

An Efficient Numerical Algorithm for Exact Inference in Meta Analysis

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ARTICLE HISTORY

Compiled April 5, 2017

ABSTRACT

The performance of commonly used asymptotic inference procedures for the random effects model used in meta analysis relies on the number of studies. When the number of studies is moderate or small, the exact inference procedure is more reliable than the asymptotic counterparts. However, the related numerical computation may be demanding and an obstacle of routine use of the exact method. In this paper, we proposed a novel numerical algorithm for constructing the exact 95% confidence interval of the location parameter in the random effects model. The algorithm is much faster than the naive method and may greatly facilitate the use of the more appropriate exact inference procedure in meta analysis. Numerical studies and real data examples are used to illustrate the advantage of the proposed method.

KEYWORDS

Meta analysis; exact inference; random effects model.

1. Introduction

Meta analysis is often used to combine evidence from multiple studies in order to make more informative statistical inference on the association of interest. Oftentimes, the association of interest is summarized by a single parameter, which, for example, can be the mean difference between two groups or hazard ratio measuring the benefit of a new treatment on patient's survival. In a typical meta analysis, the point estimator of this parameter and associated precision measure such as the standard error or confidence interval are available for a group of relevant studies. Thus, the analytical goal is to construct a more accurate estimator of the parameter of interest by combining the observed estimators from those studies. The statistical model used to construct such a combination can be classified into two classes: the fixed effects model and random effects model [1,2]. For the former, the point estimator of each study estimates a study-specific population parameter, which is constant across different studies. For the latter, the population parameters from different studies are not necessarily identical due to, for example, variations of employed intervention and study population under investigation. Normally, the study-specific population parameters are assumed to follow an unknown random distribution, whose center becomes the parameter of the

primary interest in the meta analysis. Clearly, the random effects model degenerates into the fixed effects model, when the distribution of the study-specific population parameter concentrates on a single mass point. The simplest random effects model assume that the population parameters from each study follow a normal distribution, i.e.,

$$Y_i|\mu_i \sim N(\mu_i, \sigma_i^2)$$

where observed data consist of $(Y_i, \sigma_i), i = 1, \dots, K$, Y_i is the point estimator of μ_i in the i th study, σ_i is the corresponding standard error and μ_i is the population parameter to be estimated at the same study. The random effects model further assumes that

$$\mu_1, \dots, \mu_K \sim N(\mu_0, \tau_0^2),$$

where μ_0 is the parameter of interest. Various methods have been proposed to estimate μ_0 [3,4]. DL method is the earliest and probably the most popular choice in practice [3]. DL method is essentially a two-step procedure: estimate τ_0^2 first via a simple moment estimator and then construct the optimal linear combination of Y_i to estimate μ_0 . The weights used in the optimal linear combination depend on the estimator of τ_0^2 obtained at the first step. When K , the number of studies goes to infinity, DL estimator is the most efficient estimator of μ_0 and the corresponding 95% confidence interval has a proper coverage level of μ_0 . Unfortunately, K is often fairly small in practice and the optimality and even the validity of the DL method becomes questionable. For example, it is well known that the confidence interval constructed using DL method can severely undercover the true parameter when K is too small [5,6]. A series of methods have been proposed to correct this problem. However, the proposed solutions are either pretty ad-hoc, such as approximating the distribution of the combined estimator using the wide-tailed t -distribution rather than the normal distribution, or still rely on asymptotic approximation requiring a large K , such as the higher order asymptotic inference based on the profile likelihood function of μ_0 . More recently, Liu et al. have proposed a class of exact inference procedure, whose validity doesn't depend on the number of studies [7]. While the exact method is valid even for small or moderate K , the necessary computation using brute force can be quite cumbersome and slow. The purpose of the current paper is to propose an efficient numerical algorithm for implementing the aforementioned exact method.

