

Age as a moderator of brain age gap effects across the lifespan: a systematic review and meta-analysis of case-control and longitudinal neuroimaging studies

INPLASY2026100075

doi: 10.37766/inplasy2026.10.0075

Received: 16 October 2026

Published: 16 October 2026

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ADMINISTRATIVE INFORMATION**Support** - No external funding was received for this work.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100075**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 October 2026 and was last updated on 16 October 2026.**INTRODUCTION**

Review question / Objective The primary objective is to determine whether sample mean age (lifespan stage) moderates the direction and magnitude of the between-group brain age gap (BAG) effect. Secondary objectives are: (1) to examine whether the strength of the BAG-outcome association (Fisher's z) varies with age; and (2) to examine whether the rate of longitudinal BAG change (standardized β) varies with age.

PICO framework:

Population: Humans across the lifespan (developmental, middle-aged, and aging populations).

Exposure/Prognostic factor: Brain Age Gap (BAG).

Comparator: Healthy controls (for case-control designs); no comparator for single-arm association studies.

Outcomes: Cognition, dementia conversion, mortality, clinical severity, and neuroimaging biomarkers.

Rationale Brain age gap (BAG), the difference between predicted and chronological age, is a widely used biomarker for atypical brain development and neurodegeneration. However, the biological meaning of BAG may fundamentally differ across the lifespan, with negative BAG potentially reflecting developmental delay in children and positive BAG indicating accelerated aging in older adults. Despite this theoretical premise, no systematic review or meta-analysis has yet specifically evaluated whether age stage moderates the direction and magnitude of the BAG effect. This study aims to bridge this critical gap by synthesizing existing case-control and longitudinal neuroimaging studies across the entire lifespan, providing the first comprehensive quantitative test of lifespan moderation on BAG effects. It will also clarify whether BAG offers incremental validity beyond traditional morphometric measures.

Condition being studied The condition being studied is the Brain Age Gap (BAG), defined as the difference between machine-learning predicted brain age and chronological age. This biomarker is

studied across a wide range of neuropsychiatric and neurodegenerative conditions (e.g., ADHD, autism, schizophrenia, depression, Alzheimer's disease, Parkinson's disease) as well as in healthy aging. This review will examine how BAG differs between patients and controls, and how its association with clinical outcomes (e.g., cognition, dementia conversion, mortality) varies across the lifespan.

METHODS

Search strategy Electronic databases: MEDLINE (PubMed), Web of Science Core Collection, ScienceDirect (Elsevier), Cochrane Library (CENTRAL), CNKI, and WanFang. Supplementary searches will include reference lists, cited-by searches, and preprint servers (medRxiv/bioRxiv). Search terms combine three blocks using AND logic:

(1) Brain age: "brain age" OR "brain-age" OR "brain age gap" OR "BAG" OR "brain-predicted age difference" OR "brain age delta";
 (2) Machine learning: "machine learning" OR "deep learning" OR "neural network" OR "prediction model" OR "estimation";
 (3) Imaging: "MRI" OR "neuroimaging" OR "imaging". Full search strings for each database are provided in the attached SAP v1.1.

Participant or population Participants across the entire human lifespan. The population will be divided into developmental (<25 years), middle-aged (25–59 years), and aging (≥60 years) groups. The review includes both clinical populations (patients diagnosed with neurodevelopmental, psychiatric, or neurodegenerative disorders) and healthy controls. Studies must report BAG or the brain-predicted age difference.

Intervention Not applicable. This is a prognostic review, not an intervention review. There is no health intervention being assessed. The primary prognostic factor is the Brain Age Gap (BAG). This study investigates whether BAG predicts clinical outcomes (e.g., cognitive decline, dementia conversion) and whether the sample age stage moderates this prognostic effect.

Comparator For case-control studies, the comparator is healthy control participants (e.g., individuals without the diagnosis of interest). For single-arm association studies or longitudinal cohorts (e.g., UK Biobank, ADNI), there is no concurrent comparator; these analyses examine within-group associations between BAG and clinical outcomes (e.g., cognition, dementia conversion, mortality).

Study designs to be included Observational studies only, including: cross-sectional case-control studies, longitudinal cohort studies, and the baseline cross-sectional data from randomized controlled trials (if BAG and clinical outcomes are reported). We will exclude animal studies, cell studies, post-mortem studies, reviews, conference abstracts, editorials, and case reports.

