Review / Derleme

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Systematic review and meta-analysis of the efficacy of acupuncture as an adjunct to IVF cycles in China and the world

Akupunkturun Çin ve dünyada IVF döngülerine yardımcı olarak etkinliğinin sistematik incelemesi ve meta-analizi

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Abstract

Acupuncture has been introduced as an adjuvant therapy to in vitro fertilization (IVF) cycles in many randomized controlled trials (RCTs). However, there has been a debate among trials regarding the effectiveness and safety of the procedure. To determine how effective and safe acupuncture is as an adjunct to IVF cycles for primary and secondary female infertility. We conducted a literature search for relevant RCTs and ultimately included nine studies. The main selected outcomes included the rates of clinical pregnancy, ongoing pregnancy, miscarriage, live birth, and side effects. Patients receiving acupuncture were grouped together regardless of the acupuncture points used or the protocol for the insertion of needles. We performed a subgroup analysis according to whether studies originated inside and outside China to investigate the results of the different RCTs. We pooled outcomes as a risk ratio (RR) with 95% confidence interval (CI). The analysis revealed that in China, acupuncture led to lower clinical [RR=0.80, 95% CI (0.66, 0.97), p=0.02] and ongoing [RR=0.78, 95% CI (0.63, 0.97), p=0.03] pregnancy rates than placebo. Outside China, acupuncture increased clinical pregnancy rates [RR=1.38, 95% CI (1.11, 1.71), p=0.003] and ongoing [RR=1.73, 95% CI (1.29, 2.31), p<0.001] pregnancy rates. Rates of live birth and miscarriage did not significantly differ between the arms. Regarding side effects, acupuncture groups had a significantly higher rate of puncture site itching compared to control groups [RR=1.51, 95% CI (1.12, 2.04), p=0.007]. Overall analysis does not show a statistically significant increase in clinical pregnancy rates worldwide when using acupuncture as an adjunct therapy to IVF. There were no issues regarding patient safety from any included study. Subgroup results indicated that better rates for clinical pregnancy seem to be occurring more often in RCTs performed outside China than within.

Keywords: Acupuncture, Chinese medicine, in vitro fertilization, traditional medicine, traditional Chinese medicine, alternative medicine, integrative medicine

Öz

Akupunktur, birçok randomize kontrollü çalışmada (RKÇ) in vitro fertilizasyon (IVF) döngülerine adjuvan bir tedavi olarak sunulmuştur. Ancak, prosedürün etkinliği ve güvenliği ile ilgili çalışmaların tartışmalı sonuçları mevcuttur. Biz bu sistematik inceleme ve meta-analizde, primer ve sekonder kadın kısırlığında IVF döngülerine ek olarak akupunkturun ne kadar etkili ve güvenli olduğunu belirlemek istedik. İlgili RKÇ'ler için bir literatür taraması yaptık ve sonuçta 9 çalışmayı dahil ettik. Seçilen ana sonlanımlar, klinik gebelik, devam eden gebelik, düşük, canlı doğum ve yan etki oranlarını içermekteydi. Akupunktur alan hastalar, kullanılan akupunktur noktalarından veya iğnelerin yerleştirilmesi protokolünden bağımsız olarak gruplandırıldı. Farklı RKÇ'lerin sonuçlarını araştırmak için çalışmaların Çin içinden mi yoksa Çin dışından mı kaynaklandığına göre bir alt grup analizi yaptık. Sonuçları %95 güven aralığı (GA) ve bir risk oranı (RR) şeklinde havuzladık. Analiz, Çin'de akupunkturun plasebo ile kıyaslandığında daha düşük oranda klinik gebeliğe [RR=0,80, %95 GA (0,66, 0,97), p=0,02] ve devam eden gebeliğe [RR=0,78, %95 GA (0,63, 0,97), p=0,03] yol açtığını ortaya koydu. Çin dışında akupunktur klinik gebelik oranlarını [RR=1,38, %95 GA (1,11, 1,71), p=0,003] ve devam eden gebelik oranlarını [RR=1,73, %95 GA (1,29, 2,31), p<0,001] artırdı. Canlı doğum ve düşük oranları kollar arasında anlamlı farklılık göstermedi. Yan etkilerle ilgili olarak, akupunktur gruplarında, kontrol gruplarına kıyasla anlamlı olarak daha fazla

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oranda ponksiyon yerinde kaşıntı vardı [RR=1,51, %95 GA (1,12, 2,04), p=0,007]. Genel analiz, IVF'ye ek tedavi olarak akupunktur kullanıldığında dünya çapında klinik gebelik oranlarında istatistiksel olarak anlamlı bir artış olmadığını göstermektedir. Dahil edilen hiçbir çalışmada hasta güvenliği ile ilgili herhangi bir sorun yoktu. Alt grup sonuçları, klinik gebelik için daha iyi oranların Çin dışında gerçekleştirilen RKÇ'lerde daha sık ortaya çıktığını gösterdi.

Anahtar Kelimeler: Akupunktur, Çin tıbbı, tüp bebek, geleneksel tıp, geleneksel Çin tıbbı, alternatif tıp, bütünleştirici tıp

Introduction

Infertility is defined as the failure of a couple to achieve pregnancy after 12 months of attempting. A recent analysis showed that 48.5 million couples are suffering from infertility worldwide, with a global incidence of 9-18%[1,2]. The causes for infertility vary widely, with polycystic ovarian syndrome, and advanced maternal age being some of the more common causes, and secondary infertility being more common than primary[3-5]. Even with extensive workup, greater than 15% of couples suffering from secondary infertility will not find a cause[6].

As treatment, the rate of couples seeking assisted reproductive technology (ART), particularly in vitro fertilization (IVF), has been increasing since the development of these technologies[7]. Although the cost of these procedures has been decreasing, they are still unaffordable for many couples in many countries[8].