2. Method

2.1. Exact Confidence Interval of μ_0

Under the random effects model,

$$Y_i \sim N(\mu_0, \sigma_i^2 + \tau_0^2), i = 1, \dots, K,$$

and we are interested in constructing the 95% exact confidence interval of the location parameter μ_0 based on the observed data $(Y_i, \sigma_i), i = 1, \dots, K$.

To this end, we may consider a simple test statistics

$$T(\mu) = \sum_{i=1}^K \frac{\text{sign}(Y_i - \mu)}{\hat{\sigma}_i(\mu)},$$

where $\hat{\sigma}_i^2(\mu) = \sigma_i^2 + \max\left(0, K^{-1} \sum_{i=1}^K \{(Y_i - \mu)^2 - \sigma_i^2\}\right)$. We plan to construct a 95% confidence interval by inverting an exact test based on $T(\mu)$ for testing the null hypothesis $H_0 : \mu = \mu_0$. To this end, we need to find the 2.5 and 97.5 percentiles of the null distribution of $T(\mu)$. Specifically, let the 2.5 and 97.5 percentiles be denoted by $c_L(\mu)$ and $c_U(\mu)$, respectively. The statistical significance level for testing $\mu_0 = \mu$ can then be determined by comparing $c_L(\mu)$ and $c_U(\mu)$ with the observed value of $T(\mu)$. The 95% confidence interval of μ_0 consists all μ s at which we can't reject $H_0 : \mu_0 = \mu$ at the significance level of 0.05. The overall algorithm to construct the 95% exact confidence interval can be summarized as following:

- (1) Consider the grid points μ_1, \dots, μ_m over the potential range of μ_0 .
- (2) For $j = 1, \dots, m$
 - Calculate $T(\mu_j)$
 - Calculate $c_L(\mu_j)$ and $c_U(\mu_j)$
- (3) The 95% confidence interval for μ_0 is

$$\left(\min \left\{ \mu_j \mid T(\mu_j) < c_U(\mu_j) \right\}, \max \left\{ \mu_j \mid T(\mu_j) > c_L(\mu_j) \right\} \right)$$

Note that under the null hypothesis $H_0 : \mu_0 = \mu$,

$$\text{sign}(Y_i - \mu) \perp |Y_i - \mu|, i = 1, \dots, K$$

and thus the conditional distribution

$$T(\mu) \mid \{\hat{\sigma}_i^2(\mu), i = 1, \dots, K\} \sim \sum_{i=1}^K \frac{V_i}{\hat{\sigma}_i(\mu)},$$

where $V_i, i = 1, \dots, K$ are K i.i.d random variables and $V_i = 1$ or -1 with equal probability.

The choice of the test statistics is not unique. For example, one may also consider

$$T(\mu) = \sum_{i=1}^K \frac{(Y_i - \mu)}{\hat{\sigma}_i^2(\mu)} \quad \text{or} \quad \sum_{i=1}^K \left(\Phi \left\{ \frac{Y_i - \mu}{\hat{\sigma}_i(\mu)} \right\} - \frac{1}{2} \right),$$

where $\Phi(\cdot)$ is the cumulative distribution function of the standard normal. The latter is tightly related to the robust testing procedure proposed in [8]. In general, the test statistics can be written in the form of

$$T(\mu) = \sum_{i=1}^K g\{Y_i - \mu, \hat{\sigma}_i(\mu)\}$$

for a given bivariate function $g(x, y)$ such that $g(-x, y) = -g(x, y)$. Under the null

hypothesis, the distribution of $T(\mu)$ conditional on $\{|Y_i - \mu|, i = 1, \dots, K\}$ is the same as that of

$$T_{\mathbf{V}}(\mu) = \sum_{i=1}^K V_i g\{|Y_i - \mu|, \hat{\sigma}_i(\mu)\} = \sum_{i=1}^K V_i w_i(\mu),$$

where $w_i(\mu) = g\{|Y_i - \mu|, \hat{\sigma}_i(\mu)\}$. Note that the transformed random variable

$$\tilde{T}(\mu) = \frac{1}{2} \left\{ T_{\mathbf{V}}(\mu) + \sum_{i=1}^K w_i(\mu) \right\} = \sum_{V_i > 0} w_i(\mu)$$

