

## **SUPPLEMENTARY INFORMATION**

### **Efficacy of Transcranial Alternating Current Stimulation for Major Depressive Disorder and the Role of Intensity: A Systematic Review and Exploratory Meta-Analysis**

Qi *et al.*

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## Supplementary Tables

### Supplementary Table 1. PRISMA 2020 Checklist.

| Section and Topic             | Item # | Checklist item                                                                                                                                                                                                                                                                                       | Location where item is reported |
|-------------------------------|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| <b>TITLE</b>                  |        |                                                                                                                                                                                                                                                                                                      |                                 |
| Title                         | 1      | Identify the report as a systematic review.                                                                                                                                                                                                                                                          | #1                              |
| <b>ABSTRACT</b>               |        |                                                                                                                                                                                                                                                                                                      |                                 |
| Abstract                      | 2      | See the PRISMA 2020 for Abstracts checklist.                                                                                                                                                                                                                                                         | #1                              |
| <b>INTRODUCTION</b>           |        |                                                                                                                                                                                                                                                                                                      |                                 |
| Rationale                     | 3      | Describe the rationale for the review in the context of existing knowledge.                                                                                                                                                                                                                          | #2                              |
| Objectives                    | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses.                                                                                                                                                                                                               | #2                              |
| <b>METHODS</b>                |        |                                                                                                                                                                                                                                                                                                      |                                 |
| Eligibility criteria          | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.                                                                                                                                                                                          | #2-3                            |
| Information sources           | 6      | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.                                                                                            | #3, Figure S1                   |
| Search strategy               | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used.                                                                                                                                                                                 | #3, Table S2                    |
| Selection process             | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.                     | #3                              |
| Data collection process       | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | #3                              |
| Data items                    | 10a    | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.                        | #3                              |
|                               | 10b    | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.                                                                                         | #3                              |
| Study risk of bias assessment | 11     | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.                                    | #4                              |

| Section and Topic             | Item # | Checklist item                                                                                                                                                                                                                                              | Location where item is reported |
|-------------------------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Effect measures               | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.                                                                                                                         | #3                              |
| Synthesis methods             | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).                                        | #3                              |
|                               | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.                                                                                                       | #3                              |
|                               | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses.                                                                                                                                                      | Fig. 1-2, S5-S9                 |
|                               | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | #3-4                            |
|                               | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).                                                                                                                        | #3                              |
|                               | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results.                                                                                                                                                                | Fig. S8-S9                      |
| Reporting bias assessment     | 14     | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).                                                                                                                                     | #4, Fig. S4                     |
| Certainty assessment          | 15     | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.                                                                                                                                                       | #9                              |
| <b>RESULTS</b>                |        |                                                                                                                                                                                                                                                             |                                 |
| Study selection               | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.                                                                | #4, Fig. S1                     |
|                               | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.                                                                                                                                 | #4                              |
| Study characteristics         | 17     | Cite each included study and present its characteristics.                                                                                                                                                                                                   | #4-5                            |
| Risk of bias in studies       | 18     | Present assessments of risk of bias for each included study.                                                                                                                                                                                                | #4, Table S3                    |
| Results of individual studies | 19     | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.                            | #4-7, Fig. 1, Fig. S5-S7        |
| Results of                    | 20a    | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.                                                                                                                                                      | #4-5                            |

| Section and Topic                              | Item # | Checklist item                                                                                                                                                                                                                                                                       | Location where item is reported |
|------------------------------------------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| syntheses                                      | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | #4-7, Fig. 1, Fig. S5-S7        |
|                                                | 20c    | Present results of all investigations of possible causes of heterogeneity among study results.                                                                                                                                                                                       | #4-9, Fig. 1, Fig. S5-S7        |
|                                                | 20d    | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.                                                                                                                                                                           | NA                              |
| Reporting biases                               | 21     | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.                                                                                                                                                              | #4, Table S3                    |
| Certainty of evidence                          | 22     | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.                                                                                                                                                                                  | #9, Fig. 1, Fig. S5-S7          |
| <b>DISCUSSION</b>                              |        |                                                                                                                                                                                                                                                                                      |                                 |
| Discussion                                     | 23a    | Provide a general interpretation of the results in the context of other evidence.                                                                                                                                                                                                    | #6-8                            |
|                                                | 23b    | Discuss any limitations of the evidence included in the review.                                                                                                                                                                                                                      | #8-9                            |
|                                                | 23c    | Discuss any limitations of the review processes used.                                                                                                                                                                                                                                | #8-9                            |
|                                                | 23d    | Discuss implications of the results for practice, policy, and future research.                                                                                                                                                                                                       | #8-9                            |
| <b>OTHER INFORMATION</b>                       |        |                                                                                                                                                                                                                                                                                      |                                 |
| Registration and protocol                      | 24a    | Provide registration information for the review, including register name and registration number, or state that the review was not registered.                                                                                                                                       | #2                              |
|                                                | 24b    | Indicate where the review protocol can be accessed, or state that a protocol was not prepared.                                                                                                                                                                                       | #2                              |
|                                                | 24c    | Describe and explain any amendments to information provided at registration or in the protocol.                                                                                                                                                                                      | NA                              |
| Support                                        | 25     | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.                                                                                                                                                        | #10                             |
| Competing interests                            | 26     | Declare any competing interests of review authors.                                                                                                                                                                                                                                   | #10                             |
| Availability of data, code and other materials | 27     | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.                                           | NA                              |

*Note.* Adapted from Page et al. (2021).

