Repetitive Transcranial Magnetic Stimulation (RTMS) on Chronic Tinnitus: a Systematic Review and Meta-Analysis

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Abstract

**Background:** Although the clinical efficacy and safety of repeated transcranial magnetic stimulation (rTMS) on the treatment of chronic tinnitus have been frequently reported, the results remain controversial. Therefore, its related clinical efficacy and safety were systematically evaluated and meta-classified in this study.

**Methods:** Literature on repeated transcranial magnetic stimulation (rTMS) on chronic tinnitus was retrieved in PubMed, Embase and Cochrane Library due April 2020. Review Manager 5.3 software was applied to data synthesis, and Stata 13.0 software was adopted for analyses of publication bias and sensitivity.

**Results:** A total of 29 randomized studies with 1,228 patients were included. Compared with sham rTMS, rTMS showed statistical significance in tinnitus handicap inventory (THI) scores 1 week after intervention (MD -7.92, 95% confidence interval [CI] -14.18, -1.66), THI scores 1 month after intervention (MD -8.52, 95% CI -12.49, -4.55), THI scores 6 months after intervention (MD -6.53, 95% CI -11.406, -1.66), TQ scores 1 week after intervention (MD -8.54, 95% CI -15.56, -1.52), mean change in THI scores 1 month after intervention (MD -14.86, 95% CI -21.42, -8.29) and mean change in THI scores 6 months after intervention (MD -16.37, 95% CI -20.64, -12.11). There was no statistical difference between rTMS and sham rTMS in THI scores 2 weeks after intervention (MD -1.51, 95% CI -13.42, -10.40), tinnitus questionnaire (TQ) scores 1 month after intervention (MD -8.97, 95% CI -20.41, 2.48), TQ scores 6 months after intervention (MD -7.02, 95% CI -18.18, 4.13), mean change in TQ scores 1 month after intervention (MD -3.67, 95% CI -8.56, 1.22) and adverse events (OR 1.11, 95% CI 0.51, 2.42). Egger's and Begg's tests indicated no publication bias (P = 0.925).

**Conclusion:** It was demonstrated that rTMS on chronic tinnitus has certain clinical curative effect and high safety, however, due to the lack of included studies and the small sample size, more large-sample, multi-center, randomized double-blind trials are needed for further verification.

1. Background

Tinnitus is a common auditory symptom that can cause severe stress when co-existing with other symptoms. Studies have shown that the incidence of tinnitus in adults ranges from 10 to 19 percent[^1^-^2^], characterized by an abnormal auditory perception in the brain or ear in the absence of external acoustic or electrical stimulation. In the 2019 European multidisciplinary tinnitus guidelines, tinnitus lasting more than 6 months is defined as chronic tinnitus[^3^]. Long-term tinnitus not only brings the influence of noise to patients, but also is often accompanied by varying degrees of mood disorders. Studies have found that tinnitus seriously damages the quality of life of 1–2% of people[^4^]. According to the neurophysiological model of tinnitus, tinnitus is the abnormal electrical activity of neurons in the peripheral and central auditory pathways (including the cerebral cortex), reshaping the detection and perception process of the cortex or subcortical center, and thus causing tinnitus[^5^].
In recent years, the incidence of tinnitus has increased year by year, and in most cases, there is no cure, and there is a lack of effective standardized treatment. In recent years, several studies have shown that repetitive transcranial stimulation is effective in the treatment of chronic tinnitus. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that enables electromagnetic pulses to reach the scalp and brain to cause changes in neuronal excitability and neurotransmitter systems. In other words, it is through repetitive rTMS and different frequency of stimulation, the auditory neurons are adjusted, reduce the abnormal electrical activity of hearing central neurons, reduce the occurrence of tinnitus, thus to achieve the treatment of tinnitus. The clinical efficacy and safety of rTMS on the treatment of chronic tinnitus have been reported by many lately, but the results of studies are divergent and even controversial. So far, a Cochrane review included 5 randomized studies and concluded that rTMS was useful for tinnitus, but the sample size is relatively small and the safety of rTMS treatment was not reported in five studies. The most recent of these, a systematic review of 15 studies showed that rTMS therapy had a significant effect on tinnitus, but large-scale experimental studies were lacking.

In this study, we retrieved the published literature on rTMS on the treatment of chronic tinnitus, extracted high-relevant data for a systematic review and meta-analysis to evaluated the efficacy and safety, in a bid to provide a reference for the prevention and treatment of chronic tinnitus.

2. Methods
2.1. Search strategies

- This study was executed in line with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and reported based on the guidelines developed by the Meta-Analysis of Observational Studies in Epidemiology group. Because all the analyses were performed on the basis of previous published studies, no ethical approval or patient consent was required. In the initial screening, 2 investigators (Z-RL and GC) conducted the main search in the electronic databases of PubMed, Embase and Cochrane Library to retrieve eligible randomized controlled trial articles about rTMS on the treatment of chronic tinnitus from the inception of the databases to April 2020, without restrictions to languages or regions. The combined terms of Medical Subject Headings (MeSH) and non-MeSH were searched as follows: 'Transcranial magnetic stimulation', 'Transcranial Magnetic Stimulations', 'Magnetic Stimulation, Transcranial', 'Magnetic Stimulations, Transcranial', 'Stimulation, Transcranial Magnetic', 'Stimulations, Transcranial Magnetic', 'Transcranial Magnetic Stimulation, Single Pulse', 'Transcranial Magnetic Stimulation, Paired Pulse', 'Transcranial Magnetic Stimulation, Repetitive', 'Tinnitus', 'Ringing-Buzzing-Tinnitus', 'Ringing Buzzing Tinnitus', 'Tinnitus, Tensor Palatini Induced', 'Tensor Palatini Induced Tinnitus', 'Tinnitus, Tensor Tympani Induced', 'Tensor Tympani Induced Tinnitus', 'Pulsatile Tinnitus', 'Tinnitus, Pulsatile', 'Tinnitus, Spontaneous Oto-Acoustic Emission', 'Tinnitus, Spontaneous Oto Acoustic Emission', 'Spontaneous Oto-Acoustic Emission Tinnitus', 'Spontaneous Oto Acoustic
Emission Tinnitus’, ‘Tinnitus, Clicking’,'Clicking Tinnitus'‘Tinnitus, Leudet’,'Leudet Tinnitus’,'Tinnitus, Leudet's’,‘Leudet's Tinnitus’,'Tinnitus, Leudets’,'Tinnitus, Noise Induced’,'Induced Tinnitus, Noise’,'Noise Induced Tinnitus’,'Tinnitus, Objective’,'Objective Tinnitus’,'Tinnitus, Subjective’,'Subjective Tinnitus’,'Tinnitus of Vascular Origin’,'Tinnitus of Vascular Origin','Vascular Origin Tinnitus’,'Tinnitus, Vascular Origin’. A third investigator irrelevant to the initial procedure was consulted in case of any discrepancy. Taking the pubmed database as an example, the literature search strategy is shown in Table 1.
### Table 1
The Pubmed database literature search strategy