takes 2^K (may have ties in special settings) values with equal probability. Therefore, finding the 2.5% percentile of $T_{\mathbf{V}}(\mu)$, $c_L(\mu)$, is equivalent to identifying the $[2^K \times 0.025]$ th smallest element of these 2^K values of $\tilde{T}(\mu)$. Here, $[x]$ represents the largest integer no greater than x . This can be achieved by sorting all 2^K values from the smallest to the biggest and finding the corresponding order statistics. However, when K is big, the computational burden can be heavy. Since we need to repeat the test for many different μ s to construct the confidence interval, it is important to have a more efficient algorithm identifying $c_L(\mu)$ and $c_U(\mu)$.

2.2. Efficient Algorithm to Find $c_L(\mu)$ and $c_U(\mu)$

In this section, we propose a fast algorithm to find the appropriate cut off values. To this end, define the set

$$\Omega(\mathbf{w}_K) = \left\{ \sum_{i \in \mathcal{N}} w_i \mid \mathcal{N} \subset \{1, 2, \dots, K\} \right\}$$

containing 2^K elements, where $\mathbf{w}_K = (w_1, \dots, w_K)'$, $w_1, \dots, w_K > 0$ and \mathcal{N} traverses all the 2^K subsets of $\{1, \dots, K\}$. Our goal is finding the $[2^K \times 0.025]$ th smallest element of $\Omega(\mathbf{w}_K)$.

The key observation to design such an efficient algorithm is that we do not need to compute all 2^K values in $\Omega(\mathbf{w}_K)$, if we are only interested in finding the $[2^K \times 0.025]$ th smallest value. To illustrate this, consider a simple case, where $K = 8$ and we want to find the 6th smallest value of the $2^8 = 256$ elements in $\Omega(\mathbf{w}_K)$. Without the loss of generality, we assume that

$$w_K > \dots > w_1 > 0. \quad (1)$$

We don't need to compute the value of $w_2 + w_3$, since it is always ≥ 0 , $w_1, w_2, w_3, w_1 + w_2, w_1 + w_3$ and $w_2 + w_3$, already seven elements from $\Omega(\mathbf{w}_8)$, and can't be the 6th smallest element we are looking for. Similarly, we don't need to consider values such as $w_2 + w_4$ and $w_1 + w_2 + w_3$, which are even greater than $w_2 + w_3$. Actually, to find the 6th smallest member, one only needs to consider $0, w_1, w_2, w_3, w_4, w_5, w_1 + w_2$, and $w_1 + w_3$ as a potential candidate. All the other values can be excluded since they are greater than at least 7 members in $\Omega(\mathbf{w}_8)$.

The question is reduced to how to pinpoint the subset of all potential candidates for the $[2^K \times 0.025]$ th smallest value in general. For any $1 \leq i_1 < i_2 < \dots < i_j \leq K$,

we use $a_L(i_1, i_2, \dots, i_j)$ to denote the number of elements from $\Omega(\mathbf{w}_K)$, which are always $\leq \sum_{l=1}^j w_{i_l}$, regardless of the value of \mathbf{w}_K . If $a_L(i_1, \dots, i_j) > [2^K \times 0.025]$, then there are at least $[2^K \times 0.025] + 1$ elements in $\Omega(\mathbf{w}_K) \leq \sum_{l=1}^j w_{i_l}$ due to (1) and $\sum_{l=1}^j w_{i_l}$ is strictly greater than the $[2^K \times 0.025]$ th smallest value in $\Omega(\mathbf{w}_K)$. Therefore, a candidate set for the cut off value is

$$\Omega_R(\mathbf{w}_K) = \left\{ \sum_{j \in \mathcal{N}} w_j \mid \mathcal{N} \in \mathcal{M}_K \right\},$$

where

$$\mathcal{M}_K = \left\{ \{i_1, \dots, i_k\} \mid a_L(i_1, \dots, i_k) \leq [2^K \times 0.025], 1 \leq i_1 < \dots < i_k \leq K \right\}.$$

It is clear that the $[2^K \times 0.025]$ th smallest element in $\Omega_R(\mathbf{w}_K)$ is also the $[2^K \times 0.025]$ th smallest element in $\Omega(\mathbf{w}_K)$.

