



Harnessing Gamma: Randomized Placebo-Controlled Evidence for 40 Hz Sensory Stimulation in Alzheimer's Disease

Jamir Pitton Rissardo¹, Saleha Khan², Ana Letícia Fornari Caprara¹, Ammarah Tayyebah², Aleena Zobairi², Nesa Ansari²



¹Cooper University Hospital, Camden, New Jersey, USA, ²Batterjee Medical College, Jeddah, Saudi Arabia

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Meta-analysis of 5 randomized placebo-controlled trials indicates 40 Hz sensory stimulation is safe and feasible in Alzheimer's disease, with inconsistent signals toward structural, cognitive, and functional benefit

Background

1. Gamma-band (40 Hz) neural oscillations are implicated in cognition and synaptic plasticity
2. Preclinical studies suggest 40 Hz sensory stimulation may modify Alzheimer's disease(AD) pathology
3. Clinical efficacy and safety of this approach remain uncertain

Objective: to systematically evaluate randomized, placebo-controlled trials of 40Hz sensory stimulation on neuroimaging, cognitive, functional, and safety outcomes in AD

Methodology

1. Systematic review and meta-analysis of PubMed-indexed randomized, placebo-controlled trials. Included studies evaluating 40 Hz neuromodulation in patients with AD.
2. Screening and study selection were performed according to predefined eligibility criteria.
3. Data extracted on:
 - Whole-brain volume
 - Cognitive performance
 - Activities of daily living (ADLs)
 - Adverse events
4. Continuous outcomes were analyzed using standardized mean differences (SMD; Hedges' g) with 95% confidence intervals (CIs).
5. Dichotomous outcomes were analyzed using risk ratios (RRs) with 95% CIs. Heterogeneity was assessed using the I^2 statistic.
6. Fixed-effects models are used for low heterogeneity; random-effects models are used when heterogeneity is substantial. Statistical significance is defined as $p < 0.05$.