| #1 | "Transcranial magnetic stimulation"[Mesh] |
|----|----------------------------------------|
| #2 | Transcranial magnetic stimulation       |
| #3 | Transcranial Magnetic Stimulations      |
| #4 | Magnetic Stimulation, Transcranial      |
| #5 | Magnetic Stimulations, Transcranial     |
| #6 | Stimulation, Transcranial Magnetic     |
| #7 | Stimulations, Transcranial Magnetic    |
| #8 | Transcranial Magnetic Stimulation, Single Pulse |
| #9 | Transcranial Magnetic Stimulation, Paired Pulse |
| #10| Transcranial Magnetic Stimulation, Repetitive |
| #11|
| #12| "Tinnitus"[Mesh]                        |
| #13| Tinnitus                              |
| #14| Ringing-Buzzing-Tinnitus               |
| #15| Ringing Buzzing Tinnitus               |
| #16| Tinnitus, Tensor Palatini Induced      |
| #17| Tensor Palatini Induced Tinnitus       |
| #18| Tinnitus, Tensor Tympani Induced       |
| #19| Tensor Tympani Induced Tinnitus        |
| #20| Pulsatile Tinnitus                     |
| #21| Tinnitus, Pulsatile                    |
| #22| Tinnitus, Spontaneous Oto-Acoustic Emission |
| #23| Tinnitus, Spontaneous Oto Acoustic Emission |
| #24| Spontaneous Oto-Acoustic Emission Tinnitus |
| #25| Spontaneous Oto Acoustic Emission Tinnitus |
| #26| Tinnitus, Clicking                     |
| #27| Clicking Tinnitus                      |
2.2. Study Selection Criteria

- Two independent investigators (Z-RL and GC) analyzed the initially selected articles to verify their relevance with the topic of rTMS on the treatment of chronic tinnitus. Studies had to fulfill the following criteria for inclusion: outcome was clinical efficacy and safety of rTMS on the treatment of chronic tinnitus; study design was randomized controlled trial; participants were selected without limitations to regions, ages or social status. Trials were excluded according to following identifications: non-randomized controlled, trial duplicate or overlapping data, animal experiments, conference abstracts, letters and review articles. In case of any disagreement the results were discussed and unified by senior authors.
2.3. Data Extraction

- Data from the included studies were extracted and independently categorized by 2 of the authors (Z-RL and GC) in a predefined data extraction form. All disagreements were resolved by discussion. Design information, baseline population characteristics (mean age, sample size, course of the disease and country), interventions, clinical efficacy score, adverse events, etc from all included studies were stratified into a standardized evidence table. All the data were rechecked to ensure accuracy. Study selections were shown in a PRISMA flow diagram.

2.4. Methodological Quality Assessment

- The methodological quality of the included studies was evaluated by 2 independent reviewers (Z-RL and GC) based on the Cochrane Handbook Version 5.3 that include Random sequence generation; Allocation concealment; The blinding of participants, Personnel and outcome assessor; Incomplete outcome data; Selective reporting and other sources of bias.

2.5. Statistical Analysis

- The meta-analysis and statistical analysis were performed using Cochrane Collaboration Review Manager software (RevMan version 5.3, Nordic Cochrane center, Copenhagen, Denmark). For Dichotomous data, we used the risk ratios (RRs) or odds ratios (ORs) as the analysis of statistics. For continuous data, we used the weighted mean difference (WMD) as the analysis of statistics. The $I^2$-square ($\hat{I}^2$) test was adopted to evaluate the influence of heterogeneity on the output of meta-analysis. $\hat{I}^2$ values of 0%, 25%, 50% and 75% represented no, low, medium and high heterogeneity, respectively. According to the Cochrane review guidelines, severe heterogeneity of $\hat{I}^2 \geq 50\%$ required the utilization of random-effect models. Otherwise, the fixed effect model was approved. $P$ value less than 0.05 was accepted as statistical significance. Sensitivity analysis$^{[14]}$ was conducted by study removal approach to evaluate the quality and consistency of the results. Funnel plots were visually checked, and Egger and Begg linear regression tests of publication bias were carried out by Stata 13.0 software.

3. Results

3.1. Study selection process

As a result, 897 references were initially retrieved, 524 were left after eliminating duplicate literature; and then 477 without high-relevant to our topic were discarded by reading titles and abstracts, and 47 studies remained. Finally, 18 full-text articles were abandoned because of the following reasons: 4 studies on irrelevant topics; 1 study was viewpoint; 2 studies were protocol; 8 studies were no randomized controlled
trial; 3 studies without free online full-text materials. Therefore, 29 randomized controlled studies with 1,228 patients were included in the A Systematic Review and Meta-Analysis. The flow chart describing the selection process of the study was shown in Fig. 1.