Furthermore, we don't even need to compute all the values in $\Omega_R(\mathbf{w})$. In the example of $K = 8$, w_3 is smaller than the 6th smallest member, since there are at most 5 elements in $\Omega(\mathbf{w}_8)$, $0, w_1, w_2, w_1 + w_2$, and w_3 , which are less than or equal to w_3 . It is obvious that $0, w_1$ and w_2 are also smaller than the 6th smallest element and should not be considered. More formally, we define

$$\Omega_L(\mathbf{w}_K) = \left\{ \sum_{j \in \mathcal{N}_K} w_j \mid \mathcal{N}_K \in \mathcal{N}_K \right\},$$

where

$$\mathcal{N}_K = \left\{ \{i_1, \dots, i_k\} \mid a_U(i_1, \dots, i_k \mid K) > 2^K - [2^K \times 0.025] + 1, 1 \leq i_1 < \dots < i_k \leq K \right\},$$

where $a_U(i_1, i_2, \dots, i_j \mid K), 1 \leq i_1 < \dots < i_j \leq K$ is the number of elements in $\Omega(\mathbf{w}_K)$, which are always $\geq \sum_{l=1}^j w_{i_l}$, regardless of the value of \mathbf{w}_K . For any member in $\Omega_L(\mathbf{w}_K)$, it is less than or equal to at least $2^K - [2^K \times 0.025] + 2$ elements in $\Omega(\mathbf{w}_K)$ and thus bigger than at most $[2^K \times 0.025] - 2$ elements in $\Omega(\mathbf{w}_K)$. Therefore, all elements in $\Omega_L(\mathbf{w}_K)$ are smaller than the $[2^K \times 0.025]$ th smallest value in $\Omega(\mathbf{w}_K)$. Coupled with the fact that $\mathcal{N}_K \subset \mathcal{M}_K$, it implies that the $[2^K \times 0.025]$ th smallest element in $\Omega(\mathbf{w}_K)$ is the same as the $([2^K \times 0.025] - n_K)$ th smallest value in the reduced set

$$\Omega_S(\mathbf{w}_K) = \left\{ \sum_{j \in \mathcal{N}} w_j \mid \mathcal{N} \in \mathcal{M}_K - \mathcal{N}_K \right\},$$

where n_K is the cardinality of \mathcal{N}_K .

To find \mathcal{M}_K and \mathcal{N}_K , we need to compute $a_U(i_1, \dots, i_k)$ and $a_L(i_1, \dots, i_k)$. Let $b_k(i_1, \dots, i_k), 1 \leq i_1 < \dots < i_k \leq K$ be the number of distinct sets $\{j_1, \dots, j_k\}$ such that $1 \leq j_1 < \dots < j_k \leq K$ and $j_l \leq i_l, l = 1, \dots, k$. We have the following equalities,

which can be used for the fast computation of $a_L(i_1, i_2, \dots, i_k)$

$$\begin{aligned} b_1(i_1) &= i_1, \\ b_2(i_1, i_2) &= \sum_{l=1}^{i_1} b_1(i_2 - l), \\ &\dots \\ b_k(i_1, i_2, \dots, i_k) &= \sum_{l=1}^{i_1} b_{k-1}(i_2 - l, \dots, i_k - l) \end{aligned}$$

and

$$a_L(i_1, \dots, i_k) = 1 + \sum_{l=1}^k b_{k-l+1}(i_l, i_{l+1}, \dots, i_k).$$

The justification is given in the Appendix.

