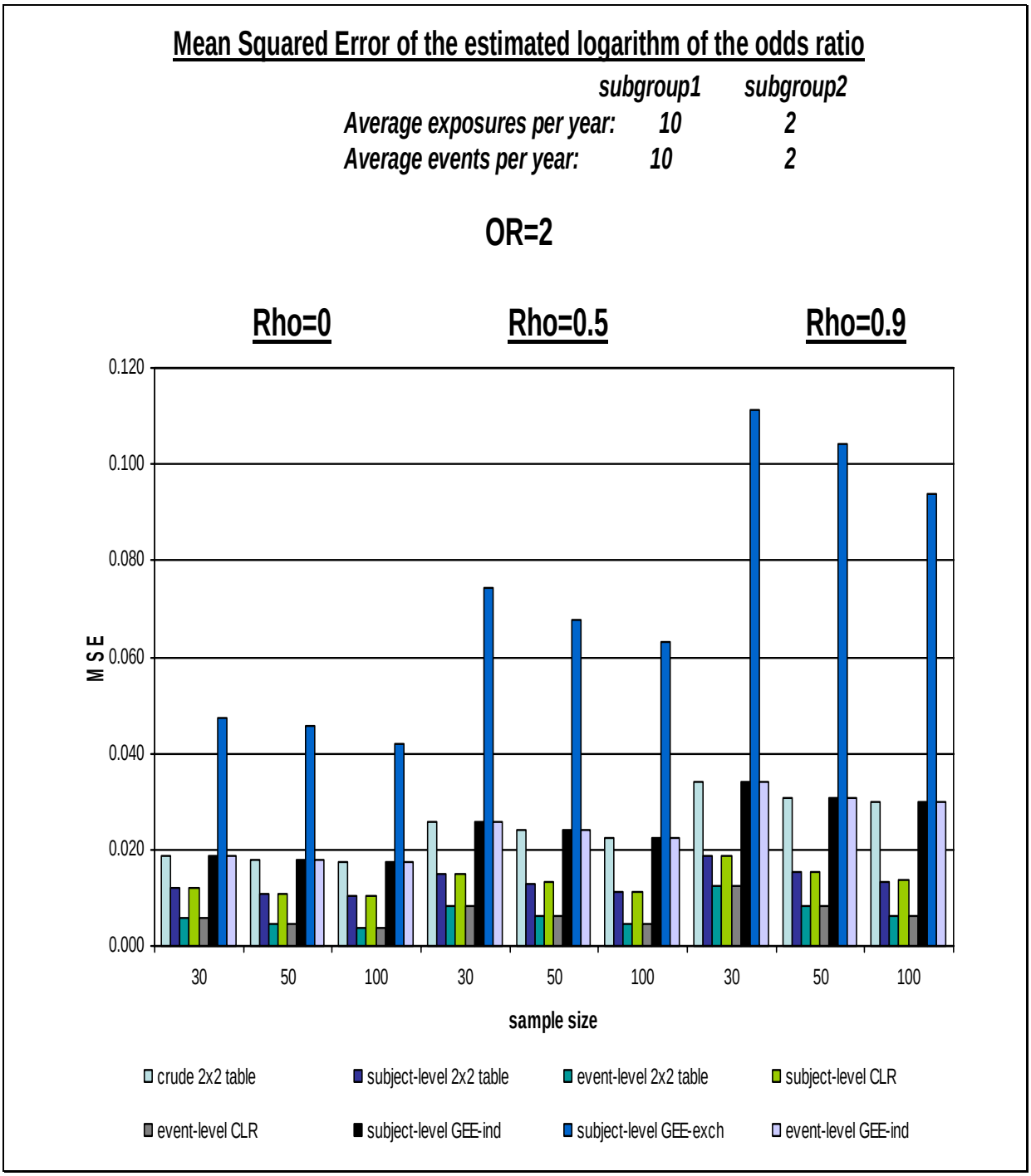


Figure 5.3.5.2: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

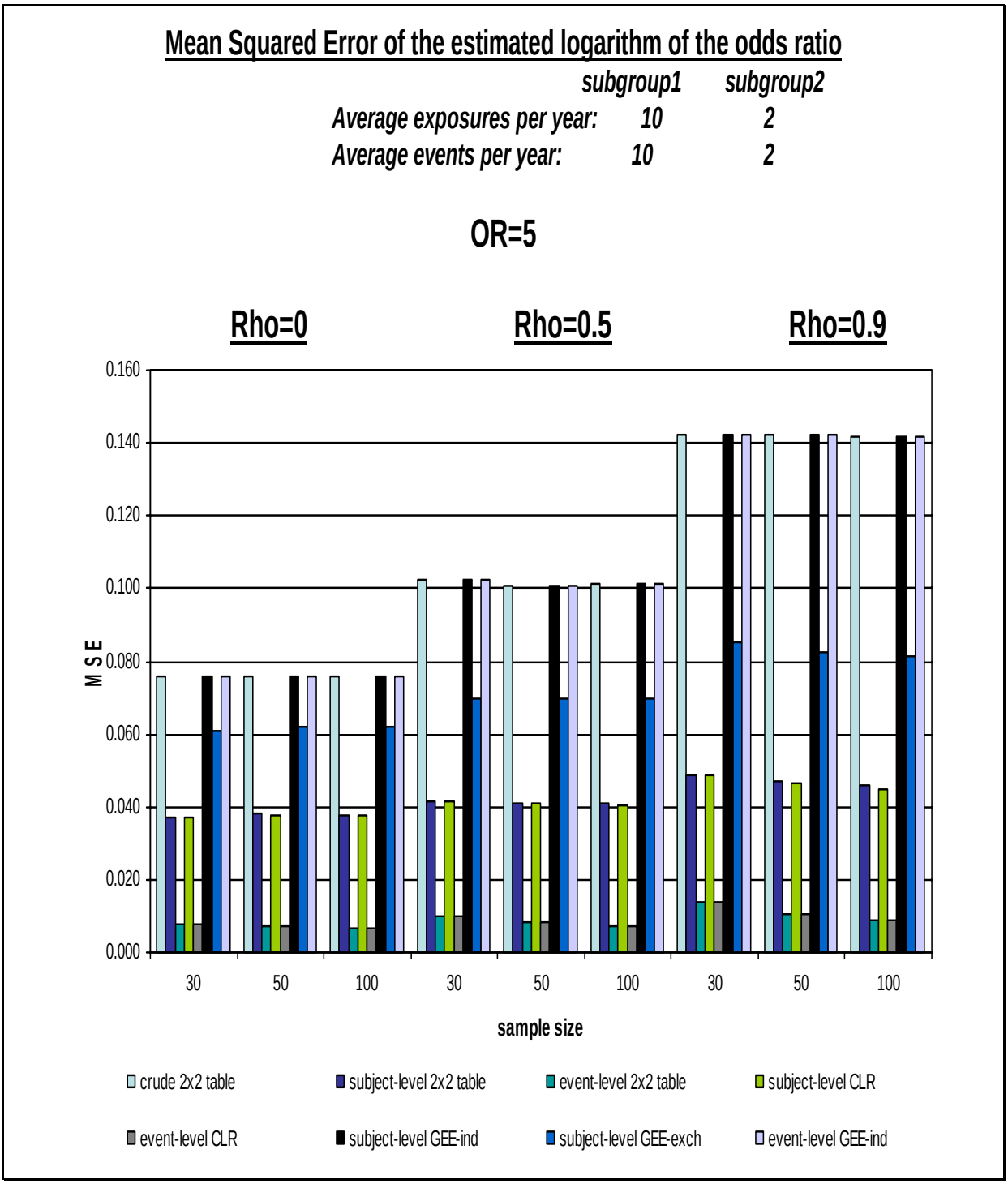


Figure 5.3.5.3: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

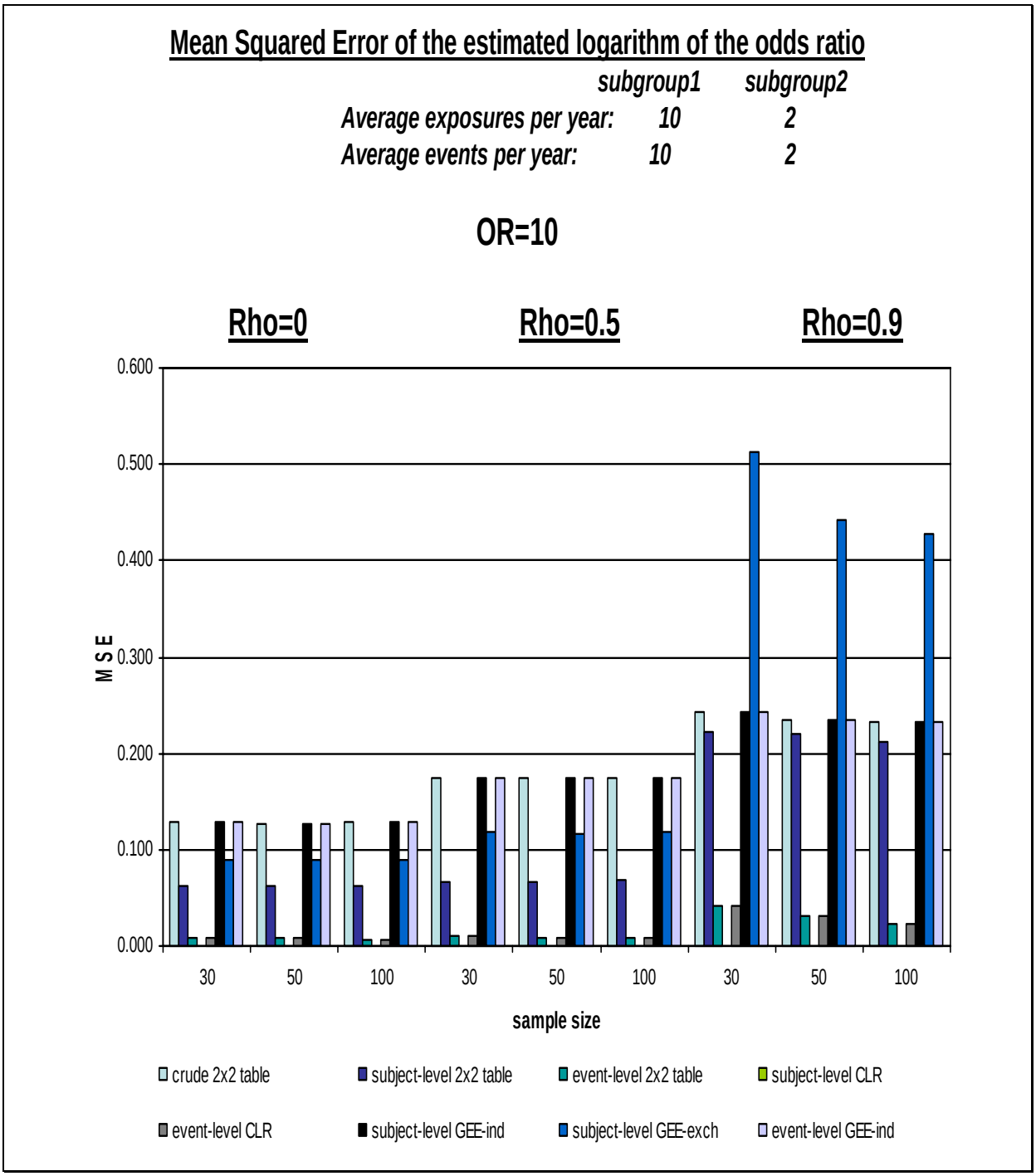


Figure 5.3.5.4: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

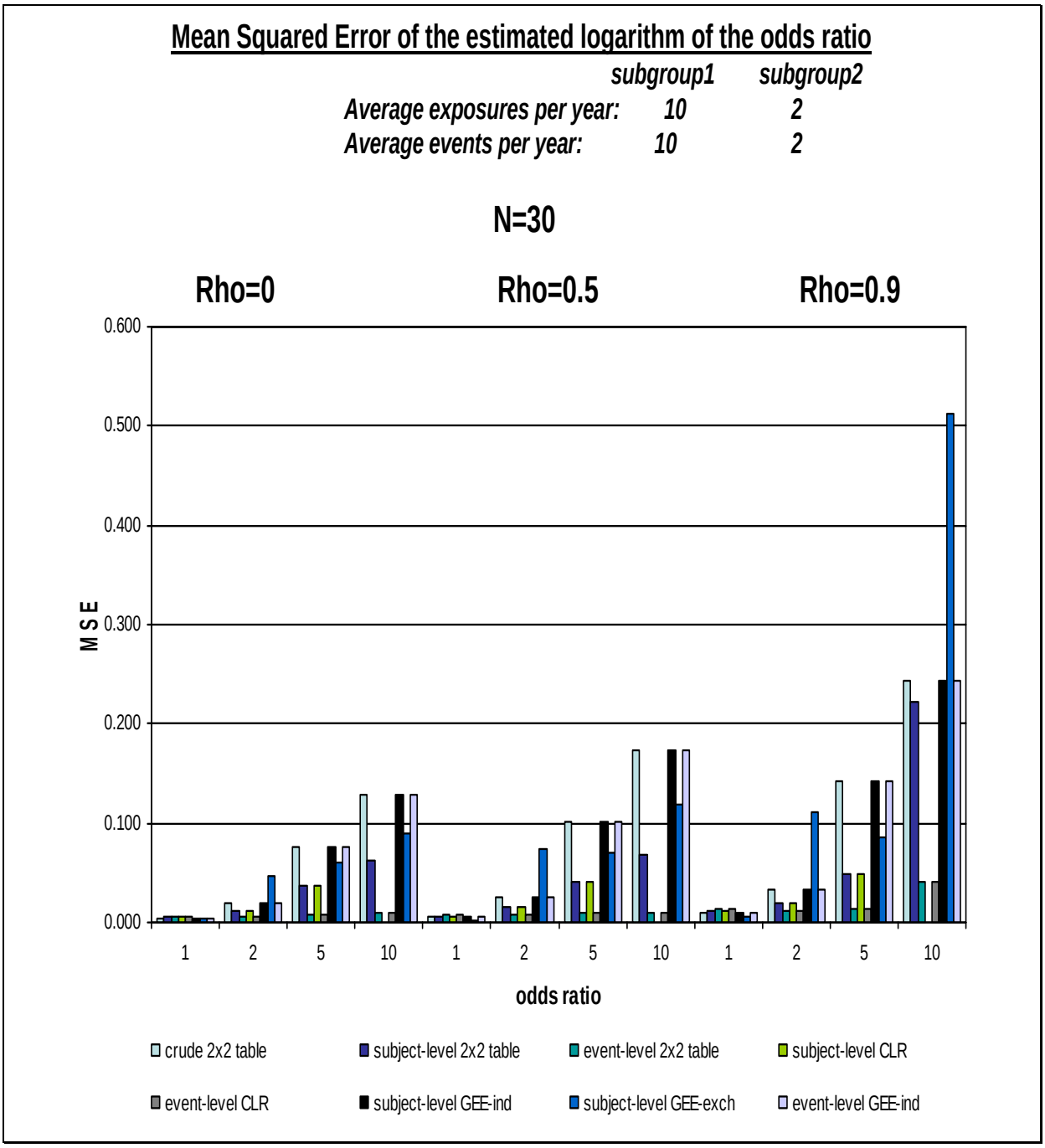


Figure 5.3.5.5: Relationship among the mean squared error, odds ratio and correlation coefficient with respect to different statistical models

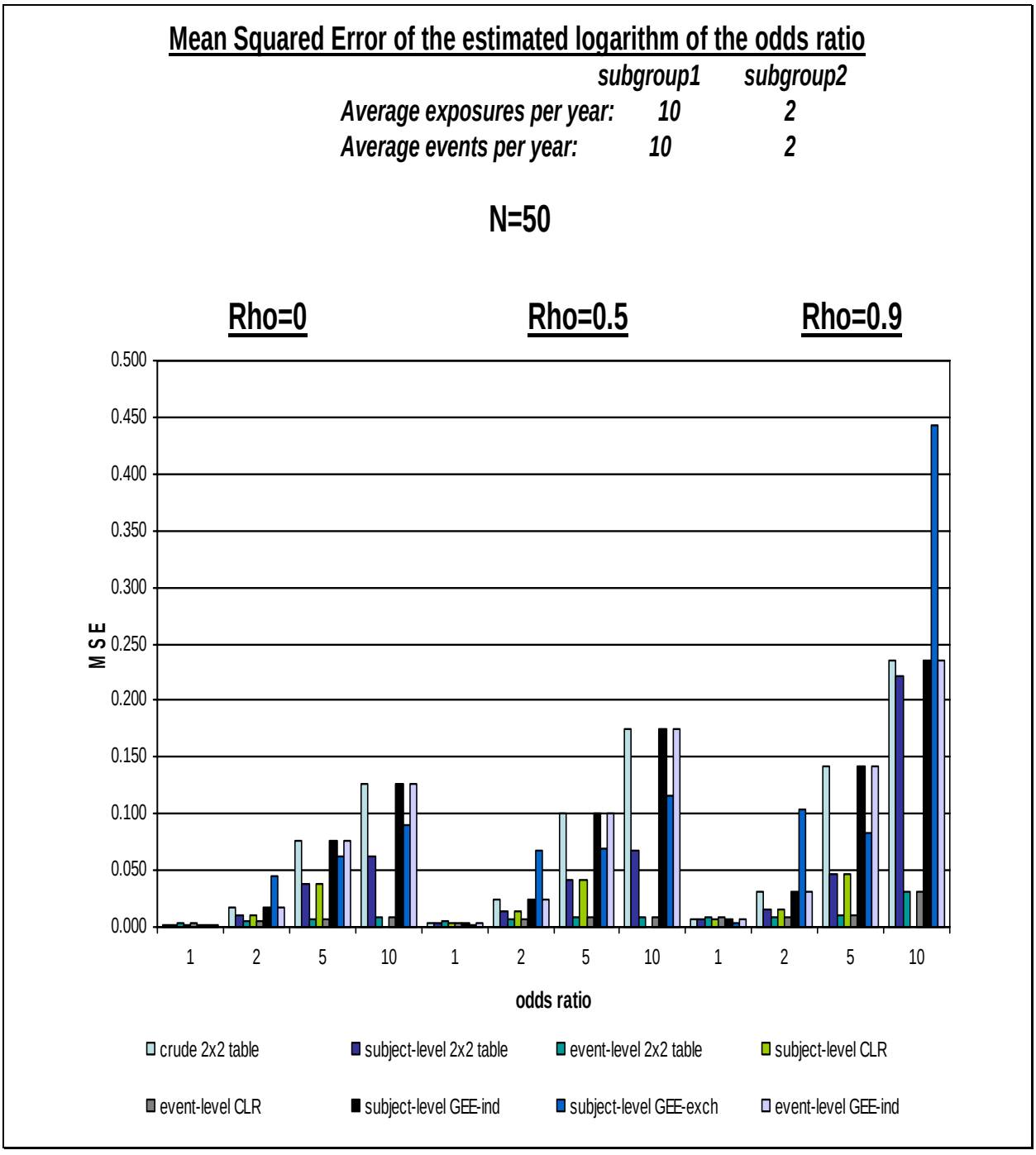


Figure 5.3.5.6: Relationship among the mean squared error, odds ratio and correlation coefficient with respect to different statistical models

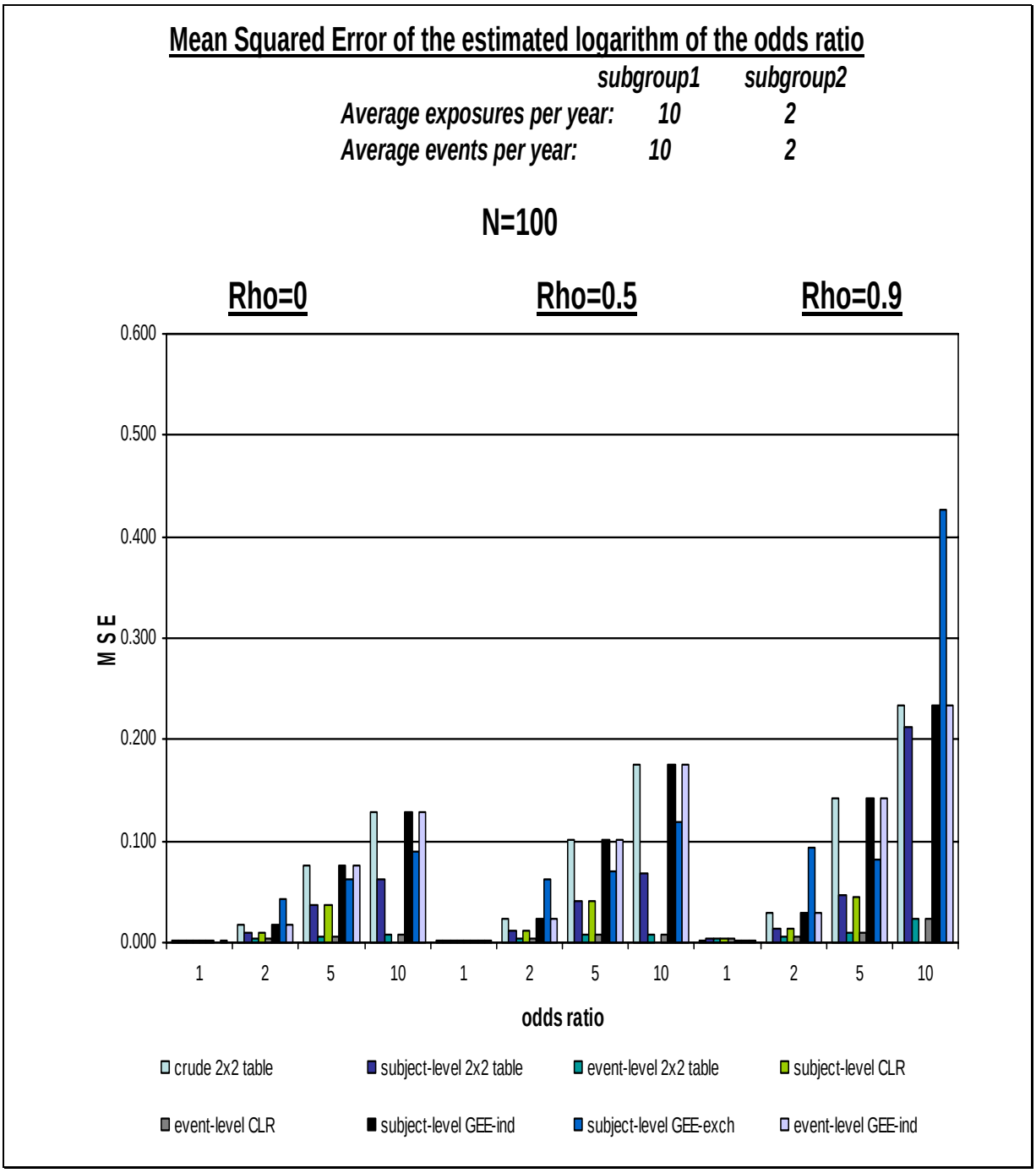


Figure 5.3.5.7: Relationship among the mean squared error, odds ratio and correlation coefficient with respect to different statistical models