Due to the high cost of IVF in developed countries, low-cost complimentary procedures that may increase the efficacy of IVF cycles are widely sought after[9,10].

In Chinese medicine, acupuncture is a well-known therapeutic approach that depends on the insertion of fine special needles at certain points of pressure through the human body. Several studies have proven the benefits of acupuncture in limited circumstances, including improvement of digestive and emotional health, therefore the risk to infertile couples seem minimal[11]. Complications with acupuncture are exceedingly rare, with sporadic reports in the literature of pneumothorax and nerve injury[11]. As for the benefits related to reproductive organs, increased blood flow to the female reproductive organs is seen through the application of acupuncture in the lower limbs and parts of the abdomen; therefore, increasing and enriching the lining of the uterus[11]. Additionally, as inferred indirectly through laboratory analysis, several authors have postulated that acupuncture can increase ovarian follicle reserve[11,12]. As a result, acupuncture has become one of the most popular complementary therapies to IVF, used widely by couples hoping to increase their chance of success[13].

Several trials have attempted to study the effect of acupuncture on IVF cycles[14,15]. In 2020, Coyle et al.[16] conducted a systematic review and meta-analysis on the role of acupuncture versus placebo acupuncture in IVF. Building on the work of previous researchers, we endeavored to create the broadest systematic review to date, by including many new randomized controlled trials (RCTs), and including an analysis of adverse events that has not previously been studied.

Materials and Methods

To perform this systematic review and meta-analysis, the authors followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement[17]. All the steps were performed in strict accordance with the Cochrane Handbook of systematic reviews of interventions[18].

Eligibility Criteria

Retrieved studies were marked as included if they met the following inclusion criteria: 1) studies that are RCTs, 2) population: Women with primary or secondary infertility, 3) intervention: Acupuncture as an adjuvant to IVF, 4) comparator: Placebo acupuncture, sham acupuncture, or no intervention, and 5) outcome: Clinical pregnancy, ongoing pregnancy, live birth, rate of miscarriage, and side effects. The following studies were excluded: 1) non-RCTs, 2) women receiving acupressure, laser acupuncture, or other types of acupuncture that excluded needle penetration of the skin, 3) other comparator arms than placebo acupuncture, sham acupuncture, or laying quietly, and 4) studies with no accessible data, conference abstracts, and animal studies.

Literature Search

We searched the following databases for published articles from inception to February 2020: EBSCO, PubMed, Embase, COCHRANE, MEDLINE, the Menstrual Disorders and Subfertility Group (MDSG, Specialized Register), and Clinical Trial registers (CENTRAL, clinicaltrial.gov, and the WHO International Clinical Trials Registry Platform). We also searched opengrey.eu for gray literature and Google Scholar for additional sources. No language restrictions were applied.

We used a combination of medical subject headings and text words to include a) acupuncture studies: "acupuncture", "moxibustion", "TCM", "traditional Chinese medicine", "electroacupuncture", "electro-acupuncture"; and b) the intervention: "IVF", "in vitro fertilization", "in vitro fertilization", "assisted reproduction technologies", "ART", "embryo transfer", "ET". Supplemental Figure S1 shows the PRISMA flowchart for our literature search. We developed the following search strategy for all databases: (acupuncture OR moxibustion OR "traditional Chinese medicine" OR electroacupuncture OR "electro-acupuncture") AND (IVF OR "in vitro fertilization" OR "assisted reproduction technologies" OR "embryo transfer").

Data Collection and Analysis

Screening of Results

Following the literature search of selected databases, eligible studies and relevant controlled trials were exported and

screened in two steps. The first step involved title and abstract screening to exclude other study designs and animal trials. The second step involved full-text screening to ensure that the controlled trials met the inclusion criteria. After screening and reaching the full-text of the included papers, we performed an additional step through searching the references of the studies for possible missed trials.

Data Extraction

After a thorough reading of the included trials, we used Microsoft Excel for extracting data. Extracted data included three main groups: 1) baseline characteristics of participants, 2) data for outcomes to be incorporated in the analysis, 3) data for the assessment of the risk of bias among trials. Demographic data included patients' age, infertility duration, sample size, country, number of retrieved oocytes, percentage of patients with primary infertility, and body mass index. Outcome analysis included clinical pregnancy as the primary outcome, in addition to other secondary outcomes such as ongoing pregnancy, live birth, rate of miscarriage, and side effects.

Quality Assessment

Only RCTs were included to ensure high-quality evidence. We used Cochrane's risk of bias tool[19] for the assessment of the risk of bias. The Cochrane risk of bias tools works by assessing the risk of bias over seven stated domains. These domains include the proper randomization of patients (Domain #1), the blinding of the allocation of patients into the study's treatment arms (also called allocation concealment) (Domain #2), whether the intentional blinding of patients only (also termed single blinding) or the intentional blinding of both personnel and participants (also termed double-blinding) was used (Domain #3), Attrition bias (Domain #4), whether the outcomes used in the protocol are all reported (also termed selection bias) (Domain #5), blinding of outcome assessors to prevent underestimation or overestimation of outcome values (Domain #6), and other bias (Domain #7). Each domain was judged as a low, high, or unclear risk of bias.

Data Synthesis

Dichotomous data were pooled as a risk ratio (RR) and 95% confidence intervals (CI). We used Review Manager Software (Version 5.3) to perform the data analysis[20]. We used the method of inverse variance for the analysis of continuous outcomes and the Mantel-Haenszel method for the analysis of dichotomous outcomes. We used two main tests to measure inconsistency among the studies[21]. These tests included the I-square test (I^2) and the p-value of the chi-square test. Values of $I^2>50\%$ and $p<0.1$ were considered significant identifiers of heterogeneity, as found within the Cochrane Handbook[18]. We analyzed homogeneous data under a fixed-effects model. As recommended by the Cochrane Handbook, a random-effects model was employed when necessary to solve for heterogeneous data. We performed a subgroup analysis according to the country in which each RCT was conducted and included two main groups, China group, and the outside China group.