Similarly, we may let $c_k(i_1, \dots, i_k | K)$, $1 \leq i_1 < \dots < i_k \leq K$ be the number of distinct sets $\{j_1, \dots, j_p\}$, $p \geq k$ such that $1 \leq j_1 < \dots < j_p \leq K$, $i_l \leq j_{p-k+l}$, $l = 1, \dots, k$, and $j_{p-k+1} = i_1$. We have

$$c_k(i_1, \dots, i_k | K) = 2^{i_1-1} b_{k-1}(K - i_k, \dots, K - i_2)$$

and

$$a_U(i_1, \dots, i_k | K) = \sum_{l=i_1}^{K-k+1} c_k \{l, \max(l+1, i_2), \dots, \max(l+k-1, i_k)\}.$$

The corresponding recursive computation for $a_L(i_1, \dots, i_k)$ and $a_U(i_1, \dots, i_k)$ is straightforward. For example,

$$\begin{aligned} a_L(1, 2, 3) &= 1 + b_1(3) + b_2(2, 3) + b_3(1, 2, 3) \\ &= 1 + b_1(3) + \{b_1(2) + b_1(1)\} + b_2(1, 2) \\ &= 1 + 3 + 3 + 1 = 8 \end{aligned}$$

and

$$\begin{aligned} a_U(3 | 8) &= c_1(3 | 8) + c_1(4 | 8) + c_1(5 | 8) + c_1(6 | 8) + c_1(7 | 8) + c_1(8 | 8) \\ &= 2^2 + 2^3 + 2^4 + 2^5 + 2^6 + 2^7 \\ &= 252. \end{aligned}$$

In practice, \mathcal{M}_K and \mathcal{N}_K can be calculated in advance and stored. For any given \mathbf{w}_K , we can compute all the values in $\Omega_S(\mathbf{w}_K)$ and find the $(\lceil 2^K \times 0.025 \rceil - n_K)$ th smallest element among them. Since $\#\Omega_S(\mathbf{w}_K) \ll 2^K$ for all K , the computation can be greatly accelerated. Again taking $K = 8$ as an example, it is not difficult to verify that

$$\mathcal{M}_8 = \{\phi, \{1\}, \{2\}, \{3\}, \{4\}, \{5\}, \{1, 2\}, \{1, 3\}\}$$

$$\mathcal{N}_8 = \{\phi, \{1\}, \{2\}, \{3\}\}$$

and

$$\Omega_S(\mathbf{w}_8) = \{w_4, w_5, w_1 + w_2, w_1 + w_3\}.$$

Therefore, in order to determine the cut off value, one only needs to compute 4 values (instead of 256 values in $\Omega(\mathbf{w}_8)$) and find the 2nd smallest element. To conduct a two-sided test, we also need to find the $[2^K \times 0.025]$ th largest element of $\Omega(\mathbf{w}_K)$. Since the set $\Omega(\mathbf{w}_K)$ is symmetric at $\sum_{i=1}^K w_i/2$, the $[2^K \times 0.025]$ th largest element is simply the difference between $\sum_{i=1}^K w_i$ and the $[2^K \times 0.025]$ th smallest element of $\Omega(\mathbf{w}_K)$.

In summary, for any given μ , we may first calculate the $([2^K \times 0.025] - n_K)$ th smallest value in $\Omega_S(\{w_1(\mu), \dots, w_K(\mu)\})$ denoted by $\tilde{c}_L(\mu)$ and then let $c_L(\mu) = 2\tilde{c}_L(\mu) - \sum_{i=1}^K w_i(\mu)$ and $c_U(\mu) = \sum_{i=1}^K w_i(\mu) - 2\tilde{c}_L(\mu)$.

Remarks: The proposed method is for the fast calculation of the precise values of $c_L(\mu)$ and $c_U(\mu)$. If we aim to approximate these cut off values, then the Monte-Carlo method can be used. Specifically, we can simulate a large number of $\{V_1, \dots, V_K\}$ and calculate the corresponding $T_{\mathbf{V}}(\mu)$. The 2.5% and 97.5% percentiles of the simulated $T_{\mathbf{V}}(\mu)$ s can then be used as approximations of $c_L(\mu)$ and $c_U(\mu)$, respectively. One drawback of the Monte-Carlo method is that the cut off value and thus the final confidence interval of μ_0 may vary from run to run due to Monte-Carlo variations.