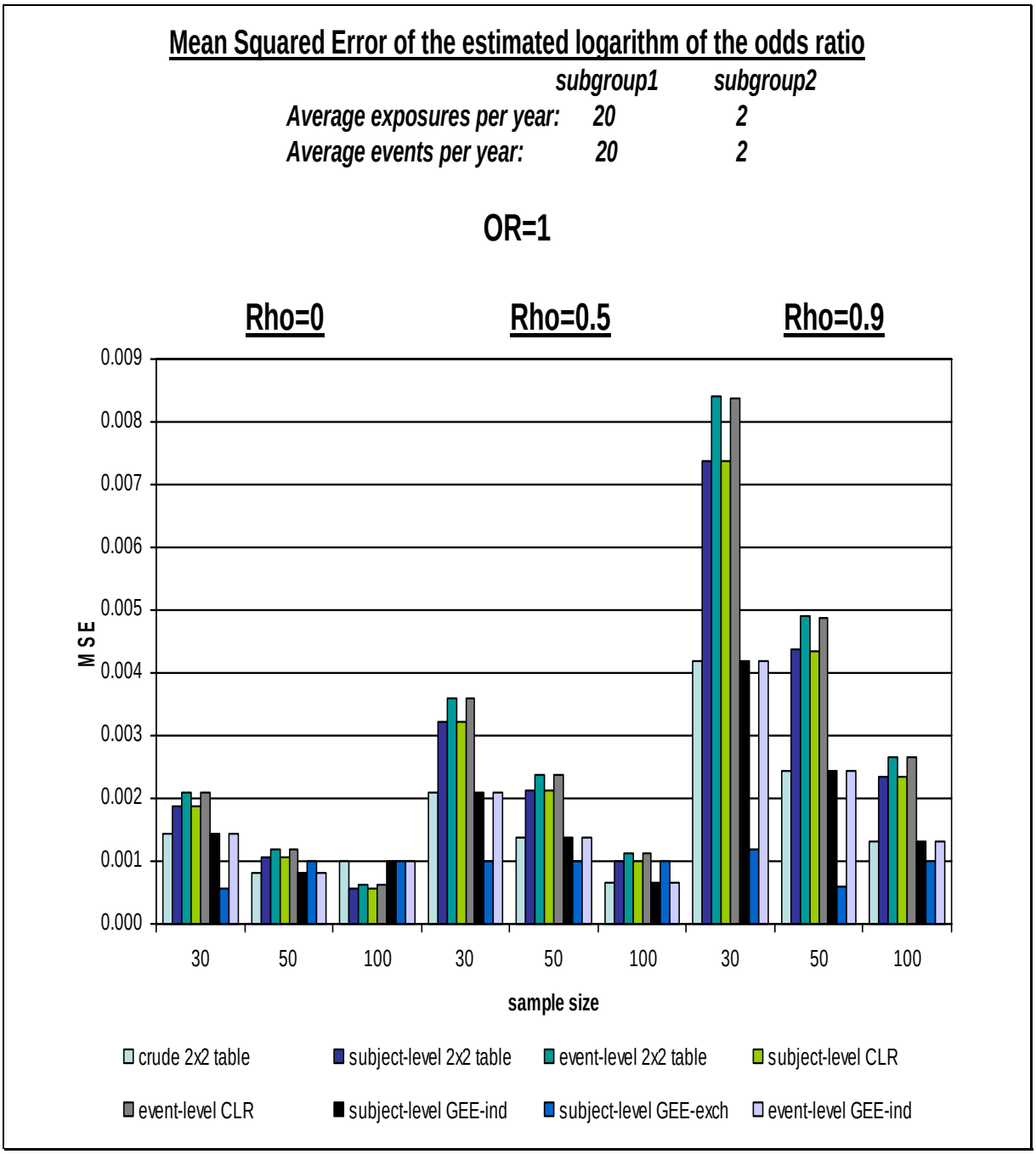


Figure 5.3.6.1: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

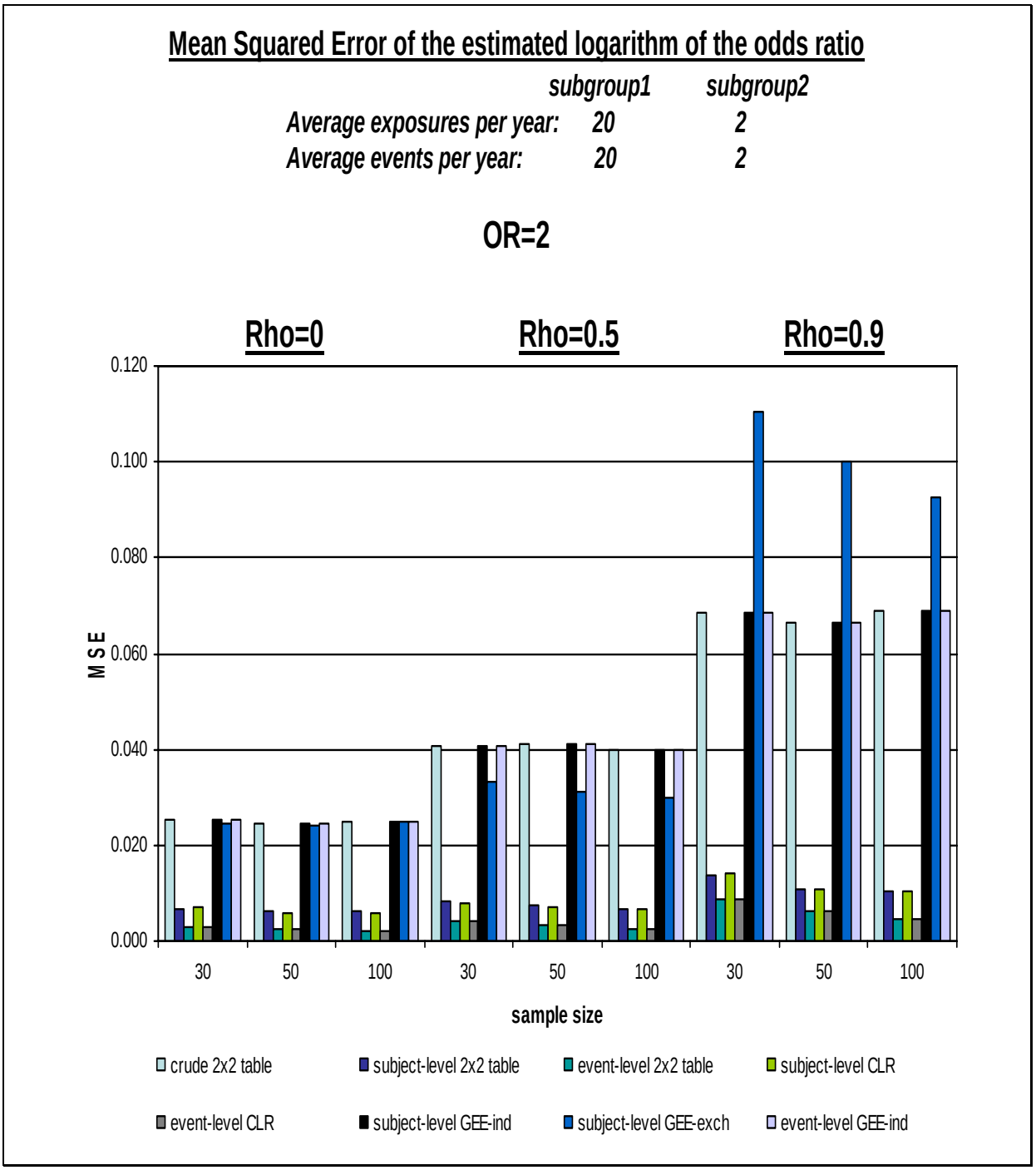


Figure 5.3.6.2: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

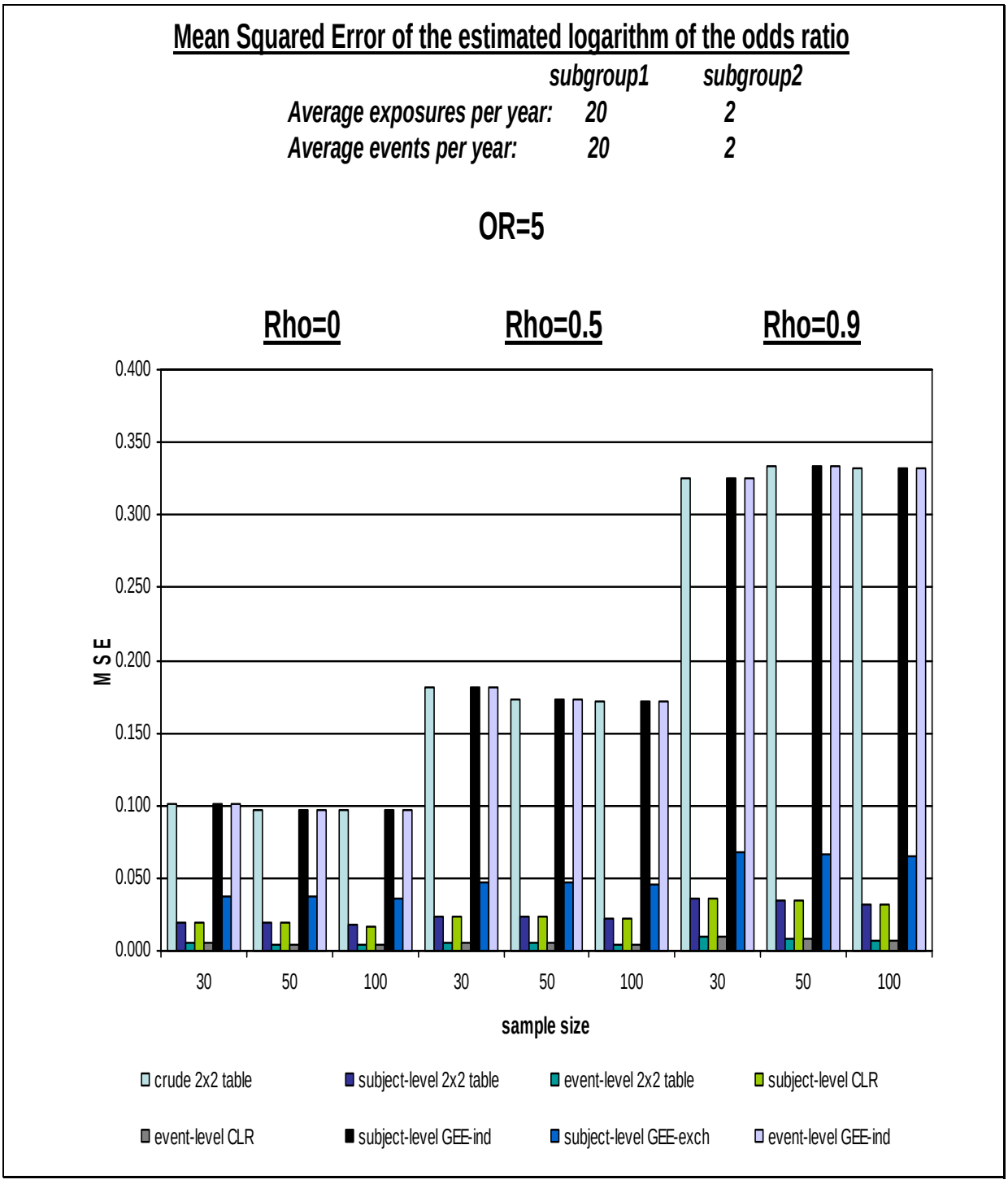


Figure 5.3.6.3: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

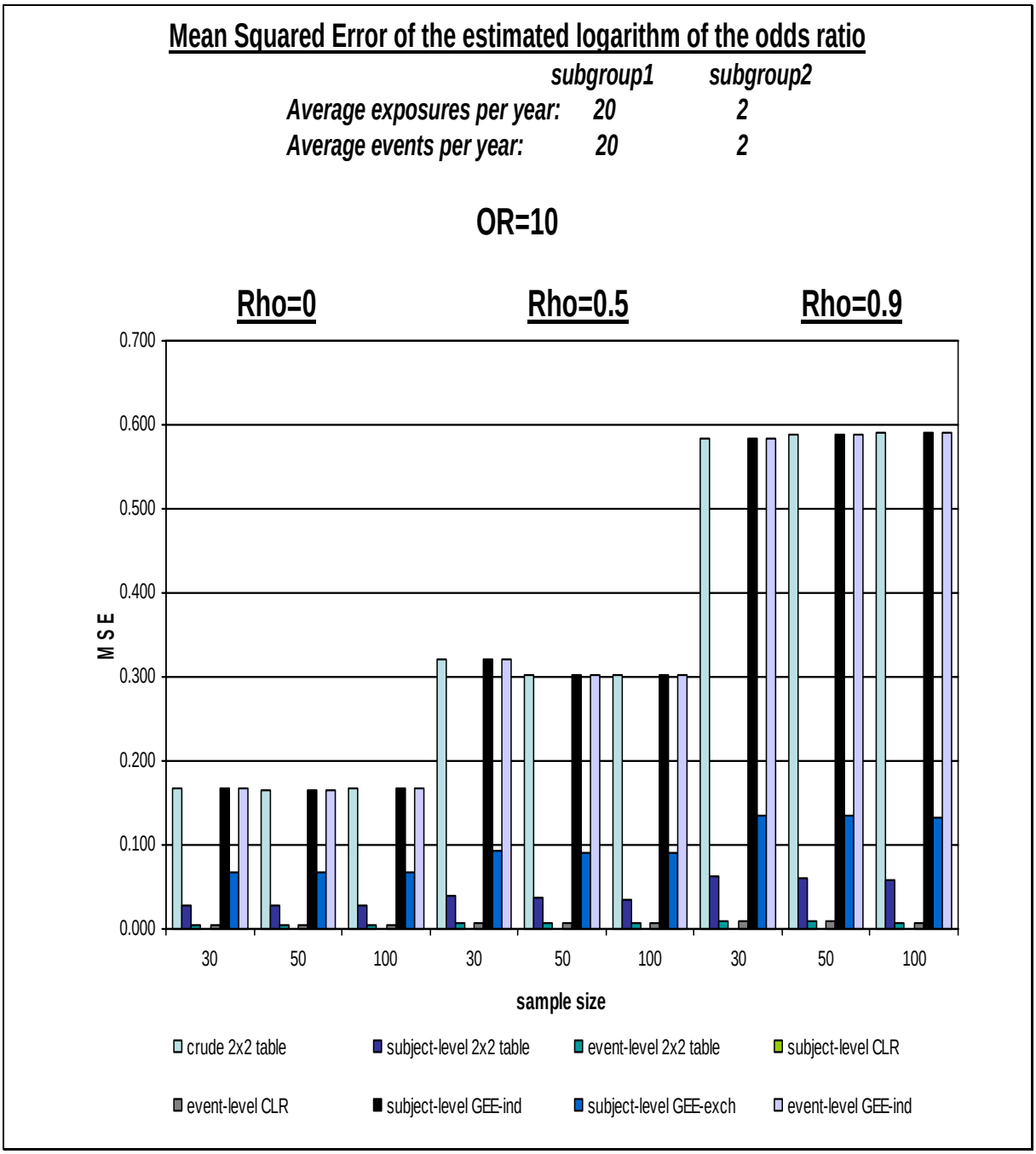


Figure 5.3.6.4: Relationship among the mean squared error, sample size and correlation coefficient with respect to different statistical models

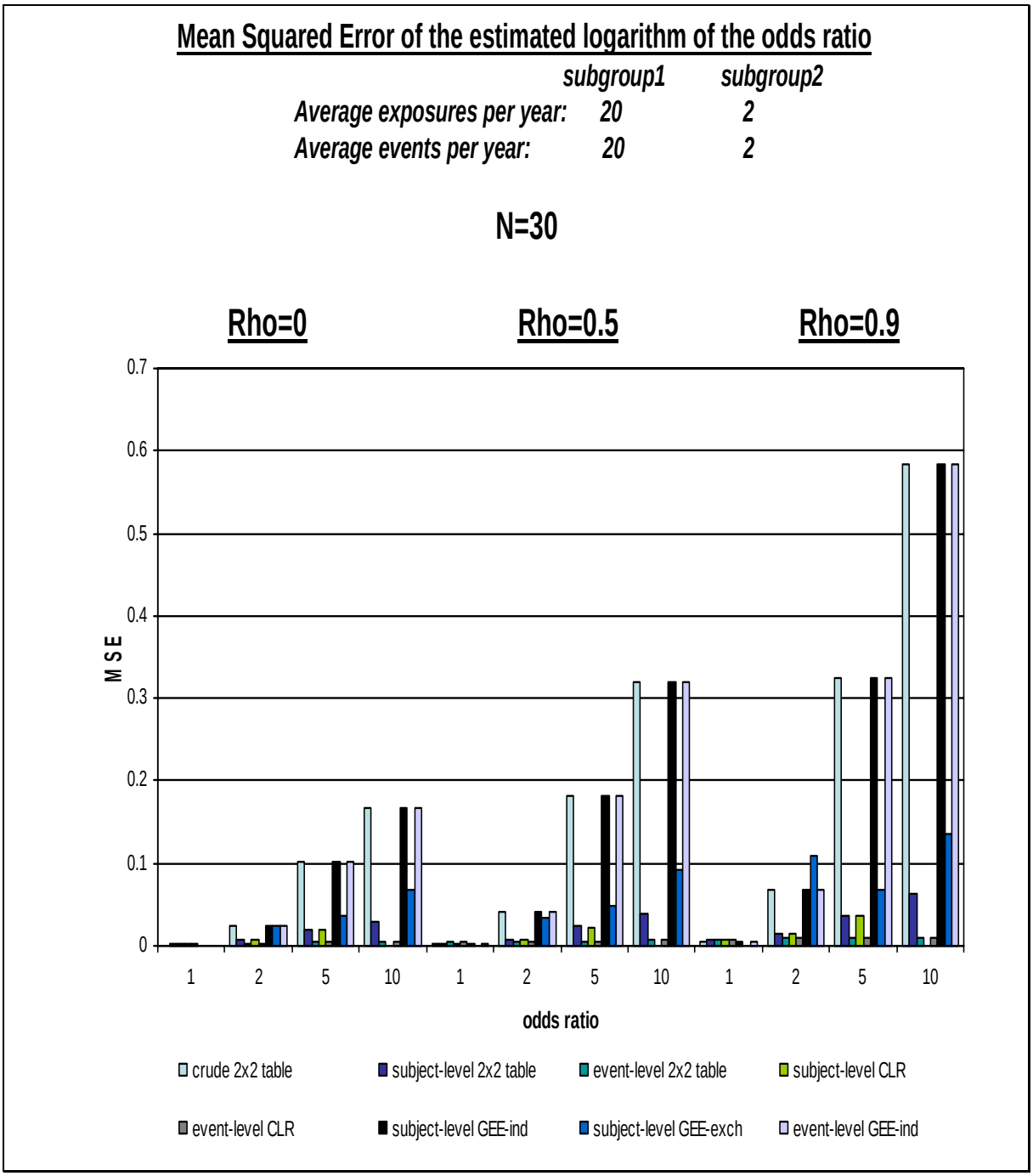


Figure 5.3.6.5: Relationship among the mean squared error, odds ratio and correlation coefficient with respect to different statistical models

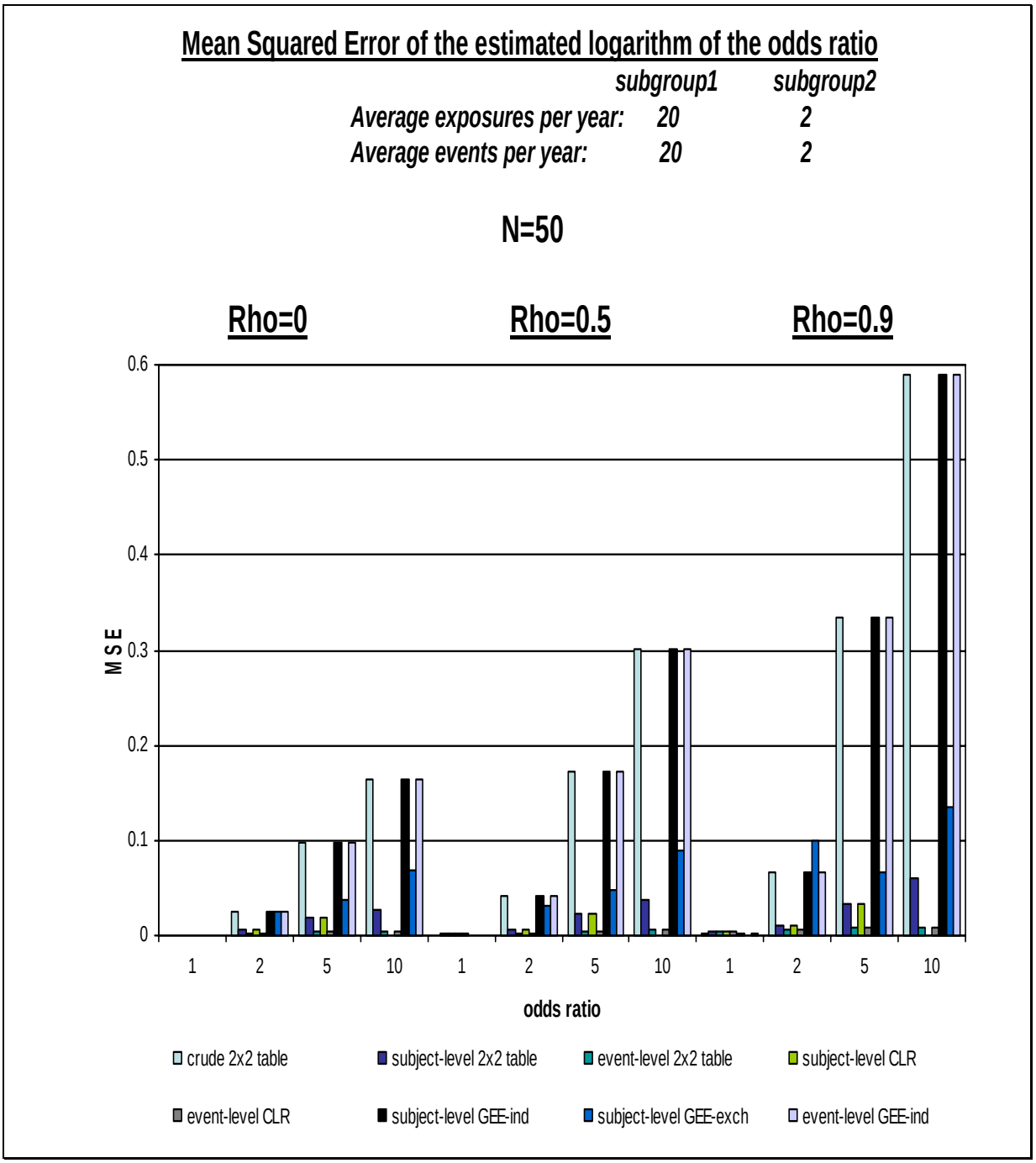


Figure 5.3.6.6: Relationship among the mean squared error, odds ratio and correlation coefficient with respect to different statistical models

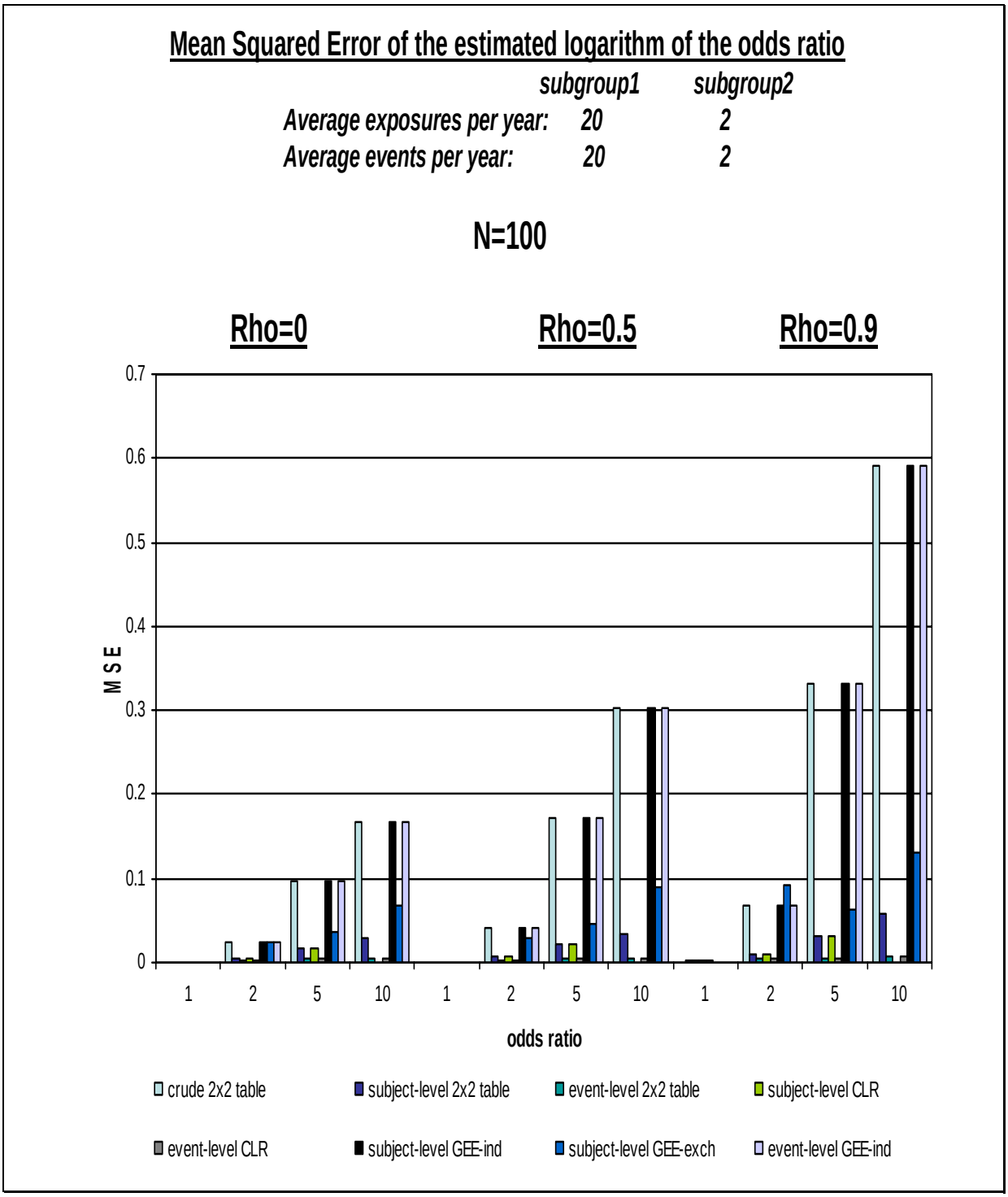


Figure 5.3.6.7: Relationship among the mean squared error, odds ratio and correlation coefficient with respect to different statistical models

CHAPTER 6

A CASE-CROSSOVER STUDY OF BENZODIAZEPINE USE AND REPEATED MOTOR VEHICLE CRASHES (MVCS) IN THE ELDERLY POPULATION

Overview

In Chapter 5, we concluded that the M-H method and the CLR method with the *event-level* data analyses are the best for analyzing data from a case-crossover study with repeated events in the same subject, under certain assumptions. In this chapter, we will apply these methods to a real dataset to study the association between benzodiazepine use and repeated MVCs in the elderly population. In particular, we will first review the study databases (SAAQ and RAMQ) that were used to obtain the information with respect to benzodiazepine use and the multiple MVCs in the same subject. Second, we will define the study population, the multiple MVCs ("cases"), and the matched control periods ("controls"). Third, we will examine the performance of the estimators while comparing the 'multiple event' with the 'first event' approaches and the 'event-level' with the 'subject-level' in the data analyses. In the same section, we will also compare the results from this real data study with those from the simulation study. Finally, we will discuss some limitations of this MVCs study and provide some recommendations on analyzing data from a case-crossover study with repeated events in the same subject.

The main purpose of this exercise is to compare results from these statistical methods in analyzing a real case-crossover data for individuals with multiple events of interest, and verify the consistency of the study findings between the study results from the MVCs study and those from the simulation study as presented in Chapter 5.

6.1 Introduction: the significance of studying the association between benzodiazepine use and the MVCs of interest

Benzodiazepines, one of the most frequently prescribed medications in the elderly population, are known to impair memory function and cognitive skills. It is reported that use of benzodiazepines may cause damage to human brain, such as the cerebral cortex. Since the cerebral cortex is important for decision-making and movement, it is suggested that benzodiazepine use may increase the risk of impairment of driving ability (Gudex, 1991). Injuries due to MVCs are major causes of morbidity and mortality in the elderly population. According to a report by Millar and Adams (1991), MVCs are the leading cause of fatal injuries in Canada.

Accidents from MVCs among elderly drivers are expected to increase due to the increasing numbers of elderly drivers. In the province of Québec, the number of licensed drivers 65 years of age or older increased from 542,595 in 2002 to 637,555 in 2006 - a 18% increase in about 5 years (Société de l'assurance automobile du Québec, 2007). It is projected that by the year 2015 more than 35% of all drivers would be over 65 years of age (Société de l'assurance automobile du Québec, 2006). Thus, it is important to determine risk factors which may cause MVC or repeated MVCs in the elderly population so that preventive measures can be undertaken to prevent or reduce the morbidity and mortality from MVCs.

In the next section, we review the study databases (SAAQ and RAMQ) that were used to define benzodiazepine use and the multiple MVCs in the same subject.

6.2 Methods

6.2.1 Sources of data

We obtained the study database for the outcome of interest (MVCs) from the Société de l'assurance automobile du Québec (SAAQ). We also obtained the database on benzodiazepine use (the exposure of interest) from the Régie de l'assurance maladie du Québec (RAMQ). Individuals' health care numbers (numéro d'assurance maladie) were used to link these two databases for the purpose of the study.

The study subjects were drivers and residents of the province of Québec. The subjects had an age range between 67 and 84 (inclusive) on June 1, 1990. The study covered the period between June 1, 1990 and May 31, 2000.

As stated previously, the outcome of interest of the study was the repeated MVCs from study subjects. The outcome information was ascertained from the database provided by the SAAQ by identifying a subject's involvement in more than one serious motor vehicle crash during the study period. A serious motor vehicle crash is defined in this study as a motor vehicle accident involving bodily injuries and material damages valued at least $500.