Results

Summary of Included Studies

This review presents the analysis of 3.020 patients (1.515 and 1.505 were allocated to the acupuncture and control group, respectively). The mean age of patients in the acupuncture group was 34.3 years, and 34.5 in the control groups. A total of 990 patients (489 in the intervention arm, and 501 in the control group) had not experienced any prior IVF cycles, and an average of 10.3 oocytes was retrieved from the patients. All studies included the previously described acupuncture procedures and acupoints, and were performed by appropriately licensed or trained personnel. There was a variation in chosen acupoints and temporal relationship to the planned IVF cycle.

Acupoints Used in the Included Trials

Regarding the included trials, Paulus et al.[22] were the first to conduct a randomized controlled trial comparing acupuncture with placebo in women receiving IVF cycles. The study included 160 patients and found acupuncture to be effective in increasing pregnancy rates ($p<0.01$). The following points were chosen for needle insertions before embryo transfer: Cx6 (Neiguan), Sp8 (Diji), Liv3 (Taichong), Gv20 (Baihui), and S29 (Guilai). After embryo transfer, the following points were selected: S36 (Zusanli), Sp6 (Sanyinjiao), Sp10 (Xuehai), Li4 (Hegu), ear point 55 (Shenmen), ear point 58 (Zhigong), ear point 22 (Neifenmi), and ear point 34 (Naodian). Dieterle et al.[23] included 116 patients in the acupuncture group, and 109 in the control group, and found that acupuncture increased clinical pregnancy rates ($p<0.01$). The needles were inserted at the following points: Guanyuan [ren (RN)4], Qihai (RN6), Guilai [stomach (ST)29], Neiguan [pericardium (PC)6], Xuehai [spleen (SP)10], and Diji (SP8). During the same year, two additional trials were initiated. Smith et al.[24] performed a similar trial in Australia with the same points as Paulus et al.[22], except for liver 4 and governing vessel 20, which were excluded. The study found no significant differences between the groups ($p=0.08$). Westergaard et al.[25] conducted a trial in Denmark and found that acupuncture leads to more pregnancy rates ($p<0.01$) using the same acupuncture points as Paulus et al.[22]. Later studies initiated by Domar et al.[26] and Andersen et al.[27] found no significant effect of acupuncture ($p=0.69$ and $p>0.05$ respectively) depending on the same acupuncture points as Paulus et al.[22]. Contrary to the previous results, two controlled trials were initiated in China by So et al.[28,29], the trials found that acupuncture has no effect on increasing clinical pregnancy rates [95% CI (0.898, 1.561)] and $p=0.06$ respectively. The points of acupuncture were similar to the previous trials, including PC6 (Neiguan), SP8 (Diji), LR3 (Taichong), GV20 (Baihui) and ST29 (Guilai) before embryo transfer. After embryo transfer,

the needles were inserted at ST36 (Zusanli), SP6 (Sanyinjiao), SP10 (Xuehai) and LI4 (Hegu).

Results of the Risk of Bias Assessment

The risk of bias assessment revealed an overall low risk of bias. All included trials reported adequate randomization of patients and allocation concealment. Regarding the blinding of participants and personnel, two studies[24,26] were single-blind, therefore they were classified as high risk of bias. Four studies[22,23,25,30] did not report enough evidence to ensure double-blinding, and therefore were put at "unclear" risk. The remaining three studies[27-29] were double-blind studies. All studies reported proper blinding of outcome assessment, except three studies[22,23,25], which did not report enough evidence. All studies were at low risk of bias regarding other domains, and no other bias was found as well. Supplemental Figure S2 shows a risk of bias graph and a summary of the risk of bias assessment among included studies.

Analysis of Efficacy Endpoints

Clinical Pregnancy

The clinical pregnancy outcome was reported in the nine studies. The overall RR did not reveal any significant difference between the groups [RR=1.14, 95% CI (0.93, 1.40), p=0.21]. Pooled results were heterogeneous (I^2=70%, p<0.001). Therefore, subgroup analysis according to the country was conducted.

In China, the results significantly favored the control group over the acupuncture arm [RR=0.80, 95% CI (0.66, 0.97), p=0.02]. Pooled data were homogeneous (I^2=0%, p=0.86). Conversely, the combined RR conducted outside China revealed that there was no significant difference between both groups [RR=1.28, 95% CI (1.02, 1.61), p=0.03]. Pooled results were heterogeneous (I^2=62%, p=0.02) (Figure 1A). According to Cochrane's leave-one-out method, inconsistency was best solved by excluding the Andersen et al.[27] study and the homogeneous results favored the acupuncture group significantly [RR=1.38, 95% CI (1.11, 1.71), p=0.003] (Figure 1B).

Ongoing Pregnancy

The ongoing pregnancy outcome was reported in seven studies[23-25,27-30]. The combined effect estimate showed no significant difference between both arms [RR=1.12, 95% CI (0.81, 1.82), p=0.34]. Pooled results were heterogeneous (I^2=79%, p<0.001). Subgroup analysis showed that in China, the control group was significantly associated with more clinical pregnancies than the acupuncture group [RR=0.78, 95% CI (0.63, 0.97), p=0.03]. Data were homogeneous (I^2=0%, p=0.94). While outside China, ongoing pregnancies were not different between the groups [RR=1.41, 95% CI (0.89, 2.23), p=0.14]. Pooled results were heterogeneous (I^2=79%, p=0.003), (Figure 2A). Heterogeneity was best solved after excluding the Andersen et al.[27] study (citation) and homogeneous results favored the acupuncture group [RR=1.73, 95% CI (1.29, 2.31), p<0.001] (Figure 2B).

