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Does Comparator Design Systematically Influence Treatment Effect Estimates in Randomized Trials of Post-Stroke Non-Pharmacological Interventions? A Cross-Domain Meta-Epidemiological Study

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 September 2026 and was last updated on 28 September 2026.

INTRODUCTION

Study aim To quantify whether comparator design is associated with the magnitude of treatment effect estimates in randomized controlled trials of non-pharmacological interventions intended to improve post-stroke recovery, function, symptoms, participation, or quality of life. The primary meta-epidemiological contrast will compare trials using matched comparators with trials using unmatched/non-equated comparators within the same prespecified clinical-question clusters. Secondary objectives are to estimate effects of specific comparator architectures and protocol-specified treatment-time matching, and to validate the main association within multi-arm randomized controlled trials that compare the same experimental intervention against comparators of different design stringency.To quantify whether comparator design is associated with the magnitude of treatment effect estimates in randomized controlled trials of post-stroke non-pharmacological interventions. The primary meta-epidemiological comparison will evaluate matched versus unmatched/non-equated comparators within prespecified clinically coherent intervention–outcome clusters. Secondary objectives are to examine specific comparator-design architectures and protocol-specified treatment-time matching, and to validate the main association within eligible multi-arm trials in which the same experimental intervention is compared against comparator arms of different design stringency.

Background Treatment effects in rehabilitation and other non-pharmacological stroke trials are defined relative to the comparator. However, comparator conditions vary substantially across trials and may include matched sham or attention controls, time- or dose-matched active controls, usual care, wait-list or no-additional-treatment controls, and pure add-on designs. Stroke-specific methodological research has demonstrated substantial variability and incomplete reporting of control interventions, while recent Stroke Recovery and Rehabilitation Roundtable recommendations have emphasized that comparator content, dose, active ingredients,

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and reporting can materially affect trial interpretation. Nevertheless, the extent to which comparator design systematically influences estimated treatment effects across post-stroke non-pharmacological randomized trials has not been quantified. This study will address that gap using prespecified within-clinical-question comparisons across multiple post-stroke domains, thereby reducing confounding by intervention type and outcome construct.

Rationale Comparator selection is a potentially important but underexamined source of heterogeneity in randomized trials of complex non-pharmacological interventions. A treatment compared with usual care, wait-list, or no additional treatment may produce a different estimated effect from the same or a similar treatment compared with a matched sham, attention control, or time- and dose-matched active comparator. Such differences may arise from unequal treatment exposure, attention, expectancy, co-interventions, or overlap in active treatment ingredients.

A stroke-specific cross-domain meta-epidemiological study is therefore needed to quantify whether comparator design is systematically associated with treatment-effect magnitude. The primary analysis will compare matched with unmatched/non-equated comparators within prespecified clinically coherent intervention–outcome clusters, rather than pooling fundamentally different clinical questions directly. This within-cluster design is intended to reduce confounding by intervention modality and outcome construct. In addition, eligible multi-arm trials in which the same experimental intervention is compared with comparator arms of different design stringency will provide a prespecified within-trial validation analysis that further reduces between-trial confounding. The findings may improve interpretation of existing stroke rehabilitation evidence and inform design and reporting of future non-pharmacological randomized trials.

METHODS

Search strategy A two-stage search strategy will be used.

Stage 1 will identify systematic reviews and meta-analyses in order to construct an exhaustive evidence map of eligible post-stroke non-pharmacological randomized controlled trial clinical-question clusters. Databases will include MEDLINE/PubMed, Embase, the Cochrane Database of Systematic Reviews, Web of Science Core Collection, Scopus, Epistemonikos, CINAHL, PsycINFO, CNKI, Wanfang Data, VIP Database, and SinoMed. Searches will combine controlled vocabulary and free-text terms for stroke with terms for rehabilitation/non-pharmacological treatment, prespecified post-stroke clinical domains, and systematic review/meta-analysis methodology.

Stage 2 will retrieve all primary RCT reports identified from eligible evidence syntheses and update the randomized evidence from the final search date of the relevant index review to the final project search date. Databases will include MEDLINE/PubMed, Embase, Cochrane CENTRAL, Web of Science Core Collection, Scopus, CINAHL, PsycINFO, CNKI, Wanfang Data, VIP Database, and SinoMed. Intervention- and outcome-specific terms derived prospectively from each eligible clinical-question cluster will be combined with stroke terms and validated RCT filters.