The exposure of interest of the study was the use of short or long half-life benzodiazepines as recorded in the database provided by the RAMQ. In this study, we do not attempt to separate these two types of benzodiazepine uses from the database in order to maintain sufficient study power. The short half-life benzodiazepines include alprazolam, bromazepam, lorazepam, oxazepam, temazepam, and triazolam. The long half-life benzodiazepines include clonazepam, diazepam, clorazepate, chlordiazepoxide, flurazepam, and nitrazepam.

6.2.2 The database from the Régie de l'assurance maladie du Québec (RAMQ)

The RAMQ is responsible for administering insured health care services for the entire province of Québec. Residents of Québec are eligible for health care coverage after they have established their residences and registered with the RAMQ for a health card. Visitors, international students, and individuals living outside of Québec for more than 183 days in a given year are not eligible for health care coverage.

There are three computerized databases that contain health care information:

1. **The demographic database:** The demographic database contains information on a medicare cardholder's name, date of birth, gender, and home address.

2. **The medical service database:** This database includes information on the nature of the service provided, specific treatment, the name of the attending physician, the date and location of the treatment, and the diagnostic code of the service (ICD-9 code).

3. **The prescription database:** This database includes information on out-patient prescriptions. Before 1997, the government provided insurance plan for medications for the Quebecers who satisfied one of the following two conditions: 1) persons aged 65 and over; and, 2) recipients of last-resort financial assistance and other holders of a claim slip. Since 1997, the government has extended the medication insurance plan to those who satisfy one of the following four conditions: 1) persons aged 65 and over; 2) recipients of last-resort financial assistance and other holders of a claim slip; 3) persons who do not have access to a private plan; and 4) children of persons covered by the public plan. This program is fee-for-service (the pharmacy claims reimbursement for the drugs dispensed). This database also contains other data which are important to the study including: 1) Patient identification number (a 12 digit health care number); 2) Date of prescription; 3) Benzodiazepine class (categorized by the American Hospital Formulary System); 4)

Benzodiazepine code (an eight digit drug identification number (DIN)); 5) Quantity dispensed; and, 6) Duration of treatment prescribed.

The prescription database does not record information on medications available over-the-counter, it only contains information on those medications identified in the RAMQ formulary (a provincial formulary of insured drugs published every six months).

The accuracy and completeness are some of the major strengths of the RAMQ computerized prescription database. The RAMQ reimbursement policies require that pharmacists must fill all mandatory fields of the claim forms in order to obtain the reimbursement. Errors in recording information about drugs dispensed are further reduced through the use of billing agencies by the pharmacies. In order to guarantee the quality of the recorded information, the RAMQ routinely conduct internal audits. After an extensive review of the accuracy and comprehensiveness for more than two million records of prescriptions dispensed to the elderly, Tamblyn et al. (1995) found only less than one percent of the values for key fields to be missing or out of range.

6.2.3 The Database from the Société de l'assurance automobile du Québec (SAAQ)

The SAAQ is a provincial government agency responsible for driver's license registration, vehicle registration, recording reports of motor vehicle traffic accidents, as well as administering the universal insurance system which provides financial compensation to those residents of the province who were injured in MVCs. The SAAQ provided the computerized dataset to identify the study cohort and to ascertain the study outcome of interest (i.e., the repeated MVCs).

The computerized database was created by the SAAQ in March 1978 and has been used for various research purposes since, including, for example, an investigation to

determine the prognostic factors for the recovery of whiplash injuries sustained in MVCs by Suissa et al. (1995).

Report forms for motor vehicle accidents were completed by Québec police officers and the information was entered in the "Fichier Accident" computerized files of the SAAQ. Based on Québec law, a police officer who responded to the accident call must hand in the accident report form to the SAAQ within eight days of the accident. To qualify for this mandated report, the accident must have involved bodily injury, as well as those with material damage valued at a minimum of $500.

The current version of the report form for a motor vehicle crash accident was revised on September 1, 1988, to include the following information: 1) The date, time and location of the crash accident; 2) The type of crash (such as rear-end collision, head-on collision, and side impact collision); 3) The weather and road conditions; 4) The number and type of vehicles involved; 5) The estimated amount of vehicle and property damage; 6) The number of individuals involved in the crash accident; 7) The use of seat belt; 8) The nature of injuries; and, 9) The health insurance card number(s) of the individual(s) involved.

Laberge-Nadeau et al. (1984) evaluated the accuracy and completeness of the SAAQ accident data and reported a 3% overall error between the accident report forms and the computerized data. The study by Laberge-Nadeau et al., however, did not evaluate the differences between the actual accident and reported event by the law enforcement officials.

As stated previously, we used personal health care number to link the SAAQ database with the RAMQ database to create a new dataset which contains the information on both the repeated MVCs and benzodiazepine use for each of the study subjects.

6.3 Study population

Source Population: From the SAAQ and RAMQ databases, we first identified a total of 163,607 subjects who had at least one motor vehicle crash accident as the source population. The study source population includes beneficiaries who aged between 67 and 84 on June 1, 1990, possessed a valid class 5 driver's license (authorized to operate a two-axle passenger vehicle), and had resided in Québec for at least two years prior to the first accident. In January 1997, the government of Québec implemented a public / private prescription drug program that covered the entire population of the province. In order to obtain a complete history of medication use during a two year period, subjects must have been 65 years of age and older in 1988. We set the upper age range to 84 because subjects beyond this age were less likely to drive, and thus, unlikely to be the candidates for the outcome of interest.

The eligible date for being a member of the source population is June 1, 1990 (the date for cohort entrance). A driver who had a valid driver's license and satisfied the other criteria for the study population would be a member of the source population. On the other hand, a member would exit the study either on May 31, 2000, or at age 85, or the time of death, or the date of migration from the province (at which time the Québec driver's license is no longer valid).

Study Population: Since the outcome of interest is repeated MVCs, subjects with a single MVC (e.g., those who died in accident were excluded) or with light accidents (as defined above) were excluded from the study population. From the source population, we identified a total of 3,304 subjects who had serious and multiple MVCs (at least two

MVCs). One of the reasons we included only those with multiple MVC accidents in the study is that we would like to maintain the same study subjects when we compare the approaches for the first event and for the multiple events. Use of different members of the study population for the first event and for the multiple event approaches could make the results uninterpretable when examining the variances of the odds ratio between different statistical methods.

Of these 3,304 subjects, 2,466 subjects were excluded because no information on benzodiazepine use was recorded in the database. The database only contained the information on medication use covered by the government prescription drug insurance plan. 838 of them had detailed information on benzodiazepine use, and these subjects formed the final study population (Figure 6.3.1).

6.4 Definition of repeated MVCs (cases), matched control periods, and exposure of interest

Multiple MVCs (Cases): The study outcome of interest in this study was repeated motor vehicle crash accidents by study subjects. As stated previously, the definition of outcome of interest requires that at least one individual (not necessarily the driver) sustained bodily injuries in the crash and that the overall damage was valued at least $500.

Matched Control Period(s): As illustrated in Figure 4.4.1 (Chapter 4), the ending date of the control period was defined as the event date minus the length of the risk period. The length of the risk period was defined as 30 days. We adopted a period of 30 days as the length for the risk period because the mean duration of benzodiazepine use is about 30 days in the RAMQ prescription database. The length of the control period was

defined as the same length as the risk period (30 days). The association between benzodiazepine use and the MVCs of interest in this study was evaluated by comparing the rates of exposure between the risk period(s) and the control period(s).

Exposure: In this study, we used two variables (the date of last prescribed benzodiazepine before a specific MVC and "the duration of treatment") to define whether a study subject was exposed to benzodiazepine during the risk period or the selected control period. For example, consider a subject for whom the date of MVC was January 1, 1995 and the date of benzodiazepine prescription was December 10, 1994. Since benzodiazepine prescription lasts for 30 days, this subject would be considered to have been exposed to benzodiazepine during the risk period. The same method can be used to define the exposure status for the selected control period(s).

6.5 Data analysis

The main purposes of the study are to (1) compare the estimates of the odds ratio; and, (2) compare the estimated variances of the odds ratio between any two different statistical methods in estimating the association between benzodiazepine use and the MVCs of interest. In particular, we will compare the ratios of the estimated odds ratios and their corresponding variances from different statistical methods based on the following two scenarios:

1) First event vs. multiple events; and,
2) 1:1 vs. 1:2 matching ratio for risk and control periods.

We will use the ratios of the estimated odds ratios and the corresponding variances to compare the performance of two different statistical methods. Because the estimated

odds ratios were obtained from multiplicative models (rather than additive models), the ratio of the estimated odds ratios would be the most reasonable way to measure the discrepancy between different statistical methods. The size of the variance of the odds ratio reflects the precision of the estimators. The smaller the variance, the higher the precision of the estimators.

6.6 Results

In Tables 6.6.1 and 6.6.2, we illustrate the data structure of the MVCs study according to the three different units of data analyses. In Table 6.6.3, we summarize the estimates of the odds ratio from three different statistical methods, while comparing the *first event* with the *multiple event* approaches. In Table 6.6.4, we compare the discrepancies of the estimates of the odds ratio and variance from three different statistical methods, while comparing the *subject-level* with the *event-level* data analyses. Similar to Tables 6.6.3 and 6.6.4, Tables 6.6.5 and 6.6.6 present the results when the matching ratio between the risk period and the control period is set to 1:2.

As shown in Table 6.6.1, there were a total of 1,682 multiple MVC accidents from 838 study subjects during a ten-year study period. Out of the 1,682 multiple MVC accidents, 822 occurred within 30 days after the study subjects received benzodiazepine prescriptions. Thus, these 822 MVCs were considered to be exposed to benzodiazepine use. Likewise, for the 1,682 matched control periods (1:1 matching ratio), 445 of them were considered to be exposed to benzodiazepine use.

If the study only considers the first MVC accident, 441 risk periods were considered to be exposed to benzodiazepine use while 231 matched control periods were

considered to be exposed to benzodiazepine use. According to the *subject-level* and the *event-level* data analyses, the data were regrouped into 838 small and 1676 (838×2) mini 2×2 tables. Table 6.6.2 shows the same data structure as presented in Table 6.6.1 but with 1:2 matching ratio.

- **Comparison of the Results from the *Multiple Event* vs. the *First Event* Approaches with 1:1 Matching (Table 6.6.3)**

• ***Multiple event approach*:**

1) The M-H method and the CLR method provided numerically almost identical estimates of the odds ratio (OR=4.0 for the former and 4.1 for the latter) when the data analyses were conducted at the *subject-level*. Moreover, the estimated variances from these two statistical methods were also numerically identical.

2) The *crude overall* M-H method and the *subject-level* GEE method with an independent w.c.s. yielded numerically identical point estimates. The GEE method, however, produced an estimate with a much narrower confidence interval.

3) The *subject-level* GEE method with an exchangeable w.c.s. produced the smallest point estimate with the smallest variance compared with the other four estimators (Table 6.6.3).

• ***First event approach*:**

1) Like the multiple event approach, the *subject-level* M-H method and the CLR method provided numerically identical estimates of the odds ratios (OR=3.69 for the former and 3.69 for the latter). The *overall crude* M-H method and the *subject-level* GEE

method with an independent w.c.s. also produced numerically identical point estimates.

2) At the *subject-level* data analysis, the GEE method with an independent w.c.s. yielded a smaller estimate of the odds ratio but with a much narrower confidence interval compared with the M-H method and the CLR method.

3) When the first event approach is used, the *subject-level* GEE method with an exchangeable w.c.s. cannot produce an estimate for the odds ratio estimation because in this case the estimated working residual correlation became negative one (-1).

- **Comparison of the Results from the Analyses Conducted at the *Subject-level* vs. the *Event-level* with 1:1 Matching (Table 6.6.4)**

As shown in Table 6.6.4, the M-H method and the CLR method produced numerically identical estimates of the odds ratio and their variance, no matter the analyses were conducted at the *subject-level* or at the *event-level*. Both the M-H method and the CLR method at the *event-level* analyses, however, produced larger odds ratios and their corresponding variances. If one assumes that these two statistical methods at the *event-level* data analyses provide the true estimations of the underlying association, then, these two methods at the *subject-level* data analyses would have underestimated the association between benzodiazepine use and the risk of the repeated MVC accidents in the same subject by about 6 to 9%.

Table 6.6.4 also shows the results from the analyses by using the GEE method. We can see that the GEE method produced numerically identical estimates of the odds ratio regardless of the units of data analyses, even though the *event-level* data analysis yielded a 10% larger variance than the *subject-level* data analyses.

- **Comparison of the Results Using the *Multiple Event* vs. the *First Event* Approaches, and the Analyses Conducted at the *Subject-level* vs. the *Event-level* with 1:2 Matching (Tables 6.6.5 and 6.6.6)**

While similar conclusions can be drawn in Tables 6.6.5 and 6.6.6 as those summarized for the results with 1:1 matching (presented in Tables 6.6.3 and 6.6.4), the 95% CIs for the odds ratios from the dataset with 1:2 matching ratio were narrower than those from the dataset with 1:1 ratio. This is because the dataset with one risk period to match two control periods (1 to 2 matching) has a larger sample size which produces higher precision for the odds ratio estimators. For example, the OR and corresponding 95% CI from the *subject-level* CLR method are 4.11 (3.41, 4.95) in Table 6.6.3 (1:1 matching ratio) vs. 4.16 (3.55, 4.87) in Table 6.6.5 (1:2 ratio). Both results are calculated by using the multiple event approach.

6.7 Comparison of the results from the MVCs study with those from the simulation study

- **Comparison of the *Multiple Event* vs. the *First Event* Approaches:**

In the simulation study (Chapter 5), we have demonstrated that the empirical estimates of the odds ratio from the eight estimators increase as the propensities of exposure and the outcome of interest increase from $2 \rightarrow 10 \rightarrow 20$ instances per year. We also showed that the estimates of the empirical variance from these eight estimators decrease with the propensities of exposure and the outcome increase. Higher propensity of exposure and the outcome of interest could generate more outcome events compared with lower

propensity of exposure and the outcome of interest. The higher or lower propensity could be compared to the *multiple event* or *first event* approach in our data analyses.

In the real data study of benzodiazepine use and the risk of the MVCs of interest (Table 6.6.3), we have demonstrated that, with the same statistical method and the same unit of data analysis, the *multiple event* approach can produce larger odds ratios than the *first event* approach. For example, the estimated odds ratio with *multiple event* approach is 10% larger than that from the *first event* approach with the CLR method at the *subject-level*.

Table 6.6.3 also shows that the *multiple event* approach can substantially reduce the variances of the estimates of the odds ratio, regardless of the units of data analyses and the statistical methods used. For example, the ratio of the variances from *first event* approach to the *multiple event* approach is 2.11 for the CLR method at the *subject-level*. The *multiple event* approach produces smaller variance (i.e., higher precision) compared with the *first event* approach. These results are consistent with what has been shown in the simulation study.

• **Comparison of the *Subject-level* vs. the *Event-Level* Data Analyses**

In Chapter 5, we concluded that the M-H method and the CLR method with the *event-level* data analyses are the best for analyzing data from a case-crossover study with repeated events in the same subject, because both statistical methods at the *event*-level yielded the smallest MSEs. We also demonstrated that all three statistical methods with the *subject-level* data analyses could substantially underestimate the underlying odds ratio although these methods with *subject-level* data analyses produce smaller variances of the odds ratio than the *event-level* data analyses.

In this real data study of benzodiazepine use and the risk of the MVCs of interest (Table 6.6.4), we also showed that, for each statistical method, the *event-level* data analysis yields a larger estimate of the odds ratio with a wider confidence interval (larger variance). For example, the ratio of the odds ratio from the *event-level* to the *subject-level* CLR method is 1.06, and the ratio of the variance from the *event-level* to the *subject-level* CLR method is 1.21. These results indicates that the odds ratio from the *event-level* CLR method is 6% larger than that from the *subject-level*, while the variance of the odds ratio from the *event-level* CLR method is 21% larger than that from the *subject-level.* These results again are consistent with what have been shown in the simulation study.

6.8 Discussion

6.8.1 Brief summary of the results from the MVCs study

In the next section, we summarize the major findings from the application to a study of the association between benzodiazepine use and the repeated MVCs in the same subject.

Compared with the *first event* approach, the *multiple event* approach with the same statistical method and the same unit of data analysis can produce a slightly larger estimate of the odds ratio with a narrower confidence interval. However, the magnitude of the difference (<10%) in the odds ratio between these two approaches is not large enough for us to recommend that *multiple event* approach rather than the *first event* approach should be used to analyze data from a case-crossover study with repeated events in the same subject. On the other hand, as expected, the estimated variance from the *multiple event* approach is smaller than that from the *first event* approach due to the sample size efficiency.

In addition, compared with the *subject-level* data analysis, the *event-level* M-H method and the CLR method can yield a larger estimate of the underlying odds ratio with a slightly wider confidence interval (larger variance). With the same statistical method and the same unit of data analysis, the estimated variances of the odds ratios from the data with a higher matching ratio are smaller than those from the data with a lower one. Simply, larger sample size results in a higher precision for the odds ratio estimation.

6.8.2 Limitations

Several potential limitations need to be considered in interpreting the study results linking benzodiazepine use and the MVCs in this study. First potential limitation is related to the exposure information on benzodiazepine use. The information on benzodiazepine use by study subjects (including date of prescription and duration of treatment) was based on the data recorded in the RAMQ drug database. The assumption for using this database to define exposure to benzodiazepine is that the patient consumed benzodiazepine on a regular basis as prescribed. Consequently, if patients did not actually take the medication on a regular basis as prescribed, misclassification of exposure could occur. However, for this misclassification of exposure to create systematic bias to the observed association between benzodiazepine use and the MVCs of interest, the misclassification has to be systematically different between the risk period and the control period(s). This is very unlikely because the exposure definition is purely based on historical records that were established long before the study. Therefore, if there was any misclassification of benzodiazepine use, the misclassification should be non-differential, and non-differential misclassification would cause an underestimation of the association between benzodiazepine use and the MVCs of interest.

The second potential limitation is related to the information on the outcome of interest. As discussed in section 6.4, the MVC accidents of the study subjects were constructed based on the SAAQ accident file. To be considered as a MVC accident in this study, the accident must involve bodily injury and material damages valued at a minimum of $500. Not all the MVC accidents were reported by law enforcement officials. There is a potential bias if the unreported MVCs were also associated with benzodiazepine use. However, for this under reporting of the MVCs to cause a systematic bias in this study, the exclusion of the MVCs from being reported by the law enforcement officials had to be affected by benzodiazepine use, that is, reporting the MVCs by police officers had to be systematically different for those who had accidents and took the medication from those who had accidents but did not take the medication.

6.9 Final remarks

In this chapter, we have applied three different statistical methods to investigate the association between benzodiazepine use and repeated MVCs in the elderly population in Québec, Canada. The results have shown that benzodiazepine use had increased the risk of developing multiple MVCs in this elderly population.

In this study, we have also compared the results from the simulation study and those from the study based on real dataset linking benzodiazepine use with repeated MVCs. Our conclusion is that the major findings from the MVCs study are consistent with what have been shown in the simulation study as described in Chapter 5.

Based on the study results, we have recommended that the *M-H method* and the *CLR method* with the *event-level* data analyses should be used to analyze the data from a

case-crossover study with repeated events in the same subject, because these two statistical methods can produce better estimates of the underlying association. Moreover, when repeated events along with multiple levels of clusters are present in the research data, the data analysis should be conducted at the finest level of cluster to obtain a better estimate of the odds ratio. In our study, the finest level of data analysis is the so-called the '*event-level'* data analysis.

In reality, the *multiple event* approach should be recommended to improve the precision of the estimate of the odds ratio, if applicable.

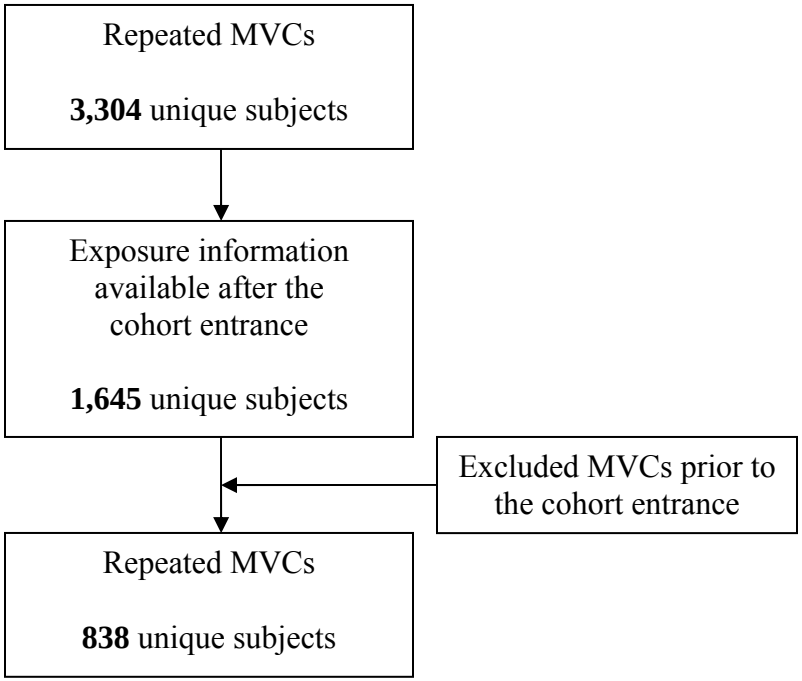


Figure 6.3.1: Recruitment of the study subjects

Type of event	Structure of data	Unit of analysis		
		Overall Crude	Subject-Level (Time-Unmatched)	Event-Level (Time-Matched)
Multiple event	2×2 table E $\overline{E}$ D $\overline{D}$	822 860 445 1237	*(1)* $\begin{bmatrix}1 & 1\\ 1 & 1\end{bmatrix}$ *(838)* $\begin{bmatrix}2 & 0\\ 2 & 0\end{bmatrix}$	*(1.1)* $\begin{bmatrix}0 & 1\\ 1 & 0\end{bmatrix}$ *(838.1)* $\begin{bmatrix}1 & 0\\ 1 & 0\end{bmatrix}$ *(1.2)* $\begin{bmatrix}1 & 0\\ 0 & 1\end{bmatrix}$ *(838.2)* $\begin{bmatrix}1 & 0\\ 1 & 0\end{bmatrix}$
	number of subjects number of events		1 1 (2) (2)	1 1 (2) (2)
First event	2×2 table E $\overline{E}$ D $\overline{D}$	411 427 231 607	*(1)* $\begin{bmatrix}0 & 1\\ 1 & 0\end{bmatrix}$ *(838)* $\begin{bmatrix}1 & 0\\ 1 & 0\end{bmatrix}$	*(1.1)* $\begin{bmatrix}0 & 1\\ 1 & 0\end{bmatrix}$ *(838.1)* $\begin{bmatrix}1 & 0\\ 1 & 0\end{bmatrix}$
	number of subjects number of events		1 1 (1) (1)	1 1 (1) (1)

Table 6.6.1: Illustration of the data structure using the multiple event vs. the first event approaches (1 risk period vs. 1 control period)

Type of event	Structure of data	Unit of analysis		
		Overall Crude	Subject-Level (Time-Unmatched)	Event-Level (Time-Matched)
Multiple event	2×2 table E $\overline{E}$ D $\overline{D}$	822 860 896 2468	*(1)* $\begin{bmatrix}1 & 1\\3 & 1\end{bmatrix}$ *(838)* $\begin{bmatrix}2 & 0\\4 & 0\end{bmatrix}$	*(1.1)* $\begin{bmatrix}0 & 1\\2 & 0\end{bmatrix}$ *(838.1)* $\begin{bmatrix}1 & 0\\2 & 0\end{bmatrix}$ *(1.2)* $\begin{bmatrix}1 & 0\\1 & 1\end{bmatrix}$ *(838.2)* $\begin{bmatrix}1 & 0\\2 & 0\end{bmatrix}$
	number of subjects		1 1	1 1
	number of events		(2) (2)	(2) (2)
First event	2×2 table E $\overline{E}$ D $\overline{D}$	411 427 465 1211	*(1)* $\begin{bmatrix}0 & 1\\2 & 0\end{bmatrix}$ *(838)* $\begin{bmatrix}1 & 0\\2 & 0\end{bmatrix}$	*(1.1)* $\begin{bmatrix}0 & 1\\2 & 0\end{bmatrix}$ *(838.1)* $\begin{bmatrix}1 & 0\\2 & 0\end{bmatrix}$
	number of subjects		1 1	1 1
	number of events		(1) (1)	(1) (1)

Table 6.6.2: Illustration of the data structure using the multiple event vs. the first event approaches (1 risk period vs. 2 control periods)

Unit of analysis	Statistical method		*Multiple event*		*First event*		Ratio of odds ratio	Ratio of Variance
			Odds ratio (95%CI) $\hat{\psi}_{me}$	variance $\hat{V}_{me}$	Odds ratio (95%CI) $\hat{\psi}_{fe}$	variance $\hat{V}_{fe}$	$\frac{\hat{\psi}_{fe}}{\hat{\psi}_{me}}$	$\frac{\hat{V}_{fe}}{\hat{V}_{me}}$
Crude	M-H		2.66(2.30, 3.07)	.0054	2.53(2.06, 3.10)	.0107	.95	1.98
Subject level	M-H		4.00(3.32, 4.81)	.0090	3.69(2.81, 4.83)	.0190	.92	2.11
	CLR		4.11(3.41, 4.95)	.0090	3.69(2.81, 4.83)	.0190	.90	2.11
	GEE	Ind.	2.66(2.34, 3.02)	.0042	2.53(2.13, 3.01)	.0079	.95	1.88
		Exch.	1.65(1.46, 1.87)	.0039				

M-H: Mantel-Haenszel; CLR: conditional logistic regression; GEE: generalized estimating equations; Ind.: independent working correlation structure; Exch.: exchangeable working correlation structure; $\hat{\psi}_{me}$, $\hat{\psi}_{fe}$ and $\hat{V}_{me}$, $\hat{V}_{fe}$ are the estimated odds ratios and variances, respectively.