Live Birth

Four studies[27-30] reported the outcome of a live birth. The overall RR showed no significant difference between both groups [RR=0.87, 95% CI (0.75, 1.01), p=0.06]. Pooled results were homogenous (I^2=0%, p=0.58), (Figure 3).

Miscarriage

Miscarriage was reported in five studies[24,27-30]. No statistically significant difference was found between both groups [RR=1.23, 95% CI (0.89, 1.70), p=0.21]. Pooled results were homogenous (I^2=0%, p=0.37) (Figure 4).

Analysis of Side Effects

Three studies[28-30] reported the intervention-related side effects (Figure 5). The results showed that the acupuncture group was associated with a significantly increased incidence rate of puncture site itching [RR=1.51, 95% CI (1.12, 2.04), p=0.007]. There were no statistically significant differences between the groups regarding nausea (p=0.21), dizziness (p=0.34), fainting (p=0.07), tiredness (p=0.75), drowsiness (p=0.55), headache (p=0.08), and chest pain (p=0.26).

Discussion

The results of this research suggest that outside China, acupuncture is an effective adjuvant approach that leads to increased rates of clinical and ongoing pregnancies, while contrary results are revealed for studies conducted within China, in which acupuncture actually leads to lower clinical and ongoing pregnancy rates. Other secondary outcomes, such as live birth were significantly lower in the acupuncture groups as well. Regarding side effects, acupuncture increases the incidence of headache and puncture site itching, while there was no difference between the two groups regarding the incidence of miscarriage, nausea, dizziness, fainting, tiredness, drowsiness, and chest pain.

The results of the subgroup analyses are consistent with the findings of other studies in the literature. A clinical trial[28] conducted in China found that the placebo acupuncture group was associated with higher overall pregnancy rates than the real acupuncture group. Another trial conducted a year later found that patients who received placebo acupuncture intervention had more ongoing pregnancy and implantation rates than those who discontinued the trial[29]. Another recent meta-analysis, Quan et al.[31] in 2022 agreed with our findings of a benefit to acupuncture in their analysis of 27 studies. Their analysis included studies from worldwide without a specific subgroup analysis. Differing from our findings, Tyler et al.[32] in 2022 found no significant difference in patients undergoing acupuncture versus those who did not, although this analysis included fewer studies than ours secondary to their goal of analyzing many factors outside acupuncture with IVF.

The exact explanation of why acupuncture decreases pregnancy rates among Chinese patients while increasing them among

other populations remains unclear. However, increasing evidence supports the effect of placebo acupuncture. A study by Birch[33] has shown that placebo acupuncture may induce a clinical response and is not an inert control. Vincent and Lewith[34] obtained the same results. Lund et al.[35] found that placebo acupuncture is not an inactive control. A large controlled trial[36] studied the effect of acupuncture in reducing chronic back pain. The study included three arms: Real acupuncture,