3.2. Study Characteristics And Methodological Quality

- The 29 included references were randomized controlled studies, with the publication years differing from 2004 to 2017. 3 were conducted in China (including 1 in Taiwan), 4 in Germany, 3 in Turkey, 3 in South Korea, 6 in USA, 2 in Czech Republic and 1 in Italy, Egypt, Brazil, Australia, Netherlands, Finland, UK, Belgium, respectively. In the selected clinical trials, the sample sizes varied between 8 and 146 participants. The mean duration of tinnitus in these studies ranged from 6 to 420 months. The mean treatment Course in these studies ranged from 5 to 20 days. The basic characteristics of the 29 of them were shown in Table 2 and Table 3. In addition, the methodological quality graph (Figs. 2 and 3) presents each item for each included study as well as each item presented as percentages across all included trails according to our established quality evaluation standard.
| Inclusive trials | Country | Study design | Gender (male/female) | Age (years) | Duration of tinnitus (month) |
|------------------|---------|--------------|----------------------|-------------|-----------------------------|
| Landgrebe M 2017 | Germany | Sham-controlled, randomized multi center trial | 54/17 51/24 | 48.1 ± 12.5 49.9 ± 13.2 | 6.2 ± 5.3 8.1 ± 8.4 |
| Formánek M 2018 | Czech Republic | Randomized double-blinded controlled trial | 13/7 10/2 | 47.9 ± 14.31 51.8 ± 10.34 | 53.4 ± 61.89 76.8 ± 76.85 |
| Chung HK 2012 | China | Parallel randomized controlled study | 11/1 11/1 | 53.83 ± 18.4 51.90 ± 15.5 | 6–24 0 6–24 0 |
| Yilmaz 2014 | Turkey | Randomized controlled trial | 27/33 27/33 | 49.8 ± 8.03 (36–66) 49.8 ± 8.03 (36–66) | > 6 > 6 |
| Rossi S 2007 | Italy | Randomized, double blind, cross over, placebo controlled trial | 7/1 4/2 | 52.63 (35–72) 52.33 (37–62) | 12–300 12–300 |
| Included trials | Country       | Study design                                                                 | Gender (male/female) | Age (years) | Duration of tinnitus (month) |
|-----------------|---------------|-------------------------------------------------------------------------------|----------------------|-------------|-----------------------------|
|                 |               |                                                                               | T  | C           | T   | C           | T   | C           |
| Langguth B 2014 (1) [4] | Germany       | Randomized, double-blind, parallel-group, controlled clinical trial          | 35/13 | 31/14       | 44.9 | ± 11.5     | 50.3 | ± 12.9     | 68.0 | ± 97.0     | 74.4 | ± 74.2     |
| Langguth B 2014 (2) [4] | Germany       | Randomized, double-blind, parallel-group, controlled clinical trial          | 32/16 | 31/14       | 50.4 | ± 12.5     | 50.3 | ± 12.9     | 78.3 | ± 64.9     | 78.3 | ± 64.9     |
| Bilici S 2015   | Turkey        | Randomized, double-blind, placebo-controlled study                           | 33/42 | 33/42       | 40 ± 13.2 (20–62) | 40 ± 13.2 (20–62) | > 12 | > 12       |
| Khedr E 2009    | Egypt         | Randomized controlled trial                                                  | Unclear              | Unclear    | Unclear                   | Unclear | Unclear | Unclear | Unclear |
| Included trials | Country       | Study design                                      | Gender(male/female) | Age(years) | Duration of tinnitus(month) |
|-----------------|---------------|---------------------------------------------------|---------------------|------------|--------------------------|
| Marc ondes RA 2010[21] | Brazil        | Randomized, double-blind, parallel design, study | Unclear             | > 18       | > 6                      |
| Folmer RL 2015[22]        | USA           | Randomized, participant and clinician or observer-blinded, placebo-controlled clinical trial | 25/7 26/6           | 58.3 ± 9.5 | 62.8 ± 8.3               |
| Li LPH 2019[23]           | Taiwan, China | Randomized controlled trial                       | 7/5                 | 57 ± 10.1  | 54 ± 7.5                 |
| Noh TS 2019[24]          | South Korea   | Double-blind randomized controlled trial          | 14/3 7/6            | 51.9 ± 12.4| 55.8 ± 6.9               |

|                           |               |                                                   | 76.1 ± 129.3        | 70.1 ± 70.4|
| Included trials                  | Country               | Study design                                                   | Gender (male/female) | Age (years) | Duration of tinnitus (month) |
|---------------------------------|-----------------------|----------------------------------------------------------------|----------------------|-------------|------------------------------|
| Ander s M 2010[25]              | Czech Republic        | Randomized, placebo controlled study                          | 12/10 17/3           | 48.09       | 106.8 ± 81.6 88.4 ± 67.5    |
| Hoekstra CEL 2013[26]           | The Netherlands       | Randomized, double-blind placebo controlled clinical trial    | 26/0 15/9            | 50 ± 12     | 58(8-240) 38(12-420)        |
| Sahls ten H 2017[27]            | Finland               | Randomized, placebo controlled study                         | 13/6 14/6            | 48.9 ± 13.1 | > 6 > 6                     |
| Wang H 2016[28]                 | China                 | Randomized controlled trial                                   | 6/8 3/7              | 62.1 ± 9.81 | 6-72 6-72                   |
| Caca ce AT 2017[29]             | USA                   | Randomized single blinded sham controlled crossover study     | 30/0 30/0            | 54.2 ± 14.2 | Unclear Unclear             |
| Inclued trials | Country | Study design | Gender(male/female) | Age(years) | Duration of tinnitus(month) |
|----------------|---------|--------------|---------------------|------------|---------------------------|
|                |         |              | T       | C       | T     | C     | T     | C     |
| Piccirillo JF 2013[30] USA | Cross over, double-blind, randomized controlled trial | 9/5 | 9/5 | Median 42(22–59) | Median 42(22–59) | 6–36 | 0 | 6–36 | 0 |
| James G 2018[31] USA | Double-blind, randomized clinical trial with participant crossover | 9/3 | 9/3 | 49.2 ± 15.3 | 49.2 ± 15.3 | > 6 | > 6 |
| Kyong JS 2019(1)[32] Korea | Randomized controlled trial | 4/4 | 6/2 | 56 ± 4.9 | 50.9 ± 7.1 | > 6 | > 6 |
| Kyong JS 2019(2)[32] Korea | Randomized controlled trial | 6/2 | 6/2 | 50.9 ± 7.1 | 50.9 ± 7.1 | > 6 | > 6 |
| Roland LT 2016[33] USA | Randomized, double-blind, controlled clinical trial | 11/5 | 10/4 | Median 50 | Median 53 | > 6 | > 6 |
| Included trials | Country        | Study design                                      | Gender (male/female) | Age (years) | Duration of tinnitus (month) |
|-----------------|----------------|--------------------------------------------------|----------------------|-------------|------------------------------|
| Barwood CHS 2013 [34] | Australia     | Single blind, randomized controlled trial        | T: 2/2               | T: 29–58    | C: >12                       |
| Godbehere J 2019 [35] | UK             | A two-arm, single-blind, randomized controlled trial | Unclear              | Unclear     | Unclear                      |
| Mennemeier M 2011 [36] | USA            | Randomized, sham-controlled crossover           | Unclear              | Unclear     | 28–75                        |
| Lee HY 2013 [37]   | Korea          | Randomized controlled trial                      | 8/7                  | 53          | Mean 48                      |
| Lorenz I 2013 [38] | Germany        | Randomized, single-blind, sham-controlled trial  | 7/3                  | 49.8        | Mean 21.6                    |
| Included trials | Country       | Study design                     | Gender(male/female) | Age(years)    | Duration of tinnitus(month) |
|-----------------|---------------|----------------------------------|---------------------|--------------|----------------------------|
|                 |               |                                  | T/C                 | T/C          | T/C                        |
| Vanneste S 2012[39] | Belgium       | Randomized controlled trial      | Unclear Unclear     | 50.05 ± 11.77 | 50.05 ± 11.77 >12          |
| Plewnia C 2012(1)[40] | Germany       | Randomized controlled trial      | 10/6 8/8            | 46.4 ± 13.0   | 45.6 ± 10.3 27 ± 14 22 ± 14 |
| Plewnia C 2012(2)[40] | Germany       | Randomized controlled trial      | 7/9 8/8             | 55.8 ± 9.7    | 45.6 ± 10.3 28 ± 13 22 ± 14 |
Table 3
Characteristics of the Included Studies