Table 6.6.3: Performance of the estimators using the multiple event vs. the first event approaches (1 risk period vs. 1 control period)

Statistical method		*Subject-level*		*Event-level*		Ratio of odds ratio $\frac{\hat{\psi}_{e-l}}{\hat{\psi}_{s-l}}$	Ratio of Variance $\frac{\hat{V}_{e-l}}{\hat{V}_{s-l}}$
		Odds ratio (95%CI) $\hat{\psi}_{s-l}$	variance $\hat{V}_{s-l}$	Odds ratio (95%CI) $\hat{\psi}_{e-l}$	variance $\hat{V}_{e-l}$		
M-H		4.00(3.32, 4.81)	.0090	4.34(3.53, 5.32)	.0109	1.09	1.21
CLR		4.11(3.41, 4.95)	.0090	4.34(3.53, 5.32)	.0109	1.06	1.21
GEE	Ind.	2.66(2.34, 3.02)	.0042	2.66(2.36, 3.00)	.0038	1.00	.90
	Exch.	1.65(1.46, 1.87)	.0039				

M-H: Mantel-Haenszel; CLR: conditional logistic regression; GEE: generalized estimating equations; Ind.: independent working correlation structure; Exch.: exchangeable working correlation structure; $\hat{\psi}_{s-l}$, $\hat{\psi}_{e-l}$ and $\hat{V}_{s-l}$, $\hat{V}_{e-l}$ are the estimated subject-level or event-level odds ratios and variances, respectively.

Table 6.6.4: Performance of the estimators using the subject-level vs. the event-level analyses (1 risk period vs. 1 control period)

Units of analysis	Statistical method		*Multiple event*		*First event*		Ratio of odds ratio $\frac{\hat{\psi}_{fe}}{\hat{\psi}_{me}}$	Ratio of Variance $\frac{\hat{V}_{fe}}{\hat{V}_{me}}$
			Odds ratio (95%CI) $\hat{\psi}_{me}$	variance $\hat{V}_{me}$	Odds ratio (95%CI) $\hat{\psi}_{fe}$	variance $\hat{V}_{fe}$		
Crude	M-H		2.63(2.33, 2.98)	.0039	2.51(2.11, 2.98)	.0078	.95	2.00
Subject level	M-H		4.02(3.43, 4.71)	.0065	3.88(3.08, 4.89)	.0139	.97	2.14
	CLR		4.16(3.55, 4.87)	.0065	4.06(3.22, 5.11)	.0139	.98	2.14
	GEE	Ind.	2.63(2.35, 2.94)	.0033	2.51(2.16, 2.91)	.0059	.95	1.79
		Exch.	1.68(1.45, 1.94)	.0055				

M-H: Mantel-Haenszel; CLR: conditional logistic regression; GEE: generalized estimating equations; Ind.: independent working correlation structure; Exch.: exchangeable working correlation structure; $\hat{\psi}_{me}$, $\hat{\psi}_{fe}$ and $\hat{V}_{me}$, $\hat{V}_{fe}$ are the estimated odds ratios and variances, respectively.

Table 6.6.5: Performance of the estimators using the multiple event vs. the first event approaches (1 risk period vs. 2 control periods)

Statistical method		*Subject-level*		*Event-level*		Ratio of odds ratio $\frac{\hat{\psi}_{e-l}}{\hat{\psi}_{s-l}}$	Ratio of Variance $\frac{\hat{V}_{e-l}}{\hat{V}_{s-l}}$
		Odds ratio (95%CI) $\hat{\psi}_{s-l}$	variance $\hat{V}_{s-l}$	Odds ratio (95%CI) $\hat{\psi}_{e-l}$	variance $\hat{V}_{e-l}$		
M-H		4.02(3.43, 4.71)	.0065	4.38(3.70, 5.20)	.0076	1.09	1.17
CLR		4.16(3.55, 4.87)	.0065	4.61(3.88, 5.46)	.0076	1.11	1.17
GEE	Ind.	2.63(2.35, 2.94)	.0033	2.63(2.37, 2.92)	.0029	1.00	.88
	Exch.	1.68(1.45, 1.94)	.0055				

M-H: Mantel-Haenszel; CLR: conditional logistic regression; GEE: generalized estimating equations; Ind.: independent working correlation structure; Exch.: exchangeable working correlation structure; $\hat{\psi}_{s-l}$, $\hat{\psi}_{e-l}$ and $\hat{V}_{s-l}$, $\hat{V}_{e-l}$ are the estimated subject-level or event-level odds ratios and variances, respectively.

Table 6.6.6: Performance of the estimators using the subject-level vs. the event-level analyses (1 risk period vs. 2 control periods)

CHAPTER 7

CONCLUSIONS AND DISCUSSIONS

Overview

This chapter summarizes the results from this thesis study and discusses future directions for research in this area. In particular, we focus on the following five areas:

1. The need to extend case-crossover study from a study of a single outcome event to a study of multiple outcome events;
2. The dependencies between repeated exposures and the outcome events in a case-crossover study and their potential impact on results of this thesis and other studies;
3. The performance of the three statistical methods (the M-H method, the CLR method and the GEE method) in analysis of data with repeated events in the same subject;
4. The potential limitations of the simulation study and the real dataset study; and,
5. The recommendations on types of statistical methods and levels of data analyses when multiple levels of clusters exist in research data.

7.1 The need to extend a case-crossover study from a study of a single event to a study of multiple events

The case-crossover study was first proposed by Maclure (1991) to study the relationship between transient exposure and acute outcome with only the 'first event' of interest. There is a need to extend the case-crossover study design from a study of a single outcome event to a study of multiple outcome events in the same subject, because

multiple events simply provide more insight into the causes, the patterns and the mechanisms leading to the outcome of interest.

In a study involving the association between repeated exposures and multiple outcome events, the association can be evaluated in the longitudinal setting as in the classical case-crossover study design. Three statistical methods can be used to analyze the data from a case-crossover study with multiple events in the same subject: the M-H method, the CLR method, and the GEE method. For each statistical method to be used for the data analysis, there are three different choices of the unit of data analysis in analyzing the data: the overall crude, the subject-level, and the event-level.

Issues related to the dependencies between the repeated exposures, confounder, and the outcome of interest in a case-crossover study are discussed below.

7.2 The dependency between the repeated exposures and the outcome events in a case-crossover study

Traditional statistical methods such as *GLM* (McCullagh and Nelder, 1989) implicitly assume that the study exposure does not affect any covariate used as a regressor in the model. However, these assumptions are often questionable when exposure and covariates vary over time. For example, in a study of the association between coffee use and the risk of myocardial infarction (MI), serum cholesterol might act as a confounder because coffee drinkers may have more unmeasured factors which are associated with elevated serum levels of cholesterol and serum cholesterol is highly associated with MI risk. At the same time, serum cholesterol level may be simply an intermediate step in the causal pathway between coffee drinking and risk of MI because coffee drinking changes serum

levels of cholesterol and then affects the risk of MI in an individual. In this case, the time-dependent confounder variables will not only function as confounders in the study, but also act as an intermediate variable (Rothman and Greenland, 1998). A biased estimate may result whether the covariate is controlled by traditional methods (Robins, 1987, 1989).

In a case-crossover study of repeated exposures and outcome events, exposure itself may affect the probability of subsequent exposure to the same agent. For example, an individual may be less likely to take medicine after experiencing side effects of a specific medication from first use. Or, the individual may change from a regular user to an irregular user due to the side effects. Other than the dependency among the repeated exposures, one also needs to consider the interrelationship between the exposure and the potential confounders in a case-crossover study, where past exposure to the time-dependent confounder variables may be related to the study exposure of interest and vice versa. In this type of study, as pointed out by Rothman and Greenland (1998), time-varying exposures and time-varying covariates that play a dual role of confounder and intermediate need to be considered in the data analysis. Otherwise, it would result in a biased estimate if we adjust for the effect of exposure on the confounder and vice versa.

Rothman and Greenland also pointed out another interrelationship which needs to be considered in a case-crossover study with repeated exposures and multiple outcome events, i.e., a case-crossover study should pay attention to the issue of "early outcome event" of interest. This is because earlier outcome event of interest may not only be an outcome, but also act as a potential confounder for evaluating the effect of exposure on the subsequent outcomes. For example, in a study of the relationship between repeated

use of oral corticosteroids and the risk of multiple asthma hospitalizations, subsequent use of oral corticosteroids would be affected by the event of previous asthma hospitalization.

The three statistical methods used in this study (the M-H method, the CLR method, and the GEE method) do not take these three dependencies into consideration. Applying these three statistical methods to the data from a case-crossover study with repeated exposures and the outcome events could result in biased estimates if strong dependencies between these variables indeed exist. It is warranted to develop or extend statistical methods to address the issue related to the dependency between exposure and intermediate variable, between exposure and early outcome, and earlier outcomes and later outcomes (e.g., Robins et al., 1999; Robins et al., 2000).

7.3 The performance of the estimators in analyzing the data with multiple outcome events per person

In the next section, we first summarize the results from the simulation study and the MVCs real data study. Next, we will discuss possible explanations for the discrepancy in the odds ratio estimation for each individual estimator.

7.3.1 Summary of the major findings from the simulation study and the real data study

We applied eight estimators to analyze the data from simulation study or from the real data involving benzodiazepine use to the risk of MVCs. As shown in Chapter 5, all of the eight estimators can produce consistent estimates of the odds ratio and the corresponding variance. However, based on the MSE criterion, we concluded that the M-H method and the CLR method with the *event-level* data analyses are the best to analyze the data from a

case-crossover study with multiple events in the same subject. This is because these two estimators produce the smallest MSEs, i.e., these two estimators can bring in a significant reduction in bias with only a slight increase in the variance estimation.

In Chapter 6, we examined the performance of the eight estimators via the MVCs study. In particular, we compared the estimates of the odds ratio and variance between any two estimators and concluded that the major findings from the real data study are consistent with those from the simulation study. That is, 1) the M-H method and the CLR method with the *event-level* data analyses can produce a larger estimate of the odds ratio with a slightly larger variance relative to the *subject-level* data analyses; and, 2) with the same statistical method and the same unit of data analysis, the *multiple event* approach can produce smaller variance (i.e., higher precision) for the odds ratio estimation relative to the *first event* approach. We now provide some details of these comparisons.

7.3.2 Comparison of the performance of the three statistical methods

- **The M-H method, the CLR method, and the GEE method**

In considering the bias and precision from these three different statistical methods, the discussion will be made only for the CLR method and the GEE method. This is because the M-H method at various levels of data analyses provides an estimate of the odds ratio that is numerically identical to that produced by the CLR method. That is, the value of the ratio of $\frac{\sum_{i=1}^{n} a_i d_i / n_i}{\sum_{i=1}^{n} b_i c_i / n_i}$ from the M-H method is identical to that from the CLR method (matched odds ratio=B/C, where 'B' represents the total number of discordant pairs with 'case exposed but control unexposed'; likewise, 'C' denotes the total number of

discordant pairs with 'case unexposed but control exposed'). The estimated variance of the log odds ratio from the M-H method is also similar to that derived from the CLR method, where the variance of the log odds ratio from the former is calculated based on the Woolf's formula (Var(log(OR))=1/a+1/b+1/c+1/d), and the latter is computed based on the formula: Var(log(OR))=1/B+1/C. In fact, these two formulas yield numerically identical results in the estimates of the empirical variance.

While the point estimates are the same, the corresponding model-based variances are identical for the overall crude M-H method, the subject-level and event-level GEE methods with an independent w.c.s. to analyze the data from a case-crossover study with multiple outcomes of interest in a subject.

Although the *event-level* GEE method with an independent w.c.s. could produce the estimates of the underlying odds ratio in various settings, as shown in the simulation study, the point estimates significantly underestimated the underlying odds ratio. In particular, the magnitude of the bias from the *event-level* GEE method had the same degree of bias as that observed at the *subject-level* data analyses. Thus, the event-level GEE method with an independent w.c.s. is considered to be a type of "unadjusted" data analyses rather than an "adjusted" data analyses (e.g., the *event-level* M-H method and the CLR method).

In the following, we will compare the results from the event-level CLR method and the GEE method. In particular, we will present some observations from the GEE method when used to analyze the data from a case-crossover study with multiple outcome events per subject.

➢ **Comparison of the performance of the CLR method and the GEE method**

- **Bias and precision of the odds ratio in the simulation study and major findings from the real data study**

1) As described in Chapter 3, the GEE method produces a population-averaged effect. Consequently, if the population is not homogenous, the heterogeneity of the study population would affect the estimate of the underlying association. If there is a substantial difference in the propensity of developing the outcome of interest in the two comparison populations, the GEE method would underestimate the underlying subject-specific odds ratio. For example, if we assume $\rho = 0.5$, $HR = 10$, $N = 100$ for both group 1 and group 2, but we set $I = 20$ instances per year for group 1 while $I = 2$ for group 2, the odds ratio from the *event-level* GEE method will be 42.0% smaller than the hazard ratio. Under the same conditions, however, the *event-level* CLR method would produce an odds ratio which is only 6.7% smaller than the true value. This demonstrates that the odds ratio from the GEE method is much more likely affected by the heterogeneity of the study population (Neuhaus, 1992).

2) In the simulation study, we hypothesized that, in using the GEE method to analyze the data from a case-crossover study where there exists a large difference in the propensities of exposure and the outcome of interest between the two comparison populations, the GEE method would produce a large reduction in the point estimate of the odds ratio, and thus, cause a significant bias in the estimate of the association between the exposure and the outcome of interest. As the propensities of exposure and the outcome of interest increase between the two comparison populations, the bias will increase. The results from the simulation study support the hypothesis. For example, 1) when

$\rho = 0.5, HR = 10, N = 100$, the bias from the GEE method at *event-level* analysis increases from 34.0% $\rightarrow$ 42.0%, as the propensity of the outcome increases from 10 $\rightarrow$ 20 instances per year on average. On the contrary, under the same conditions, the bias from the CLR method at the *event-level* analysis decreases from 7.9% $\rightarrow$ 6.7%. In fact, the difference in the propensities of exposure and the outcome of interest between two comparison populations does not have a major impact on the magnitude of the bias when the CLR method at the *event-level* is used to analyze the data.

3) As shown in the simulation study and the real data study, the CLR method produces larger variance for the estimated odds ratio than the GEE method when the hazard ratio is small (1 to 2). This is because the CLR method only utilizes the discordant pairs in analyzing pair-matched data. However, as the hazard ratio is set to a value greater than 2, the CLR method at the *event-level* analysis actually produces smaller variances than the GEE method at the *event-level* analysis.

4) In the simulation study and the real data study, the risk period and matched control period(s) are selected to form pair-matched sets. If the GEE method at the *event-level* analysis with an exchangeable w.c.s. is used to analyze these data, the GEE method will not be able to produce an estimate of the odds ratio because, under this condition, the estimated working residual correlation becomes negative one (perfect negative correlation within cluster) (Allison, 1999).

In summary, compared with the GEE method, the CLR method is a much more desirable statistical method in estimating the association between the exposure and the outcome in a case-crossover study when there is substantial heterogeneity in the propensities of exposure and developing the outcome of interest between the comparison

populations. Although the GEE method may produce a smaller variance for the estimated odds ratio, however, it is important to keep in mind that the validity of epidemiological study should be the primary objective, not precision.

- **Discussion of the Subject-level and the Event-level GEE methods**

In the following, we will present some observations from the GEE method when used to analyze the data from a case-crossover study with multiple outcomes of interest in a subject. In addition, we will discuss under what conditions the GEE method would expected to have better performance.

1) In analyzing the data from a case-crossover study with repeated measurements, the subject-level GEE method with an exchangeable working correlation structure (w.c.s.) produced inconsistent results for the MSEs as shown in Tables 5.3.1(a) $\rightarrow$ 5.3.3(c). The reason(s) for the inconsistency is currently not fully understood. However, based on our study results, it seems that the HR and the propensity of developing the outcome of interest appear to be at least partially responsible for the inconsistent results for the MSEs. Some of the observations based on our simulation study are discussed below:

- The value of HR and its potential impact on the observed MSEs:

  a) When the hazard ratio is set to the null value (HR=1), as shown from Tables 5.3.1(a) to 5.3.3(c), the subject-level GEE method with an exchangeable w.c.s. provides the smallest MSEs compared with the other three estimators (the overall crude M-H method, the subject-level and the event-level GEE method with an independent w.c.s.). This is true no matter which combination of the design parameters (the propensity of developing the outcome of interest, the correlation coefficient, and the sample size) is implemented in the simulation study.

b) When the hazard ratio is increased (e.g., from 2 to 10), but we keep the propensity of developing the outcome of interest small as shown in Tables 5.3.1(a) to 5.3.1(c), the subject-level GEE method with an exchangeable w.c.s. produces the largest MSEs compared with the other three estimators. These results indicate that the hazard ratio has a significant impact on the observed MSEs from the subject-level GEE method with an exchangeable w.c.s..

- The propensity of developing the outcome of interest and its potential impact on the observed MSEs:

  The propensity of developing the outcome of interest appears also to have a significant impact on the observed MSEs as shown in Table 5.3.2(a). For example, if we assume that there are two comparison groups, one group has a higher propensity while the other has a lower propensity of developing the outcome of interest. For the higher propensity group, each individual has a likelihood of developing 10 or 20 events per year, on average. On the other hand, each individual in the other group has a likelihood of developing 2 events per year. As shown in Table 5.3.2(a), when $I_1 = 10$, $I_2 = 2$, $\rho = 0$, $n = 100$, and $HR = 2$, the subject-level GEE method with an exchangeable w.c.s. produced a MSE of 0.042 which is larger than those from the other three estimators (0.018). However, when the propensity of developing the outcome of interest in the higher propensity group is further increased from 10 to 20 and remain the other design parameters the same ($I_2 = 2$, $\rho = 0$, $n = 100$, and $HR = 2$), the subject-level GEE method produced the identical MSE to those from the other three estimators (0.025 vs.0.025).

In summary, these results show that the MSE from the subject-level GEE method with an exchangeable w.c.s. appears to be likely influenced by the value of the hazard ratio and the propensity of developing the outcome of interest. Future studies are warranted to investigate other potential factors which cause the subject-level GEE method with an exchangeable w.c.s. to provide inconsistent estimates in analyzing the data from a case-crossover study with multiple outcome events in a subject. For example, the potential impact from incorporating a continuous exposure variable in the model fitting should be considered when quantitative information about the exposure of interest is available.

2) Two observations about the estimated $\hat{\alpha}$ from the subject-level GEE method with an exchangeable w.c.s. are summarized below: 1) the estimated $\hat{\alpha}$ is always negative; and 2) the estimated $\hat{\alpha}$ increases and approaches 0 as the difference in the propensity of developing the outcome of interest between the two comparison groups increases (e.g., $I_1 = I_2 = 2, \rho = 0, n = 100 \Rightarrow \hat{\alpha}$ =-0.0096; $I_1 = 2, I_2 = 10, \rho = 0, n = 100 \Rightarrow \hat{\alpha}$ =-0.0023; and, $I_1 = 2, I_2 = 20, \rho = 0, n = 100 \Rightarrow \hat{\alpha}$ =-0.0015). The corresponding explanations for these observations are as follows:

a) Due to the specific structure of the case-crossover study, where the risk period is coded as "1" and the corresponding control period is coded as "0", the product of the residuals between the Ys and $\hat{Y}$s is always negative ((1- $\hat{y}_{risk\ period}$) × (0- $\hat{y}_{control\ period}$)). The negative product of residuals from the fitted model resulted in the $\hat{\alpha}$s that are always negative when the GEE method is used to analyze the data from a case-crossover study with repeated measurements in a subject.

b) As the difference in the propensity of developing the outcome of interest between the two comparison groups increases, the estimated $\hat{\alpha}$ increases and approaches zero. A large number of the outcome events result in a more stable $\hat{\beta}$, when the subject-level GEE method with an exchangeable w.c.s. is used to analyze the data from a case-crossover study with multiple outcomes of interest in a subject.

3) The conditions for better performance of the GEE method are discussed separately for the subject-level and the event-level data analyses:

a) For the GEE method at the subject-level data analysis, we expect that this method should work better under a higher propensity of developing the outcome of interest. This is the case because, as the propensity of developing the outcome of interest increases, more outcome events of interest would develop in an individual. A large number of the outcomes of interest would help to produce a more stable estimate of β. As stated previously, the estimated $\hat{\alpha}$ increases and approaches 0 as the propensity of developing the outcome of interest increases.

b) For the GEE method at the event-level data analysis, the GEE method with an exchangeable w.c.s. does not produce an estimate of the odds ratio of interest because the working residual correlation between the risk period and corresponding control period becomes -1, which results in an undefinable V^{-1} in the estimating equation for β. Other approaches can also be tested to see whether the performance of the event-level GEE method could be improved in analyzing the data from a case-crossover study with multiple outcomes of interest. For example, we may add a weighted exposure variable into the model or treat the exposure as a continuous variable when quantitative data about the exposure are available.

However, as described in Chapter 6, our data on benzodiazepine use and MVCs do not have quantitative data on the medication use. That is, the exposure on benzodiazepine use could only be treated as either '1' for ever use or '0' for never use.

7.4 The potential limitations of the study and future research direction

Caution must be exercised in interpreting the results from this study because of the following potential limitations:

1. The results presented in Chapter 6 were based entirely on the data obtained from the administrative files of the SAAQ and RAMQ. We did not attempt to conduct a validation study to confirm the accuracy of the information on motor vehicle accidents and on benzodiazepine use as recorded in the databases. However, as stated previously, several validation studies have been conducted since the early 1980s and have evaluated the consistency between the accidents reported by the police officers and the computerized data files. For example, a study by Laberge-Nadeau et al. (1984) reported an overall error rate of 3% in the SAAQ data. Another study by Tamblyn et al. (1995) also found that less than one percent of the values in key fields of the RAMQ data that were either missing or out of range.

As described previously, misclassification of exposure is likely in this study. For example, the data on benzodiazepine use is solely based on dispensed prescriptions. It is quite possible that prescription may not reflect the reality whether the medication was actually taken by the prescription recipients. However, while misclassification of exposure is likely, this misclassification is likely to be non-differential, and non-

differential misclassification would only cause an underestimation of the association observed in this study.

In studying the relationship between benzodiazepine use and motor vehicle accidents, we also did not attempt to differentiate benzodiazepines into short or long half-life medications. A recent study by Mannering et al. (2007) has shown that the association between benzodiazepine use and motor vehicle accidents may vary based on the subtype of the medication. Thus, further studies are needed to investigate the relationship by subtype of benzodiazepines.

2. Another potential limitation is related to the selection of the risk period, particularly the assumption of the length of the risk period. We assumed that the length of the risk period in our simulation study was 12 days based on the prior knowledge of the exposure and the outcome of interest as described in Chapters 2 and 4. It should be noted that different assumptions for the lengths of the risk period may affect the estimation of the underlying association and their corresponding variances. Further studies are warranted to evaluate the performances of these statistical methods under different assumptions for the lengths of the risk period.

3. Another potential limitation of the study is related to the selection of the control period. The classical case-control study design is facing tremendous challenge in selecting a valid control group. This is particularly true in these days when people are increasingly using cellular phone rather than using a wall-plug home phone. In this regards, the case-crossover study design has the advantage over the classical case-control study because the former does not have to select another group of subjects to form the control group. However, the validity of a case-crossover study depends on how validly the control period is defined.

A valid definition of control period(s) may be affected by the assumption of the length of the induction period and the length of the carry-over effects from the exposure of interest. One potential solution for the carry-over effect is to have a washout period between the risk period and the control period. However, while a washout period may help to avoid potential carry-over effects, the time trend in exposure and differential recall between the risk period and the control period may still raise concerns if the selected control period is substantially later in time than the risk period.

4. Another potential concern is related to the early outcome event of interest. An early outcome event may change an individual's likelihood for subsequent exposure to the same agent during the study period. For example, the side effect from the use of one specific medication could make a regular user change to an irregular user or even a non-user. If this phenomenon indeed occurred, in our study of benzodiazepine use and the risk of MVCs, this impact would cause an underestimation of the association between benzodiazepine use and MVC accidents. On the other hand, we should also realize that, in many cases, outcome events may not have a major impact on the probability of an individual's subsequent exposure. For example, a person who is addicted to pain-killer medications may not change his or her addiction from a motor vehicle accident.

The three statistical methods (the M-H method, the CLR method, and the GEE method) do not address the issue of dependency (correlations) between the variables as stated previously. Since the dependency between the variables may result in biased estimation of the association and their corresponding variances, statistical methods need to be developed to address this issue.

7.5 Conclusions and recommendations

The main purpose of the study is to evaluate the performance of eight estimators in analyzing the data from a case-crossover study with repeated events in the same subject. In the simulation study, we have demonstrated that the M-H method and the CLR method with the *event-level* data analyses can produce a better less biased estimate of the underlying odds ratio with a slightly larger variance. Based on the MSE criterion, the smaller MSE the better estimator performs, we concluded that the M-H method and the CLR method with the *event-level* data analyses produce the better estimation of the underlying association than the *subject-level* data analyses. Moreover, with the same statistical method and the same level of data analysis, the *multiple event* approach consistently yields an odds ratio which is 5% to 10% larger than that from the *first event* approach. In most circumstances, the estimated variance of the odds ratio from the *multiple event* approach is only the half size of that from the *first event* approach (i.e., higher precision).

Based on these study results, we make the following recommendations:

1. If multiple levels of clusters exist in the research data, the data analysis should be conducted at the finest level of clusters (such as at the *event-level* rather than at the *subject-level* in this study).
2. The conditional probability model approach (e.g., the conditional logistic regression method) should be used when the significant heterogeneities in the propensity of exposure and the propensity of developing the outcome of interest exist in the study population.
3) If feasible, the multiple outcome events of interest should be included in the data analysis.

The first two recommendations are related to the validity of the study, i.e., to avoid bias in the estimate of the odds ratio; the third recommendation is related to the precision of the estimate of the odds ratio.

BIBLOGRAPHY

Alison, P. D. *Survival analysis using the SAS system: A practical guide*, Cary, NC: SAS Institute Inc., 1995. 292 pp.

Alison, P. D. *Logistic regression using the SAS system: Theory and Application*, Cary, NC: SAS Institute Inc., 1999. 304 pp.

Barbone, F., McMahon, A. D., Davey, P. G., Morris, A. D., Reid, I. C., McDevitt, D. G. & MacDonald, T. M. Association of road-traffic accidents with benzodiazepine use. *Lancet* 352: 1331-1336, 1998.

Bateson, T. & Schwartz, J. Control for seasonal variation and time trend in case-crossover studies of acute effects of environmental exposures. *Epidemiology* 1999, 10:539-544.

Breslow, NE. & Day, NE.. *Statistical methods in cancer research. Vol. 1. The analysis of case-control studies.* Lyon, France: International Agency for Research on Cancer, 1980.

Breslow, NE. (1974) Covariance analysis of censored survival data. *Biometrics* 30, 89-99.

Burton, P., Gurrin, L., & Sly, P. Extending the simple linear regression model to account for correlated responses: an introduction to the generalized estimating equations and multi-level mixed modeling. *Statistics in Medicine*, 17, 1261-1291 (1998).