**Supplementary Table 2. Detailed search strategy and results for each database.**

| Database             | Search Strategy                                                                        |                                                                                                                                                                                                 | Results    |
|----------------------|----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| PubMed               | #1                                                                                     | "Depressive Disorder"[Mesh] OR "Depressive Disorder, Major"[Mesh] OR "depression":ti,ab,kw OR "MDD":ti,ab,kw                                                                                    | 551,995    |
|                      | #2                                                                                     | "Transcranial Electrical Stimulation"[Mesh] OR "transcranial alternating current stimulation":ti,ab,kw OR "tACS":ti,ab,kw                                                                       | 2,627      |
|                      | #3                                                                                     | #1 AND #2                                                                                                                                                                                       | <b>116</b> |
| Embase               | #1                                                                                     | 'depression'/exp OR 'depression' OR 'depressive disorder'/exp OR 'depressive disorder' OR 'major clinical depression' OR 'major depression':ab,ti OR 'depressive disorder':ab,ti OR 'mdd':ab,ti | 1,118,856  |
|                      | #2                                                                                     | 'transcranial alternating current stimulation'/exp OR 'transcranial alternating current stimulation':ab,ti OR 'tacs':ab,ti OR (('alternating' NEAR/3 'current stimulation'):ab,ti)              | 4,984      |
|                      | #3                                                                                     | #1 AND #2                                                                                                                                                                                       | <b>355</b> |
| Web of Science       | #1                                                                                     | TS=("Major Depressive Disorder" OR "Depression" OR "Depressive Disorder" OR "MDD" OR "Unipolar Depression" OR "Affective Disorder")                                                             | 678,603    |
|                      | #2                                                                                     | TS=("Transcranial Alternating Current Stimulation" OR "tACS" OR "Alternating Current Stimulation" OR "cranial alternating current stimulation")                                                 | 3,165      |
|                      | #3                                                                                     | #1 AND #2                                                                                                                                                                                       | <b>192</b> |
| The Cochrane Library | #1                                                                                     | [mh "Depressive Disorder, Major"] OR "major depressive disorder":ti,ab,kw OR "major depression":ti,ab,kw                                                                                        | 18,326     |
|                      | #2                                                                                     | [mh "Transcranial Electrical Stimulation"] OR "transcranial alternating current stimulation":ti,ab,kw OR "tACS":ti,ab,kw                                                                        | 971        |
|                      | #3                                                                                     | #1 AND #2                                                                                                                                                                                       | <b>51</b>  |
| ClinicalTrials.gov   | #1                                                                                     | AREA[ConditionSearch](Major Depressive Disorder OR Depression)                                                                                                                                  | 11,970     |
|                      | #2                                                                                     | AREA[InterventionSearch](Transcranial Alternating Current Stimulation OR tACS)                                                                                                                  | 306        |
|                      | #3                                                                                     | #1 AND #2                                                                                                                                                                                       | <b>30</b>  |
| WHO ICTRP            | "depression AND tACS" OR "depressive AND transcranial alternating current stimulation" |                                                                                                                                                                                                 | <b>6</b>   |

*Note.* Latest updated search was conducted on January 5, 2026. Three major bibliographic databases (Embase, PubMed, and Web of Science) and three registration databases (The Cochrane Library, ClinicalTrials.gov, and WHO ICTRP) were searched. The search strategies were adapted to the specific syntax of each database to ensure maximum sensitivity and specificity.

**Supplementary Table 3. Assessment of study quality.**

| Study                   | Random sequence generation                                                                                                         | Allocation concealment                                                                            | Blinding of participants and personnel                                                             | Blinding of outcome assessment                                                                     | Incomplete outcome data                                                                     | Selective reporting                            | Other bias                           |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------|--------------------------------------|
| Alexander et al. (2019) | Randomized study codes prepared by a member of the research lab, who was not involved in the study otherwise.                      | Stimulation protocol controlled by a custom Matlab interface based on the study code.             | All authors and study team members were blinded to group assignments until the study's completion. | All authors and study team members were blinded to group assignments until the study's completion. | Attrition rate 18.8% (>10%). ITT analysis employed to handle missing data.                  | All predefined outcome measures were reported. | No other sources of bias identified. |
| Gehrmann et al. (2024)  | No restrictions on randomization for the initial 250 participants; excess randomizations beyond 250 were balanced in blocks of 10. | Randomization performed by an unblinded investigator who had no direct contact with participants. | Not explicitly mentioned.                                                                          | Not explicitly mentioned.                                                                          | Missing data was minimal and did not impact the results.                                    | All predefined outcome measures were reported. | No other sources of bias identified. |
| Wang et al. (2022)      | According to a computer-generated list of random numbers.                                                                          | Randomization based on a computer-generated list of random numbers.                               | Participants were assigned a group via sealed envelopes containing randomization codes.            | Blinding was maintained for participants, staff, and assessors to the group allocation.            | Low attrition rate . Data were analyzed using the ITT principle with worst-case imputation. | All predefined outcome measures were reported  | No other sources of bias identified. |
| Zhou et al. (2024)      | Randomization sequence generated using a random number table in SAS 9.4 by a statistician not involved in the trial.               | Group assignments were placed in sealed envelopes and opened by researchers at enrollment.        | Device operators aware of allocation codes; participants and outcome assessors remained blinded.   | Blinding maintained for both participants and operators regarding the type of stimulation.         | Attrition rate 13.6% (>10%). ITT analysis employed to handle missing data.                  | All predefined outcome measures were reported  | No other sources of bias identified. |