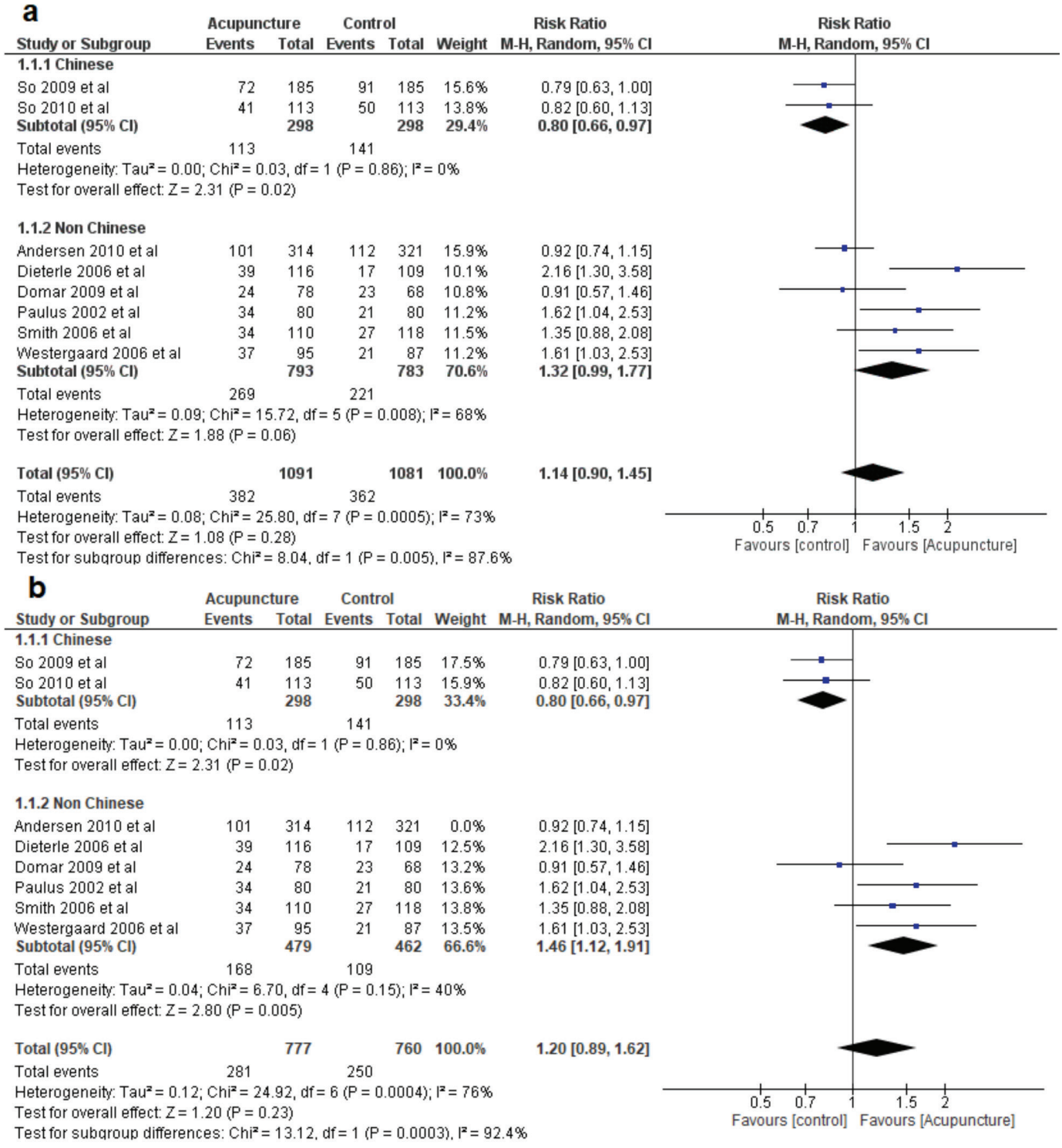

Figure 1. Shows a forest plot for the analysis of the clinical pregnancy outcomes, **a)** results before leave-one-out analysis, **b)** after leave-one-out analysis

CI: Confidence interval

a placebo acupuncture group, and a control group receiving conventional care. The study found that both real and placebo acupuncture had the same efficacy, which was superior to conventional care methods.

Contrary results were found in controlled trials performed outside China. Three RCTs[22,23,25] reported that acupuncture led to increased clinical and ongoing pregnancy rates, while another three RCTs found no significant difference between both groups[24,26,27]. A previous meta-analysis found that acupuncture increased pregnancy rates in patients undergoing IVF[37]. Another meta-analysis[38] found higher live birth and pregnancy rates in the real acupuncture group. Although the exact pathogenesis of how acupuncture increases pregnancy rates remains unknown, these studies relied on the evidence that acupuncture has been suggested to stimulate the release of several neurotransmitters (including serotonin and

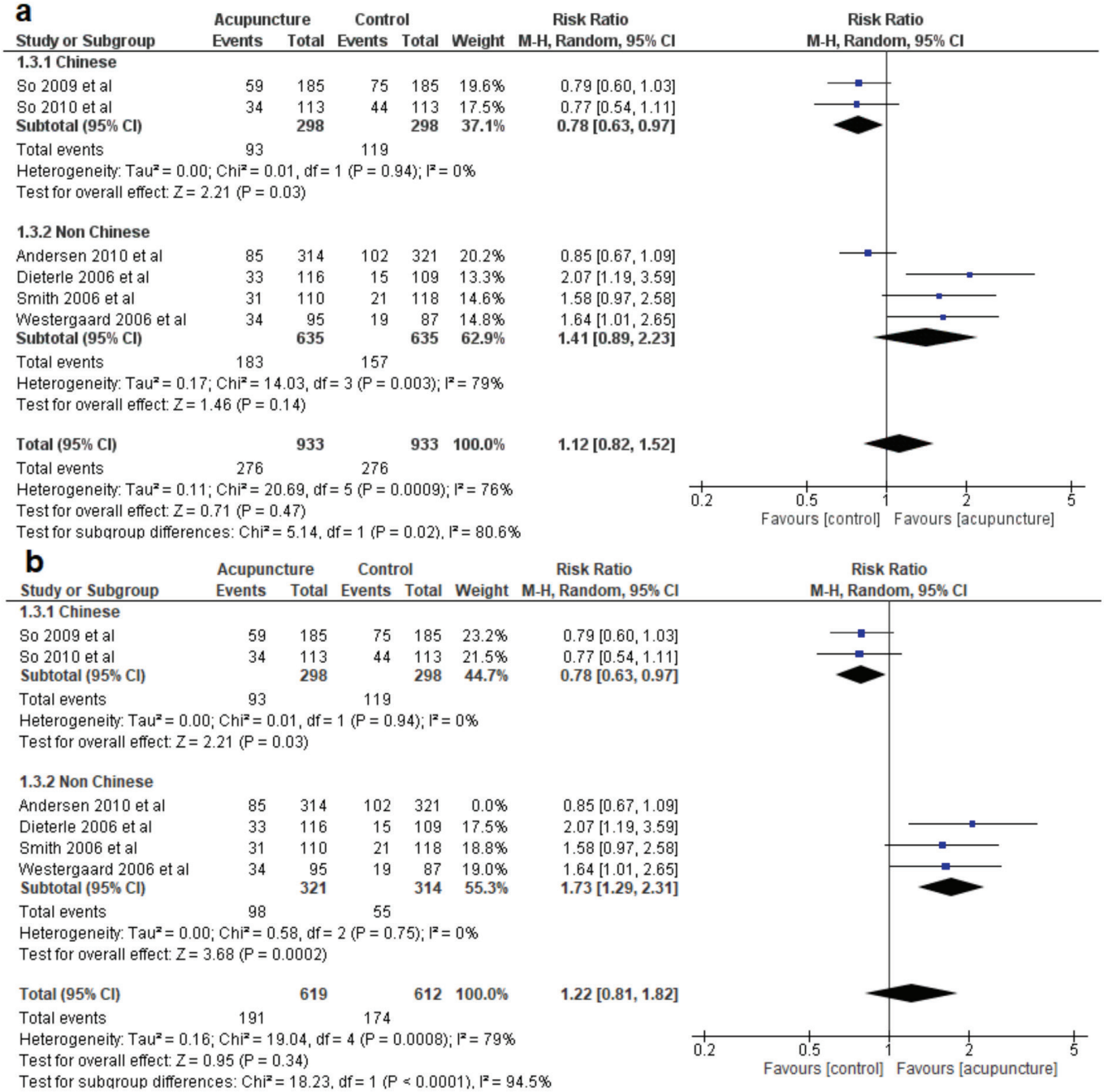

Figure 2. Shows a forest plot for the analysis of ongoing pregnancy outcome, **a)** before leave-one-out analysis, and **b)** after leave-one-out analysis

CI: Confidence interval

endorphins). These neurotransmitters enhance the production of gonadotropin-releasing hormones from the hypothalamus, which in turn increase the production of follicular-stimulating hormone that leads to stimulating and improving female ovulation[39-41]. It is also possible that these same processes lead to improved egg quality and ovarian follicle reserve, which would produce the same results[41].