Carey, V., Zeger, SL. & Diggle, P. (1993) Modeling multivariate binary data with alternating logistic regression. *Biometrika* 80, 517-526.

Cox, DR. (1970) *The analysis of binary data,* London, Methuen.

Cox, DR. & Hinkley, DV. (1974) *Theoretical statistics*, London, Chapman & Hall.

Cox, DR. (1975) Partial likelihood. *Biometrika* 62, 269-276.

Cox, DR. & Oakes, D. *Analysis of survival data.* New York: Chapman and Hall, 1984.

Collett, D. *Modelling binary data. Second Edition*. Chapman & Hall / CRC, 2003.

Crane, J., Pearce, N., Burgess, C., Woodman, K., Robson, B. & Beasley, R. (1992) Markers of risk of asthma death or readmission in the 12 months following a hospital admission for asthma. *Int J Epidemiol* 21, 737-744.

Diggle, PJ., Liang, KY. & Zeger, SL. *The analysis of longitudinal data.* New York: Oxford University Press, 1994.

Efron, B. (1977) The efficiency of Cox's likelihood function for censored data. *Journal of the American statistical association* 72, 557-565.

Farewell, VT. & Prentice, RL. (1980) The approximation of partial likelihood with emphasis on case-control studies. *Biometrika* 67, 273-278.

Feller, W. (1971) *An introduction to probability theory*, 2, 2nd edition. New York: Wiley.

Gail, M., & Mantel, N. (1977) Counting the number of $r \times c$ contingency tables with fixed margins. *Journal of the American Statistical Association*, 72, 859–862.

Greenland, S. & Robins, JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* Vol. 41, No. 1. (Mar., 1985), pp. 55-68.

Greenland, S. A unified approach to the analysis of case-distribution (case-only) studies. *Statistics in Medicine* 18: 1-15, 1999.

Gudex, C. Adverse effects of benzodiazepines. *Soc Sci Med* 1991, 33, 587-596.

Hanley, JA., Negassa, A., Edwardes, MD. & Forrester, JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. American Journal of Epidemiology, Vol 157, 4, 364-375.

Hosmer, DW. & Lemeshow, S. *Applied logistic regression.* 2nd edition. John Wiley & Sons, Inc. 2000.

Hsieh, FY. (1995) A cautionary note on the analysis of extreme data with Cox regression. *The American Statistician* 49: 226-228.

Li, D., German, D., Lulla, S., Thomas, RG. & Wilson, SR. (1995) Prospective study of hospitalization for asthma: A preliminary risk factor model. *Am J Resp Crit Care Med* 151, 647-655.

Liang, KY. & Zeger, SL. Longitudinal data analysis using generalized linear models. *Biometrika* Vol 73, Issue 1(Apr., 1986), 13-22.

Lumley, T., Levy, D. Bias in the case-crossover design: implications for studies of air pollution. *NRCSE technical report series.* No. 031.

Maclure, M. The case-crossover design: a method for studying transient effects on the risk of acute events. *American Journal of Epidemiology* 133: 144-153, 1991.

Mannering F. (2007) Age, gender major factors in severity of auto-accident injuries. *News Purdue University*.

Marshall, RJ. & Jackson, RT. Analysis of case-crossover designs. *Statistics in Medicine* 12, 2333-2341 (1993).

McCullagh, P. & Nelder, JA. *Generalized linear models*, 2nd edition. New York: Chapman and Hall, 1989.

McCullagh, P. Quasi-likelihood and estimating functions. In: Hinkley, DV, Reid, N, Snell, EJ, eds. *Statistical theory and modeling.* London: Chapman and Hall, 1991.

Meier, C. R., Jick, S. S., Derby, L. E., Vasilakis, C. & Jick, H. Acute respiratory-tract infections and risk of first-time acute myocardial infarction. *Lancet* 351: 1467-1471, 1998.

Millar, W. & Adams, O. Accidents in Canada: general social survey analysis series. *Ottawa: Minister of Supply and Services Canada,* 1991.

Mitchell, EA., Bland, JM. & Thompson, JM. (1994) Risk factors for readmission to hospital for asthma in childhood. *Thorax* 49, 33-36.

Mittleman, MA., Maclure, M. & Robins, JM. Control sampling strategies for case-crossover studies: An assessment of relative efficiency. *American Journal of Epidemiology* 142: 91-98, 1995.

Muller, JE., Mittleman, A., Maclure, M., Sherwood, JB. & Tofler, GH. Triggering myocardial infarction by sexual activity. Low absolute risk and prevention by regular physical exertion. Determinants of Myocardial Infarction Onset Study Investigators. *JAMA* 275: 1405-1409, 1996.

Navidi, W. Bidirectional case-crossover designs for exposures with time trends. *Biometrics* 1998, 54: 596-605.

Navidi, W. & Weinhandl, E. (2001) Risk set sampling for case-crossover designs. *Epidemiology* 13, 1, 100-105.

Neuhaus, JM. Statistical methods for longitudinal and clustered design with binary responses. *Stat Methods Med Res.* 1992; 1(3): 249-73.

Peto, R. (1972). Contributions to the paper by D.R Cox. *Journal of the Royal Statistical Society* Series B 34: 205-207.

Prentice, RL. & Breslow, NE. Retrospective studies and failure-time models. *Biometrika* 1978, 65: 153-158.

Robins JM. A graphical approach to the identification and estimation of causal parameters in mortality studies with sustained exposure periods. *J Chronic Dis* 1987; 40(suppl 2): 139S-161S.

Robins JM. The control of confounding by intermediate variables. *Stat Med* 1989; 8: 679-701.

Robins JM, Greenland, S. & Hu, F. Estimation of the causal effect of a time-varying exposure on the marginal mean of a repeated binary outcome (with discussion). *J Am Stat Assoc* 1999; 94: 687-712.

Robins JM, Hernan, MA. & Brumback, B. Marginal Structural Models and Causal. Inference in Epidemiology. *Epidemiology*, 11, 550–560. (2000)

Rothman, KJ. & Greenland, S. (1998) *Modern epidemiology,* 2nd edition, Lippincott Williams & Wilkins.

Société de l'assurance automobile du Québec. Dossier statistique bilan 1991: Accidents, parc automobile, permis de conduire. Société de l'assurance automobile du Québec (Québec), 1992a.

Suissa, S., Ernst, P., Boivin, JF., Horwitz, RI., Habbick, B., Cockroft, D., Blais, L., McNutt, M., Buist, AS. and Spitzer, WO. (1994) A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Resp Crit Care Med* 149, 604-610.

Suissa, S. The case-time-control design. *Epidemiology* 6: 248-253, 1995.

Suissa, S., Harder, S. & Veilleux, M. The québec whiplash-associated disorders cohort study. *Spine* 1995, 20, 12s-20s.

Twisk, JWR. (2003) *Applied longitudinal data analysis for epidemiology: A practical guide.* Cambridge University Press.

Wang, YG. & Carey, V. Working correlation structure misspecification, estimation and covariate design: Implications for generalized estimating equations performance. *Biometrika* 2003, 90, 1, pp.29-41.

Wedderburn, RWM. (1974) Quasi-likelihood functions, generalized linear models, and the Gauss-Newton method. *Biometrika* 61, 439-447.

APPENDIX I: DERIVATION OF THE VARIANCE OF THE ESTIMATOR USING THE WITHIN-SUBJECT VS. BETWEEN-SUBJECT STUDY DESIGNS

Burton et al. stated that "when interest centres on a change in response under different conditions or over time, the longitudinal correlation between repeated observations means that within-person changes can be highly informative because they minimize the 'noise' arising from between-person variability".

In the following, we will demonstrate that the within-subject design, relative to the between-subject design, will produce an estimator with lower standard error. For the purpose of demonstration, let's assume we are to conduct a study investigating the effect of using a medication on the weight change in a group of middle-aged adults. We could use two different study designs to estimate the effect, that is the within-subject design and the between-subject design.

Within-subject design Ten subjects will be studied in the within-subject design group. For each study subject, the weight will be measured twice, once right before the treatment and the other 2 months after the treatment (assuming that the medication takes at least 2 months to have an effect on weight). In total, there are 10 study subjects with 20 weight measurements.

Between-subject design Ten subjects will be studied in the between-subject design. These will be randomly allocated into either treatment group or control (untreated) group with 5 subjects each. Body weight will be measured twice for each person as in the within-subject design. Thus, there are 10 study subjects with a total of 20 weight measurements.

The weight (Y) during the study period is assumed to follow the following model:

$$y_{jk} = \alpha_j + \beta_j x_{jk} + \varepsilon_{jk},$$

X is the new medical treatment of interest (X =1 if treatment; X =0 if not).

$\alpha_j \sim N\left(\mu_\alpha, \sigma_\alpha^2\right)$ is the intercept for the jth subject, and $\beta_j \sim N\left(\mu_\beta, \sigma_\beta^2\right)$ is the effect for jth person who receiving treatment and μ_β is the parameter of interest.

$\varepsilon_{jk} \overset{iid}{\sim} N\left(0, \sigma_e^2\right)$ is assumed to be the measurement error. $\varepsilon_{j1}, \varepsilon_{j2}$ ($k = 1, 2$) are the pre-treatment and post-treatment measurement errors for the jth subject. The layout of the data is as follows:

Within-subject approach:

Study subject	Pre-treatment	Post-treatment	Diff. between two measurements
1	Y_{11}	Y_{12}	$(Y_{12} - Y_{11})$
2	Y_{21}	Y_{22}	$(Y_{22} - Y_{21})$
…			
10	$Y_{10,1}$	$Y_{10,2}$	$(Y_{10,2} - Y_{10,1})$

Between-subject approach:

Study subject	Untreated group			Treated group		
1*	Y_{11}	Y_{12}	$\bar{Y}_{1.}$	Y'_{11}	Y'_{12}	$\bar{Y}'_{1.}$
2	Y_{21}	Y_{22}	$\bar{Y}_{2.}$	Y'_{21}	Y'_{22}	$\bar{Y}'_{2.}$
..						
5	Y_{51}	Y_{52}	$\bar{Y}_{5.}$	Y'_{51}	Y'_{52}	$\bar{Y}'_{5.}$
	$\bar{\bar{Y}}_{j.} = \frac{1}{5}\sum_{j=1}^{5}\bar{Y}_{j.}; X = 0$			$\bar{\bar{Y}}_{j.}' = \frac{1}{5}\sum_{j=1}^{5}\bar{Y}'_{j.}; X = 1$		

*: Subject 1 in untreated group is a different person from subject 1 in treated group.

<u>Within-subject approach</u>:

$$\Delta(Y_{within-subject}) = \frac{1}{10}\left[(Y_{12} - Y_{11}) + (Y_{22} - Y_{21}) + \ldots + (Y_{102} - Y_{101})\right]$$

The variance of $\Delta(Y_{within-subject})$ is:

$$Var\left(\Delta(\hat{Y}_{within-subject})\right) = \frac{1}{100}Var\left((Y_{12} - Y_{11}) + \ldots + (Y_{102} - Y_{101})\right)$$

$$= \frac{1}{100}\left[Var\left(Y_{12} - Y_{11}\right) + Var\left(Y_{22} - Y_{21}\right) + \ldots + Var\left(Y_{102} - Y_{101}\right)\right]$$

(Changes in weight between study subjects are mutually independent)

$$= \frac{1}{100}\left[Var\left(\beta_1 + \left(\varepsilon_{12} - \varepsilon_{11}\right)\right) + \ldots + Var\left(\beta_{10} + \left(\varepsilon_{10,\,2} - \varepsilon_{10,\,1}\right)\right)\right] \qquad \left(\varepsilon_{jk} \overset{iid}{\sim} N\left(0,\ \sigma_e^2\right)\right)$$

$$= \frac{1}{10}\left[\sigma_\beta^2 + \sigma_e^2 + \sigma_e^2\right]$$

$$= \frac{\sigma_\beta^2}{10} + \frac{2\sigma_e^2}{10} \qquad (1)$$

<u>Between-subject approach</u>:

$$\Delta(Y_{between-sibject}) = \overline{\overline{Y}}_{j.}{}' - \overline{\overline{Y}}_{j.} \qquad (2)$$

The variance of (2):

$$Var\left(\Delta(\hat{Y}_{between-subject})\right) = Var\left[\frac{1}{5}\left(\left(\frac{Y_{12}' + Y_{11}'}{2}\right) + \ldots + \left(\frac{Y_{52}' + Y_{51}'}{2}\right) - \left(\frac{Y_{12} + Y_{11}}{2}\right) - \ldots - \left(\frac{Y_{52} + Y_{51}}{2}\right)\right)\right]$$

$$= \frac{1}{25}\left[Var\left(\frac{Y_{12}^{'} + Y_{11}^{'}}{2} \right) + \ldots + Var\left(\frac{Y_{52}^{'} + Y_{51}^{'}}{2} \right) + 2Cov\left(\left(\frac{Y_{12}^{'} + Y_{11}^{'}}{2} \right), \left(\frac{Y_{22}^{'} + Y_{21}^{'}}{2} \right) \right) + \ldots + Var\left(\frac{Y_{12} + Y_{11}}{2} \right) + \ldots + Var\left(\frac{Y_{52} + Y_{51}}{2} \right) + \ldots + 2Cov\left(\left(\frac{Y_{42} + Y_{41}}{2} \right), \left(\frac{Y_{52} + Y_{51}}{2} \right) \right) \right]$$

$$= \frac{1}{25}\left[5Var\left(\left(\alpha + \beta + \frac{\varepsilon_2 + \varepsilon_1}{2} \right) + \left(\alpha + \frac{\varepsilon_2 + \varepsilon_1}{2} \right) \right) \right]$$

$$= \frac{1}{5}\left[\sigma_\alpha^2 + \sigma_\beta^2 + \frac{\sigma_e^2}{4} + \frac{\sigma_e^2}{4} + \sigma_\alpha^2 + \frac{\sigma_e^2}{4} + \frac{\sigma_e^2}{4} \right]$$

$$= \frac{2\sigma_\alpha^2}{5} + \frac{\sigma_\beta^2}{5} + \frac{2\sigma_e^2}{10} \qquad (3)$$

In comparing (3) with (1), we can obtain:

$$Var\left(\Delta(\hat{Y}_{between-subject})\right) = \frac{2\sigma_\alpha^2}{5} + \frac{2\sigma_\beta^2}{10} + \frac{2\sigma_e^2}{10} > Var\left(\Delta(\hat{Y}_{within-subject})\right) = \frac{\sigma_\beta^2}{10} + \frac{2\sigma_e^2}{10}$$

In summary, in a hypothetical longitudinal study of assessing the changes in weight from medication use, we have demonstrated here that the within-subject design can be highly informative because it eliminates between-subject variability.

APPENDIX II: HAND CALCULATIONS FOR THE ESTIMATORS

I). Data set:

	Obs	subject	rep_sub	outcome	exposure	
Subject 1 (Cluster 1)	1	1	1.01	1	0	Matched pair 1
	2	1	1.01	0	1	
	3	1	1.02	1	0	Matched pair 2
	4	1	1.02	0	1	
	5	1	1.03	1	0	
	6	1	1.03	0	0	
	7	1	1.04	1	1	⋮
	8	1	1.04	0	1	⋮
	9	1	1.05	1	0	
	10	1	1.05	0	0	
Subject 2 (Cluster 2)	11	2	2.01	1	0	
	12	2	2.01	0	1	
	13	2	2.02	1	1	
	14	2	2.02	0	0	
	15	2	2.03	1	0	
	16	2	2.03	0	1	
	17	2	2.04	1	0	Matched pair 9
	18	2	2.04	0	0	

Table 1
Subject 1
(Cluster 1)

	Exposure$^+$	Exposure$^-$	
Outcome$^+$	1	4	5
Outcome$^-$	3	2	5
	4	6	10

Table 2
Subject 2
(Cluster 2)

	Exposure$^+$	Exposure$^-$	
Outcome$^+$	1	3	4
Outcome$^-$	2	2	4
	3	5	8

The data presented here will be used to illustrate each individual estimator, except for the GEE method. The data for the GEE method will be introduced in the GEE hand calculation section. The SAS outputs and the hand calculations for each estimator are summarized below.

II) The overall crude M-H method SAS output:

The FREQ Procedure

Table of outcome by exposure

outcome	exposure		
Frequency,			
Col Pct	0	1	Total
0	4	5	9
	36.36	71.43	
1	7	2	9
	63.64	28.57	
Total	11	7	18

Statistics for Table of outcome by exposure

Statistic	DF	Value	Prob
Chi-Square	1	2.1039	0.1469
Likelihood Ratio Chi-Square	1	2.1569	0.1419
Continuity Adj. Chi-Square	1	0.9351	0.3336
Mantel-Haenszel Chi-Square	1	1.9870	0.1587
Phi Coefficient		-0.3419	
Contingency Coefficient		0.3235	
Cramer's V		-0.3419	

WARNING: 50% of the cells have expected counts less than 5. Chi-Square may not be a valid test.

Fisher's Exact Test

Cell (1,1) Frequency (F)	4
Left-sided Pr <= F	0.1674
Right-sided Pr >= F	0.9751
Table Probability (P)	0.1425
Two-sided Pr <= P	0.3348

The FREQ Procedure

Statistics for Table of outcome by exposure

Statistic	Value	ASE
Gamma	-0.6279	0.3166
Kendall's Tau-b	-0.3419	0.2192
Stuart's Tau-c	-0.3333	0.2160
Somers' D C|R	-0.3333	0.2160

Somers' D R|C	-0.3506	0.2240
Pearson Correlation	-0.3419	0.2192
Spearman Correlation	-0.3419	0.2192
Lambda Asymmetric C|R	0.1429	0.3968
Lambda Asymmetric R|C	0.3333	0.3009
Lambda Symmetric	0.2500	0.3014
Uncertainty Coefficient C|R	0.0897	0.1175
Uncertainty Coefficient R|C	0.0864	0.1136
Uncertainty Coefficient Symmetric	0.0880	0.1155

Estimates of the Relative Risk (Row1/Row2)

Type of Study	Value	95% Confidence Limits	
Case-Control (Odds Ratio)	0.2286	0.0295	1.7736
Cohort (Col1 Risk)	0.5714	0.2543	1.2840
Cohort (Col2 Risk)	2.5000	0.6450	9.6895

Sample Size = 18

The FREQ Procedure

Summary Statistics for outcome by exposure

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)

Statistic	Alternative Hypothesis	DF	Value	Prob
1	Nonzero Correlation	1	1.9870	0.1587
2	Row Mean Scores Differ	1	1.9870	0.1587
3	General Association	1	1.9870	0.1587

Estimates of the Common Relative Risk (Row1/Row2)

Type of Study	Method	Value	95% Confidence Limits	
Case-Control	**Mantel-Haenszel**	**0.2286**	**0.0295**	**1.7736**
(Odds Ratio)	Logit	0.2286	0.0295	1.7736
Cohort	Mantel-Haenszel	0.5714	0.2543	1.2840
(Col1 Risk)	Logit	0.5714	0.2543	1.2840
Cohort	Mantel-Haenszel	2.5000	0.6450	9.6895
(Col2 Risk)	Logit	2.5000	0.6450	9.6895

Total Sample Size = 18

The overall crude M-H method (hand calculation):

When combining tables 1 and 2, we have:

	exposure$^+$	exposure$^-$	
outcome$^+$	2 (a)	7(b)	9
outcome$^-$	5(c)	4(d)	9
	7	11	18

Summary odds ratio:

$$\hat{OR} = \frac{ad}{bc} = \frac{2 \times 4}{5 \times 7} \approx 0.2286$$

95% CI: Woolf's formula:

$$\begin{aligned} \hat{Var} \log \hat{OR} &= \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d} \\ &= \frac{1}{2} + \frac{1}{7} + \frac{1}{5} + \frac{1}{4} \approx 1.0928 \end{aligned}$$

$$\Rightarrow \hat{SD}\left(\log \hat{OR} \right) \approx 1.045$$

Therefore, variance of the odds ratio:

$$\begin{aligned} &\left(\underline{OR}\ \overline{OR} \right) = \left(\hat{OR} e^{-1.96 \hat{SD}(\log \hat{OR})},\ \hat{OR} e^{+1.96 \hat{SD}(\log \hat{OR})} \right) \\ &\Rightarrow \left(\underline{OR}\ \overline{OR} \right) = \left(0.2286 e^{-1.96 \times 1.045},\ 0.2286 e^{+1.96 \times 1.045} \right) \\ &\Rightarrow \left(\underline{OR}\ \overline{OR} \right) = \left(0.0295, 1.7725 \right) \\ &\therefore OR(95\%CI): \quad 0.2286 \left(0.0295, 1.7725 \right) \end{aligned}$$

The odds ratio and the corresponding 95% CI by hand are practically identical to the SAS output.

The subject-level M-H method:

The FREQ Procedure

Table 1 of outcome by exposure
Controlling for pt=1

outcome exposure

Frequency, Col Pct	0	1	Total
0	2 33.33	3 75.00	5
1	4 66.67	1 25.00	5
Total	6	4	10

Statistics for Table 1 of outcome by exposure
Controlling for pt=1

Statistic	DF	Value	Prob
Chi-Square	1	1.6667	0.1967
Likelihood Ratio Chi-Square	1	1.7261	0.1889
Continuity Adj. Chi-Square	1	0.4167	0.5186
Mantel-Haenszel Chi-Square	1	1.5000	0.2207
Phi Coefficient		-0.4082	
Contingency Coefficient		0.3780	
Cramer's V		-0.4082	

WARNING: 100% of the cells have expected counts less than 5. Chi-Square may not be a valid test.

Fisher's Exact Test

Cell (1,1) Frequency (F)	2
Left-sided Pr <= F	0.2619
Right-sided Pr >= F	0.9762
Table Probability (P)	0.2381
Two-sided Pr <= P	0.5238

.....

Estimates of the Relative Risk (Row1/Row2)

Type of Study	Value	95% Confidence Limits	
Case-Control (Odds Ratio)	0.1667	0.0098	2.8213
Cohort (Col1 Risk)	0.5000	0.1568	1.5942
Cohort (Col2 Risk)	3.0000	0.4516	19.9278

Sample Size = 10

The FREQ Procedure

Table 2 of outcome by exposure
Controlling for pt=2

outcome exposure

Frequency, Col Pct	0	1	Total
0	2 40.00	2 66.67	4
1	3 60.00	1 33.33	4
Total	5	3	8

Statistics for Table 2 of outcome by exposure
Controlling for pt=2

Statistic	DF	Value	Prob
Chi-Square	1	0.5333	0.4652
Likelihood Ratio Chi-Square	1	0.5412	0.4620
Continuity Adj. Chi-Square	1	0.0000	1.0000
Mantel-Haenszel Chi-Square	1	0.4667	0.4945
Phi Coefficient		-0.2582	
Contingency Coefficient		0.2500	
Cramer's V		-0.2582	

WARNING: 100% of the cells have expected counts less than 5. Chi-Square may not be a valid test.

Fisher's Exact Test

Cell (1,1) Frequency (F)	2
Left-sided Pr <= F	0.5000

Estimates of the Relative Risk (Row1/Row2)

Type of Study	Value	95% Confidence Limits	
Case-Control (Odds Ratio)	0.3333	0.0167	6.6544
Cohort (Col1 Risk)	0.6667	0.2150	2.0670
Cohort (Col2 Risk)	2.0000	0.2817	14.1981

Sample Size = 8

The FREQ Procedure

Summary Statistics for outcome by exposure
Controlling for pt

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)

Statistic	Alternative Hypothesis	DF	Value	Prob
1	Nonzero Correlation	1	1.8713	0.1713
2	Row Mean Scores Differ	1	1.8713	0.1713
3	General Association	1	1.8713	0.1713

Estimates of the Common Relative Risk (Row1/Row2)

Type of Study	Method	Value	95% Confidence Limits	
Case-Control	**Mantel-Haenszel**	**0.2308**	**0.0299**	**1.7791**
(Odds Ratio)	Logit	0.2311	0.0296	1.8065
Cohort	Mantel-Haenszel	0.5714	0.2538	1.2864
(Col1 Risk)	Logit	0.5794	0.2578	1.3022
Cohort	Mantel-Haenszel	2.5000	0.6430	9.7201
(Col2 Risk)	Logit	2.4667	0.6320	9.6279

Breslow-Day Test for
Homogeneity of the Odds Ratios

Chi-Square	0.1092
DF	1
Pr > ChiSq	0.7411

Total Sample Size = 18

The subject-level M-H method (hand calculation):

Based on the two tables (as shown in "data set" section), the M-H estimator for the odds ratio:

$$\hat{\psi}_{MH} = \frac{\sum_{j=1}^{2} \frac{a_j d_j}{n_j}}{\sum_{j=1}^{2} \frac{b_j c_j}{n_j}} = \frac{\frac{1\times 2}{10} + \frac{1\times 2}{8}}{\frac{3\times 4}{10} + \frac{2\times 3}{8}}$$

$$= \frac{\frac{1}{5} + \frac{1}{4}}{\frac{6}{5} + \frac{3}{4}} = \frac{0.45}{1.9}$$

$$\approx 0.2308$$

A robust variance formula for the M-H estimator can be obtained from Robins et al., Biometrics, 42, 311-323. SAS uses Robin's formula (so-called "RBG" (Robin-Breslow-Greenland) formula) to obtain the 95% CI for the M-H estimator.

The corresponding 95% CI for the odds ratio is as follow:

$$\left(\hat{\psi}_{MH} \exp(-1.96\hat{\sigma}), \hat{\psi}_{MH} \exp(+1.96\hat{\sigma})\right)$$

Where $\hat{\sigma}^2 = \hat{Var}\left(\ln(\hat{\psi}_{MH})\right)$

$$\therefore \hat{\sigma}^2 = \frac{\frac{(1+2)\times 1\times 2}{10^2} + \frac{(1+2)\times 1\times 2}{8^2}}{2(\frac{2}{10} + \frac{2}{8})^2} + \frac{\frac{(1+2)\times 3\times 4 + (3+4)\times 1\times 2}{10^2} + \frac{(1+2)\times 3\times 2 + (3+2)\times 1\times 2}{8^2}}{2(\frac{1\times 2}{10} + \frac{1\times 2}{8})(\frac{3\times 4}{10} + \frac{3\times 2}{8})} + \frac{\frac{(3+4)\times 3\times 4}{10^2} + \frac{(3+2)\times 3\times 2}{8^2}}{2(\frac{3\times 4}{10} + \frac{3\times 2}{8})^2}$$

$$\approx 0.3796 + 0.1721 + 0.5342$$

$$\approx 1.0859$$

$$\Rightarrow \hat{\sigma} = 1.042$$

$$\begin{aligned}\left(\underline{\psi_{MH}}, \overline{\psi_{MH}}\right) &= \left(\hat{\psi}_{MH}\exp(-1.96\times 1.042), \hat{\psi}_{MH}\exp(+1.96\times 1.042)\right)\\ &\approx \left(0.2308\exp(\text{-}2.0424), 0.2308\exp(2.0424)\right)\\ &\approx (0.0299, 1.7793)\end{aligned}$$

The odds ratio and the corresponding 95% CI by hand are numerically identical to the SAS output.