*Note.* ITT: Intention-to-Treat analysis; SAS: Statistical Analysis System.

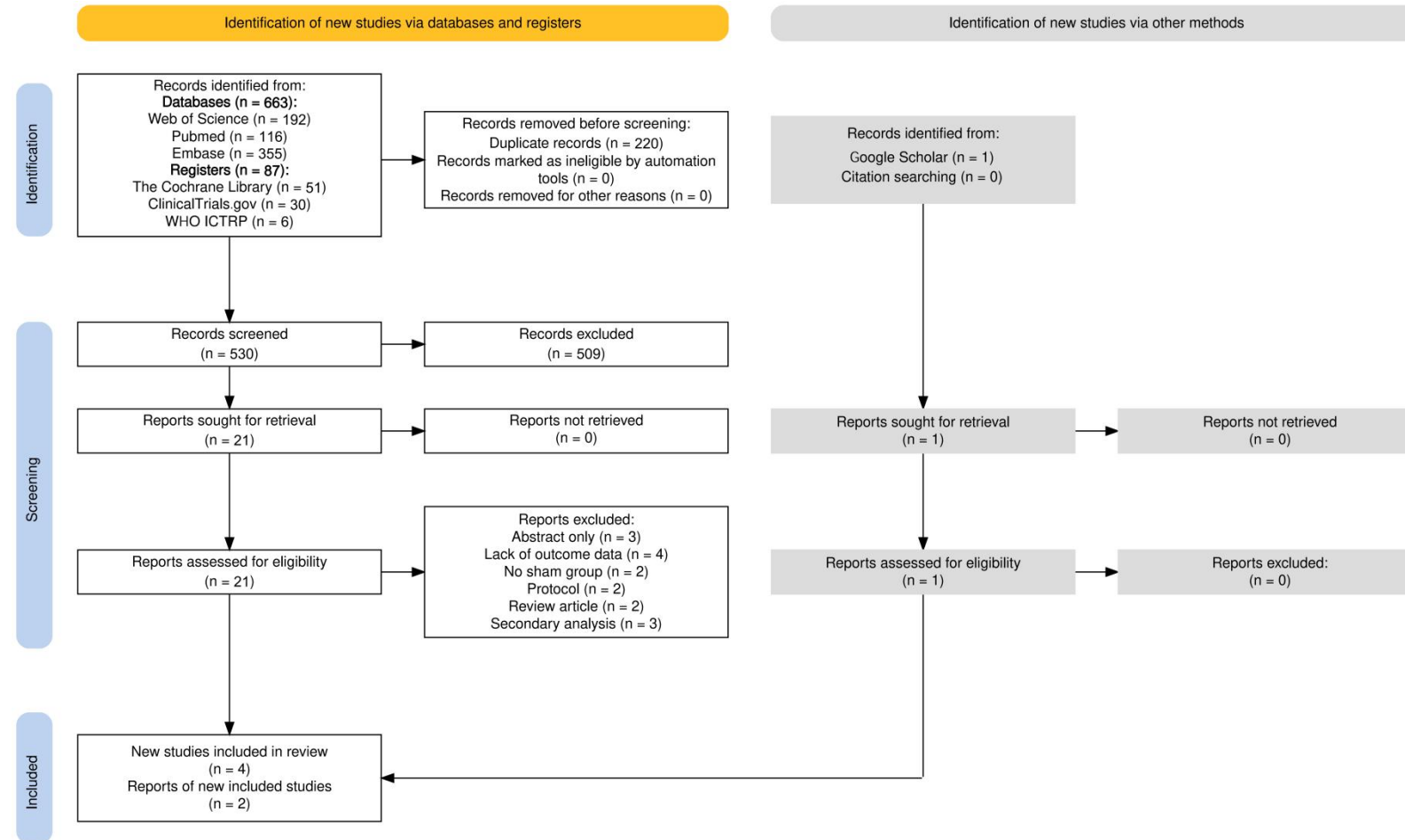
**Supplementary Table 4. Conceptual Comparison of Parameters and Theoretical Rationale Across Neuromodulation Technologies (Peterchev et al., 2010; Deng et al., 2011; Sackeim, 2017; Pan et al., 2023).**

| Modality                      | Typical Current                  | Primary Therapeutic Rationale                                                 |
|-------------------------------|----------------------------------|-------------------------------------------------------------------------------|
| Historical ECT<br>(Sine-wave) | Variable (Constant Voltage)      | Induction of a generalized seizure                                            |
| Modern ECT<br>(Brief-pulse)   | 800 to 900 mA (Constant Current) | Induction of a generalized seizure with minimal energy to reduce side effects |
| LI-tACS                       | ~2 mA                            | Modulation of cortical neural oscillations                                    |
| HI-tACS                       | ~15 mA                           | Modulation of cortical and deep structure neural oscillations                 |

