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# Effectively Combining Independent 2 x 2 Tables for Valid Inferences in Meta Analysis with all Available Data but no Artificial Continuity Corrections for Studies with Zero Events and its Application to the Analysis of Rosiglitazone's Cardiovascular Disease Related Event Data

Lu Tian* Tianxi Cai† Nikita Piankov‡

Pierre-Yves Cremieux** L. J. Wei††

*Northwestern University, lutian@northwestern.edu

†Harvard University, tcai@hsph.harvard.edu

‡Analysis Group, npiankov@analysisgroup.com

**Analysis Group, pcremieux@analysisgroup.com

††Harvard University, wei@hsph.harvard.edu

# Effectively combining independent $2 \times 2$ tables for valid inferences in meta analysis with all available data but no artificial continuity corrections for studies with zero events and its application to the analysis of Rosiglitazone's Cardiovascular disease related event data

**Authors:** Lu Tian[1], Tianxi Cai[2], Nikita Piankov[3], Pierre-Yves Cremieux[3,4] and L. J. Wei[2]

**Affiliations:**

[1] *Department of Preventive Medicine, Northwestern University, Chicago IL*

[2] *Department of Biostatistics, Harvard University, Boston, MA*

[3] *Analysis Group, Boston MA*

[4] *Department of Economics, University of Quebec at Montreal, Montreal, Quebec, Canada*

## Abstract

Recently meta analysis has been widely utilized to combine information across comparative clinical studies for evaluating drug safety profile. The standard meta analysis procedures, based on large sample approximations, may give misleading or invalid results when the sample sizes of individual studies are not large or the total number of studies is small, or when the event rates are low. Moreover, when dealing with rather rare events, a substantial proportion of studies may not have any events of interest. Conventional methods either exclude such studies or add arbitrary positive values to the corresponding $2 \times 2$ tables in the analysis. In this article, we present a simple, effective procedure to make *valid* inferences about the parameter of interest with all available data without continuity corrections. We then use the procedure to analyze the data from 48 comparative trials involving Rosigliazone, a type 2 diabetes drug, with respect to its possible cardiovascular toxicity. The results are markedly different from those of the meta analysis reported in Nissen and Wolski[1]. For example, based on the data from entire 48 studies, the 95% confidence interval for the *risk difference* with respect to MI is $(-0.08, 0.38)$% (p-value=0.27) and the interval estimate with respect to CVD related death is $(-0.13, 0.23)$% ($p$-value=0.83). On the other hand, excluding studies which do not have any events of interest, Nissen and Wolski reported that for the *odds ratio* the corresponding intervals are $(1.03, 1.98)$ ($p$-value=0.03) for MI and $(0.98, 2.74)$ ($p$-value=0.06) for CVD death.



**Key words:** Meta analysis, Cardiovascular toxicity, Combining $2 \times 2$ tables, Continuity correction for zero events, Type 2 diabetes

## 1. Background

Meta analysis provides a framework for combining information across a number of independent, but "similar" clinical studies to make inferences about a common parameter[2,3]. For example, to compare two treatment groups with a binary outcome variable (either yes or no), the parameter of interest may be the risk difference, relative risk or odds ratio. Standard statistical procedures for combining study-specific estimates of such a parameter can be implemented with, for example, software in Review Manager (Update Software, Oxford) or commercial statistical package such as STATA (Stata Corp., College Station, Texas). Almost all existing methods rely on *large* sample approximations to the distributions of the combined point estimators. Such approximations may be rather inaccurate and lead to invalid conclusions when the individual study sample sizes are small, or the total number of studies is not large, or when the event rates are low[4]. Moreover, when the events of interest are very rare, often many studies which satisfy the entry criteria for the meta analysis do not have any events of interest. The standard procedures either apply continuity corrections to the studies with zero events or simply exclude these studies from the analysis[5,6,7]. For example, recently Nissen and Wolski performed a meta analysis to examine whether Rosiglitazone, a drug for treating type 2 diabetes mellitus, significantly increases the risk of myocardial infarction (MI) or cardiovascular disease (CVD) related death. Of 116 screened studies, 48 trials (not 42 as reported in their paper) satisfied the inclusion criteria for their analysis. There are 10 studies with zero MI events and 25 studies with zero CVD related deaths. Nissen and Wolski simply excluded those studies from their meta analysis. On the other hand, instead of excluding studies which do not have any events of interest, one may add an arbitrary value, for example, 0.5, to each cell of the corresponding $2 \times 2$ tables. Unfortunately, different continuity corrections may result in different conclusions about the contrast of two treatment groups[8].