3. Numerical Study

The improvement of the computational efficiency of the proposal depends on the cardinality of \mathcal{M}_K and \mathcal{N}_K . In Table 1, we summarized the cardinality of $\mathcal{M}_K - \mathcal{N}_K$ for $K = 7, 8, \dots, 20$, the range, in which the exact method is useful. Since the cardinality of $\mathcal{M}_K - \mathcal{N}_K$ is only a small fraction of 2^K , it is expected that the time needed for implementing the exact test with the new algorithm is substantially less than the time of using the naive method. We have performed a set of numerical studies to investigate the empirical performance of the proposal. Specifically, we simulated 50 sets of data via the following model:

$$\sigma_i^2 \sim U(0.5, 2) \quad \text{and} \quad Y_i \sim N(\theta_i, \sigma_i^2),$$

where $\theta_i = \Phi^{-1}\{i/(K+1)\}$, $i = 1, \dots, K$. For each set of generated data, we constructed the 95% exact confidence interval of μ_0 with the proposed as well as naive algorithm. To this end, we have considered three test statistics:

$$T(\mu) = \begin{cases} T_{median}(\mu) = \sum_{i=1}^K \text{sign}(Y_i - \mu)/\hat{\sigma}_i(\mu) \\ T_{mean}(\mu) = \sum_{i=1}^K (Y_i - \mu)/\hat{\sigma}_i^2(\mu) \\ T_{wang}(\mu) = \sum_{i=1}^K (\Phi\{(Y_i - \mu)/\hat{\sigma}_i(\mu)\} - 0.5) \end{cases}.$$

The mean elapse times in R used in analyzing the data by different algorithms are summarized in Table 2. As anticipated, the proposed method is much faster than its naive counterpart especially for $K \geq 13$.

Table 1. The cardinality of $\mathcal{M}_K - \mathcal{N}_K$ for selected K s

K	2^K	$\#\mathcal{M}_K - \#\mathcal{N}_K$
7	128	1
8	256	4
9	512	14
10	1,024	35
11	2,048	94
12	4,096	224
13	8,192	516
14	16,384	1,181
15	32,768	2,598
16	65,536	5,693
17	131,072	12,359
18	262,144	26,415
19	524,288	56,357
20	1,048,576	119,039

Table 2. The average elapse time of constructing the 95% exact confidence interval using the naive as well as proposed algorithms

K	$T_{median}(\mu)$		$T_{mean}(\mu)$		$T_{wang}(\mu)$	
	naive	new	naive	new	naive	new
8	0.044	0.044	0.041	0.041	0.044	0.043
9	0.053	0.044	0.047	0.042	0.050	0.045
10	0.063	0.047	0.058	0.042	0.061	0.045
11	0.093	0.047	0.081	0.045	0.086	0.048
12	0.144	0.052	0.133	0.049	0.138	0.055
13	0.268	0.063	0.236	0.060	0.242	0.064
14	0.501	0.090	0.459	0.085	0.463	0.088
15	1.099	0.149	1.041	0.140	1.125	0.145
16	2.233	0.258	2.227	0.265	2.241	0.271
17	4.797	0.521	4.549	0.594	4.617	0.564
18	9.948	1.224	10.04	1.335	9.793	1.303
19	21.02	2.993	21.28	3.373	21.18	3.209
20	42.39	6.270	42.74	6.219	43.56	6.268

4. Example

Atrial fibrillation (AF) is one of the primary causes of cardiovascular disease including stroke and death. Literature suggests that women and men experience many cardiovascular risk factors differently. However, it is unclear whether AF is a stronger (or weaker) risk factor of stroke and death in women than in men. A meta-analysis is conducted to estimate and compare the gender-specific association between AF and all cause mortality. Specifically, results from 19 studies are pooled to estimate the interaction between AF and gender [9]. The detailed information of the 19 studies can be found in Table 3. Based on the asymptotic DL method, the ratio of relative risks (AF vs non-AF) for women compared with men is 1.12 with a 95% confidence interval 1.07 to 1.17. Therefore, the association between AF and all cause mortality in women is statistically significantly stronger than that in men.