*Note.* ECT: Electroconvulsive Therapy; LI-tACS: Low-Intensity Transcranial Alternating Current Stimulation; HI-tACS: High-Intensity Transcranial Alternating Current Stimulation; mA: milliamperes.



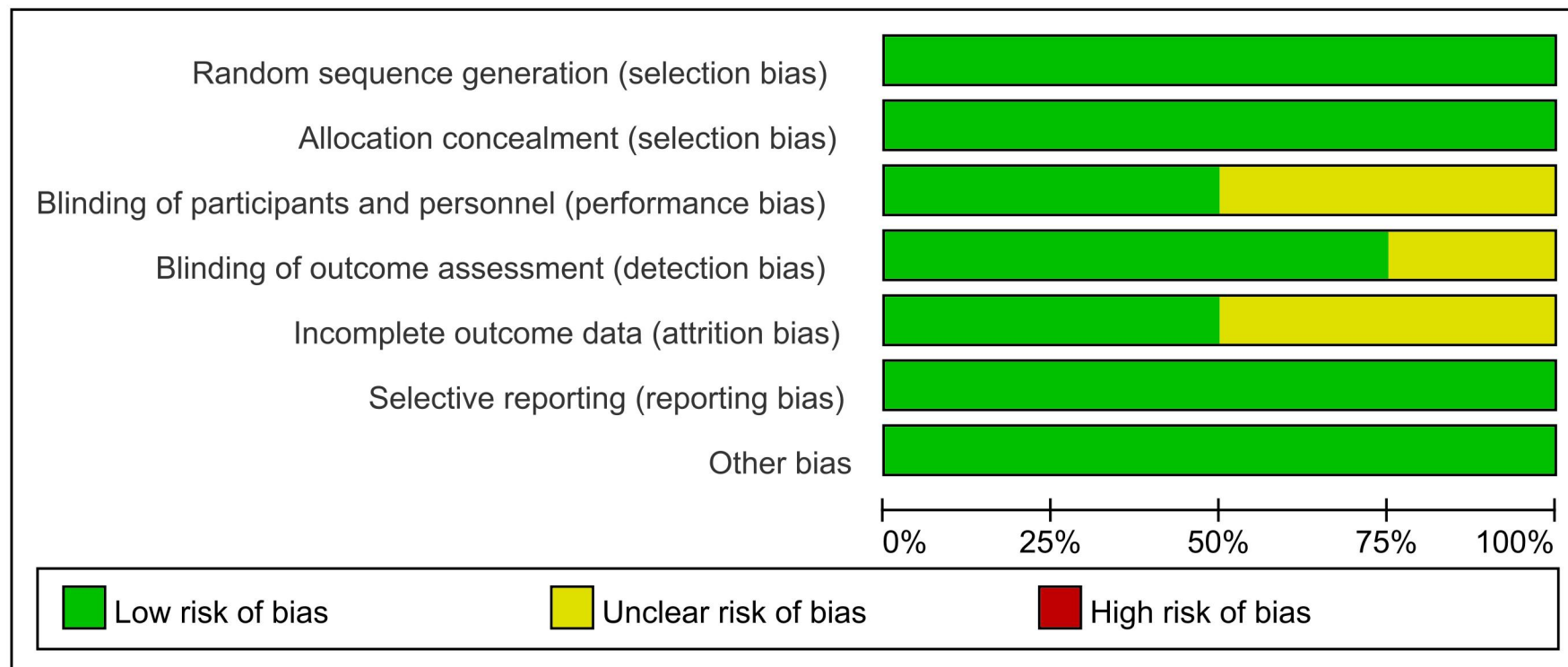
## Supplementary Figures



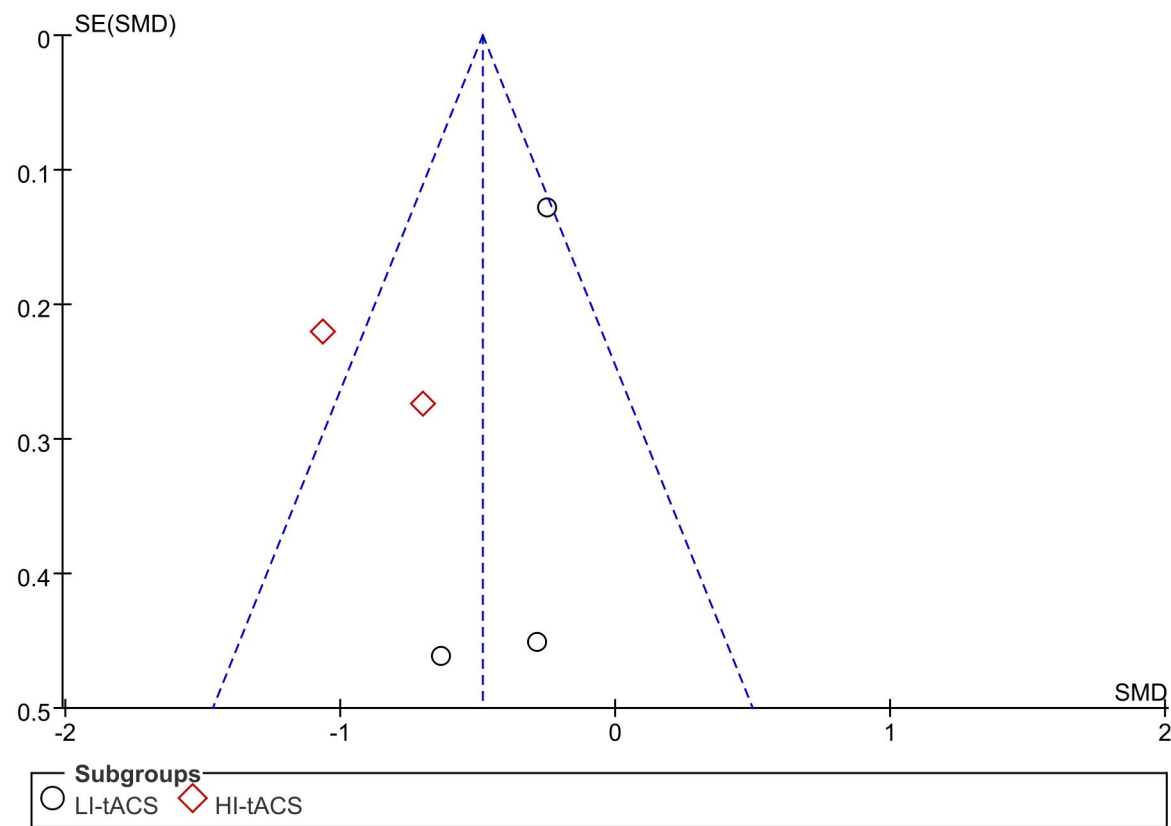
**Supplementary Fig. 1. PRISMA 2020 flow diagram illustrating the search results and study selection process.** The flowchart complied with PRISMA 2020 and was generated using the method provided by Haddaway et al. (2022).

|                | 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 |
|----------------|---------------------------------------------|-----------------------------------------|-----------------------------------------------------------|-------------------------------------------------|------------------------------------------|--------------------------------------|------------|
| Alexander 2019 | +                                           | +                                       | +                                                         | +                                               | ?                                        | +                                    | +          |