The event-level M-H method SAS output:

```
                        The FREQ Procedure

                   Table 1 of outcome by exposure
                    Controlling for rep_pt=1.01

          outcome     exposure

          Frequency,
          Col Pct  ,       0,       1,  Total
          ƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒˆ
                 0 ,      0 ,      1 ,      1
                   ,   0.00 , 100.00 ,
          ƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒˆ
                 1 ,      1 ,      0 ,      1
                   , 100.00 ,   0.00 ,
          ƒƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒˆƒƒƒƒƒƒƒˆ
          Total           1        1        2


              Statistics for Table 1 of outcome by exposure
                       Controlling for rep_pt=1.01

        Statistic                     DF       Value      Prob
        ƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒƒ
        Chi-Square                     1      2.0000    0.1573
        Likelihood Ratio Chi-Square    1      2.7726    0.0959
        Continuity Adj. Chi-Square     1      0.0000    1.0000
        Mantel-Haenszel Chi-Square     1      1.0000    0.3173
        Phi Coefficient                      -1.0000
        Contingency Coefficient               0.7071
        Cramer's V                           -1.0000

.....

        One or more risk estimates not computed --- zero cell.

                        Sample Size = 2
```

.....

Table 5 of outcome by exposure
Controlling for rep_pt=1.05

outcome exposure

Frequency, Col Pct	0	1	Total
0	1 50.00	0 .	1
1	1 50.00	0 .	1
Total	2	0	2

Table 6 of outcome by exposure
Controlling for rep_pt=2.01

outcome exposure

Frequency, Col Pct	0	1	Total
0	0 0.00	1 100.00	1
1	1 100.00	0 0.00	1
Total	1	1	2

.....

Table 9 of outcome by exposure
Controlling for rep_pt=2.04

outcome exposure

Frequency, Col Pct	0	1	Total
0	1 50.00	0 .	1
1	1 50.00	0 .	1
Total	2	0	2

The FREQ Procedure

Statistics for Table 9 of outcome by exposure
Controlling for rep_pt=2.04

Row or column sum zero. No statistics computed for this table except for the summary calculations.

Sample Size = 2
The FREQ Procedure

Summary Statistics for outcome by exposure
Controlling for rep_pt

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)

Statistic	Alternative Hypothesis	DF	Value	Prob
1	Nonzero Correlation	1	1.8000	0.1797
2	Row Mean Scores Differ	1	1.8000	0.1797
3	General Association	1	1.8000	0.1797

Estimates of the Common Relative Risk (Row1/Row2)

Type of Study	Method	Value	95% Confidence Limits	
Case-Control	**Mantel-Haenszel**	**0.2500**	**0.0279**	**2.2367**
(Odds Ratio)	Logit **	0.2676	0.0353	2.0257
Cohort	Mantel-Haenszel	0.5714	0.2496	1.3082
(Col1 Risk)	Logit **	0.5173	0.1668	1.6039
Cohort	Mantel-Haenszel	2.5000	0.6252	9.9961
(Col2 Risk)	Logit **	1.9332	0.6235	5.9940

** These logit estimators use a correction of 0.5 in every cell of those tables that contain a zero. Tables with a zero row or a zero column are not included in computing the logit estimators.

Breslow-Day Test for
Homogeneity of the Odds Ratios

Chi-Square	8.0000
DF	4
Pr > ChiSq	0.0916

Total Sample Size = 18

The event-level M-H method (hand calculation):

Since the calculation processes on the odds ratio and the corresponding variance are the same for both the event-level and the subject-level data analyses. For simplicity, we ignore it here.

The subject-level CLR method SAS output:

The PHREG Procedure

Model Information

Data Set	WORK.CASS_10
Dependent Variable	time
Censoring Variable	outcome
Censoring Value(s)	0
Ties Handling	**DISCRETE**

Number of Observations Read	18
Number of Observations Used	18

Summary of the Number of Event and Censored Values

Stratum	pt	Total	Event	Censored	Percent Censored
1	1	10	5	5	50.00
2	2	8	4	4	50.00
Total		18	9	9	50.00

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates

-2 LOG L	19.556	17.646
AIC	19.556	19.646
SBC	19.556	19.843

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	1.9102	1	0.1669
Score	1.8713	1	0.1713
Wald	1.7851	1	0.1815

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
exposure	1	-1.30156	0.97417	1.7851	0.1815	**0.272**	**0.040**	**1.836**

The subject-level CLR method (hand calculation):

Since the calculation processes on the odds ratio and variance are the same for both levels of data analyses (the subject-level and the event-level). We only show how to obtain the estimates of the odds ratio at the event-level data analyses in the next section.

The event-level CLR method SAS output:

The PHREG Procedure

Model Information

Data Set	WORK.CASS1_10
Dependent Variable	time
Censoring Variable	outcome
Censoring Value(s)	0
Ties Handling	**DISCRETE**

Number of Observations Read	18
Number of Observations Used	18

Summary of the Number of Event and Censored Values

Stratum	rep_pt	Total	Event	Censored	Percent Censored
1	1.01	2	1	1	50.00
2	1.02	2	1	1	50.00
3	1.03	2	1	1	50.00
4	1.04	2	1	1	50.00
5	1.05	2	1	1	50.00
6	2.01	2	1	1	50.00
7	2.02	2	1	1	50.00
8	2.03	2	1	1	50.00
9	2.04	2	1	1	50.00
Total		18	9	9	50.00

Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Model Fit Statistics

Criterion	Without Covariates	With Covariates
-2 LOG L	12.477	10.549
AIC	12.477	12.549
SBC	12.477	12.746

The PHREG Procedure

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq

Likelihood Ratio	1.9274	1	0.1650
Score	1.8000	1	0.1797
Wald	1.5374	1	0.2150

Analysis of Maximum Likelihood Estimates

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
exposure	1	-1.38627	1.11803	1.5374	0.2150	**0.250**	**0.028**	**2.237**

The event-level CLR method (hand calculation):

First method:

Assume that the conditional likelihood for the J[th] matched set is known as follows (see Chapter 3, the CLR review section):

$$L_j^*\left(\beta_1,\cdots\beta_p\right)=\frac{e^{\sum_{k=1}^{p}\beta_k X_{j1k}}}{\sum_{\mu=1}^{M+1}e^{\sum_{k=1}^{p}\beta_k X_{juk}}}$$

The conditional likelihood for the sample is the product of the J^{th} matched sets specific likelihoods:

$$L^*\left(\beta_1,\cdots\beta_p\right)=\prod_{j=1}^{J}L_j^*\left(\beta_1,\cdots\beta_p\right)$$

Now, for this data set, we have j = 2, p = 1, 1:1 matching (case: control ratio) and unique dichotomous exposure (1, 0). Therefore, the J^{th} conditional likelihood can be simplified as:

$$L_j^*(\beta)=\frac{e^{\beta X_{j1}}}{\sum_{\mu=1}^{M+1}e^{\beta X_{ju}}}=\frac{OR^{X_{j1}}}{\sum_{\mu=1}^{M+1}OR^{X_{ju}}}$$ (X_{j1} is the case exposure in the J^{th} matched set)

The conditional likelihood in the J^{th} matched set can be described as follows:

Case	Control	L_j^*		
exposure$^+$	exposure$^+$	$OR/(OR+OR)$	$=1/2$	$\leftarrow$ concordant pair
exposure$^+$	exposure$^-$	$OR/(OR+1)$		$\leftarrow$ disconcordant. pair
exposure$^-$	exposure$^+$	$1/(1+OR)$		$\leftarrow$ disconcordant. pair
exposure$^-$	exposure$^-$	$1/(1+1)$	$=1/2$	$\leftarrow$ concordant pair

$\therefore$ The conditional likelihood for the data can be written as:

$$L^*(\beta_{(OR)}) = \underbrace{\frac{1}{1+OR}}_{pair\,1} \times \underbrace{\frac{1}{1+OR}}_{pair\,2} \times \underbrace{\frac{1}{2}}_{pair\,3} \times \underbrace{\frac{1}{2}}_{pair\,4} \times \underbrace{\frac{1}{2}}_{\cdots} \times \underbrace{\frac{1}{1+OR}}_{\cdots} \times \underbrace{\frac{OR}{OR+1}}_{\cdots} \times \underbrace{\frac{1}{1+OR}}_{\cdots} \times \underbrace{\frac{1}{2}}_{pair\,9}$$

$$= \left(\frac{1}{1+OR}\right)^4 \times 8 \times \frac{OR}{1+OR}$$

$\Rightarrow$ $\ln L^*$ = -4 ln(1+OR) +lnOR - ln(1+OR)

= lnOR – 5 ln(1+OR)

Differentiate both sides w.r.t OR $\Rightarrow$ $\dfrac{\partial \ln L^*}{\partial OR_{(\beta)}} = \dfrac{1}{OR} - \dfrac{5}{1+OR}$

Assume $\dfrac{\partial \ln L^*}{\partial OR} = 0$

$$\Rightarrow 5\hat{OR} = 1 + \hat{OR} \qquad 4\hat{OR} = 1$$

$$\Rightarrow \hat{OR} = \frac{1}{4} = 0.25$$

$\Rightarrow$ The maximize likelihood estimate of the odds ratio is 0.25, which is numerically identical to the estimate provided by SAS.

Second method:

Intuitively:
$$\hat{OR}_{MH} = \frac{B}{C} = \frac{\#\ of\ pairs\ where\ "case\ exposed\ and\ control\ unexposed"}{\#\ of\ pairs\ where\ "case\ unexposed\ and\ control\ exposed"} = \frac{1}{4} = 0.25$$

This might be recognized as the classical matched-pair odds ratio estimator, the ratio of the two types of exposure-discordant pairs.

The SD estimate of "RBG" formula for $\ln(\hat{OR}_{MH})$ simplifies to $(\frac{1}{B}+\frac{1}{C})^{1/2}$ for matched-pair data (Rothman and Greenland, 1998).

Therefore, $\hat{SD}(\ln \hat{OR}_{MH}) = (\frac{1}{1}+\frac{1}{4})^{1/2} = (1.25)^{1/2} = 1.11803$

$$\left(\underline{OR}_{MH}, \overline{OR}_{MH}\right) = \exp\left(\ln \hat{OR}_{MH} \pm Z_{\alpha/2}\, \hat{SD}(\ln \hat{OR}_{MH})\right)$$
$$= \exp(\ln 0.25 \pm 1.96 \times 1.11803)$$
$$= \exp(-1.38629 \pm 2.191338)$$
$$\approx (0.028,\ 2.237)$$

The odds ratio and the corresponding 95% CI by hand are identical to those provided by SAS.

III) In the following, we will use the subject-level GEE with an exchangeable w.c.s., as an example, to illustrate the GEE estimation process (hand calculation):

The estimating equation is solved by iterating between quasi-likelihood methods for estimating β and method of moments estimation of α as a function of β as follows:

1) compute an initial estimate of β using a GLM model;
2) computer the standardized Pearson residuals:

$$\gamma_{ij} = \frac{y_{ij} - \hat{\mu}_{ij}}{\sqrt{V(\hat{\mu}_{ij})}}$$

and obtain the estimates for the ϕ and α using moment estimation;

3) update $\hat{\beta}$ with the following formula:

$$\hat{\beta}^{(r+1)} = \hat{\beta}^{(r)} - \left[\sum_{i=1}^{K} \frac{\partial \mu_i^{'}}{\partial \beta} V_i^{-1} \frac{\partial \mu_i}{\partial \beta}\right]^{-1} \times \left[\sum_{i=1}^{K} \frac{\partial \mu_i^{'}}{\partial \beta} V_i^{-1} (Y_i - \mu_i)\right]; \text{ and,}$$

4) Iterate until convergence.

For simplicity, we only used 4 repeated outcome events in the first cluster and 6 in the second cluster (total 2 clusters) and we will show 1 iterate on how to get the updated β by hand as well.

The first cluster:

Y1= (1, 0, 1, 0) -----Y denotes the outcome of interest---case coded as 1, control coded as 0 (pair –matched);

X1= (1, 0, 1, 0) -----1: exposed; 0 unexposed---representing the exposure status.

Likewise, **the second cluster:**

Y2= (1, 0, 1, 0, 1, 0) and X2= (1, 0, 0, 1, 1, 1).

In this example, i=1, 2, and j=1, 2, 3, 4 for the first cluster and 1, 2,…, to 6 for the second cluster. All the formula used to calculate the parameters of interest can be found in Chapter 3, the GEE review section.

1> data set:

$$Y_1 = (1,\ 0,\ 1,\ 0) \qquad X_1 = (1,\ 0,\ 1,\ 0) \qquad \leftarrow cluster\,1$$
$$Y_2 = (1,\ 0,\ 1,\ 0,\ 1,\ 0) \qquad X_2 = (1,\ 0,\ 0,\ 1,\ 1,\ 1) \qquad \leftarrow cluster\,2$$

2> model:

$$\log\frac{P}{1-P}=\beta_0+\beta_1 X_{ij} \qquad i=1,\ 2 \qquad j=1,\ 2,\ 3,\ 4 \quad \leftarrow \textit{for cluster 1}$$

$$1,\ 2,\ 3,\ 4,\ 5,\ 6 \leftarrow \textit{for cluster 2}$$

3> initial values of β_0, β_1 estimated from least square estimate (assumed known) based on the above data $\Rightarrow \hat{\beta}_0^{(0)}=0.25, \quad \hat{\beta}_1^{(0)}=0.4167$

4> according to logistic model $\log\frac{P}{1-P}=\beta_0+\beta_1 X_{ij} \ \Rightarrow\ P=\frac{e^{\beta_0+\beta_1 X_{ij}}}{1+e^{\beta_0+\beta_1 X_{ij}}}$

Cluster 1:

$$\hat{\mu}_{11}=\frac{e^{\hat{\beta}_0+\hat{\beta}_1}}{1+e^{\hat{\beta}_0+\hat{\beta}_1}}=\frac{e^{0.25+0.4167}}{1+e^{0.25+0.4167}}\approx 0.661 \quad (X_{11}=1)$$

$$\hat{\mu}_{12}=\frac{e^{\hat{\beta}_0}}{1+e^{\hat{\beta}_0}}=\frac{e^{0.25}}{1+e^{0.25}}\approx 0.562 \quad (X_{12}=0)$$

$$\hat{\mu}_{13}=\frac{e^{\hat{\beta}_0+\hat{\beta}_1}}{1+e^{\hat{\beta}_0+\hat{\beta}_1}}\approx 0.661 \quad (X_{13}=1)$$

$$\hat{\mu}_{14}\approx 0.562 \quad (X_{14}=0);$$

Cluster 2:

$$\hat{\mu}_{21}\approx 0.661 \quad (X_{21}=1)$$

$$\hat{\mu}_{22}\approx 0.562 \quad (X_{22}=0)$$

$$\hat{\mu}_{23}\approx 0.562 \quad (X_{23}=0)$$

$$\hat{\mu}_{24}\approx 0.661 \quad (X_{24}=1)$$

$$\hat{\mu}_{25}\approx 0.661 \quad (X_{25}=1)$$

$$\hat{\mu}_{26}\approx 0.661 \quad (X_{26}=1)$$

The corresponding variance $Var(y_{ij})$

Cluster 1:

$$\hat{Var}(y_{11})=\hat{\mu}_{11}(1-\hat{\mu}_{11})=0.661\times 0.339=0.224$$

$$\hat{Var}(y_{12})=\hat{\mu}_{12}(1-\hat{\mu}_{12})=0.562\times 0.438=0.246$$

$$\hat{Var}(y_{13})=\hat{\mu}_{13}(1-\hat{\mu}_{13})=0.224$$

$$\hat{Var}(y_{14})=\hat{\mu}_{14}(1-\hat{\mu}_{14})=0.246$$

Cluster 2:

$$\hat{Var}(y_{21})=0.224$$

$$\hat{Var}(y_{22})=0.246$$

$$\hat{Var}(y_{23})=0.246$$

$$\hat{Var}(y_{24})=0.224$$

$$\hat{Var}(y_{25})=0.224$$

$$\hat{Var}(y_{26})=0.224$$

5> the standardized Pearson residuals

$$\hat{\gamma}_{ij}=\frac{y_{ij}-\hat{\mu}_{ij}}{\hat{v}\left(\hat{\mu}_{ij}\right)} \qquad i=1,\ 2 \quad j=\begin{matrix}1\to4 & \textit{for cluster 1}\\ 1\to6 & \textit{for cluster 2}\end{matrix}$$

$$\hat{\gamma}_{11}=\frac{1-0.661}{\sqrt{0.224}}=0.7163 \qquad \hat{\gamma}_{21}=\frac{1-0.661}{\sqrt{0.224}}=0.7163$$

$$\hat{\gamma}_{12}=\frac{0-0.5622}{\sqrt{0.246}}=-1.1335 \qquad \hat{\gamma}_{22}=\frac{0-0.5622}{\sqrt{0.246}}=-1.1335$$

$$\hat{\gamma}_{13}=\frac{1-0.661}{\sqrt{0.224}}=0.7163 \qquad \hat{\gamma}_{23}=\frac{1-0.5622}{\sqrt{0.246}}=0.8831$$

$$\hat{\gamma}_{14}=\frac{0-0.5622}{\sqrt{0.246}}=-1.1335 \qquad \hat{\gamma}_{24}=\frac{0-0.661}{\sqrt{0.224}}=-1.3966$$

$$\hat{\gamma}_{25}=\frac{1-0.661}{\sqrt{0.224}}=0.7163$$

$$\hat{\gamma}_{26}=\frac{0-0.661}{\sqrt{0.224}}=-1.3966$$

The estimates for the nuisance parameters

$$\hat{\phi}^{-1}=\sum_{i=1}^{2}\sum_{t=1}^{j}\hat{\gamma}_{it}^{2}\Big/N-P \qquad j=\begin{matrix}1\to4 & \textit{for cluater 1}\\ 1\to6 & \textit{for cluster 2}\end{matrix}$$

Where $N=\sum n_i=4+6=10$

$P=2$ (*# of parameters needs to be estimated*)

$$\therefore \hat{\phi}^{-1}=\frac{\hat{\gamma}_{11}^2+\hat{\gamma}_{12}^2+\hat{\gamma}_{13}^2+\hat{\gamma}_{14}^2+\hat{\gamma}_{21}^2+\hat{\gamma}_{22}^2+\hat{\gamma}_{23}^2+\hat{\gamma}_{24}^2+\hat{\gamma}_{25}^2+\hat{\gamma}_{26}^2}{10-2}$$

$$=\left(4\times0.7163^2+3\times1.1335^2+2\times1.3966^2+0.8831^2\right)/8$$

$$=1.323$$

$$\Rightarrow \hat{\phi}=0.756$$

To estimate α consistently, we have to borrow strength over the 2 subjects. α can be estimated by the following simple function

$$\hat{R}_{\mu\nu}=\sum_{i=1}^{2}\hat{\gamma}_{i\mu}\hat{\gamma}_{i\nu}\Big/(N'-P) \qquad N'\textit{: sum of all } n_i(n_i-1)/2$$

$\therefore$ for cluster 1, we have 6 products of $\hat{\gamma}_{1\mu} \cdot \hat{\gamma}_{1\nu}$; for cluster 2, we have 15 products of $\hat{\gamma}_{2\mu} \cdot \hat{\gamma}_{2\nu}$.

If we assume an exchangeable working correlation matrix, the estimate of α is the sum of all cross-products $\hat{\gamma}_{i\mu} * \hat{\gamma}_{i\nu}$ over all μ different from ν within each i and subsequently over all i as well.

$$\hat{\alpha} = \begin{pmatrix} \hat{\gamma}_{11}\hat{\gamma}_{12} + \hat{\gamma}_{11}\hat{\gamma}_{13} + \hat{\gamma}_{11}\hat{\gamma}_{14} + \hat{\gamma}_{12}\hat{\gamma}_{13} + \hat{\gamma}_{12}\hat{\gamma}_{14} + \hat{\gamma}_{13}\hat{\gamma}_{14} + \hat{\gamma}_{21}\hat{\gamma}_{22} \\ + \hat{\gamma}_{21}\hat{\gamma}_{23} + \hat{\gamma}_{21}\hat{\gamma}_{24} + \hat{\gamma}_{21}\hat{\gamma}_{25} + \hat{\gamma}_{21}\hat{\gamma}_{26} + \hat{\gamma}_{22}\hat{\gamma}_{23} + \hat{\gamma}_{22}\hat{\gamma}_{24} + \hat{\gamma}_{22}\hat{\gamma}_{25} \\ + \hat{\gamma}_{22}\hat{\gamma}_{26} + \hat{\gamma}_{23}\hat{\gamma}_{24} + \hat{\gamma}_{23}\hat{\gamma}_{25} + \hat{\gamma}_{23}\hat{\gamma}_{26} + \hat{\gamma}_{24}\hat{\gamma}_{25} + \hat{\gamma}_{24}\hat{\gamma}_{26} + \hat{\gamma}_{25}\hat{\gamma}_{26} \end{pmatrix} \Big/ (21-2)$$

$$\Rightarrow \hat{\alpha} = \frac{0.7163 \times (-1.1335) + \cdots\cdots + 0.7163 \times (-1.3966)}{19}$$

$$= -0.1451$$

GEE is to estimate the parameter vector β and its covariance matrix. Let A_i be the $t_i * t_i$ diagonal matrix with $V(\mu_{ij})$ as the j^{th} diagonal element. The working covariance matrix for y_i is $V_i(\alpha) = \phi A_i^{1/2} R_i(\alpha) A_i^{1/2}$.

Therefore,

Cluster 1	Cluster 2
$V_1(\alpha) = \phi A_1^{1/2} R_1(\alpha) A_1^{1/2}$	$V_2(\alpha) = \phi A_2^{1/2} R_2(\alpha) A_2^{1/2}$

The working correlation matrix

Cluster 1:

$$R_1(\hat{\alpha}) = \begin{pmatrix} 1 & -0.1451 & -0.1451 & -0.1451 \\ -0.1451 & 1 & -0.1451 & -0.1451 \\ -0.1451 & -0.1451 & 1 & -0.1451 \\ -0.1451 & -0.1451 & -0.1451 & 1 \end{pmatrix}_{4\times 4}$$

Cluster 2:

$$R_2(\hat{\alpha}) = \begin{pmatrix} 1 & -0.1451 & \cdots & & & -0.1451 \\ -0.1451 & 1 & & & & \\ & & 1 & & & \vdots \\ \cdots & \vdots & & 1 & & \\ & & & & 1 & -0.1451 \\ -0.1451 & & \cdots & & -0.1451 & 1 \end{pmatrix}_{6\times 6}$$

$$A_1 = \begin{pmatrix} 0.224 & & & \\ & 0.246 & & \\ & & 0.224 & \\ & & & 0.246 \end{pmatrix}_{4\times 4}$$

Off-diagonal elements are 0s.

$$\Downarrow$$

$$A_1^{\frac{1}{2}} = \begin{pmatrix} 0.473 & & & \\ & 0.496 & & \\ & & 0.473 & \\ & & & 0.496 \end{pmatrix}_{4\times 4}$$

Off-diagonal elements are 0s.

$$A_2 = \begin{pmatrix} 0.224 & & & & & \\ & 0.246 & & & & \\ & & 0.246 & & & \\ & & & 0.224 & & \\ & & & & 0.224 & \\ & & & & & 0.224 \end{pmatrix}_{6\times 6}$$

Off-diagonal elements are 0s.

$$\Downarrow$$

$$A_2^{\frac{1}{2}} = \begin{pmatrix} 0.473 & & & & & \\ & 0.496 & & & & \\ & & 0.496 & & & \\ & & & 0.473 & & \\ & & & & 0.473 & \\ & & & & & 0.473 \end{pmatrix}_{6\times 6}$$

Off-diagonal elements are 0s.

$$\Rightarrow\ V_1(\hat{\alpha}) = \hat{\phi} A_1^{1/2} R_1(\hat{\alpha}) A_1^{1/2}$$

$$= 0.756 \times \begin{pmatrix} 0.473 & & & \\ & 0.496 & & \\ & & 0.473 & \\ & & & 0.496 \end{pmatrix}_{4\times 4} \times \begin{pmatrix} 1 & -0.1451 & -0.1451 & -0.1451 \\ -0.1451 & 1 & -0.1451 & -0.1451 \\ -0.1451 & -0.1451 & 1 & -0.1451 \\ -0.1451 & -0.1451 & -0.1451 & 1 \end{pmatrix}_{4\times 4} \times \begin{pmatrix} 0.473 & & & \\ & 0.496 & & \\ & & 0.473 & \\ & & & 0.496 \end{pmatrix}_{4\times 4}$$

$$= \begin{pmatrix} 0.1690 & -0.0257 & -0.0245 & -0.0257 \\ -0.0257 & 0.1858 & -0.0257 & -0.0269 \\ -0.0245 & -0.0257 & 0.1690 & -0.0257 \\ -0.0257 & -0.0269 & -0.0257 & 0.1858 \end{pmatrix}_{4\times 4}$$

$$V_2(\hat{\alpha}) = \hat{\phi} A_2^{1/2} R_2(\hat{\alpha}) A_2^{1/2}$$

$$= 0.756 \times \begin{pmatrix} 0.473 & & & & & \\ & 0.496 & & & & \\ & & 0.496 & & & \\ & & & 0.473 & & \\ & & & & 0.473 & \\ & & & & & 0.473 \end{pmatrix}_{6\times 6} \times \begin{pmatrix} 1 & -0.1451 & -0.1451 & \cdots & & -0.1451 \\ -0.1451 & 1 & & & & \\ \vdots & & 1 & & & \\ & & & \ddots & & \\ & & & & & -0.1451 \\ -0.1451 & \cdots & & & & 1 \end{pmatrix}_{6\times 6}$$

$$\times \begin{pmatrix} 0.473 & & & & & \\ & 0.496 & & & & \\ & & \ddots & & & \\ & & & & & \\ & & & & & \\ & & & & & 0.473 \end{pmatrix}_{6\times 6}$$

The GEE estimate of β is the solution of the estimating equation

$$U(\beta)=\sum_{i=1}^{n}\left(\frac{\partial\mu_i}{\partial\beta}\right)'\left[V_i(\hat{\alpha})\right]^{-1}\left(Y_i-\mu_i\right)=O_p \qquad (p=2)$$

Where $\mu_1=\left(\mu_{11},\cdots\mu_{14}\right)'$, $\mu_2=\left(\mu_{21},\cdots\mu_{26}\right)'$, O_2 is the 2×1 vector and $\hat{\alpha}$ is a consistent estimate of α.