There have been no reported serious adverse events with acupuncture. However, RCTs have shown that many patients may experience mild-to-moderate side effects of nausea and headache[28,29]. Other RCTs have reported that acupuncture leads to positive side effects such as the feeling of relaxation, calm and peace[24]. Therefore, acupuncture is considered a safe therapeutic approach.

In the present systematic review and meta-analysis, only RCTs were included. This gave the review a significant strength. The risk of bias assessment revealed an overall low risk of bias, which further supports the results of this study. However, several limitations need to be considered. The results of the analysis, though it is correct, may not represent the "true effect" of acupuncture. This may be primarily due to the small number of included studies in the China group (two studies). More controlled trials are needed with a larger sample size to provide solid evidence to solve this debate. Moreover, double-blinding may play a critical role in affecting the results. This is supported by the fact that sham acupuncture has been effective in increasing pregnancy rates in double-blind studies only[28,29]. Other trials included in this analysis were either single-blind[24,26] or did not report data about blinding[22,23,25]. Heterogeneity is the most important limitation, nevertheless, pooled homogeneous analysis was obtained. One final limitation is the lack of data required to conduct a true subgroup analysis of the different acupuncture sites to draw a connection between each individual point and the likely benefit or adverse effect associated with that point. Massive numbers of RCTs would be necessary to begin obtaining those answers on even a preliminary level of evidence.

Conclusion

As a conclusion, there is no clear evidence at this time to support the role of acupuncture. Results indicate that acupuncture reduces clinical and ongoing pregnancy rates among Chinese patients, while increasing them among patients outside China. The overall analysis of live birth and miscarriage outcomes showed no significant difference between the groups. As for the side effects, no side effects were associated with the procedure, except for puncture site itching.

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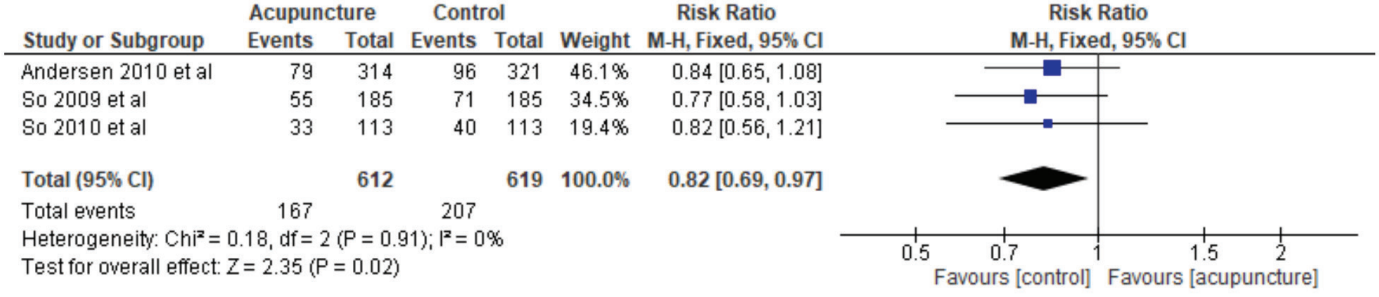