| Gehrman 2024   | +                                           | +                                       | ?                                                         | ?                                               | +                                        | +                                    | +          |
| Wang 2022      | +                                           | +                                       | +                                                         | +                                               | +                                        | +                                    | +          |
| Zhou 2024      | +                                           | +                                       | ?                                                         | +                                               | ?                                        | +                                    | +          |

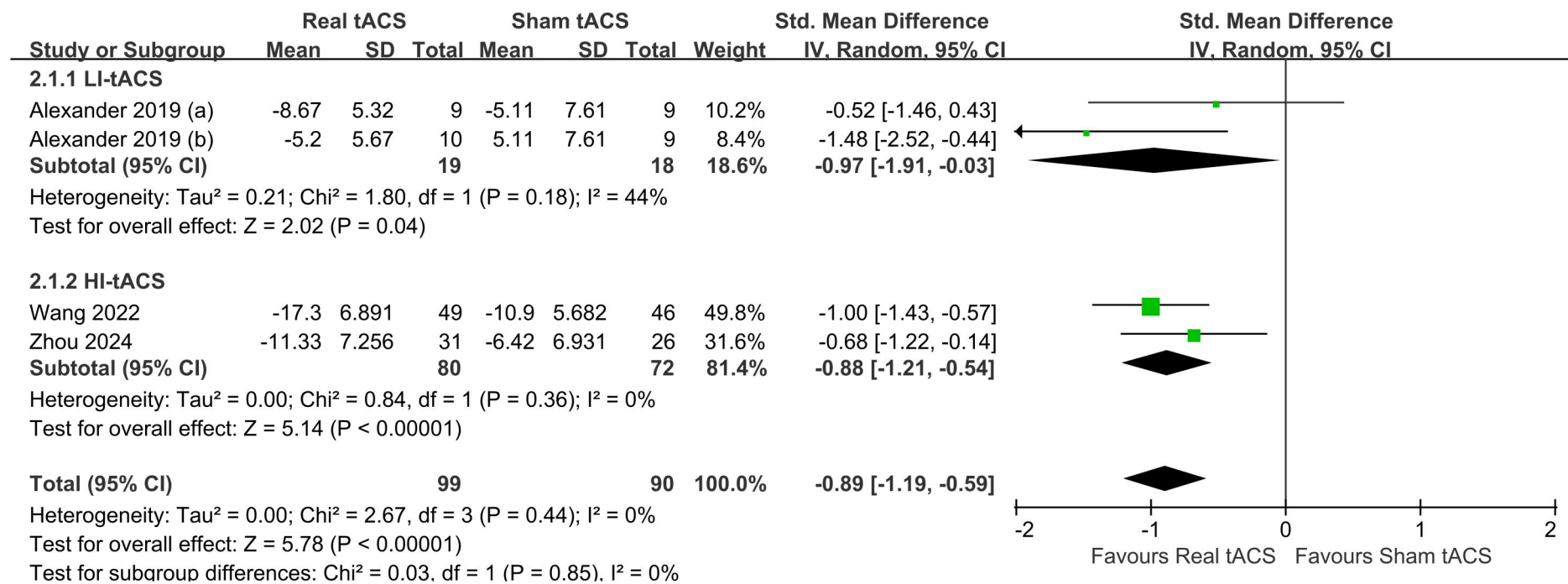
**Supplementary Fig. 2. Risk of bias assessment for individual studies.**