In this article, under the fixed-effects modeling assumption, we present a simple procedure to construct *valid* confidence intervals for the parameter using all available data. The procedure only requires that for each study, *valid* individual study-specific confidence intervals for the parameter are available. The new proposal does not rely on the large sample approximation nor arbitrary continuity corrections to obtain interval estimates. For example, when combining multiple $2 \times 2$ tables, for each study, one may construct *exact* confidence intervals for the risk difference between two comparative groups, which are always available even when the study has zero events in both groups. Here, the coverage probability of an exact confidence interval is guaranteed to be no less than the pre-specified nominal level under any setting. Our procedure can then provide an overall *exact* interval estimate of the parameter by combining

these study-specific exact confidence intervals. We analyze the cardiovascular disease (CVD) related event data from 48 Rosiglitazone studies (see Table 1 for details) which satisfy the inclusion criteria in the meta analysis conducted by Nissen and Wolski.

## 2. Methods

Suppose that we are interested in making inferences about a parameter $\Delta$, for example, the risk difference between two treatment groups for the above diabetes studies with respect to MI incidences. To be specific, assume that we would like to construct a $(1-\alpha)$, for example, 0.95, one-sided confidence interval $(a, \infty)$ of $\Delta$ from the data of $n$ independent studies. For a given confidence level $\eta$ (for example, $\eta = 0.8$), there are $n$ study-specific one-sided $\eta$-level confidence intervals for the risk difference. Each interval is constructed based on the data only from its corresponding study. Now, let us pick up a value, say, zero and ask ourselves whether $\Delta = 0$ is the true value of the risk difference. If it is, by the definition of $\eta$-level confidence intervals, on average, 0 should belong to at least $100\eta\%$ of the above $n$ independent intervals. The decision on whether the interval $(a, \infty)$ should include zero can be made easily via a simple hypothesis testing procedure. That is, we test for a Bernoulli probability being at least $\eta$ with the sample size $n$ and a Type I error rate of $\alpha$. To this end, let $y_i = 1$, if $\Delta = 0$ belongs to the observed $\eta$ interval from the $i$th study, and $y_i = 0$, otherwise. Then, we include $\Delta = 0$ in $(a, \infty)$ if

$$t(\eta) = \sum_{i=1}^{n} w_i(y_i - \eta) \geq c, \tag{1}$$

where $w_i$ is a study specific positive weight, $c$ is chosen such that $\text{pr}(T(\eta) < c) \leq \alpha$,

$$T(\eta) = \sum_{i=1}^{n} w_i(B_i - \eta), \tag{2}$$

and $\{B_i, i = 1, \cdots, n\}$ are $n$ independent Bernoulli random variables with a "success" probability of $\eta$. We repeat this process with all other possible values for $\Delta$ and obtain the final $(1-\alpha)$ confidence interval $(a, \infty)$. Here, the weight $w_i$ may be the sample size for the $i$th study.

One may further improve the aforementioned interval estimate for $\Delta$ by utilizing multiple intervals with various levels of confidence from each study. Specifically, let $J_{ij} = (a_{ij}, \infty)$ denote the $\eta_j$-level one-sided confidence interval based on the $i$th study, for $j = 1, ..., K$. Without loss of generality, we assume that $0 < \eta_1 < \cdots < \eta_K < 1$ and $a_{i1} \geq \cdots \geq a_{iK}$. For any given $\Delta$, we would include $\Delta$ in the final combined

interval $(a, \infty)$ if

$$\sum_{j=1}^{K} \tilde{w}_j t(\eta_j) \geq d, \tag{3}$$

where $\tilde{w}_j$ is a positive weight for the $\eta_j$-level intervals, $t(\eta_j)$ is obtained by replacing $y_i$ and $\eta$ in (1) with $y_{ij}$ and $\eta_j$, respectively. Here, the critical value $d$ is chosen such that