Figure 3. Shows a forest plot for the analysis of the live birth outcome

CI: Confidence interval

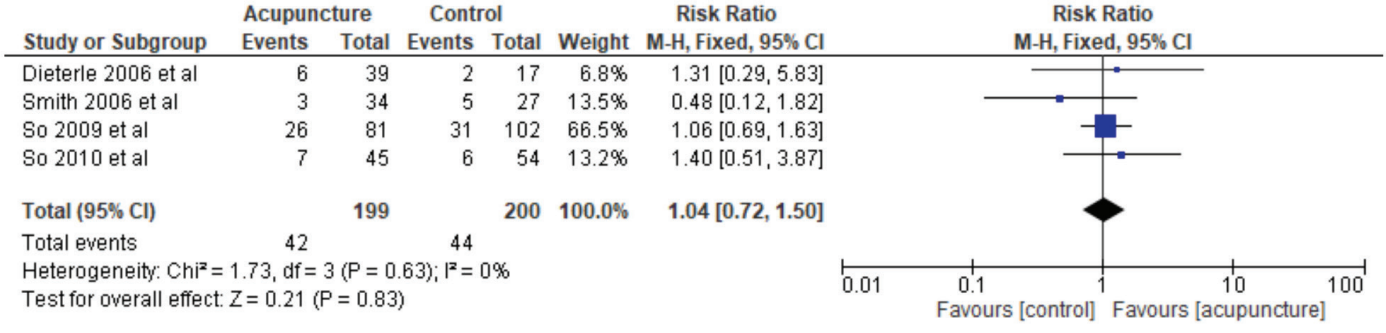

Figure 4. Shows a forest plot for the analysis of the miscarriage outcome

CI: Confidence interval

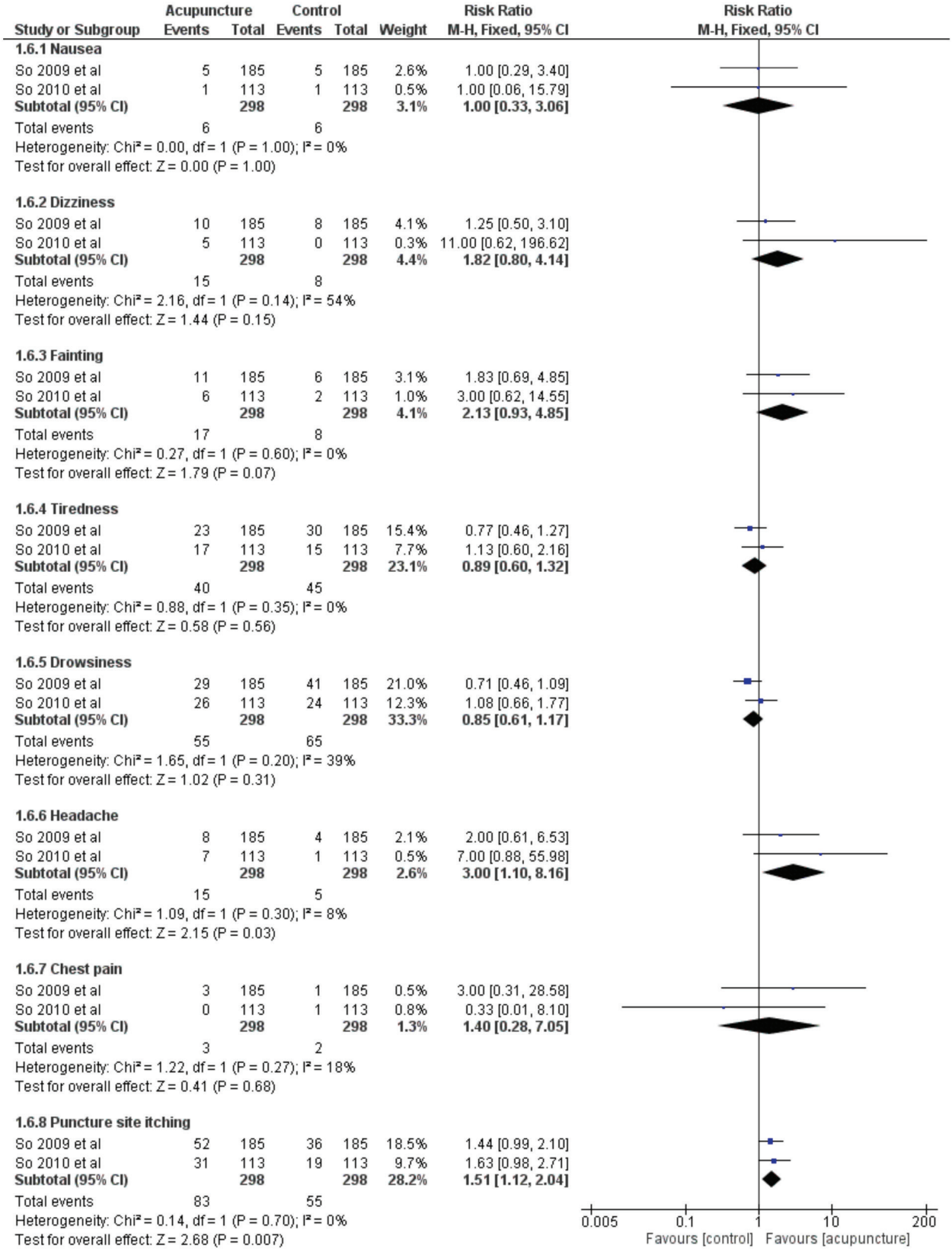

Figure 5. Shows a forest plot for the analysis of intervention-related side effects including nausea, dizziness, fainting, tiredness, drowsiness, headache, chest pain, and puncture site itching

CI: Confidence interval

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: G.M., A.M., A.A.Z., F.E., Data Collection or Processing: G.M., R.L., M.J., Analysis or Interpretation: F.E., A.A.Z., M.J., Initial Draft: G.M., R.L., B.L., A.M., M.J., Final Draft: G.M., A.M., B.L., R.L., Writing: G.M., A.M., B.L., R.L.