Since there are only 19 studies, we constructed the 95% exact confidence interval for the log-transformed ratio of the relative risk for women to that for men. Both naive and the proposed methods yield the identical result as expected. The 95% exact confidence interval of the ratio of the relative risk is (1.051, 1.220) based on $T_{median}(\mu)$; (1.059, 1.181) based on $T_{mean}(\mu)$ and (1.053, 1.232) based on $T_{wang}(\mu)$. The resulting exact confidence intervals are slightly wider than (1.07, 1.17), the asymptotic counterpart reported in [9]. Since all three confidence intervals exclude zero, the relative risk of AF in women is also statistically significantly different from that in men based on the “exact” inference. We have also examined the gain of the proposed method in terms of the computational speed. While the elapse time of constructing the three confidence intervals is approximately 24 seconds using the naive method, its counterpart using the proposed method is 3.14-3.47 seconds. Therefore, the improvement in computational speed is fairly substantial.

As we discussed in the previous section, the null distribution also can be approximated by a Monte Carlo simulation. One limitation of the Monte Carlo approach is the random variability of the resulting inference result. We constructed the 95% confidence interval of the ratio of relative risks with the null distribution being approximated by 1000 simulated test statistics. We repeated the same process of constructing the confidence interval 100 times. The lower and upper ends of the confidence interval based on $T_{mean}(\mu)$ varies from 1.047 to 1.076 and from 0.170 to 0.214, respectively. Similarly, the lower and upper ends of the confidence interval based on $T_{wang}(\mu)$ varies from 1.042 to 1.066 and from 1.218 to 0.247, respectively. Therefore, the inference result varies moderately depending on the Monte-Carlo runs.

5. Conclusion

We have proposed a fast numerical algorithm to find the desired percentile of the null distribution of interest. The method can be used to construct the exact 95% confidence interval for the location parameter of a random effects model. The similar method can be used to construct the exact 90% confidence interval as well. However, the gain in terms of computational time would be smaller in such a case. The R-code implementing the proposed method can be found at “<http://web.stanford.edu/~luttian/Software.HTML>”.

Table 3. The estimated the ratio of relative risk in women to that in men from 19 studies

Study	Ratio of relative risk (RRR) (95% CI)	log(RRR)	SE of log(RRR)
Stortecky	0.69 (0.25 to 1.88)	-0.37	0.51
Wolfe	0.70 (0.09 to 5.58)	-0.36	1.05
Siontis	0.86 (0.63 to 1.18)	-0.15	0.16
Kaarisalo	0.87 (0.67 to 1.13)	-0.14	0.13
Bejot	0.97 (0.73 to 1.28)	-0.03	0.14
Saposnik	1.05 (0.91 to 1.20)	0.05	0.07
Hamaguchi	1.08 (0.58 to 2.01)	0.08	0.32
Wolf	1.10 (1.03 to 1.18)	0.10	0.03
Chamberlain	1.12 (0.86 to 1.44)	0.11	0.13
Hippisley-Cox 2010	1.15 (1.07 to 1.23)	0.14	0.04
Andersson	1.17 (0.99 to 1.38)	0.16	0.08
Guize	1.20 (0.60 to 2.39)	0.18	0.35
Ruigomez	1.22 (0.85 to 1.74)	0.20	0.18
van Wijk	1.27 (0.89 to 1.81)	0.24	0.18
Benjamin	1.27 (0.96 to 1.66)	0.24	0.14
Bouzas-Mosquera	1.42 (0.92 to 2.18)	0.35	0.22
Stewart	1.47 (0.90 to 2.38)	0.39	0.25
Ohsawa	1.64 (0.85 to 3.17)	0.49	0.34
Friberg	1.65 (1.07 to 2.54)	0.50	0.22
Random effects model	1.12 (1.07 to 1.17)	0.11	0.023