$$\text{pr}\{\sum_{j=1}^{K} \tilde{w}_j T(\eta_j) < d\} \leq \alpha, \tag{4}$$

where $T(\eta_i)$ is obtained by replacing $B_i$ and $\eta$ in (2) by $B_{ij}$ and $\eta_j$, respectively, and $\{(B_{i1}, \cdots, B_{iK})', i = 1, \cdots, n\}$ are $n$ independent random vectors whose components are correlated Bernoulli variables such that $B_{i1} \leq B_{i2} \leq \cdots \leq B_{iK}$ and $\text{pr}(B_{ij} = 1) = \eta_j$. We repeat the above process for all possible values for $\Delta$ and obtain the final interval $(a, \infty)$. In the appendix, we show that if the coverage levels of all intervals $J_{ij}, i = 1, \cdots, n$ are at least $\eta_j$, the coverage probability of the resulting interval $(a, \infty)$ is at least $(1 - \alpha)$. The choice of the weights $\{\tilde{w}_j\}$ for a linear combination of $K$ dependent test statistics such as (3) or (4) has been discussed extensively via the large sample theory[9,10,11]. For the present case, one may let $\tilde{w}_j$ be proportional to the inverse of the variance of $T(\eta_j)$ in (4), which is, $\{\eta_j(1 - \eta_j)\}^{-1}$.

Similarly, we can obtain combined $(1 - \alpha)$ one-sided interval $(-\infty, b)$ based on the corresponding one-sided study-specific intervals. It follows that $(a, b)$ would be a $(1 - 2\alpha)$ two-sided interval for the risk difference.

## 3. Results

We use the above procedure to quantify the difference between Rosiglitazone and other diabetes drugs with respect to the risk of MI and the risk of CVD related death based on data from the 48 studies listed in Table 1. In Nissen and Wolski, 48 randomized comparative studies met their pre-defined inclusion criteria. However, six studies did not report any MI or death (Studies #43-48 in Table 1). Therefore only 42 studies were considered in the Nissen and Wolski meta analysis (see their Table 1) . We are able to confirm that there are no CVD related events for those six studies from the GlaxoSmithKline clinical trial registry website (http://ctr.gsk.co.uk/welcome.asp). It is important to note that Nissen and Wolski did not utilize the information from studies which reported zero events of interest. Thus their analysis only included 38 studies for the MI endpoint and 23 studies for the CVD related mortality. On the other hand, our analysis includes data from all 48 studies as listed in Table 1.

Using large-sample-approximation based procedures for meta analysis, with respect to MI, Nissen and

Wolski obtained a 95% confidence interval of $(1.03, 1.98)$ with p-value of 0.03 for the odds ratio between Rosiglitazone and the control arm (in favor of the control). With respect to mortality, the 95% confidence interval for odds ratio is $(0.98, 2.74)$ with p-value of 0.06, an almost statistically significant result in favor of the control arm.

Unless we have prior information about the underlying event rates, it is not clear how to utilize studies with zero events without arbitrary continuity corrections to obtain an over-all assessment for the odds ratio in meta analysis. On the other hand, we are able to use all data for making inference about the heuristically appealing risk difference as a measure of the treatment difference. To this end, we let $\Delta$ (Rosiglitazone minus control) be the risk difference in our analysis. We construct 95% confidence intervals for $\Delta$ based on the data from 48 studies via the procedure described in (1)-(4). Here, we let $\{\eta_k, k = 1, \cdots, 20\}$ be 20 equally spaced $\eta$-levels from 0.1 to 0.95. The cut-off point $d$ in (4) is determined by randomly generating 50,000 independent samples $\{(B_{i1}, \cdots, B_{iK}), i = 1, \cdots, n\}$. Moreover, for each study, the $\eta_j$-level confidence interval for the risk difference is obtained via the popular mid-$p$-value method, which has correct coverage level even when the underlying event rates for both arms are small or each study size is not large[12,13,14,15]. For comparison, we also obtain the corresponding 95% intervals based on the large sample approximation method, for example, the Mantel-Haenszel (MH) weighted confidence interval estimates for the risk difference. This method is recommended for practical usage when the event rates are low[16]. It is important to note that the large sample MH method either excludes studies which have no events or uses continuity corrections.