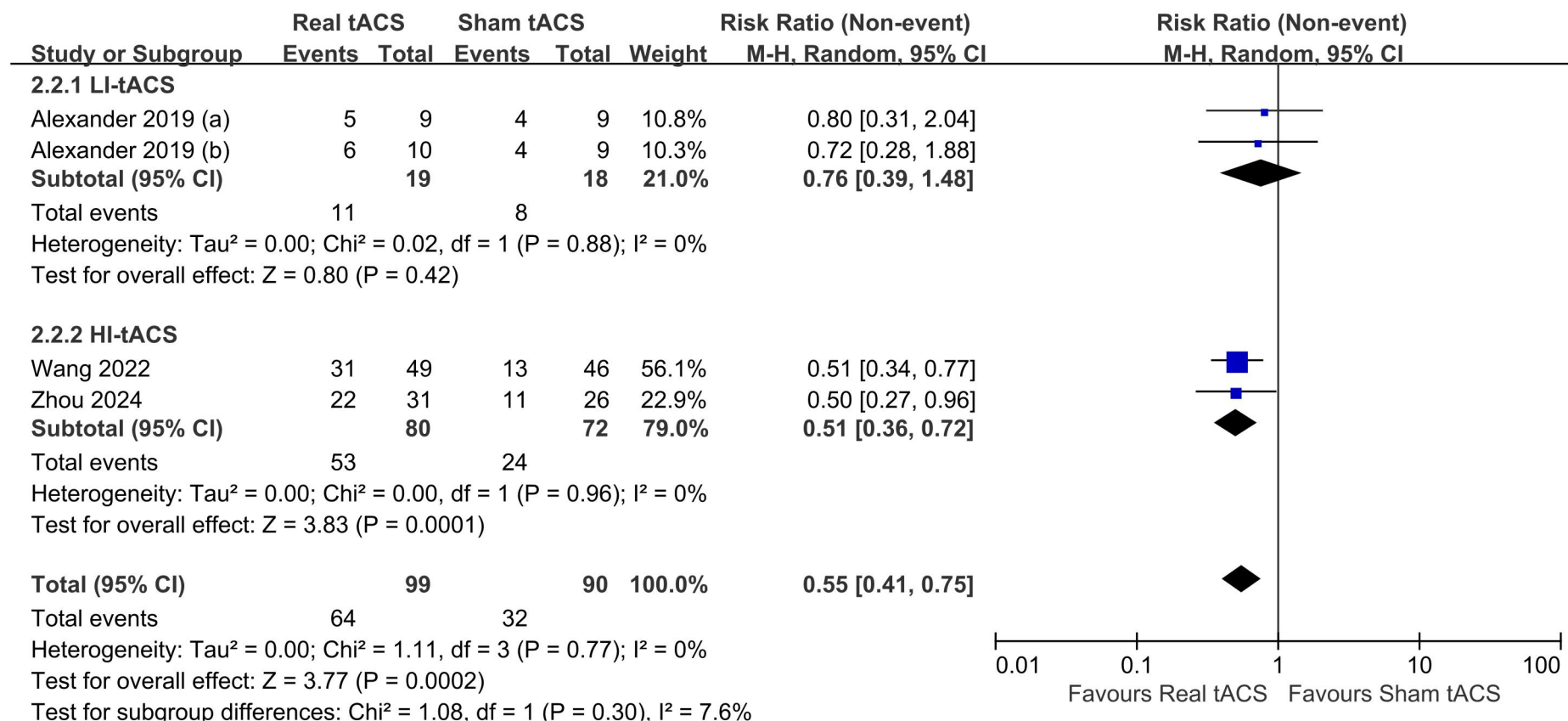
**Supplementary Fig. 3. Risk of bias summary for all included studies.**