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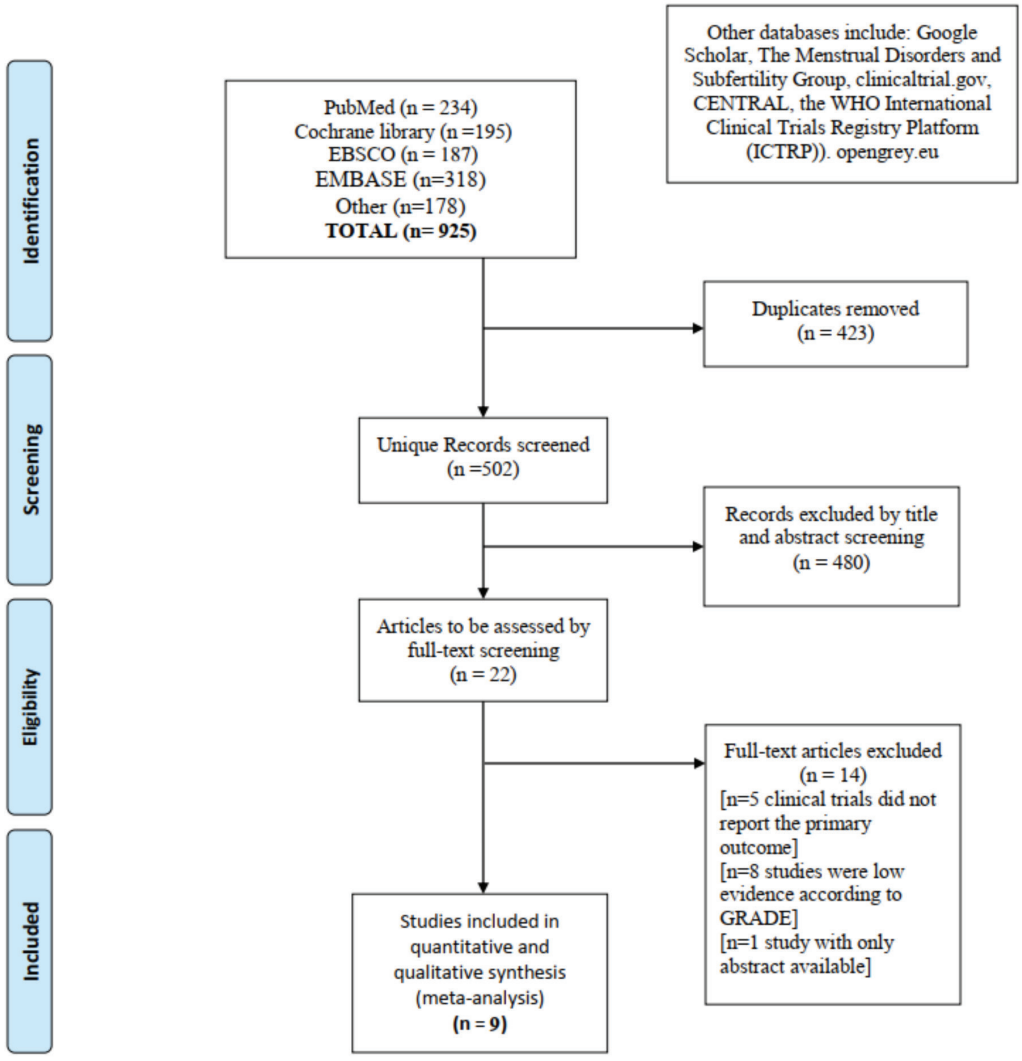
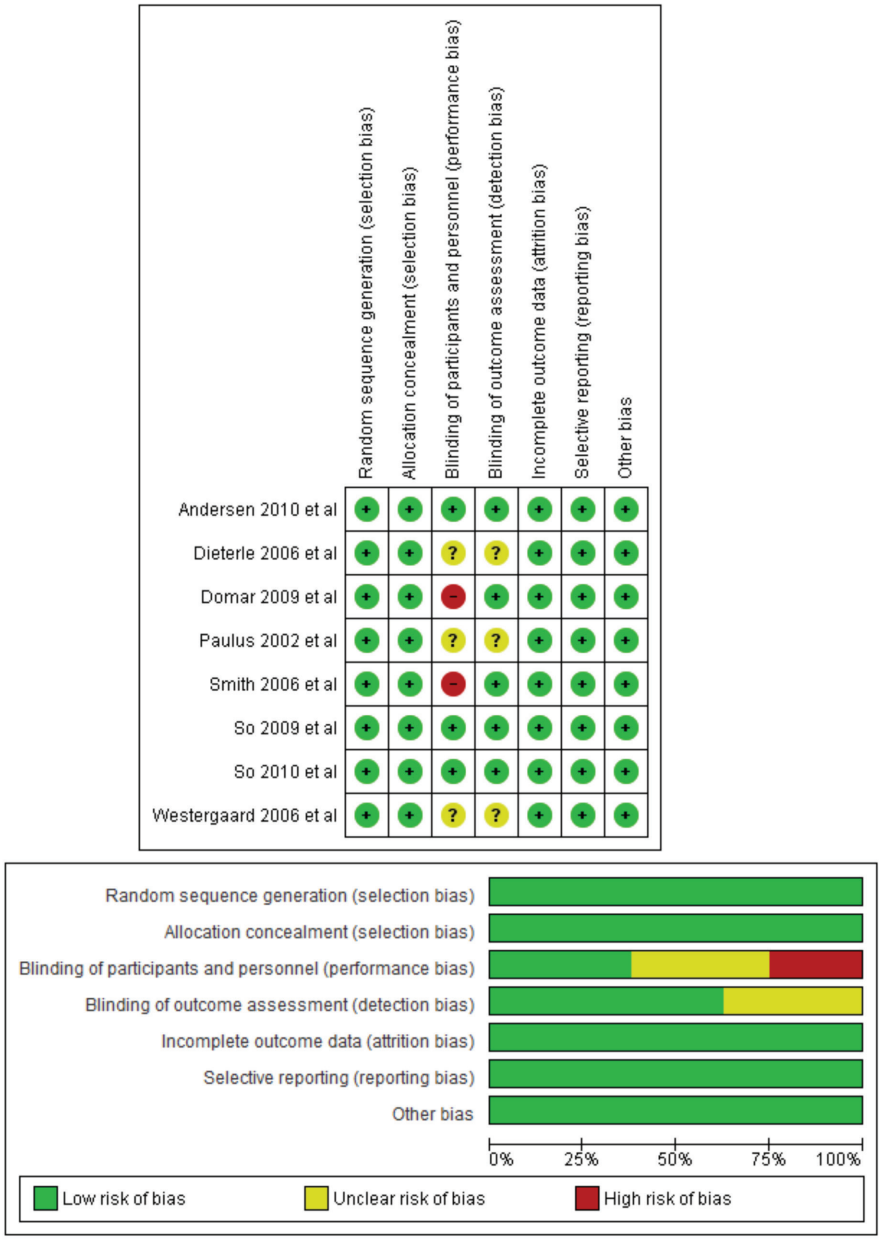


Supplemental Figure S1. Shows a PRISMA flow chart for literature search of included studies

PRISMA: Preferred reporting items for systematic reviews and meta-analyses



Supplemental Figure S2. Shows a detailed risk of bias assessment and risk of bias graph of included trials