First, for the mortality endpoint, in Figure 1(a), we present a standard tree diagram in meta analysis. The bottom horizontal line (x-axis) gives possible values of the risk difference. There are 48 thin line segments above the x-axis, each of which is a 95% study-specific confidence interval for the risk difference constructed via the mid-$p$-value method. There are 25 studies, marked by $*$ besides the study ID, which have no CVD related deaths. The corresponding 25 confidence intervals are centered about zero with various lengths. The thick line segment right above the x-axis is the combined 95% confidence interval $(-0.13, 0.23)\%$ with $p$-value of 0.83. On the other hand, in Figure 1(b), each of 23 thin line segments is a 95% study-specific large sample confidence interval (we cannot obtain the standard large sample interval for a study with no events). Note that these intervals tend to be much shorter than their exact counterparts displayed in Figure 1(a). It is well known that the validity of these large sample interval estimates is questionable when the events are rare. As Nissen and Wolski did for the odds ratio, for comparison purposes, we also combine the data only from these 23 studies. The thick line segment right

above the x-axis is the resulting 95% MH final interval $(0.00, 0.31)\%$ with a $p$-value of 0.05. Since this interval estimate does not use information from 25 studies with no events, its validity for making inference about the risk difference is questionable. Now, if we use the commonly used continuity correction of 0.5 for those 25 studies with no events, the 95% MH interval is $(-0.02, 0.24)\%$, which is tighter than the above two. However, it is not clear that this estimate has the correct coverage level of 0.95.

For the MI endpoint, there are ten studies with no events. Similar to Figure 1(a), we present forty-eight 95% "exact" study-specific intervals in Figure 2(a). The final combined 95% interval denoted by the thick line segment right above the x-axis is $(-0.08, 0.38)\%$ with $p$-value of 0.27. Again, as in Nissen and Wolski, if we exclude ten studies which have no events and use the large sample interval estimation method (see Figure 2(b)), the final 95% MH interval is $(0.02, 0.42)\%$ with $p$-value of 0.03. Moreover, with the continuity correction of 0.5 and $n = 48$, the final 95% MH interval is $(0.01, 0.37)\%$. It is not clear this interval, which is slightly shorter than our exact interval, has correct coverage level of 0.95.

Note that based on our extensive numerical study, we find that the procedure gives quite stable interval estimates when we choose twenty evenly spaced confidence levels $\{\eta_i, i = 1, \cdots, K\}$ from 0.1 to 0.9.

## 4. Conclusion

Unlike the standard meta analysis procedures, the proposed simple method provides valid inferences about the parameter of interest under any fixed effects modeling setting, for instance, when the study sizes are not large, the number of studies is small, or the event rates are small. Moreover, it effectively utilizes the data from every study in the meta analysis without artificial imputation. The parameter of interest can be the odds ratio or the relative risk. Our procedure can also be utilized to handle cases beyond the classical $2 \times 2$ tables, for example, the outcome is the incidence rate or a continuous variable[17,18]. Using the proposed method to analyze 48 comparative trials involving Rosiglitazone, the results are markedly different from those recently presented in Nissen and Wolski for evaluating cardiovascular safety of type 2 diabetes drugs. The computer code for implementing the procedure is available at "http://biosun1.harvard.edu/ tcai/MetaCode.r".

## Appendix. Justification of Validity for the Final Combined Interval

Assume that the $n$ studies in our meta analysis are realizations of a random sample from a population whose distribution is generated by a random quantity $\Pi$. For example, for the $2 \times 2$ tables, $\Pi$ consists of $\Delta_0$ (the common, fixed, unknown, true risk difference between two event rates), the underlying event rate for the control arm (which may vary from study to study), and possibly the sample sizes for two arms of the study. Let $\pi_i$ be the realization of $\Pi$ for the $i$th study, $i = 1, 2, \cdots, n$. Note that one may further assume that the number $n$ of studies is a random component $N$ of $\Pi$. Given $\pi_i$, the data $X_i$ were generated for $i = 1, \cdots, n$. The one-sided confidence interval $J_{ij}$ (the one with a lower bound) for $\Delta_0$ satisfies the condition:

$$\text{pr}(\Delta_0 \in J_{ij} | \pi_i) \geq \eta_j, \quad j = 1, \cdots, K, \tag{A.1}$$

where the probability is generated by $X_i$. Now, given $\Delta$, we test the null hypothesis that $\Delta = \Delta_0$. Let $Y_{ij} = 1$, if $\Delta \in J_{ij}; 0$, otherwise. Consider the test statistic