| Included trials | Interventions | Position | Treatment Course(days) | Follow up | Conclusi on by author |
|-----------------|---------------|----------|-----------------------|-----------|-----------------------|
| Landgrebe M 2017[15] | 1-Hz-rTMS (2000 stimuli, 110% motor threshold) | The left temporal cortex | 10d | 6 months | No significant |
| Formanek M 2018[6] | 1-Hz-rTMS (1000 stimuli, 110% motor threshold, the left side and primary auditory cortex on both sides); 25-Hz-rTMS (300 stimuli, 80% motor threshold, the dorsolateral prefrontal cortex) | The dorsolateral prefrontal cortex or the left side and primary auditory cortex on both sides | 5d | 6 months | No significant |
| Chung HK 2012[16] | 5-Hz-rTMS (900 stimuli, 80% motor threshold) | The temporoparietal | 10d | 1 month | Significant |

rTMS = repeated transcranial magnetic stimulation, AC = auditory cortex, DLPFC = dorsolateral prefrontal cortex
| Included trials | Interventions | Position | Treatment Course(d)ays | Follow up | Conclusion by author |
|-----------------|---------------|----------|------------------------|-----------|---------------------|
| Yilmaz 2014[17] | 1-Hz-rTMS sham rTMS | Unclear | 10d | 1 month | Significant |
| Rossi S 2007[18] | 1-Hz-rTMS sham rTMS | The left temporoparietal region | 5d | 6 weeks | Significant |
| langguth B 2014(1) [4] | 1-Hz-rTMS sham rTMS | PET-based neuronavigated | 10d | 11 weeks | No significant |
| langguth B 2014(2) [4] | 1-Hz-rTMS sham rTMS | The left auditory cortex | 10d | 11 weeks | No significant |
| Bilici S 2015(1) [19] | 1-Hz-rTMS sham rTMS | The left temporoparietal region | 10d | 6 months | Significant |

rTMS = repeated transcranial magnetic stimulation, AC = auditory cortex, DLPFC = dorsolateral prefrontal cortex
| Included trials | Interventions | Position | Treatment Course(days) | Follow up | Conclusion by author |
|-----------------|---------------|----------|------------------------|-----------|---------------------|
| Bilici S 2015(2) [19] | 10-Hz-rTMS (600 stimuli, 110% motor threshold) | The left temporoparietal region | 10d | 6 months | Significant |
| Khedr EM 2009(1) [20] | 1-Hz-rTMS (1500 stimuli, 100% motor threshold) | The left temporoparietal region | 10d | 12 months | No significant |
| Khedr EM 2009(2) [20] | 10-Hz-rTMS (1500 stimuli, 100% motor threshold) | The left temporoparietal region | 10d | 12 months | Significant |
| Khedr EM 2009(3) [20] | 25-Hz-rTMS (1500 stimuli, 100% motor threshold) | The left temporoparietal region | 10d | 12 months | Significant |
| Marcondes RA 2010 [21] | 1-Hz-rTMS (1020 stimuli, 110% motor threshold) | The left temporoparietal region | 5d | 6 months | Significant |

rTMS = repeated transcranial magnetic stimulation, AC = auditory cortex, DLPFC = dorsolateral prefrontal cortex
| Included trials | Interventions | Position | Treatment Course(days) | Follow up | Conclusion by author |
|-----------------|---------------|----------|-------------------------|-----------|---------------------|
| Folmer RL 2015\[22\] | 1-Hz-rTMS (2000 stimuli, 110% or lower motor threshold) | The auditory cortex | 10d | 6 months | Significant |
| Li LPH 2019\[23\] | 1-Hz-rTMS (1800 stimuli, 110% or lower motor threshold) | The left primary auditory cortex | 5d | 1 month | Significant |
| Noh TS 2019\[24\] | 1-Hz-rTMS (2,000 pulses over the AC and 1,000 pulses over the DLPFC, 110% or lower motor threshold) | The left primary auditory cortex (AC) and left dorsolateral prefrontal cortex (DLPFC) | 4d | 8 weeks | Significant |
| Anders M 2010\[25\] | 1-Hz-rTMS (1500 stimuli, 110% or lower motor threshold) | The left primary auditory cortex | 10d | 6 months | Significant |