Comparator-related terms such as sham, control, placebo, or usual care will not be mandatory search concepts because requiring such terminology could preferentially retrieve trials with better-described comparator conditions and introduce selection bias in the methodological exposure under study.

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform will be searched for completed, ongoing, or unpublished trials. Backward reference checking and forward citation tracking will be conducted, and trial registries, protocols, supplementary materials, companion publications, dissertations, conference abstracts, and preprints will be examined where relevant.

No language restriction will be applied at the search stage. Search strategies will be validated against prespecified sentinel systematic reviews and RCTs across major post-stroke domains. The MEDLINE/PubMed strategy will undergo independent peer review using PRESS principles before definitive searching. Complete database-specific search strategies, search dates, validation records, and any technical modifications will be archived and reported transparently. Searches will be rerun before the final statistical dataset is locked and again before manuscript submission if a meaningful interval has elapsed or new potentially eligible trials are identified.

Eligibility criteria Participants will be adults aged 18 years or older with ischemic or hemorrhagic stroke at any post-stroke phase. Studies with mixed neurological populations will be eligible only when stroke-specific data can be separately extracted.

Eligible interventions will be non-pharmacological therapeutic interventions intended to improve post-stroke impairment, activity, participation,

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symptoms, or quality of life, including rehabilitation and exercise therapies, speech/language and swallowing therapy, cognitive rehabilitation, psychological or behavioral interventions, acupuncture/manual approaches, virtual or robotic rehabilitation, biofeedback, and therapeutic neuromodulation. Pharmacological or nutraceutical interventions, diagnostic procedures, acute reperfusion/recanalization procedures, surgery, and interventions primarily intended for primary or secondary stroke prevention will be excluded.

Eligible primary studies will be parallel-group randomized controlled trials. Multi-arm RCTs will be eligible and decomposed into pairwise randomized contrasts while retaining a common trial_id. Quasi-randomized, crossover, cluster-randomized, non-randomized, single-arm, and observational studies will be excluded from the primary RCT dataset.

The primary analysis will use continuous validated clinical or functional outcomes measured immediately after the intervention. A clinical-question cluster will be prospectively defined as an intervention class × outcome construct × immediate post-intervention time point. The prespecified sampling frame will cover motor/physical function, swallowing, communication/language, cognition, psychological/emotional outcomes, and other clinically important post-stroke symptoms, participation, or quality-of-life outcomes when eligible randomized evidence exists.

A clinical-question cluster will contribute to the primary matched-versus-unmatched meta-epidemiological analysis only if it contains at least five independent RCTs, including at least two RCTs with matched comparators and at least two RCTs with unmatched/non-equated comparators. Cluster eligibility will be determined without reference to treatment-effect magnitude, direction, or statistical significance. Clusters failing this information threshold will remain in the evidence map and may contribute to descriptive or secondary analyses.

Data extraction Data will be extracted at trial, randomized-contrast, and clinical-question-cluster levels. Multiple reports from the same trial will be linked into a single trial family and assigned a common trial_id; each eligible randomized comparison will receive a unique contrast_id and cluster_id.

Comparator-design coding and numerical outcome extraction will be separated wherever practicable. Two reviewers will independently code comparator matching status, detailed comparator architecture, protocol-specified treatment-time matching, therapist/contact-time matching, attention matching, sham adequacy, background co-interventions, and comparator-reporting adequacy using primary reports, protocols, registries, supplements, and companion publications. Comparator codes will be reconciled and locked before numerical outcome data are merged.

Numerical extraction will include sample size, participant and stroke characteristics, intervention/comparator components and dose, outcome instrument, post-intervention means and standard deviations, analyzed sample sizes, and information required for effect-size calculation and RoB 2. Final post-intervention values will be prioritized; change-score-only data will be retained separately.

For multi-arm RCTs, original arm-level data will be retained to model shared-arm dependence and conduct prespecified within-trial validation. Unclear comparator characteristics will not be imputed. All coding changes and derived values will be documented in an auditable log.

Outcome definitions The trial-level treatment effect will be expressed as Hedges g standardized mean difference for a prespecified continuous validated clinical or functional outcome measured immediately after the intervention. Effect directions will be oriented so that positive values indicate benefit of the experimental intervention; scales in which lower scores indicate improvement will be sign-reversed before analysis.