$$T_0 = \sum_{i=1}^{n} \sum_{j=1}^{K} (Y_{ij} - \eta_j) w_i \tilde{w}_j.$$

A small observed value of $T_0$ suggests that $\Delta$ is not $\Delta_0$ and should not be in the final interval $(a, \infty)$. Since the confidence level of each individual confidence interval $J_{ij}$ may be larger than $\eta_j$, it is not clear how to derive the null distribution of $T_0$. Instead the critical value $d$ in (3) and (4) of Section 2 is derived from the test statistic

$$\tilde{T} = \sum_{i=1}^{n} \sum_{j=1}^{K} (B_{ij} - \eta_j) w_i \tilde{w}_j.$$

Note that if $\Delta = \Delta_0$, (A.1) implies

$$\text{pr}(Y_{ij} = 1 | \pi_i) \geq \eta_j, \quad j = 1, \cdots, K \tag{A.2}$$

Under this condition, we will show that

$$T_0 \gtrsim \tilde{T}, \tag{A.3}$$

where $\gtrsim$ means "stochastically greater than or equal to". It follows that conditional on any set of realizations $\{\pi_1, \cdots, \pi_n\}$, the Type I error rate of the test based on $T_0$ and the cutoff point $d$ is no larger than $\alpha$. That is, $\text{pr}(T_0 < d \mid \Delta = \Delta_0, \pi_1, \cdots, \pi_n) \leq \alpha$, where the probability is generated by $\{X_i, i = 1, \cdots, n\}$. This implies that $\text{pr}(T_0 < d \mid \Delta = \Delta_0) \leq \alpha$, where the probability is generated under the random pairs

$\{(X_i, \Pi_i), i = 1, \cdots, n\}$. Here, $X_i$ is random quantity associated with $\Pi_i$ and $\{\Pi_i\}$ is a random sample from the population $\Pi$. Again, one may generalize this by assuming that $n$ is a realization of $N$.

To show (A.3), first let $g(u_1, \cdots, u_K) = \sum_{j=1}^{K}(u_j - \eta_j)\tilde{w}_j$. Since for each individual study, the $K$ confidence intervals are nested, therefore, $g(y_{i1}, \cdots, y_{iK})$ or $g(B_{i1}, \cdots, B_{iK})$ can only assume $K+1$ possible distinct values:

$$\begin{aligned}
v_0 = &\quad (1-\eta_1)\tilde{w}_j + (1-\eta_2)\tilde{w}_2 + (1-\eta_3)\tilde{w}_3 + \cdots + (1-\eta_K)\tilde{w}_K,\\
v_1 = &\quad (0-\eta_1)\tilde{w}_j + (1-\eta_2)\tilde{w}_2 + (1-\eta_3)\tilde{w}_3 + \cdots + (1-\eta_K)\tilde{w}_K,\\
v_2 = &\quad (0-\eta_1)\tilde{w}_j + (0-\eta_2)\tilde{w}_2 + (1-\eta_3)\tilde{w}_3 + \cdots + (1-\eta_K)\tilde{w}_K,\\
&\vdots\\
v_K = &\quad (0-\eta_1)\tilde{w}_j + (0-\eta_2)\tilde{w}_2 + (0-\eta_3)\tilde{w}_3 + \cdots + (0-\eta_K)\tilde{w}_K,
\end{aligned}$$

where $y$ is the observed value of $Y$ and $v_0 > v_1 \cdots > v_K$. Furthermore, $g(y_{i1}, \cdots, y_{iK}) = v_s$ if and only if $y_{ij} = I(j > s)$. Similarly, $g(B_{i1}, \cdots, B_{iK}) = v_s$ if and only if $B_{ij} = I(j > s)$. It follows that for $v \in (v_s, v_{s-1}]$,

$$\text{pr}\{g(Y_{i1}, \cdots, Y_{iK}) \geq v\} = \text{pr}\{g(Y_{i1}, \cdots, Y_{iK}) \geq v_{s-1}\} = \text{pr}(Y_{is} = 1).$$

Under (A.2),

$$\text{pr}(Y_{is} = 1) \geq \eta_s = \text{pr}(B_{is} = 1) = \text{pr}\{g(B_{i1}, \cdots, B_{iK}) \geq v\}.$$

Consequently, $g(Y_{i1}, \cdots, Y_{iK}) \gtrsim g(B_{i1}, \cdots, B_{iK})$ and

$$T_0 = \sum_{i=1}^{n} g(Y_{i1}, \cdots, Y_{iK}\}w_i \gtrsim \sum_{i=1}^{n} g(B_{i1}, \cdots, B_{iK})w_i = \tilde{T}.$$