Results

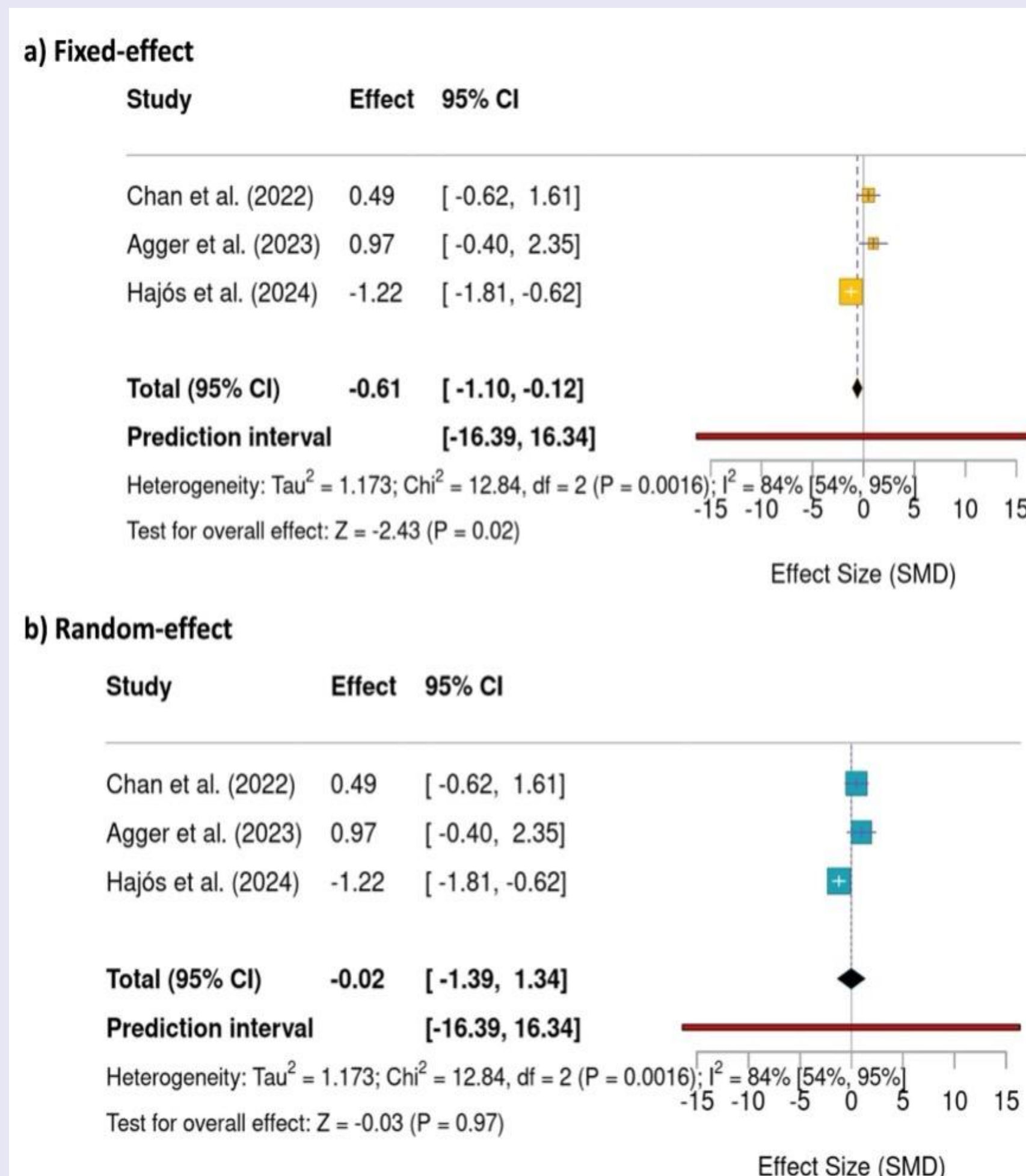


Figure 1. Meta-analysis of randomized placebo-controlled trials evaluating whole-brain volume changes following 40 Hz gamma sensory stimulation in Alzheimer's disease, using fixed- and random-effects models.

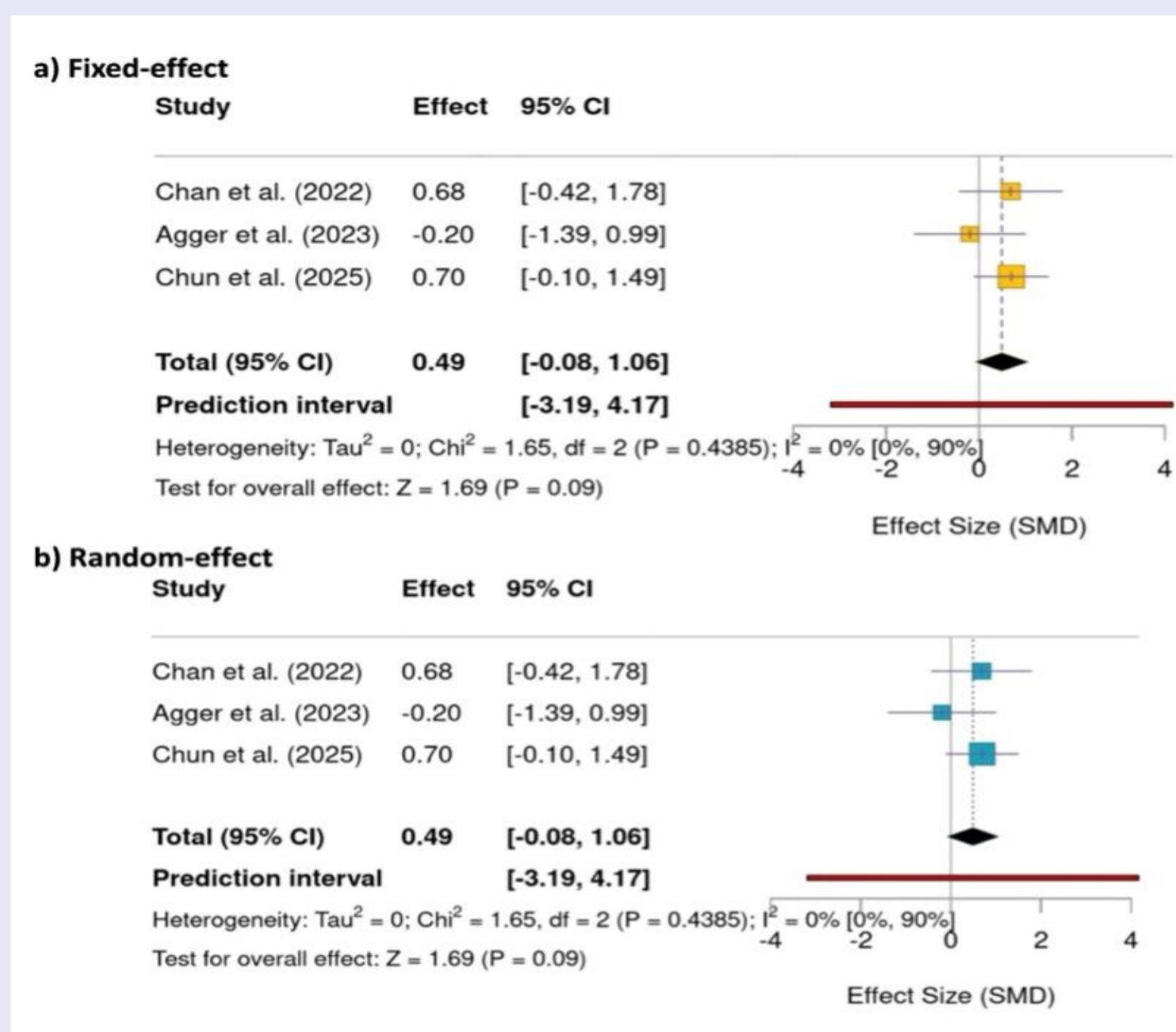


Figure 2. Meta-analysis of cognitive outcomes from randomized placebo-controlled trials assessing the effect of 40 Hz gamma sensory stimulation in Alzheimer's disease.