rTMS = repeated transcranial magnetic stimulation, AC = auditory cortex, DLPFC = dorsolateral prefrontal cortex
| Included trials | Interventions | Position | Treatment Course(days) | Follow up | Conclusion by author |
|-----------------|---------------|----------|------------------------|-----------|----------------------|
| Hoekstra CEL 2013[26] | 1-Hz-rTMS (2000 stimuli, 110% motor threshold) sham rTMS | The auditory cortex | 5d | 6 months | No significant |
| Sahlsten H 2017[27] | 1-Hz-rTMS (4000 stimuli, 100% motor threshold) sham rTMS | The left superior temporal gyrus | 10d | 6 months | No significant |
| Wang H 2016[28] | 1-Hz-rTMS (1000 stimuli, 110% motor threshold) sham rTMS | The left temporoparietal region | 10d | Unclear | Significant |
| Cacace AT 2017[29] | 1-Hz-rTMS (1200 stimuli, 110% motor threshold) sham rTMS | The temporal cortex of the left hemisphere | 5d | Unclear | Significant |
| Piccirillo JF 2013[30] | 1-Hz-rTMS (1650 stimuli, 110% motor threshold) sham rTMS | The left temporoparietal area | 20d | > 4 weeks | No significant |

rTMS = repeated transcranial magnetic stimulation, AC = auditory cortex, DLPFC = dorsolateral prefrontal cortex
| Included trials | Interventions | Position | Treatment Course(days) | Follow up | Conclusion by author |
|-----------------|---------------|----------|-------------------------|-----------|---------------------|
| James G 2018<sup>[31]</sup> | 1 OR 10-Hz-rTMS (1800 stimuli, 110% motor threshold) | The posterior superior temporal gyrus | 5d | Unclear | Significant |
| Kyong JS 2019(1)<sup>[32]</sup> | 1-Hz-rTMS | The auditory temporal cortex | Unclear | Unclear | No significant |
| Kyong JS 2019(2)<sup>[32]</sup> | 1-Hz-rTMS (stimuli: unclear, motor threshold: unclear) | The auditory temporal and the frontal regions | Unclear | Unclear | Significant |
| Roland LT 2016<sup>[33]</sup> | 1-Hz-rTMS (stimuli: unclear, 110 motor threshold) | The motor cortex | 10d or 20d | 4 weeks | No significant |
| Barwood CHS 2013<sup>[34]</sup> | 1-Hz-rTMS (2000 stimuli, 110% motor threshold) | The left primary auditory cortex | 10d | 3 months | Significant |

rTMS = repeated transcranial magnetic stimulation, AC = auditory cortex, DLPFC = dorsolateral prefrontal cortex
| Included trials    | Interventions                                      | Position                                                                 | Treatment Course(days) | Follow up | Conclusion by author |
|-------------------|---------------------------------------------------|--------------------------------------------------------------------------|------------------------|-----------|----------------------|
| Godbehere J 2019[35] | 5-Hz-rTMS (1200 stimuli, 80% motor threshold)     | The temporal-parietal region of the scalp, overlying the auditory cortex | 5d                    | 4 weeks   | No significant       |
| Mennemeier M 2011[36] | 1-Hz-rTMS (1800 stimuli, 110% motor threshold)   | The temporal cortex                                                      | 5d                    | Unclear   | Significant          |
| Lee1 HY 2013[37]    | 1-Hz-rTMS (1200 stimuli, 100% motor threshold)    | The motor cortex                                                         | 5d                    | Unclear   | Significant          |
| Lorenz I 2013[38]   | 1-Hz-rTMS (1000 stimuli, 110% motor threshold)    | The auditory cortex                                                      | 5d                    | Unclear   | Significant          |

rTMS = repeated transcranial magnetic stimulation, AC = auditory cortex, DLPFC = dorsolateral prefrontal cortex
| Included trials | Interventions | Position | Treatmen t | Follow up | Conclusion by author |
|-----------------|---------------|----------|------------|-----------|---------------------|
| Vanneste S 2012 [39] | 1 or 10 Hz-rTMS (900 stimuli, 120% motor threshold) | The left ventrolateral prefrontal cortex | 5d | 12 months | Significant (for 10 Hz) |
| Plewnia C 2012(1) [40] | 5-Hz-rTMS (2400 stimuli, 80% motor threshold) | The secondary auditory cortex | 20d | 12 weeks | No significant |
| Plewnia C 2012(2) [40] | 5-Hz-rTMS (2400 stimuli, 80% motor threshold) | The temporoparietal association cortex | 20d | 12 weeks | No significant |

rTMS = repeated transcranial magnetic stimulation, AC = auditory cortex, DLPFC = dorsolateral prefrontal cortex
Table 4
Meta-analysis results of other outcome evaluation indicators

| Outcome                                      | Included studies(n) | Included patients(T/C,n) | Heterogeneity | MD,95%CI          | P     |
|----------------------------------------------|---------------------|--------------------------|---------------|-------------------|-------|
| TQ scores 1 week after intervention         | 2                   | 38/34                    | P = 0.55, $I^2$ = 0% | -8.54(-15.56, -1.52) | 0.02  |
| TQ scores 1 month after intervention        | 2                   | 38/34                    | P = 0.15, $I^2$ = 53% | -8.97(-20.41, 2.48)   | 0.12  |
| TQ scores 6 months after intervention       | 2                   | 97/99                    | P = 0.03, $I^2$ = 79% | -7.02(-18.18, 4.13)   | 0.22  |
| Mean change in TQ scores 1 week after intervention | 3                   | 108/100                  | P = 0.04, $I^2$ = 69% | -3.67(-8.56,1.22)     | 0.14  |
| VAS scores 1 month after intervention       | 2                   | 56/54                    | P = 0.07, $I^2$ = 69% | -0.64(-1.77,0.48)     | 0.26  |
| Tinnitus loudness 1 month after intervention | 2                   | 42/40                    | P = 0.71, $I^2$ = 0%  | -1.13(-7.13,4.87)     | 0.71  |

TQ = tinnitus questionnaire, VAS = visual analogue scale, CI = confidence interval

3.3. The clinical efficacy and safety of rTMS on the treatment of chronic tinnitus

3.3.1. THI Scores 1 Week After Intervention

Of the 29 included studies, 3 reported[16,24,26] the THI scores 1 week after intervention. Because of nonsignificant heterogeneity among the studies, the fixed effect model was utilized ($I^2 = 0\%, P = 0.57$). The outcome manifested a statistically significant difference in the item between the two patient groups (MD: -7.92, 95%CI: -14.18,-1.66, $P = 0.01$). (Fig. 4)

3.3.2. THI Scores 2 Week After Intervention

Three studies[15,24,25] containing statistics on the THI scores 1 week after intervention were available for the analysis using the random effect model, with significant heterogeneity among the studies ($I^2 = 72\%, P$
The results exhibited no statistically significant differences in THI scores 1 week after intervention between the two patient groups (MD: -1.51, 95%CI: -13.42, 10.40, \( P = 0.80 \)). (Fig. 5)