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Table 1. Data listing for 48 Rosiglitazone comparative studies

| ID | Study | Rosiglitazone Group | | | Control Group | | |
|---|---|---|---|---|---|---|---|
| | | No. of Patients | Myocardial Infarction | Cardiovascular death | No. of Patients | Myocardial Infarction | Cardiovascular death |
| | | | number | | | number | |
| 1 | 49653/011 | 357 | 2 | 1 | 176 | 0 | 0 |
| 2 | 49653/020 | 391 | 2 | 0 | 207 | 1 | 0 |
| 3 | 49653/024 | 774 | 1 | 0 | 185 | 1 | 0 |
| 4 | 49653/093 | 213 | 0 | 0 | 109 | 1 | 0 |
| 5 | 49653/094 | 232 | 1 | 1 | 116 | 0 | 0 |
| 6 | 100684 | 43 | 0 | 0 | 47 | 1 | 0 |
| 7 | 49653/143 | 121 | 1 | 0 | 124 | 0 | 0 |
| 8 | 49653/211 | 110 | 5 | 3 | 114 | 2 | 2 |
| 9 | 49653/284 | 382 | 1 | 0 | 384 | 0 | 0 |
| 10 | 712753/008 | 284 | 1 | 0 | 135 | 0 | 0 |
| 11 | AVM100264 | 294 | 0 | 2 | 302 | 1 | 1 |
| 12 | BRL49653C/185 | 563 | 2 | 0 | 142 | 0 | 0 |
| 13 | BRL49653/334 | 278 | 2 | 0 | 279 | 1 | 1 |
| 14 | BRL49653/347 | 418 | 2 | 0 | 212 | 0 | 0 |
| 15 | 49653/015 | 395 | 2 | 2 | 198 | 1 | 0 |
| 16 | 49653/079 | 203 | 1 | 1 | 106 | 1 | 1 |
| 17 | 49653/080 | 104 | 1 | 0 | 99 | 2 | 0 |
| 18 | 49653/082 | 212 | 2 | 1 | 107 | 0 | 0 |
| 19 | 49653/085 | 138 | 3 | 1 | 139 | 1 | 0 |
| 20 | 49653/095 | 196 | 0 | 1 | 96 | 0 | 0 |
| 21 | 49653/097 | 122 | 0 | 0 | 120 | 1 | 0 |
| 22 | 49653/125 | 175 | 0 | 0 | 173 | 1 | 0 |
| 23 | 49653/127 | 56 | 1 | 0 | 58 | 0 | 0 |
| 24 | 49653/128 | 39 | 1 | 0 | 38 | 0 | 0 |
| 25 | 49653/134 | 561 | 0 | 1 | 276 | 2 | 0 |
| 26 | 49653/135 | 116 | 2 | 2 | 111 | 3 | 1 |
| 27 | 49653/136 | 148 | 1 | 2 | 143 | 0 | 0 |
| 28 | 49653/145 | 231 | 1 | 1 | 242 | 0 | 0 |
| 29 | 49653/147 | 89 | 1 | 0 | 88 | 0 | 0 |
| 30 | 49653/162 | 168 | 1 | 1 | 172 | 0 | 0 |
| 31 | 49653/234 | 116 | 0 | 0 | 61 | 0 | 0 |
| 32 | 49653/330 | 1172 | 1 | 1 | 377 | 0 | 0 |
| 33 | 49653/331 | 706 | 0 | 1 | 325 | 0 | 0 |
| 34 | 49653/137 | 204 | 1 | 0 | 185 | 2 | 1 |
| 35 | SB-712753/002 | 288 | 1 | 1 | 280 | 0 | 0 |
| 36 | SB-712753/003 | 254 | 1 | 0 | 272 | 0 | 0 |
| 37 | SB-712753/007 | 314 | 1 | 0 | 154 | 0 | 0 |
| 38 | SB-712753/009 | 162 | 0 | 0 | 160 | 0 | 0 |
| 39 | 49653/132 | 442 | 1 | 1 | 112 | 0 | 0 |
| 40 | AVA100193 | 394 | 1 | 1 | 124 | 0 | 0 |
| 41 | DREAM | 2635 | 15 | 12 | 2634 | 9 | 10 |
| 42 | ADOPT | 1456 | 27 | 2 | 2895 | 41 | 5 |
| 43 | 49653/044* | 101 | 0 | 0 | 51 | 0 | 0 |
| 44 | 49653/096* | 232 | 0 | 0 | 115 | 0 | 0 |
| 45 | 49653/282* | 70 | 0 | 0 | 75 | 0 | 0 |
| 46 | 49653/369* | 25 | 0 | 0 | 24 | 0 | 0 |
| 47 | 49653/325* | 196 | 0 | 0 | 195 | 0 | 0 |
| 48 | 797620/004* | 676 | 0 | 0 | 225 | 0 | 0 |