1. Five randomized placebo-controlled trials met the inclusion criteria
2. Whole-brain volume (3 trials, n=79): fixed-effect SMD -0.61 [-1.10, -0.12]; not significant under random-effects (SMD -0.02 [-1.39, 1.34]); $I^2=84\%$ (Fig. 1)
3. Cognitive outcomes (3 trials, n=51): moderate, non-significant improvement, SMD 0.49 [-0.08, 1.06]; $I^2=0\%$ (Fig. 2)
4. ADLs: significant improvement in 1 trial (SMD 3.45, $p<0.01$)
5. Adverse events comparable between groups (RR 0.91 [0.71–1.16]); headache/tinnitus infrequent, not significant (Fig. 3)

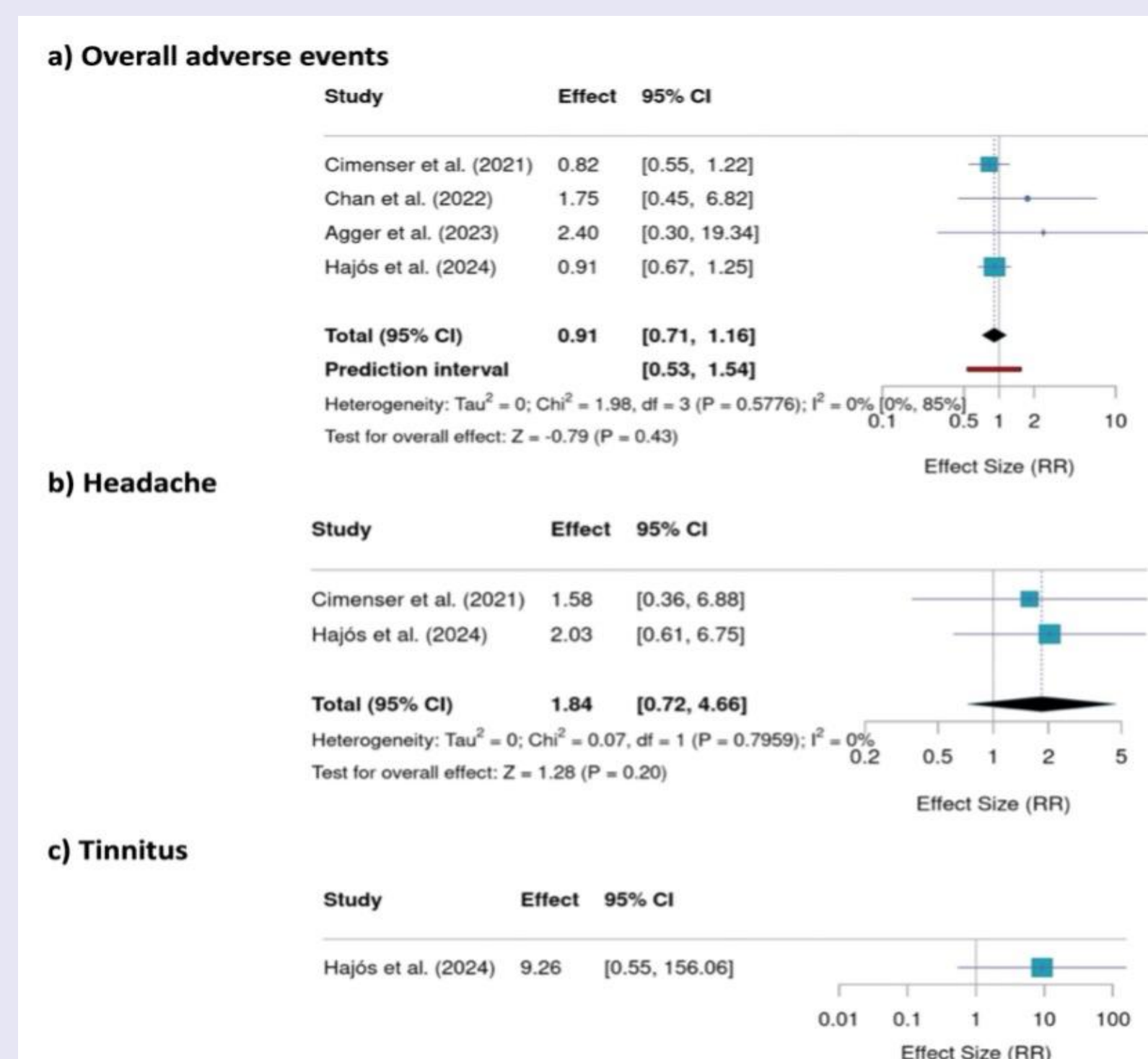


Figure 3. Safety meta-analysis of randomized placebo-controlled trials showing risk ratios for overall adverse events, headache, and tinnitus associated with 40 Hz gamma sensory stimulation.

Conclusion

1. 40 Hz sensory stimulation appears safe and feasible in AD
2. Signals toward structural, cognitive, and functional benefit were observed
3. Effects are inconsistent and limited by small sample sizes and heterogeneity
4. Larger, adequately powered trials are needed to define therapeutic efficacy and identify responsive subpopulations

References

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Contact

Saleha Khan,
salehashafi5@gmail.com