### 3.3.3. THI Scores 1 Month After Intervention

Seven studies\cite{16, 17, 19, 21, 23, 24, 26} reporting statistics on the THI scores 1 month after intervention were involved in meta-analysis. There was no significant statistical heterogeneity among the studies (\( I^2 = 0\%\), \( P = 0.53 \)) and the fixed effect model was utilized. It was found that the difference in THI scores 1 month after intervention was significant between the two patient groups (MD: -8.52, 95%CI: -12.49, -4.55, \( P < 0.0001 \)). (Fig. 6)

### 3.3.4. THI Scores 6 Months After Intervention

Four studies\cite{15, 19, 21, 26} reporting statistics on the THI scores 6 months after intervention were involved in meta-analysis. There was no significant statistical heterogeneity among the studies (\( I^2 = 21\%\), \( P = 0.28 \)) and the fixed effect model was utilized. It was found that the difference in THI scores 6 months after intervention was significant between the two patient groups (MD: -6.53, 95%CI: -11.40, -1.66, \( P = 0.009 \)). (Fig. 7)

### 3.3.5. Mean change in THI scores 1 month after intervention

Three studies\cite{19, 21, 23} containing statistics on mean change in THI scores 1 month after intervention were available for the analysis using the random effect model, with significant heterogeneity among the studies (\( I^2 = 56\%\), \( P = 0.08 \)). The results exhibited a statistically significant differences in THI scores 1 month after intervention between the two patient groups (MD: -14.86, 95%CI: -21.42, -8.29, \( P < 0.00001 \)). (Fig. 8)

### 3.3.6. Mean change in THI Scores 6 Months After Intervention

Two studies\cite{19, 21} reporting statistics on mean change in THI scores 6 months after intervention were involved in meta-analysis. There was no significant statistical heterogeneity among the studies (\( I^2 = 0\%\), \( P = 0.87 \)) and the fixed effect model was utilized. It was found that the difference in mean change in THI scores 6 months after intervention was significant between the two patient groups (MD: -16.37, 95%CI: -20.64, -12.11, \( P < 0.00001 \)). (Fig. 9)

### 3.3.7. Other Outcome Evaluation Indicators
Two studies\textsuperscript{[16,26]} reporting statistics on TQ scores 1 week after intervention, 2 studies\textsuperscript{[16,26]} reporting statistics on TQ scores 1 month after intervention were involved in meta-analysis, 2 studies\textsuperscript{[15,26]} reporting statistics on TQ scores 6 months after intervention, 3 studies\textsuperscript{[4,16]} (One study\textsuperscript{[4]} included two RCTs) reporting statistics on mean change in TQ scores 1 week after intervention, 2 studies\textsuperscript{[17,26]} reporting statistics on VAS scores 1 month after intervention and 2 studies\textsuperscript{[16,17]} reporting statistics on tinnitus loudness 1 month after intervention were involved in meta-analysis. The results exhibited a statistically significant differences in TQ scores 1 week after intervention between the two patient groups ($P = 0.02$). However, it was found that the difference in other outcome after intervention were no significant between the two patient groups (MD: -6.53, 95%CI: -11.40, -1.66, $P = 0.009$). (Table.4)

### 3.3.8. Adverse Events

Data on adverse events were available for the meta-analysis from 15 studies\textsuperscript{[4,6,15,17,19,22,23,26–30,35,38]}, and nonsignificant heterogeneity was presented among the studies ($I^2 = 37\%, P = 0.13$). Therefore, the fixed effect model was applied. However, differences in adverse events between the two patient groups were still nonsignificant (OR: 1.11, 95%CI: 0.51–2.42, $P = 0.79$). (Fig. 10)

### 3.3.9. Sensitivity Analyses

The sensitivity analysis was performed on the selected studies to assess whether individual studies would affect the overall results. The results showed that there was a nonsignificant difference in the stability of the results (Fig. 11), which validated the rationality and reliability of our analysis.

### 3.3.10. Evaluation Of Publication Bias

Visual inspection of funnel plots was adopted in the estimation (Fig. 12). Specifically, Egger\textsuperscript{s} and Begg\textsuperscript{s} analyses\textsuperscript{[16,17,19,21,23,24,26]} of publication bias showed that publication bias did not exist in our meta-analysis ($P = 0.925$). (Figs. 13 and 14)

### 4. Discussion

In this study, we report results of a systematic review and meta-analysis of 29 selected RCTs of rTMS to reduce chronic tinnitus. In order to ensure reliable conclusions, we retrieved, reviewed and summarized the previously published studies on rTMS in the treatment of chronic tinnitus to achieve high levels, good compliance, and high quality to answer various clinical questions about this disease. Overall, our results suggest that repeated transcranial magnetic stimulation is effective in the treatment of chronic tinnitus. Group analysis showed that repeated transcranial magnetic stimulation for the treatment of chronic tinnitus was statistically significant among the participants. The treatment of rTMS was safe at
the intension: serious adverse events were evenly distributed between participants randomly assigned to rTMS versus sham rTMS.

Tinnitus heterogeneity and with a high incidence in the crowd, though many treatments have been used in the treatment of tinnitus, but because most of the low level of evidence therapeutic strategy, there is a lack of widely agreed to be able to reduce tinnitus loudness, reduce the impact of tinnitus and can be copied to verify the effective treatment of tinnitus methods\cite{41}. This presents a huge challenge for the ear, nose and throat doctor. Landgrebe et al. found that by repeated low-frequency rTMS stimulation on a daily basis, its biological effects had a stacking effect, which not only caused synaptic inhibition and changes in the plasticity of auditory cortex nucleus, but also affected the series changes of hemodynamics in the auditory region, showing a significant effect in the treatment of chronic tinnitus\cite{15}. Our findings from analysing the study population as a whole are consistent with those of recent aggregate data meta-analysis of RCTs of rTMS for the chronic tinnitus\cite{42}.

Our study has several strengths. The included studies were of publication of the protocol, detailed and predefined sensitivity and subgroup analyses, comprehensive assessment of the risk of systematic and random errors, and assessment of the quality of evidence. Secondly, the rationality and reliability of our meta-analysis have been prudently and significantly improved in that the overall comprehensive estimation is based on a large sample size. In addition, sufficient sensitivity analysis has been carried out to ensure the reliability of this study.