* : Not reported in Table 1 of Nissen and Wolski (2007)

Figure 1. 95% confidence intervals of the risk difference for CVD death (Rosiglitazone minus control) with 48 studies listed in Table 1
( Small circles are the observed risk differences)

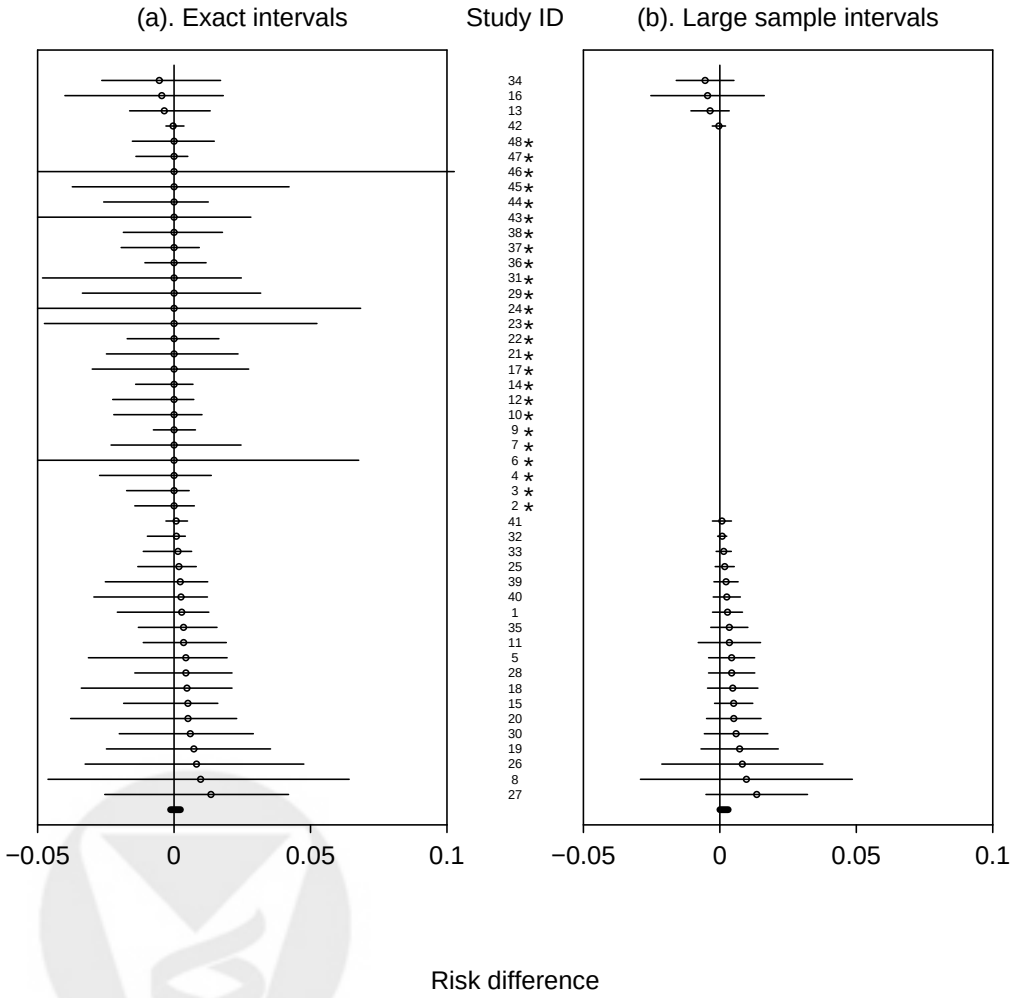

Figure 2. 95% confidence intervals of the risk difference for MI (Rosiglitazone minus control) with 48 studies listed in Table 1
( Small circles are the observed risk differences)