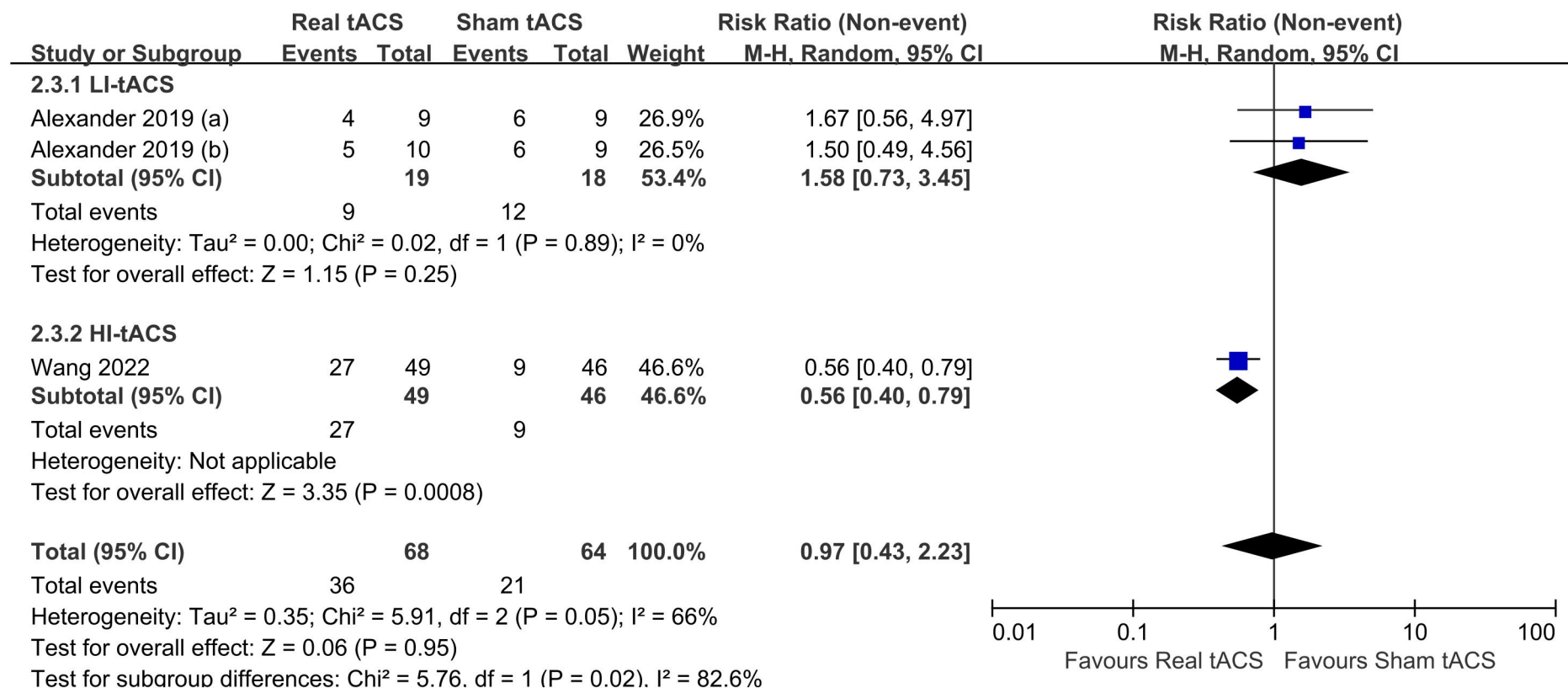
**Supplementary Fig. 4. Funnel plot of the main outcome.** Abbreviations: SE: Standard Error; SMD: Standardized Mean Difference.



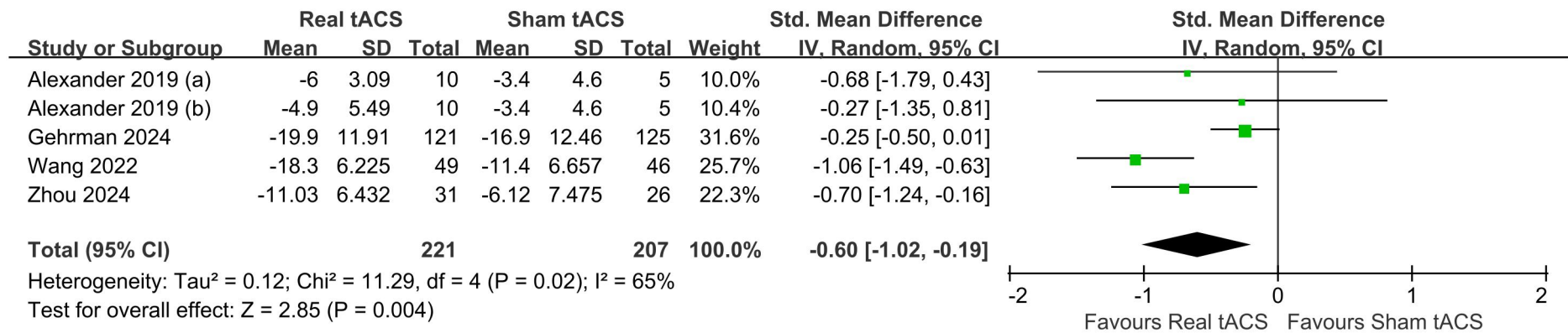
**Supplementary Fig. 5. Forest plot of the reduction in depressive symptom scores at follow-up.** Abbreviations: CI: Confidence Interval; IV: Inverse Variance; SD: Standard Deviation; df: degrees of freedom; SMD: Standardized Mean Difference.