However, our review also has some limitations. On the one hand, despite the inclusion of recent large randomized trials, our analytical capabilities are still very low, because repeated transcranial magnetic stimulation has not been widely used in the clinic, the total sample of patients included in this study is still small, resulting in the loss of statistical significance in some outcome indicators. On the other hand, this study contains only English references, which leads to lost data from those in other languages. In addition, Egger’s and Begg’s analyses of publication bias showed that publication bias did not exist in our meta-analysis, however, because few studies were included in the analysis, false negatives cannot be excluded.

### 5. Conclusion

In summary, our systematic review and meta-analysis suggests that rTMS on chronic tinnitus has certain clinical curative effect and high safety, however, due to the lack of included studies and the small sample size, more large-sample, multi-center, randomized double-blind trials are needed for further verification.

### Abbreviations

rTMS
repeated transcranial magnetic stimulation, CI = condidence interval, THI = tinnitus handicap inventory, TQ = tinnitus questionnaire, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-
Analyses, MeSH = Medical Subject Headings, AC = auditory cortex, DLPFC = dorsolateral prefrontal cortex, VAS = visual analogue scale.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and the original studies’ publications.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

ZRL conceived the study idea. ZRL, GC and LFH retrieved and screened the literature. LFH and TZ conducted data extraction and evaluation of methodological quality. ZRL and GC performed statistical analyses and interpretation of corresponding results. ZRL drafted the initial manuscript. HYJ modified the initial manuscript. HYJ and HDY had primary responsibility for the final content. All authors made critical comments for the initial manuscript. All authors read and approved the final manuscript.
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Figures
Figure 1

The flow diagram of literature selection.
Figure 2

The risk of bias graph.
| Study             | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-------------------|---------------------------------------------|----------------------------------------|----------------------------------------------------------|-----------------------------------------------|----------------------------------------|-----------------------------------|-----------|
| Anders M 2010     | ? ?                                        | +                                      | +                                                        | +                                             | +                                      | +                                 | ?         |
| Banwood CHS 2013  | ? ?                                        | ?                                      | +                                                        | +                                             | ?                                      | ?                                 | ?         |
| Biici S 2013      | ? ?                                        | +                                      | +                                                        | +                                             | ?                                      | ?                                 | ?         |
| Cacace AT 2017    | ? ?                                        | ?                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Chung HK 2012     | ? ?                                        | ?                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Fölmer RL 2015    | ? ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Formanek M 2018   | + ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Godbehere J 2019  | ? ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Hoekstra CEL 2013 | + ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| James G 2018      | ? ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Khder EM 2009     | ? ?                                        | ?                                      | ?                                                        | ?                                             | ?                                      | ?                                 | ?         |
| Kyong JS 2019     | ? ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Landgrebe M 2017  | ? ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Langguth B 2014   | ? ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Lee1 HY 2013      | ? ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Li LPH 2019       | ? ?                                        | ?                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Lorenz I 2013     | ? ?                                        | +                                      | +                                                        | ?                                             | +                                      | ?                                 | ?         |
| Marcondes RA 2010 | ? ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Mennemeier M 2011 | ? ?                                        | ?                                      | ?                                                        | ?                                             | ?                                      | ?                                 | ?         |
| Non TS 2019       | + ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
| Piccirillo JF 2013| + ?                                        | +                                      | +                                                        | +                                             | +                                      | ?                                 | ?         |
Figure 3

The risk of bias summary

| Study or Subgroup | rTMS Mean | SD | Total | sham rTMS Mean | SD | Total | Mean Difference | Mean Difference |
|-------------------|----------|----|-------|----------------|----|-------|----------------|----------------|
| Chung HK 2012     | 32       | 13.21 | 12    | 38             | 9.48 | 10    | 43.4%          | -6.00 [-15.51, 3.51] |
| Hoekstra CEL 2013 | 41       | 16   | 26    | 47             | 23   | 24    | 32.0%          | -6.00 [-17.07, 5.07] |
| Noh TS 2019       | 38.1     | 16.3 | 17    | 52.9           | 19.3 | 13    | 24.6%          | -13.90 [-26.41, -1.19] |
| Total (95% CI)    | 55       |      |       | 47             |      | 100.0%| -7.92 [-14.18, -1.66]|

Heterogeneity: \( I^2 = 1.11\), \( df = 2 (P = 0.57); I^2 = 0\%
Test for overall effect: \( Z = 2.48 (P = 0.01) \)

Figure 4

Meta-analysis results of the THI scores 1 week after intervention

| Study or Subgroup | rTMS Mean | SD | Total | sham rTMS Mean | SD | Total | Weight | IV, Random, 95% CI | Mean Difference |
|-------------------|----------|----|-------|----------------|----|-------|--------|------------------|----------------|
| Anders M 2010     | 31.32    | 22.3 | 22    | 23.1           | 19.5 | 20    | 30.3%  | 8.72 [-4.11, 21.55] |
| Landgrebe M 2017  | 50.2     | 21.3 | 71    | 49             | 20.2 | 75    | 40.6%  | 1.20 [-5.54, 7.94] |
| Noh TS 2019       | 34.4     | 17.9 | 17    | 50.3           | 18.3 | 13    | 29.2%  | -15.90 [-29.41, -2.39] |
| Total (95% CI)    | 110      |      |       | 108            |      | 100.0%| -1.51 [-3.42, 0.40] |

Heterogeneity: \( Tau^2 = 73.16\), \( Ch^2 = 7.21, df = 2 (P = 0.03); I^2 = 72\%
Test for overall effect: \( Z = 0.25 (P = 0.80) \)