The primary meta-epidemiological estimand will be the within-clinical-question difference in treatment-effect magnitude between unmatched/non-equated and matched comparator trials:

Delta g = g_unmatched – g_matched.

Positive Delta g indicates larger apparent treatment effects when unmatched/non-equated comparators are used.

A comparator will be classified as matched when the trial protocol or report demonstrates intentional equivalence of study-delivered non-specific treatment exposure apart from the experimental active ingredient(s), for example through a credible sham/attention condition or a time/dose-matched active comparator with balanced background treatment. A comparator will be classified as unmatched/non-equated when the experimental arm receives additional protocol-delivered treatment exposure, as in a pure A+B versus B design, or when usual care, wait-list, or no-additional-treatment control is used without demonstrated protocol equivalence.

Unclear classifications will be excluded from the primary binary comparison. Longer-term follow-up and change-score-only outcomes will be analyzed separately.

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Strategy of data synthesis / Statistical analysis The primary analysis will use a two-stage within-clinical-question meta-epidemiological approach.
Stage 1: within each informative clinical-question cluster, random-effects meta-regression will estimate Delta g, the difference in Hedges g between unmatched/non-equated and matched comparator trials. A cluster will contribute to the primary analysis only if it contains at least five independent RCTs, including at least two matched and two unmatched comparator RCTs. Dependence from multi-arm or shared-control trials will be handled using multivariate/multilevel methods or trial-cluster robust variance estimation with small-sample correction.
Stage 2: cluster-specific Delta g estimates will be pooled using random-effects meta-analysis with REML estimation and Hartung-Knapp-type inference where appropriate. Tau^2, I^2, and prediction intervals will be reported when estimable. A pooled cross-domain conclusion will be emphasized only if at least five informative clusters are available.
Secondary analyses will examine detailed comparator architectures and protocol-specified treatment-time matching. Therapist/contact-time matching, attention matching, sham adequacy, and comparator-reporting adequacy will be exploratory.
Prespecified within-trial multi-arm validation will compare the same experimental intervention against comparator arms of different design stringency. Sensitivity analyses will address RoB 2, comparator-reporting adequacy, unclear classifications, influential effects, and alternative multilevel models. If at least ten informative clusters are available, Bayesian hierarchical meta-regression will be performed as a sensitivity analysis.

Country(ies) involved China.

Other relevant information A preliminary methodological feasibility pilot was conducted before this registration. Fifty RCTs were initially used to assess whether key comparator-design characteristics could be extracted, followed by source-level re-coding of a subset and restructuring of multi-arm trials at the randomized-contrast level. The pilot was undertaken solely to test methodological feasibility and refine operational definitions; it will not be treated as part of the formal primary analysis.
The pilot led to several prospective refinements before formal review-wide screening and outcome extraction: the unit of analysis was changed from trial-level to contrast-level; pure add-on design was strictly defined as A+B versus B and distinguished from matched-sham designs; therapist/contact-time and attention matching were designated exploratory because of incomplete reporting; an exhaustive prespecified domain-based sampling frame was introduced; comparator-design coding will be separated from numerical outcome extraction wherever practicable; and a within-trial multi-arm validation analysis was prespecified.
No formal cross-domain primary meta-epidemiological analysis has been conducted. Published subgroup findings and pilot observations have been used only as feasibility signals and will not be carried forward as study results.

Keywords stroke; rehabilitation; non-pharmacological intervention; comparator; control group; randomized controlled trial; meta-epidemiology; meta-research; treatment effect; Bayesian hierarchical model.

Dissemination plans Findings will be submitted to a peer-reviewed journal in clinical epidemiology, evidence synthesis, stroke, or neurorehabilitation and may be presented at relevant scientific meetings. The final report will distinguish preregistered primary, secondary, confirmatory, sensitivity, and exploratory analyses. Subject to legal, ethical, copyright, and publisher restrictions, the de-identified contrast-level analytical dataset, comparator-design coding manual and dictionary, clinical-question cluster inventory, complete search strategies, data-processing scripts, and statistical-analysis code will be shared through the associated OSF project or another stable repository. Copyrighted full-text articles and private author correspondence will not be redistributed.

Contributions of each author
Author 1 - Yanpeng Miao - Conceptualization; methodology; literature searching; study screening; data extraction; comparator-design coding; statistical analysis; visualization; drafting of the manuscript; and project administration.
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