**Supplementary Fig. 6. Forest plot of response rates at follow-up.** Abbreviations: CI: Confidence Interval; df: degrees of freedom; RR: Risk Ratio; M-H: Mantel-Haenszel.

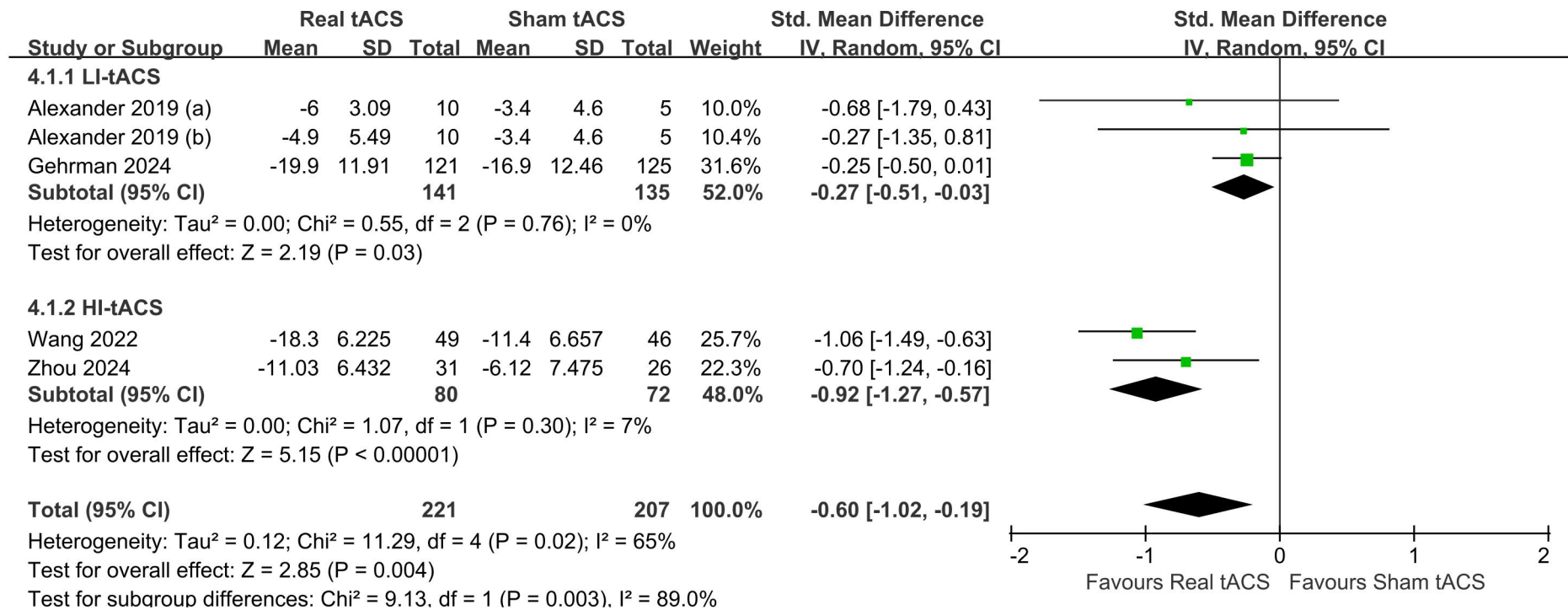


**Supplementary Fig. 7. Forest plot of remission rates at follow-up.** Abbreviations: CI: Confidence Interval; df: degrees of freedom; RR: Risk Ratio; M-H: Mantel-Haenszel.



**Supplementary Fig. 8. Sensitivity analysis of the overall effect of tACS on depressive symptoms.** This forest plot shows a sensitivity analysis correcting the unit-of-analysis error from the multi-arm Alexander et al. (2019) trial. The analysis was conducted using the Cochrane-recommended splitting the shared control group method. The overall pooled effect remains significant, confirming the robustness of the primary finding. Abbreviations: CI: Confidence Interval; IV: Inverse Variance; SD: Standard Deviation; df: degrees of freedom; SMD: Standardized Mean Difference.





**Supplementary Fig. 9. Sensitivity analysis of the subgroup analysis by current intensity.** This sensitivity analysis applies the splitting the shared control group method to the Alexander et al. (2019) study within the LI-tACS subgroup. The analysis confirms the robustness of the paper's central conclusion: the effect of HI-tACS (SMD = -0.92) remains significantly larger than that of LI-tACS (SMD = -0.27), as demonstrated by the test for subgroup differences ( $p = 0.003$ ). Abbreviations: CI: Confidence Interval; IV: Inverse Variance; SD: Standard Deviation; df: degrees of freedom; SMD: Standardized Mean Difference; RR: Risk Ratio; M-H: Mantel-Haenszel.

## Supplementary References

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