The above equations are solved by iteration. After obtaining the updated $\hat{\beta}_0$ and $\hat{\beta}_1$, we can substitute them in to recalculation α, then, based on the updated α we can calculate new β's until convergence.

$$U(\beta)=\left(\frac{\partial\mu_1}{\partial\beta}\right)'\underset{known}{V_1(\hat{\alpha})^{-1}}\underset{known}{\left(Y_1-\mu_1\right)}+\left(\frac{\partial\mu_2}{\partial\beta}\right)'\underset{known}{V_2(\hat{\alpha})^{-1}}\underset{known}{\left(Y_2-\mu_2\right)}=O_2$$

In order to solve the above equation with respect to β_0 and β_1, we have to obtain

$$\frac{\partial\mu_1}{\partial\beta_0}\ \frac{\partial\mu_1}{\partial\beta_1}\ \frac{\partial\mu_2}{\partial\beta_0}\ \frac{\partial\mu_2}{\partial\beta_1}$$

We know $\mu=\dfrac{e^{\beta_0+\beta_1x}}{1+e^{\beta_0+\beta_1x}}$

$$\frac{\partial\mu}{\partial\beta_0}=\frac{e^{\beta_0+\beta_1x}\left(1+e^{\beta_0+\beta_1x}\right)-e^{\beta_0+\beta_1x}e^{\beta_0+\beta_1x}}{\left(1+e^{\beta_0+\beta_1x}\right)^2}=\frac{e^{\beta_0+\beta_1x}}{\left(1+e^{\beta_0+\beta_1x}\right)^2}$$

$$\frac{\partial\mu}{\partial\beta_1}=\frac{xe^{\beta_0+\beta_1x}\left(1+e^{\beta_0+\beta_1x}\right)-e^{\beta_0+\beta_1x}\cdot xe^{\beta_0+\beta_1x}}{\left(1+e^{\beta_0+\beta_1x}\right)^2}=\frac{xe^{\beta_0+\beta_1x}}{\left(1+e^{\beta_0+\beta_1x}\right)^2}$$

$$\Rightarrow\quad\begin{pmatrix}\frac{\partial\mu_1}{\partial\beta_0}\\ \frac{\partial\mu_1}{\partial\beta_1}\end{pmatrix}'=\begin{pmatrix}\frac{e^{0.25+0.41667}}{\left(1+e^{0.24+0.41667}\right)^2} & \frac{e^{0.25}}{\left(1+e^{0.25}\right)^2} & \cdots & \frac{e^{0.25}}{\left(1+e^{0.25}\right)^2}\\ \frac{e^{0.25+0.41667}}{\left(1+e^{0.25+0.41667}\right)^2} & 0 & \cdots & 0\end{pmatrix}_{2\times4}$$

$$=\begin{pmatrix}0.224 & 0.246 & 0.224 & 0.246\\ 0.224 & 0 & 0.224 & 0\end{pmatrix}_{2\times4}$$

$$\begin{pmatrix} \frac{\partial \mu_1}{\partial \beta_0} \\ \frac{\partial \mu_1}{\partial \beta_1} \end{pmatrix} = \begin{pmatrix} 0.224 & 0.224 \\ 0.246 & 0 \\ 0.224 & 0.224 \\ 0.246 & 0 \end{pmatrix}_{4\times 2}$$

Likewise for the cluster 2:

$$\begin{pmatrix} \frac{\partial \mu_2}{\partial \beta_0} \\ \frac{\partial \mu_2}{\partial \beta_1} \end{pmatrix}' = \begin{pmatrix} 0.224 & 0.246 & \cdots & 0.224 \\ 0.224 & 0 & \cdots & 0.224 \end{pmatrix}_{2\times 6}$$

$$\begin{pmatrix} \frac{\partial \mu_2}{\partial \beta_0} \\ \frac{\partial \mu_2}{\partial \beta_1} \end{pmatrix} = \begin{pmatrix} 0.224 & 0.224 \\ 0.246 & 0 \\ \vdots & \vdots \\ 0.224 & 0.224 \end{pmatrix}_{6\times 2}$$

Thus, update $\hat{\beta}$ with

$$\hat{\beta}^{(r+1)} = \hat{\beta}^{(r)} - \left[\sum_{i=1}^{2} \frac{\partial \mu_i}{\partial \beta}' V_i^{-1} \frac{\partial \mu_i}{\partial \beta} \right]^{-1} \cdot \left[\sum_{i=1}^{2} \left(\frac{\partial \mu_i}{\partial \beta} \right)' V_i^{-1} (Y_i - \mu_i) \right]$$

Where $\gamma = 0$

$$\Rightarrow \hat{\beta^{(1)}} = \hat{\beta^{(0)}} - \left(\left(\frac{\partial \mu_1}{\partial \beta} \right)' V_1^{-1} \frac{\partial \mu_1}{\partial \beta} + \left(\frac{\partial \mu_2}{\partial \beta} \right)' V_2^{-1} \frac{\partial \mu_2}{\partial \beta} \right)^{-1} \times \left(\left(\frac{\partial \mu_1}{\partial \beta} \right)' V_1^{-1} (Y_1 - \mu_1) + \left(\frac{\partial \mu_2}{\partial \beta} \right)' V_2^{-1} (Y_2 - \mu_2) \right)$$

$$\begin{pmatrix}\beta_0^{(1)}\\ \beta_1^{(1)}\end{pmatrix}=\begin{pmatrix}0.25\\ 0.4167\end{pmatrix}-$$

$$\left[\begin{array}{l}\begin{pmatrix}0.224 & \cdots & 0.246\\ 0.224 & \cdots & 0\end{pmatrix}'_{2\times 4}\begin{pmatrix}0.169 & \cdots & -0.0257\\ \vdots & \ddots & \vdots\\ -0.0257 & \cdots & 0.1858\end{pmatrix}^{-1}_{4\times 4}\begin{pmatrix}0.224 & 0.224\\ \vdots & \vdots\\ 0.246 & 0\end{pmatrix}_{4\times 2}+\\ \\ \begin{pmatrix}0.224 & \cdots & 0.224\\ 0.224 & \cdots & 0.224\end{pmatrix}'_{2\times 6}\begin{pmatrix}0.169 & -0.0257 & \cdots & -0.0245\\ -0.0257 & & & \vdots\\ \vdots & & \ddots & \\ -0.0245 & \cdots & & 0.1690\end{pmatrix}^{-1}_{6\times 6}\begin{pmatrix}0.224 & 0.224\\ 0.246 & 0\\ \vdots & \vdots\\ 0.224 & 0.224\end{pmatrix}_{6\times 2}\end{array}\right]^{-1}$$

$$\times\left[\begin{array}{l}\begin{pmatrix}0.224 & \cdots & 0.246\\ 0.224 & \cdots & 0\end{pmatrix}'_{2\times 4}\begin{pmatrix}0.169 & \cdots & -0.0257\\ & & \\ -0.0257 & & 0.1858\end{pmatrix}^{-1}_{4\times 4}\begin{pmatrix}0.339\\ -0.562\\ \vdots\\ -0.562\end{pmatrix}_{4\times 1}\\ \\ +\begin{pmatrix}0.224 & \cdots & 0.224\\ 0.224 & \cdots & 0.224\end{pmatrix}'_{2\times 6}\begin{pmatrix}0.169 & -0.0257 & \cdots & 0.0245\\ -0.0257 & & & \vdots\\ \vdots & & \ddots & \\ -0.0245 & \cdots & & 0.1690\end{pmatrix}^{-1}_{6\times 6}\begin{pmatrix}0.339\\ -0.562\\ \vdots\\ -0.661\end{pmatrix}_{6\times 1}\end{array}\right]$$

$$\Rightarrow\ \begin{pmatrix}\hat{\beta}_0^{(1)}\\ \hat{\beta}_1^{(1)}\end{pmatrix}=\begin{pmatrix}-0.7898\\ 1.5187\end{pmatrix}$$

After we get a new estimated $\begin{pmatrix}\hat{\beta}_0^{(1)}\\ \hat{\beta}_1^{(1)}\end{pmatrix}$, we can recalculate $\hat{\alpha}_{new}^{(2)}$, then, update $\begin{pmatrix}\hat{\beta}_0^{(1)}\\ \hat{\beta}_1^{(1)}\end{pmatrix}$ to $\begin{pmatrix}\hat{\beta}_0^{(2)}\\ \hat{\beta}_1^{(2)}\end{pmatrix}$ and so on until convergence.

The model-based estimator of the covariance matrix for $\hat{\beta}$ is the inverse of the observed information matrix:

$$\sum_m \left(\hat{\beta}\right) = I_0^{-1} \text{ Where } I_0 = \sum_{i=1}^{2} \left(\frac{\partial \mu_i}{\partial \beta}\right)' V_i^{-1} \frac{\partial \mu_i}{\partial \beta}$$

$$\Rightarrow \quad \underbrace{I_0 = \left(\frac{\partial \mu_1}{\partial \beta}\right)' V_1^{-1} \frac{\partial \mu_1}{\partial \beta} + \left(\frac{\partial \mu_2}{\partial \beta}\right)' V_2^{-1} \frac{\partial \mu_2}{\partial \beta}}_{\textit{all the elements known}}$$

Empirical:

$$\sum_e = I_0^{-1} I_1 I_0^{-1} \qquad I_1 = \sum_{i=1}^{2} \frac{\partial \mu_i}{\partial \beta}' V_i^{-1} \operatorname{cov}(Y_i) V_i^{-1} \frac{\partial \mu_i}{\partial \beta}$$

$$\operatorname{cov}(Y_i) = \left(Y_i - \mu_i(\hat{\beta})\right)\left(Y_i - \mu_i(\hat{\beta})\right)'$$

$$\Rightarrow \operatorname{cov}(Y_1) = \left(Y_1 - \mu_1(\hat{\beta})\right)\left(Y_1 - \mu_1(\hat{\beta})\right)'$$

$$\operatorname{cov}(Y_2) = \left(Y_2 - \mu_2(\hat{\beta})\right)\left(Y_2 - \mu_2(\hat{\beta})\right)'$$

$$\underbrace{I_1 = \left(\frac{\partial \mu_1}{\partial \beta}\right)' V_1^{-1} \operatorname{cov}(Y_1) V_1^{-1} \frac{\partial \mu_1}{\partial \beta} + \left(\frac{\partial \mu_2}{\partial \beta}\right)' V_2^{-1} \operatorname{cov}(Y_2) V_2^{-1} \frac{\partial \mu_2}{\partial \beta}}_{\textit{all the elements known}}$$

We can obtain the *model-based* and *empirical* variances from the GEE method.

APPENDIX III: SAS PROGRAM FOR THE SIMULATION STUDY

Before moving to the SAS program section, we are going to introduce some design parameters (symbols) used to produce the actual SAS program.

HR (hazard ratio): HR is used to evaluate the magnitude of the association between exposure (taking medication) and the outcome (adverse outcome events) of interest. The value of this parameter is considered as the gold standard value for evaluating the bias produced from each estimator. In the simulation, the values of HR are set to be 1, 2, 5 and 10;

Pt (n, sample size): The number of individuals to be generated;

R_window: The risk period where the probability of developing the outcome of interest is elevated relative to that when not exposed;

Pvi_hi: The marginal daily probability of becoming exposed;

Poi_hi: The marginal daily probability of developing the outcome of interest if not exposed;

Phi_hi: The probability of being in subgroup "HH";

Vi_hi: The high propensity of exposure category in a 2 x 2 table, e.g., on average, 10 instances/per person year;

Vi_low: The low propensity of exposure category in a 2 x 2 table, e.g., on average, 2 instances/per person year;

Oi_hi: The high propensity of outcome category in a 2 x 2 table, e.g., on average, 10 events/per person year;

Oi_low: The low propensity outcome category in a 2 x 2 table, e.g., on average, 2 events /per person year;

Cond_p: The conditional daily propensity of developing the outcome of interest given a certain propensity of exposure;

v_ntnsty: The propensity of becoming exposed, unit: expected # of exposures per person year;

o_ntnsty: The propensity of developing the outcome, unit: expected # of outcomes per person year;

v_prob: The daily probability of becoming exposed per day;

e_prob_o: The daily probability of developing the outcome when not exposed;

e_prob: The daily probability of developing the outcome when exposed.

SAS Program for the Simulation Study

```
*options ls=75 ps=50;


libname repbin 'c:\Documents and Settings\Bin.Zhang\My Documents\case-
crossover';


%macro repbin(rr,dataset, n_pts ,
              men_exp, men_outcome,
              women_exp, women_outcome,
              pvi_hi, poi_hi, phi_hi,
              n_days, n_times,r_length,
              fseed);

data seeds;
keep seed;
do ds = 1 to &dataset;
   jump_seed = 1 + ceil(100000*ranuni(&fseed));
   do i = 1 to jump_seed;
      seed = ceil(10000000*ranuni(&fseed));
        if i = jump_seed then output;
        end;
end;
run;

/*proc datasets nolist nodetails;delete all all1 all2 all3 all4 all5
all6 all7 all8;*/

%do ds=1 %to &dataset;

ODS LISTING CLOSE;

PROC PRINTTO LOG='c:\Documents and Settings\Bin.Zhang\My Documents\case-
crossover\BIN.TXT';
RUN;

data a;
keep  pt   case1-case400 ctl1-ctl400;

Retain  seedno;

do which_seed = 1 to &ds;
    set seeds;
    if which_seed = &ds then seedno = seed;
end;

array v_t(*) vt1-vt4000;
array e_t(*) et1-et4000;
array ctl_t(*) ctlt1-ctlt4000;
array exp_case_w(*) exp_casew1-exp_casew4000;
array exp_ctl_w(*)  exp_ctlw1-exp_ctlw4000;
array exped_case(*) case1-case4000;
array exped_ctl(*)  ctl1-ctl4000;
```

```
do pt = 1 to &n_pts;

  do i = 1 to &n_times; v_t(i) = . ; e_t(i) = . ; ctl_t(i)=.;
                        exp_case_w(i)=.;exp_ctl_w(i)=.;
                                  exped_case(i)=.;exped_ctl(i)=.;
  end;

      r=ranuni(seedno);

       if r > &pvi_hi then v_ntnsty= &men_exp;

          else v_ntnsty= &women_exp;

       if v_ntnsty= &men_exp then cond_p = &phi_hi/&pvi_hi;

          else cond_p = (&poi_hi-&phi_hi)/(1-&pvi_hi);

      r1=ranuni(seedno);

       if r1 > cond_p then o_ntnsty= &men_outcome;

          else o_ntnsty= &women_outcome;

      v_prob   = 12*v_ntnsty/365;

      e_prob_0 = 12*o_ntnsty/365;

      v_no =0; e_no=0;
      v_clock = 0; e_clock =0; r_window = 0;

    do d = 1 to &n_days by 12;

       if e_no > 0 then e_clock = e_clock + 1;

       if v_no > 0 then v_clock = v_clock + 1;

       if r_window = 1 and v_clock > &r_length then r_window = 0;

          e_prob = e_prob_0 * ( 1 + (&rr-1)*r_window );

      r2=ranuni(seedno);

      v  = (r2 <v_prob);
       if v = 1 then do;
          v_no = v_no + 1;
       if v_no <= &n_times then v_t(v_no) = d;
          r_window = 1;
          v_clock = 0;
       end;

        r3=ranuni(seedno);

      e = (r3 < e_prob);
       if e = 1 then do;
        e_no = e_no + 1;
       if e_no <= &n_times then e_t(e_no) = d;
```

```
     e_clock = 0;

           ctl_t(e_no)=e_t(e_no)-&r_length;
  end;

end;

 if e_no > 0 then do;
    n_elig_w = 0; case_v=0; ctl_v=0;
       do e = 1 to e_no;
           if e_t(e) > (2*&r_length) then do;
              elig_w = 1;
              n_elig_w = n_elig_w+1;
           end;
           if  elig_w =1 and v_no > 0 then do;
              v_case_w = 0; v_ctl_w = 0;
                  do v = 1 to v_no;
                     if (0 <= e_t(e) - v_t(v) <= &r_length)
                         then do; v_case_w = 1;
                    exp_case_w(e)=e_t(e)- v_t(v);

                     if exp_case_w(e)<= &r_length then
                                    exped_case(e)=1; end;

                     if (e_t(e)-v_t(v) > &r_length)
                          then do; exp_case_w(e)=e_t(e)-v_t(v);

                     if exp_case_w(e) >&r_length then
                                   exped_case(e)=0;  end;


                     if (0 <= (ctl_t(e) - v_t(v)) <= &r_length)
                         then do; v_ctl_w  = 1;
                              exp_ctl_w(e)=ctl_t(e)- v_t(v);

                       if exp_ctl_w(e)<=  &r_length then
                                    exped_ctl(e)=1;  end;

                       if ((ctl_t(e) - v_t(v)) > &r_length)
                                     then do;
                              exp_ctl_w(e)=ctl_t(e)- v_t(v);

                       if exp_ctl_w(e) > &r_length then
                                    exped_ctl(e)=0;  end;


                   end;
           case_v = case_v + v_case_w; ctl_v = ctl_v + v_ctl_w;
           end;

       end;
    mh_num = case_v * (n_elig_w - ctl_v )/n_elig_w;
    mh_den = ctl_v  * (n_elig_w - case_v)/n_elig_w;

           output;
 end; * end of block if # events > 0;
```

```
end; * end for pt;

proc sort data=a; by pt; run;

proc transpose data=a(keep= pt case1-case400 )
               out=b(rename=(col1=exposure  ));by pt;run;

proc transpose data=a(keep= pt  ctl1-ctl400)
               out=c(rename=(col1=exposure  ));by pt;run;

data b_exp;set b;by  pt;retain count ;count=_N_;outcome=1;
run;

data c_exp;set c;by  pt;retain count ;count=_N_;outcome=0;
run;

proc append base=b_exp data=c_exp force;run;

proc sort data=b_exp;by pt count;run;

data b_exp;retain   pt  count outcome exposure _NAME_; set b_exp;run;

proc sort data=b_exp nodupkey;by count;run;

/*cases are deleted because of the corresponding controls lack of
exposure information*/

data cc;merge b_exp(where=(exposure ne .) in=a) c_exp(where=(exposure
ne .) in=b);
by count;if a ne b; run;

/*bring the cases out from the case dataset*/

data cassover ;merge b_exp(where=(exposure ne .) in=a) cc(in=b);by count;
if a ne b; run;

/*create a final case-cross-over dataset*/

proc append base=cassover
            data=c_exp(where=(exposure ne .)) force;run;
proc sort data=cassover;by  pt count;run;
/* data analyses*/

/* crude M-H 2x2 table data analysis*/

proc freq data=cassover(keep= pt outcome exposure);
tables outcome*exposure/nopercent norow measures cmh all;
ods output commonrelrisks=sasdc(where=(studytype='Case-Control'));
ods output crosstabfreqs=sasdc_freq(where=(_type_='11'));
run;

/*subject level M-H 2x2 table data analysis*/

proc freq data=cassover(keep= pt outcome exposure);
tables pt*outcome*exposure/nopercent norow measures cmh all;
ods output commonrelrisks=sasds(where=(studytype='Case-Control'));
ods output crosstabfreqs=sasds_freq(where=(_type_='11'));
```

```
run;

/*event level M-H 2x2 table data analysis*/

data test1;set cassover(where=(outcome=1));by  pt;
if first.pt then do;rep=0;end;
rep+1;
run;

data test2;set cassover(where=(outcome=0));by  pt;
if first.pt then do;rep=0;end;
rep+1;
run;

data test3;set test1;by  pt;retain rep_pt;
rep_pt=pt+rep/10000;
run;

data test4;set test2;by  pt;retain rep_pt;
rep_pt=pt+rep/10000;
run;

proc append base=test3 data=test4 force;run;
proc sort data=test3;by  pt rep rep_pt;run;
data test3;retain  pt rep_pt outcome exposure;set test3;drop rep ;run;

proc freq data=test3;
tables rep_pt*outcome*exposure/nopercent norow measures cmh all;
ods output commonrelrisks=sasde(where=(studytype='Case-Control'));
ods output crosstabfreqs=sasde_freq(where=(_type_='11'));
run;

/*conditional logistic regression---CLR*/

/*based on the subject-level ----CLR*/

data cass;set cassover(drop=count _NAME_);
time=1;run;

proc phreg data=cass /*nosummary*/;
model time*outcome(0)=exposure/ties=discrete rl;
strata pt;
ods output parameterestimates=sasds_cond;
ods output CensoredSummary=ds_cond;
run;

/*based on the event level---CLR*/

data cass1;set test3(drop=count _NAME_);
time=1;run;

proc phreg data=cass1;
model time*outcome(0)=exposure/ties=discrete rl;
strata  rep_pt;
ods output parameterestimates=sasde_cond;
ods output censoredsummary=de_cond;
run;
```

```
/*GEE approach*/

/*the subject level----GEEs---independent working correlation
structure*/

proc genmod data=cass(drop=time) descending;
class pt  ;
model outcome=exposure  /  d=binomial ;
repeated subject=pt/type=ind  covb /* corrw*/ modelse;
ods output geemodpest=sasdate101;
run;

/*subject level----GEE---exchangeable working correlation structure */

proc genmod data=cass(drop=time) descending;
class pt  ;
model outcome=exposure  /  d=binomial ;
repeated subject=pt/type=exch  covb /*corrw*/ modelse;
ods output geemodpest=sasdate131;
run;

/*GEEs*/

/*the event level-------GEEs---independent working correlation
structure*/

proc genmod data=cass1(drop=time)  descending;
class rep_pt ;
model outcome=exposure  /  d=binomial ;
repeated subject=rep_pt/type=ind  /*covb corrw*/ modelse;
ods output geemodpest=sasdate101_e;
run;

/*the event level-------GEEs---exchangeable working correlation
structure */


proc genmod data=cass1(drop=time)  descending;
class rep_pt  ;
model outcome=exposure  /  d=binomial ;
repeated subject=rep_pt/type=exch  covb corrw modelse;
ods output geemodpest=sasdate131_e;
run;



/* all the summary datasets*/

/*the crude 2x2 table variance of log odds ratio*/

data sasdc;set sasdc;retain logor vlogor;
logor=log(value);
vlogor=((log(uppercl)-log(lowercl))/2/1.96)**2;run;

/*the subject-level variance of log odds ratio*/
```

```
data sasds;set sasds;retain logor vlogor;
logor=log(value);
vlogor=((log(uppercl)-log(lowercl))/2/1.96)**2;run;

/*the event-level variance of log odds ratio*/

data sasde;set sasde;retain logor vlogor;
logor=log(value);
vlogor=((log(uppercl)-log(lowercl))/2/1.96)**2;run;

/*the subject-level variance of log hazard ratio from the CLRegression*/

data sasds_cond;set sasds_cond;retain loghazardratio vloghazardratio;
loghazardratio=log(hazardratio);
vloghazardratio=stderr**2;run;

/*the event-level variance of log hazard ratio from the CLRegression*/

data sasde_cond;set sasde_cond;retain loghazardratio vloghazardratio;
loghazardratio=log(hazardratio);
vloghazardratio=stderr**2;
run;

/*the subject-level variance of log odds ratio from the GEEs---ind
w.c.s.model*/

data sasdate81;set sasdate101(where=(parm='exposure'));retain logor
vlogor or;
logor=estimate;
vlogor=stderr**2;
or=exp(estimate);
run;

/*the subject-level variance of log odds ratio from the GEEs---exch
w.c.s. model*/

data sasdate111;set sasdate131(where=(parm='exposure'));retain logor
vlogor or;
logor=estimate;vlogor=stderr**2;or=exp(estimate);
run;

/*the event-level variance of log odds ratio from the GEEs---ind w.c.s.
model*/
data sasdate81_e;set sasdate101_e(where=(parm='exposure'));retain logor
vlogor or;
logor=estimate;vlogor=stderr**2;or=exp(estimate);
run;

/*the event-level variance of log odds ratio from the GEEs---exch w.c.s.
model*/


data sasdate111_e;set sasdate131_e(where=(parm='exposure'));retain logor
vlogor or;
logor=estimate;vlogor=stderr**2;or=exp(estimate);
run;
```

```
/*append all the datasets together*/

/*M-H estimates for the crude 2x2 table , subject and event-levels*/

proc datasets nolist nodetails;
     append base=tools.dcfreq  data=sasdc_freq;

proc datasets nolist nodetails;
     append base=tools.dsfreq  data=sasds_freq;

proc datasets nolist nodetails;
     append base=tools.defreq  data=sasde_freq;

proc datasets nolist nodetails;
     append base=tools.dscond  data=ds_cond;

proc datasets nolist nodetails;
     append base=tools.decond  data=de_cond;

proc datasets nolist nodetails;
     append base=tools.all data=sasdc;

proc datasets nolist nodetails;
     append base=tools.all1 data=sasds;

proc datasets nolist nodetails;
     append base=tools.all2 data=sasde;

/*odds ratios from the conditional logistic regression method */

proc datasets nolist nodetails;
     append base=tools.all3 data=sasds_cond;

proc datasets nolist nodetails;
     append base=tools.all4 data=sasde_cond;

/*odds ratios from the GEEs models-----subject-level*/

proc datasets nolist nodetails;
     append base=tools.all5 data=sasdate81;

proc datasets nolist nodetails;
     append base=tools.all6 data=sasdate111;

/*odds ratioes from GEE models-----event level*/

proc datasets nolist nodetails;
     append base=tools.all7 data=sasdate81_e;


proc datasets nolist nodetails;
     append base=tools.all8 data=sasdate111_e;



/*delete the datasets*/
```

```
proc datasets nolist nodetails;
      delete a  sasdc sasds sasde sasds_cond sasde_cond sasdate101
sasdate81 sasdate111 sasdate131  sasdate101_e sasdate81_e sasdate111_e
sasdate131_e;

PROC PRINTTO LOG=LOG;
RUN;

ODS LISTING ;

%end;
%mend repbin;

%repbin(rr=2, dataset=1, n_pts=4,
        men_exp=20, men_outcome=20,
        women_exp=5, women_outcome=5,
            pvi_hi=0.5, poi_hi=0.5,
            phi_hi=0.25, n_days=3650,
            n_times=4000, r_length=12,
        fseed=789654378)
quit;

/*output the results*/

proc means data=tools.all; var logor vlogor value;

output out=new mean= std(logor)= / autoname;

title1 'Estimation of Crude log-M-H odds ratio ';
run;

proc means data=tools.all1; var logor vlogor value;

output out=new1 mean= std(logor)= / autoname;

title1 'Estimation of log-M-H odds ratio based on subject-level';
run;

proc means data=tools.all2; var logor vlogor value;

output out=new2 mean= std(logor)= / autoname;

title1 'Estimation of log-M-H odds ratio based on event-level';
run;

proc means data=tools.all3;
var loghazardratio vloghazardratio hazardratio;

output out=new3 mean= std(loghazardratio)= / autoname;

title1 'Average log(OR) based on the subject-level using the Conditional
Logistic Regression ';
run;

proc means data=tools.all4;
var loghazardratio vloghazardratio hazardratio;
```

```
output out=new4 mean= std(loghazardratio)= / autoname;

title1 'Average log(OR) based on the event-level using the conditional
logistic regression';
run;

proc means data=tools.all5;
var logor vlogor or;

output out=new5 mean= std(logor)= / autoname;

title1 'AVERAGE log(OR) FROM THE GEES WITH AN INDEPENDENCE WORKING
STRUCTURE---subject-level';
run;

proc means data=tools.all6;
var logor vlogor or;

output out=new6 mean= std(logor)= / autoname;

title1 ' AVERAGE log(OR) FROM THE GEES WITH AN EXCHANGABLE WORKING
STRUCTURE---subject-level';
run;

proc means data=tools.all7;
var logor vlogor or;

output out=new7 mean= std(logor)= / autoname;

title1 ' AVERAGE log(OR) FROM THE GEES WITH AN INDEPENDENCE WORKING
STRUCTURE---event-level';
run;


proc means data=tools.all8;
var logor vlogor or;

output out=new8 mean= std(logor)= / autoname;

title1 ' AVERAGE log(OR) FROM THE GEES WITH AN EXCHANGABLE WORKING
STRUCTURE---event-level';
run;


data all_new;
set new new1 new2 new3 new4 new5 new6 new7 new8;run;
```

APPENDIX IV: DETAILED RESULTS FROM THE SIMULATION STUDY

In the following, we are going to present the results from each individual table as well as a cross comparison between tables from the simulation study, where one of the four design parameters (the sample size, the correlation coefficient, the hazard ratio and the intensities of exposure and the outcome of interest) changes the fastest and the others hold the same. For example, the effects of the correlation coefficient can be investigated from Table 5.2.1(a) $\rightarrow$ Table 5.2.1(b) $\rightarrow$ Table 5.2.1(c), where the correlation coefficient changes from $0 \rightarrow 0.5 \rightarrow 0.9$; however, the sample size, the hazard ratio and the intensities of exposure and the outcome of interest hold the same.