Figure 5

Meta-analysis results of the THI scores 2 week after intervention
Figure 6

Meta-analysis results of the THI scores 1 month after intervention

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Mean Difference | IV, Fixed, 95% CI |
|-------------------|------|----|-------|------|----|-------|----------------|------------------|
| Bilici S 2013(1)  | 40.8 | 26.7 | 25 | 43.1 | 20.7 | 25 | 13.5% | -2.20 [-15.44, 11.04] |
| Bilici S 2013(2)  | 27.5 | 18.3 | 25 | 43.1 | 20.7 | 25 | 22.2% | -15.60 [-25.93, -5.27] |
| Hoekstra CEL 2013 | 43.1 | 22.2 | 71 | 57.0 | 22.5 | 75 | 38.9% | -1.60 [-9.12, 5.92] |
| Marcondaes RA 2010| 22.8 | 13.2 | 10 | 29.6 | 23.5 | 9 | 6.5% | -6.90 [-25.85, 12.29] |
| Total (95% CI)    | 157  | 158 | 100.0% | -6.53 [-11.40, -1.66] |

Heterogeneity: Chi² = 5.06, df = 4 (P = 0.26); P = 21%
Test for overall effect: Z = 2.63 (P = 0.009)

Figure 7

Meta-analysis results of the THI scores 6 months after intervention

| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Mean Difference | IV, Random, 95% CI |
|-------------------|------|----|-------|------|----|-------|----------------|-------------------|
| Bilici S 2013(1)  | 19.1 | 21.2 | 25 | 0.7 | 5 | 25 | 26.3% | -16.70 [-27.16, -16.24] |
| Bilici S 2013(2)  | -9.1 | 8.8 | 25 | 0.7 | 5 | 25 | 41.2% | -9.80 [-13.77, -5.83] |
| Li LFH 2019       | -28.5 | 10.59 | 12 | -7.56 | 13.49 | 12 | 23.5% | -20.32 [-30.62, -11.22] |
| Marcondes RA 2010 | -10.4 | 20.2 | 10 | 0 | 24.85 | 9 | 8.5% | -10.40 [-30.90, 10.10] |
| Total (95% CI)    | 72   | 71 | 100.0% | -14.86 [-21.42, -8.29] |

Heterogeneity: Tau² = 23.15, Chi² = 8.77, df = 3 (P = 0.08); P = 56%
Test for overall effect: Z = 4.44 (P = 0.00001)

Figure 8

Meta-analysis results of the mean change in THI scores 1 month after intervention
### Figure 9

**Meta-analysis results of the mean change in THI scores 6 months after intervention**

| Study or Subgroup   | rTMS Mean SD | sham rTMS Mean SD | Mean Difference IV, Fixed, 95% CI | Heterogeneity: Chi² = 0.28, df = 2 (P = 0.87), I² = 0% | Test for overall effect: Z = 7.53 (P = 0.0001) |
|---------------------|--------------|-------------------|----------------------------------|--------------------------------------------------------|-----------------------------------------------|
| Bilici S 2013(1)    | -1.7 2.4     | 25                | 0.7 5                            | -18.40 [-27.46, -9.40]                                  |                                               |
| Bilici S 2013(2)    | -15.2 11.7   | 25                | 0.7 5                            | -15.90 [-20.68, -10.91]                                 |                                               |
| Martindale RA 2016  | -7 20.5      | 10                | 7 23.65                          | -14.00 [-24.30, 0.80]                                   |                                               |
| **Total (95% CI)**  | **60**       | **59**            | **100.0%**                       | **-16.37 [-20.64, -12.11]**                            |                                               |

### Figure 10

**Meta-analysis results of the adverse events after intervention**

| Study or Subgroup   | rTMS Events Total | sham rTMS Events Total | Odds Ratio M-H, Random, 95% CI | Total (95% CI) | Total events | Heterogeneity: Tau² = 0.42, Chi² = 11.13, df = 7 (P = 0.13), I² = 37% | Test for overall effect: Z = 0.27 (P = 0.79) |
|---------------------|-------------------|------------------------|-------------------------------|----------------|--------------|--------------------------------------------------------------------------|-----------------------------------------------|
| Bilici S 2013(1)    | 1 25              | 0 25                   | 3.12 [0.12, 80.39]            | 462            | 462          |                                                                          |                                               |
| Bilici S 2013(2)    | 5 25              | 0 25                   | 13.68 [0.71, 262.17]          |                |              |                                                                          |                                               |
| Casace AT 2017      | 0 25              | 0 25                   | Not estimable                 |                |              |                                                                          |                                               |
| Formanek M 2018     | 3 19              | 3 10                   | 0.44 [0.07, 2.73]             |                |              |                                                                          |                                               |
| Goddehove J 2019    | 3 23              | 0 20                   | 7.00 [0.34, 144.27]           |                |              |                                                                          |                                               |
| Hoekstra CEL 2013   | 5 26              | 1 24                   | 5.46 [0.50, 50.78]            |                |              |                                                                          |                                               |
| Landgrebe M 2017    | 31 74             | 43 76                  | 0.55 [0.29, 1.06]             |                |              |                                                                          |                                               |
| Langguth B 2014(1)  | 0 48              | 0 48                   | Not estimable                 |                |              |                                                                          |                                               |
| Langguth B 2014(2)  | 0 48              | 0 45                   | Not estimable                 |                |              |                                                                          |                                               |
| Li LPH 2019         | 0 12              | 0 12                   | Not estimable                 |                |              |                                                                          |                                               |
| Lorenz 2013         | 0 10              | 0 10                   | Not estimable                 |                |              |                                                                          |                                               |
| Plewnia C 2012(1)   | 5 16              | 6 16                   | 0.76 [0.18, 3.27]             |                |              |                                                                          |                                               |
| Plewnia C 2012(2)   | 5 16              | 6 16                   | 0.76 [0.18, 3.27]             |                |              |                                                                          |                                               |
| Sahilsten H 2017    | 0 19              | 0 20                   | Not estimable                 |                |              |                                                                          |                                               |
| Wang H 2015         | 0 14              | 0 10                   | Not estimable                 |                |              |                                                                          |                                               |
| Yilmaz 2014         | 0 30              | 0 30                   | Not estimable                 |                |              |                                                                          |                                               |
| **Total (95% CI)**  | **462**           | **441**                | **100.0%**                     | **1.11 [0.51, 2.42]**                                  |                                               |

**Heterogeneity: Tau² = 0.42, Chi² = 11.13, df = 7 (P = 0.13), I² = 37%**

**Test for overall effect: Z = 0.27 (P = 0.79)**
Figure 11

Influence analysis of included studies.

Figure 12

Funnel plot of the THI scores 1 month after intervention
Figure 13
Egger's funnel plot

Figure 14
Begg's funnel plot