References

- [1] Higgins J, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*. 2009; 172(1):137–159.
- [2] Schmidt FL, Oh IS, Hayes TL. Fixed-versus random-effects models in meta-analysis: Model properties and an empirical comparison of differences in results. *British Journal of Mathematical and Statistical Psychology*. 2009;62(1):97–128.
- [3] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*. 1986; 7(3):177–188.
- [4] Hardy RJ, Thompson SG. A likelihood approach to meta-analysis with random effects. *Statistics in medicine*. 1996;15(6):619–629.
- [5] Follmann DA, Proschan MA. Valid inference in random effects meta-analysis. *Biometrics*. 1999;55(3):732–737.
- [6] Jackson D, Bowden J, Baker R. How does the dersimonian and laird procedure for random effects meta-analysis compare with its more efficient but harder to compute counterparts? *Journal of Statistical Planning and Inference*. 2010;140(4):961–970.
- [7] Liu S, Lee S, Xie M, et al. Exact inference on meta-analysis with generalized fixed-effects and random-effects models. *Biostatistics & Epidemiology* (submitted). 2016;.
- [8] Wang R, Tian L, Cai T, et al. Nonparametric inference procedure for percentiles of the random effects distribution in meta-analysis. *The annals of applied statistics*. 2010;4(1):520.
- [9] Emdin CA, Wong CX, Hsiao AJ, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *bmj*. 2016;352:h7013.

Appendix A. The justification of the expression of $a_L(i_1, \dots, i_k)$

For any $1 \leq i_1 < \dots < i_k = K$, $a_L(i_1, \dots, i_k)$ is the number of distinct sets $\{j_1, \dots, j_l\}$ such that

$$i_k \geq j_l, i_{k-1} \geq j_{l-1}, \dots \quad \text{and} \quad i_{k-l+1} \geq j_1,$$

where $0 \leq l \leq k$, which implies that

$$\sum_{s=1}^l w_{j_s} \leq \sum_{s=1}^k w_{i_k}$$

considering the fact that $w_1 < \dots < w_k$. Recalling that $b_k(i_1, \dots, i_k)$ represents the number of distinct sets $\{j_1, \dots, j_k\}$ such that $i_k \geq j_k, i_{k-1} \geq j_{k-1}, \dots$ and $i_1 \geq j_1$, and letting $l = 0, 1, \dots, k$, we have

$$a_L(i_1, \dots, i_k) = 1 + b_1(i_k) + b_2(i_{k-1}, i_k) + \dots + b_k(i_1, \dots, i_k).$$

To compute $b_k(i_1, \dots, i_k)$, we need to count the number of distinct sets $\{j_1, \dots, j_k\}$ satisfying the constraint that

$$i_l \geq j_l, l = 1, \dots, k.$$

Since j_1 only takes a value from $\{1, \dots, i_1\}$, we first count the number of sets $\{l, j_2, \dots, j_k\}$ satisfying the constraint that

$$i_l \geq j_l, l = 2, \dots, k \quad \text{and} \quad j_k > j_{k-1} > \dots > j_2 > l \quad (\text{A1})$$

for given l , $1 \leq l \leq i_1$. For any such a set, $\{j_2^*, \dots, j_{k-1}^*\} = \{j_2 - l, \dots, j_k - l\}$ also satisfies the constraint that

$$i_l - l \geq j_l^*, l = 2, \dots, k \quad \text{and} \quad 1 \leq j_2^* < \dots < j_k^*.$$

Therefore, the number of sets $\{l, j_2, \dots, j_k\}$ satisfying the constraint (A) is $b_{k-1}(l, i_2 - l, \dots, i_k - l)$. Since l can only be $0, 1, \dots$, and i_1 ,

$$b_k(i_1, \dots, i_k) = b_{k-1}(1, i_2 - 1, \dots, i_k - 1) + \dots + b_{k-1}(i_1, i_2 - i_1, \dots, i_k - i_1).$$