The same ordering of the presentation, shown in Chapter 5, will be adapted here. That is, we will first present the bias in the empirical estimates of odds ratio for the eight estimators, then followed by the MSEs. Finally, we will examine the ratios of the empirical to model-based variances from each individual estimator.

5.2 Magnitude of bias in Odds Ratio from different statistical methods

SUMMARY OF THE DETAILED RESULTS FROM INDIVIDUAL TABLES

- The propensities of exposure and the outcome of interest between these two study groups are 2/2 instances per year in these three tables, while the correlation coefficient varies the fastest from $0 \rightarrow 0.5 \rightarrow 0.9$---**Results from Tables 5.2.1(a, b and c)**

1. The results from Tables 5.2.1 (a, b, and c) show that, when $N = 50$ or $N = 100$, the magnitudes of bias do not have a material change as the correlation coefficient increases from $0 \rightarrow 0.5 \rightarrow 0.9$. In fact, they are almost numerically identical. For example, the results in Tables 5.2.1 (a, b, and c) show that: the magnitude of bias from the

CLR method with the event-level data analysis changes from 10.4 $\rightarrow$ 10.6 $\rightarrow$ 10.9, when $N = 50, OR = 5$ and $\rho = 0 \rightarrow 0.5 \rightarrow 0.9$.

When the sample size is small ($N = 30$) and the hazard ratio is set to the null value; however, the magnitude of bias from the CLR method with the event-level data analyses shows an increase as the correlation coefficient increases from 0 $\rightarrow$ 0.5. On the other hand, the bias shows a decrease as the correlation coefficient increases from 0.5 $\rightarrow$ 0.9.

2. As the hazard ratio increases from 1 $\rightarrow$ 10, the biases presented in all of three tables (Tables 5.2.1 (a, b and c)) show an increase. That is, the higher the value of the hazard ratio, the larger the bias in the estimate of the odds ratio. This is true with all the different given sample sizes ($N = 30, 50$ and 100) and correlation coefficients ($\rho = 0, 0.5$ and 0.9). It is also true regardless of which statistical method or unit of data analysis is used. For example, 1) The results in Table 5.2.1(a) show that, when $\rho = 0, N = 30$, the bias from the subject-level GEE method with an exchangeable w.c.s. increases from 2.9% $\rightarrow$ 50.3% as the hazard ratio increases from 1 $\rightarrow$ 10; 2) In Table 5.2.1(b), when $\rho = 0.5, N = 50$, the bias increases from 5.4% $\rightarrow$ 49.7%; and, 3) In Table 5.2.1(c), when $\rho = 0.9, N = 100$, the bias increases from 3.3% $\rightarrow$ 47.9%.

When the hazard ratio is fixed at a value greater than 1, the biases from the other six estimators are substantially higher than those from the event-level M-H method and the CLR method. For example, the results from Table 5.2.1(a) show that, when $\rho = 0, N = 30, OR = 10$, the bias from the overall crude M-H method is 3 times (38.1% vs. 10.5%) higher than that from the event-level data analysis; when $\rho = 0, N = 30, OR = 10$, the bias from the subject-level CLR method is 3 times (36.8% vs. 10.5%) higher than that from the event-level data analysis.

- The propensities of exposure and the outcome between these two study groups are 10/2 instances per year in these three tables, while the correlation coefficient varies the fastest from 0 $\rightarrow$ 0.5 $\rightarrow$ 0.9---**Results from Tables 5.2.2(a, b and c)**

1. As the correlation coefficient increases from 0 $\rightarrow$ 0.9, the biases from all three statistical methods also show an increase. For example, when $N = 30$ and OR=10, the bias from the subject-level GEE method increase from 25.7% $\rightarrow$ 28.5% $\rightarrow$ 50.0% as the correlation coefficient increases from 0 $\rightarrow$ 0.5 $\rightarrow$ 0.9. When the hazard ratio is set to the null value; however, the changes in the bias from all three statistical analyses do not show systematically changing patterns as those that were observed in Tables 5.2.1(a, b and c).

2. In comparing the results in Table 5.2.2(a) with Table 5.2.1(a); Table 5.2.2(b) with Table 5.2.1(b); and Tables 5.2.2(c) with Table 5.2.1(c), it is clear that as the difference in the propensities of exposure and the outcome of interest between the two comparison populations increases, the biases from the M-H method and the CLR method with the event-level data analyses decrease significantly. For example, when $N = 30$, OR=10, the bias from the event-level CLR method reduces from 10.5% $\rightarrow$ 7.9% (Table 5.2.2(a) vs. Table 5.2.1(a)). The same conclusion can also be made for the overall crude M-H method and all three statistical methods (the M-H method, the CLR method, and the GEE method) with the subject-level data analyses.

3. Within a homogeneous population (Table 5.2.1(a), Table 5.2.1(b) and Table 5.2.1(c) with the same intensities of exposure and the outcome of interest between these two study groups), the magnitude of bias from each estimator is almost identical as the correlation coefficient increases from 0 $\rightarrow$ 0.9, which is true no matter whether the subject-level or the event-level data analysis is conducted.

This is not the case for a heterogeneous population (Table 5.2.2(a), Table 5.2.2(b), Table 5.2.2(c); Table 5.2.3(a), Table 5.2.3(b) and Table 5.2.3(c)) with different intensities of exposure and the outcome of interest between the two study groups. In particular, as shown in the above tables (Tables 5.2.2 (a, b and c) and Tables 5.2.3 (a, b and c)), the bias is smaller for $\rho = 0$ (Table 5.2.2(a)), while larger for $\rho = 0.5$ and $\rho = 0.9$ (Table 5.2.2(b) and Table 5.2.2(c)). For example, when $N = 30$, the bias from the subject-level GEE method with an exchangeable w.c.s. increase from 25% ($\rho = 0$) $\rightarrow$ 50% ($\rho = 0.9$). The data appear to show that if other conditions do not change, a higher correlation among repeated outcome events will have a much larger impact on the bias in a heterogeneous population than in a homogeneous population.

4. The biases (in Tables 5.2.2 (a, b and c)) from the event-level M-H method and the CLR method are smaller than the other six estimators.

The above results are presented based on the hazard ratios of 2 to 10. When the hazard ratio is set to the null value, however, the biases from the eight estimators are almost numerically identical to each other (as shown in Tables 5.2.2 (a, b and c)).

- <u>The propensities of exposure and the outcome between these two study groups are 20/2 instances per year in these three tables, while the correlation coefficient varies the fastest from 0 $\rightarrow$ 0.5 $\rightarrow$ 0.9</u>---**<u>Results from Tables 5.2.3(a, b and c)</u>**

1. Almost the same conclusions can be reached for the results presented in Tables 5.2.3 (a, b, and c) as we had previously summarized for Tables 5.2.2 (a, b, and c). In this case, however, the overall crude M-H method and the subject-level GEE method with an

independent w.c.s. produce the highest bias compared to the other estimators (including the case where the hazard ratio is set to the null value).

2. As the correlation coefficient increases from 0 $\rightarrow$ 0.9, the biases from the M-H method and from the CLR method with the event-level data analyses show a slight increase. The estimated empirical odds ratios, however, are fairly stable. This suggests that, if a proper statistical method and unit of data analysis are chosen for data analysis, the bias will not be significantly affected by the size of the correlation coefficient.

- The propensities of exposure and the outcome between these two study groups vary the fastest (2/2 $\rightarrow$ 10/2 $\rightarrow$ 20/2), while the correlation coefficient varies the slowest---

Results from a cross examination of Table 5.2.1(a), Table 5.2.2(a) and Table 5.2.3(a); Table 5.2.1(b), Table 5.2.2(b) and Table 5.2.3(b); Table 5.2.1(c), Table 5.2.2(c) and Table 5.2.3(c)

In comparing the results in the tables with the same correlation coefficient, it is clear that as the difference in the propensities of exposure and the outcome of interest between the two comparison populations increases, the bias from the M-H method and the CLR method with the event-level data analyses decrease in the various settings. The results from the overall crude M-H method and the subject-level GEE method, however, do not show such a pattern. Instead, the bias from these methods fluctuate with a decrease first, followed by an increase pattern. The results also show that, as the propensities of exposure and the outcome of interest increases, the biases from all three statistical methods (the M-H method, the CLR method, and the GEE method) decrease at the subject-level data analyses.

As discussed previously, the results in Tables 5.2.1(a, b and c) show that, within a homogeneous population and when the correlation coefficient cycles through values from $0 \rightarrow 0.9$, the bias from the subject-level data analyses with all three statistical methods are almost identical. This is, however, not the case for a heterogeneous population. In a heterogeneous population, three different statistical methods (the M-H method, the CLR method, and the GEE method) with the subject-level analyses produce higher bias as the correlation coefficient increases from $0 \rightarrow 0.9$.

When the event-level statistical analyses are conducted, the bias from the M-H method and the CLR method appear more likely to be affected by the propensities of exposure and the outcome of interest rather than the correlation among the repeated outcome events. For example, the bias decreases from 12.1% in Table 5.2.1(a) (where the study population is a homogeneous population) $\rightarrow$ 5.8% in Table 5.2.3(a) (where the study population is a heterogeneous population) while the other design parameters hold the same ($\rho=0$, $N=100$, $OR=10$).

In addition, when comparing the results presented in Tables 5.2.1(a, b and c), Tables 5.2.2(a, b and c) and Tables 5.2.3(a, b and c), we can see that, when $N = 100$, the biases from the event-level data analyses with both the M-H method and the CLR method are relatively stable ($12.1\% \rightarrow 11.4\% \rightarrow 11.5\%$, $7.7\% \rightarrow 7.9\% \rightarrow 11.3\%$ and $5.8\% \rightarrow 6.7\% \rightarrow 7.5\%$).

- <u>The propensities of exposure and the outcome (2/2 instances per year) and the correlation coefficient between these two study groups are the same in the following</u>

individual tables---**Results from each individual Tables 5.2.1(a, b and c); 5.2.2(a, b and c); 5.2.3(a, b and c)**

With the same size of the hazard ratio, the M-H method and the CLR method with the event-level data analyses produce numerically almost identical biases (identical to the second decimal point), particularly when the hazard ratio is fixed at a value between 2 and 10. When the hazard ratio is set to the null value, however, the biases from these two statistical methods change irregularly. The change in sample size from 30 $\rightarrow$ 50 $\rightarrow$ 100, however, does not bring a material change for the bias.

5.3 Mean squared error for the estimators of the log odds ratio

SUMMARY OF THE DETAILED RESULTS FROM INDIVIDUAL TABLES

- The propensities of exposure and the outcome between these two study groups are 2/2 instances per year, while the correlation coefficient varies the fastest from 0 $\rightarrow$ 0.5 $\rightarrow$ 0.9---**Results from Tables 5.3.1(a, b and c)**

1. As stated previously, when the hazard ratio is assigned a value between 1 and 10, the MSEs from all the eight estimators are almost identical to the second decimal point while cycling through the correlation coefficient from 0 $\rightarrow$ 0.5 $\rightarrow$ 0.9. When the hazard ratio is fixed at a value greater than 1, the MSEs from the M-H method and the CLR method with the event-level data analyses are smaller than the others. For example, the results from Table 5.3.1(a) show that: when $\rho = 0$, $N = 30$, $OR = 10$, the MSE from the overall crude M-H method is 5 times (.248 vs. .048) higher than that from the event-level data analysis. When $\rho = 0$ $N = 30$, $OR = 10$, the MSE from the CLR method with the

subject-level data analysis is 4 times (.229 vs. .048) higher than that from the event-level data analysis.

When the hazard ratio is set at the null value, as shown in Figure 5.3.4.1, the MSEs from the M-H method and the CLR method with the event-level data analyses are largest at various combinations of the sample size and the correlation coefficient. For example, the results from Table 5.3.1(a) show that: when $\rho = 0,\ N = 30,\ OR = 1$, the MSE from the overall crude M-H method is smaller (.049 vs. .059) than that from the event-level data analysis; when $\rho = 0\ N = 30,\ OR = 1$, the MSE from the CLR method with the subject-level data analysis is also smaller (.050 vs. .059) than that from the event-level data analysis.

2. When the hazard ratio is set at the null value, the subject-level GEE method with an exchangeable w.c.s. yields the smallest MSE. When the hazard ratio is assigned a value greater than 1, however, the subject-level GEE method with an exchangeable w.c.s. produces the highest values in MSE.

3. When the hazard ratio is assigned a value between 1 and 10, as shown in Figure 5.3.4.1, with the same size of the correlation coefficient, the MSEs from all the eight estimators decrease as the sample size increases from $30 \rightarrow 50 \rightarrow 100$.

4. The results in each individual Table 5.3.1(a), Table 5.3.1(b) and Table 5.3.1(c) (Figure 5.3.4.1 to Figure 5.3.4.4) show that, with the same sample size and correlation coefficient, the MSEs from all the eight estimators increase while cycling through the hazard ratio from $1 \rightarrow 2 \rightarrow 5 \rightarrow 10$.

5. As shown in each individual Table 5.3.1(a), Table 5.3.1(b) and Table 5.3.1(c) (Figure 5.3.4.5 to Figure 5.3.4.7), with the same sample size and hazard ratio, the MSEs from all the eight estimators do not show a material change while cycling through the correlation coefficient from 0 $\rightarrow$ 0.5 $\rightarrow$ 0.9. As presented previously, with the same values of the correlation coefficient and the hazard ratio, the MSEs from the eight estimators decrease slightly as the sample size increases from 30 $\rightarrow$ 50 $\rightarrow$ 100.

- The propensities of exposure and the outcome between these two study groups are 10/2 instances per year, while the correlation coefficient varies the fastest from 0 $\rightarrow$ 0.5 $\rightarrow$ 0.9---**Results from Tables 5.3.2(a, b and c)**

1. When the hazard ratio is assigned a value greater than 1, the MSEs from the M-H method and the CLR method with the event-level data analyses are smaller than the other six estimators. When the hazard ratio is set at the null value, as shown in Figure 5.3.5.1, the MSEs from the M-H method and the CLR method with the event-level data analyses are largest at various combinations of the sample size and the correlation coefficient.

2. When the hazard ratio is set at the null value, the subject-level GEE method with an exchangeable w.c.s. yields the smallest MSE. When the hazard ratio is assigned a value greater than 1, however, this method produces the highest values in MSE.

3. As shown in Tables 5.3.2(a, b and c), except for the M-H method and the CLR method with the event-level data analyses, the MSEs from the overall crude M-H method and all three statistical methods (the M-H method, the CLR method, and the GEE method) with the subject-level data analyses increase slightly as the correlation coefficient increases from 0 $\rightarrow$ 0.9. For example, in Table 5.3.2(a), Table 5.3.2(b) and

Table 5.3.2(c), when $OR = 5,\ N = 50,$ it is clear that the MSEs from the subject-level M-H method show a slight increase from $0.038 \rightarrow 0.041 \rightarrow 0.047$ as the correlation coefficient increases from $0 \rightarrow 0.5 \rightarrow 0.9$.

4. When the hazard ratio is fixed at the null value, as shown in Figure 5.3.5.1, the MSEs from all the eight estimators increase while cycling through the correlation coefficient from $0 \rightarrow 0.5 \rightarrow 0.9$. It can also be seen in the same figure that within the same correlation coefficient all the MSEs decrease slightly as the sample size increases from $30 \rightarrow 50 \rightarrow 100$.

5. The results in each individual Table 5.3.2(a), Table 5.3.2(b) and Table 5.3.2(c) (Figure 5.3.5.1 to Figure 5.3.5.4) show that, with the same sample size and the correlation coefficient, the MSEs from all the eight estimators increase while cycling through the hazard ratio from $1 \rightarrow 2 \rightarrow 5 \rightarrow 10$.

6. As shown in Table 5.3.2(a), Table 5.3.2(b) and Table 5.3.2(c) (Figure 5.3.5.5 to Figure 5.3.5.7), with the same sample size and the hazard ratio, the MSEs from all the eight estimators increase while cycling through the correlation coefficient from $0 \rightarrow 0.5 \rightarrow 0.9$. Likewise, with the same correlation coefficient and hazard ratio, the MSEs from all decrease slightly as the sample size increases from $30 \rightarrow 50 \rightarrow 100$.

- The propensities of exposure and the outcome between these two study groups are 20/2 instances per year, while the correlation coefficient varies fastest from $0 \rightarrow 0.5 \rightarrow 0.9$---**Results from Tables 5.3.3(a, b and c)**

Almost the same conclusions can be drawn for the results presented in Tables 5.3.3 (a, b, and c) as we summarized for Tables 5.3.2 (a, b, and c) presented above. When the hazard

ratio is set to a value greater than 1, however, the overall crude M-H method and the GEE method (including the subject-level and the event-level) with an independent w.c.s. produce the largest MSEs while cycling through the correlation coefficient from $0 \rightarrow 0.5 \rightarrow 0.9$.

The MSEs from the event-level or the subject-level M-H method and the CLR method and the subject-level GEE method with an exchangeable w.c.s. decrease while cycling through the propensities of exposure and the outcome of interest between these two study groups. For example, the MSEs from the CLR method with the event-level data analyses in Tables 5.3.1(a) $\rightarrow$5.3.2(a) $\rightarrow$5.3.3(a) are .048 $\rightarrow$.009 $\rightarrow$.005, when $\rho = 0,\ N = 30,\ OR = 10$ and $I = 2 \rightarrow 10 \rightarrow 20$

The MSEs from the overall crude M-H method and the event-level or the subject-level GEE method with an independent w.c.s. show irregular changes according to the different combinations of the hazard ratio and the propensities of exposure and the outcome of interest between these two study groups. For example, the MSEs from the overall crude M-H method in Tables 5.3.1(a) $\rightarrow$5.3.2(a) $\rightarrow$5.3.3(a) are .248 $\rightarrow$.129 $\rightarrow$.167, when $\rho = 0,\ N = 30,\ OR = 10$ and $I = 2 \rightarrow 10 \rightarrow 20$.

In summary, based on the MSE criterion, the smaller the MSE, the better the estimator performs. We can conclude that the M-H method and the CLR method with the *event-level* data analyses are the best in the various settings.

5.4 Empirical variance and model-based variance

SUMMARY OF THE DETAILED RESULTS FROM INDIVIDUAL TABLES

- The propensities of exposure and the outcome between these two study groups are 2/2 instances per year, while the correlation coefficient varies the fastest from 0 $\rightarrow$ 0.5 $\rightarrow$ 0.9---**Results from Tables 5.4.1(a, b and c)**

1. The overall crude M-H method and all three different statistical methods with the subject-level data analyses produce smaller empirical variances than those from the M-H method and the CLR method with the event-level data analyses. This finding could be explained by the fact that, at the subject-level data analyses, the four cells in a 2×2 table were artificially inflated by aggregating the repeated outcome events. Thus, the subject-level data analyses approach resulted in much larger denominators (a, b, c, d) in the Woolf's formula than those from the event-level data analyses.

2. The subject-level GEE method with an exchangeable w.c.s. yields a reasonable estimate of empirical variance of the odds ratio only when the hazard ratio is set at the null value. In addition, the estimated empirical variance from this estimator decreases as the sample size increases. The empirical variance becomes unstable when the sample size is small ($N \le 50$). For example, with a small sample size $(N = 30, \log OR = 2.303)$, the empirical variance changes from 0.034 ($\rho = 0$) $\rightarrow$ 0.0281 ($\rho = 0.5$) $\rightarrow$ 0.0268 ($\rho = 0.9$); With a medium sample size $(N = 50, \log OR = 2.303)$, the empirical variance changes from 0.0191 ($\rho = 0$) $\rightarrow$ 0.0178 ($\rho = 0.5$) $\rightarrow$ 0.0179 ($\rho = 0.9$); With a large sample size $(N = 100, \log OR = 2.303)$, however, the empirical variance changes slightly from 0.0091 ($\rho = 0$) $\rightarrow$ 0.0096 ($\rho = 0.5$) $\rightarrow$ 0.0102 ($\rho = 0.9$). As shown in Tables 5.4.1(a, b and c), the ratio of the empirical variance to model-based variance for this estimator is

substantially greater than 1, which implies that the model-based variances from the subject-level GEE method with an exchangeable w.c.s. are inaccurate.

- The propensities of exposure and the outcome between these two study groups are 10 (or 20)/2 instances per year, while the correlation coefficient varies the fastest from 0 $\rightarrow$ 0.5 $\rightarrow$ 0.9---**Results from Tables 5.4.2(a, b and c) and Tables 5.4.3(a, b and c)**

Almost the same conclusions can be drawn for the results presented in Tables 5.4.2 (a, b, and c) and Table 5.4.3 (a, b and c) as we summarized for Tables 5.4.1 (a, b, and c) presented above. When comparing the results across these tables, however, we can see that the overall crude M-H method and the GEE method with an independent w.c.s. yield the largest estimates of the empirical variance, and the ratio between the empirical variance and the model-based variance slightly increases as the correlation coefficient increases.

Results from a cross examination of Table 5.4.1(a), Table 5.4.1(b) and Table 5.4.1(c)

The empirical variances from all eight estimators are likely to be more pronounced as the correlation coefficient increases, when the sample size and the hazard ratio are small. The correlation coefficient appears to play an important role in the estimation of the empirical variance. Nevertheless, as the sample size ($N = 30 \rightarrow 100$) and the hazard ratio ($OR = 1 \rightarrow 10$) increase, the empirical variances from all the eight estimators become fairly stable. In these situations, it seems that the sample size and the hazard ratio play a more important role in the variance estimation than the correlation coefficient.

Results from a cross examination of Table 5.4.2(a), Table 5.4.2(b) and Table 5.4.2(c); Table 5.4.3(a), Table 5.4.3(b) and Table 5.4.3(c)

Almost the same conclusions can be drawn for the results presented in a cross examination of Tables 5.4.2 (a, b, and c) and Tables 5.4.3(a, b and c) as we summarized for Tables 5.4.1 (a, b, and c). The empirical variances from all the eight estimators increase as the correlation coefficient increases from $0 \rightarrow 0.5 \rightarrow 0.9$.

- The propensities of exposure and the outcome cycle through from $2 \rightarrow 10 \rightarrow 20$ instances per year between these two study groups---**Results from a cross examination of Table 5.4.1(a), Table 5.4.2(a) and Table 5.4.3(a); Table 5.4.1(b), Table 5.4.2(b) and Table 5.4.3(b); Table 5.4.1(a), Table 5.4.2(c) and Table 5.4.3(c)**

It seems that the ratios of the empirical variance to model–based variance from all three different statistical methods (the M-H method, the CLR method and the GEE method) with the crude overall and the subject-level data analyses are a function of the propensities of exposure and the outcome of interest between these two study groups and the correlation coefficient among the multiple outcome events. The ratios from the M-H method and the CLR method with the event-level data analyses, however, are fairly stable regardless of the different configurations of the intensities of exposure and outcome of interest and the correlation among the multiple outcome events. For example, the ratios between the empirical variance and the model-based variance from the overall crude M-H method in Tables 5.4.1(a) $\rightarrow$ 5.4.2(a) $\rightarrow$ 5.4.3(a) are $1.08 \rightarrow 2.78 \rightarrow 14.5$, when $\rho = 0,\ N = 30,\ OR = 10$ and $I = 2 \rightarrow 10 \rightarrow 20$. However, the ratios between the empirical variance and the model-based variance from the event-level M-H method in

Tables 5.4.1(a) $\rightarrow$ 5.4.2(a) $\rightarrow$ 5.4.3(a) are 1.08 $\rightarrow$ .91 $\rightarrow$ .92, when $\rho = 0,\ N = 30,\ OR = 10$ and $I = 2 \rightarrow 10 \rightarrow 20$.

From Table 5.4.1(a) to Table 5.4.3(c) (9 tables), we can conclude that the model-based variances from the M-H method and the CLR method with the event-level data analyses are almost identical to the corresponding empirical variances. The model-based variances from these two estimators are accurate. On the other hand, the model-based variances from the other six estimators lack the abilities to reflect real sampling variance.

In conclusion, the *event-level* M-H method and the CLR method can provide less biased estimates of the underlying odds ratio with a slight increase in the empirical variance, when compared with the other six estimators. As long as the *event-level* of data analysis is used, the M-H method and the CLR method with the event-level data analyses can produce numerically better estimates of the underlying odds ratios. On the other hand, the other six estimators are not sufficient enough to control for the bias. The model-based variances from these six estimators are inaccurate and appear to be more likely affected by the correlation among the repeated outcome events in the same subject.