Eligibility criteria Inclusion criteria: (1) Human studies reporting BAG / brain-PAD / BrainAGE; (2) must report at least one of the following: disease vs. control BAG means±SD, BAG-outcome associations (r , β , OR, HR), or longitudinal BAG change; (3) sample mean age or age range must be extractable; (4) Publications must be in English or Chinese.

Exclusion criteria: (1) No BAG data (only model performance metrics like MAE/RMSE/prediction-actual r); (2) No usable effect size; (3) Age not reported; (4) Animal/cell/post-mortem studies; (5) Reviews/editorials/conference abstracts; (6) Duplicate cohorts (only the most informative paper per cohort is retained for the main analysis); (7) Records published in languages other than English or Chinese.

Information sources Electronic databases: MEDLINE (PubMed), Web of Science Core Collection, ScienceDirect (Elsevier), Cochrane Library (CENTRAL), CNKI (China National Knowledge Infrastructure), and WanFang Database. Supplementary sources: reference lists and cited-by of included studies and previous reviews; medRxiv, bioRxiv, OSF preprints; and ClinicalTrials.gov.

Main outcome(s) The primary outcome is the between-group Brain Age Gap (BAG) difference, quantified as Hedges' g . The primary meta-regression will test whether sample mean age (in decades) moderates the direction and magnitude of this BAG effect. Effect sizes will be extracted from cross-sectional case-control studies and baseline data of longitudinal cohorts. The effect measure is Hedges' g , with variance computed from group sample sizes and standard errors.

Additional outcome(s) Secondary outcomes include: (1) the association between BAG and clinical outcomes (Fisher's z), limited to at most three pre-defined domains: cognition, clinical severity, and neuroimaging/biomarker; and (2) the rate of longitudinal BAG change (standardized β). These will be analyzed in separate exploratory models to avoid mixing different estimands.

Data management Data will be extracted using the pre-defined Extraction-template Codebook v1.1 (uploaded as a supplementary file). Two independent reviewers (Zhou Zifeng and Xu Shuyu) will extract into separate copies, with a third reviewer (Wang Xu) adjudicating disagreements. The extraction workbook contains locked computed columns to prevent manual overwriting. All data, analysis code (R), and search strategies will be deposited in the associated OSF project (<https://osf.io/4ejzh>) upon submission.

Quality assessment / Risk of bias analysis Risk of bias will be assessed using the Newcastle-Ottawa Scale (NOS) for observational studies and the PROBAST tool for prediction model studies. Two reviewers will independently assess each included study. A pre-specified sensitivity analysis will exclude studies with high risk of bias to evaluate the robustness of the primary findings.

Strategy of data synthesis Three distinct estimands will be analyzed in separate models and never pooled together. (1) Primary analysis: between-group BAG difference (Hedges' g), fitted with `metafor::rma.mv(g ~ mean_age_decade + disease_cat + model_MAE, random = ~ 1 | study_id/effect_id, method = "REML")`. Inference uses cluster-robust variance (CR2, clubSandwich) with Satterthwaite degrees of freedom. (2) Exploratory analysis B: BAG-outcome association (Fisher's z). (3) Exploratory analysis C: longitudinal BAG change (standardized β). Heterogeneity will be reported using τ^2 , I^2 , and prediction intervals.

Subgroup analysis Pre-specified subgroup analyses include: (1) Cross-period same-disease continuous moderation, tested separately for schizophrenia, depression, epilepsy, and TBI (diseases with usable lifespan coverage); (2) Modality as a main-model covariate (MRI vs. FDG-PET); (3) Age-bias-correction subgroup (studies with vs. without age-bias correction). Any disease $\times$ age-band cell with $k < 5$ will not be formally tested and will be presented descriptively only.

Sensitivity analysis Sensitivity analyses will be run in a pre-ordered chain: (1) age-matched studies only; (2) age-bias-corrected studies only; (3) structural MRI only; (4) exclude overlapping cohorts; (5) exclude high risk of bias (NOS/PROBAST); (6) leave-one-out (study-level and cohort-level). Conditional analyses (Module A: BAG vs. GMV; Two-arm decomposition) will only be executed if pre-specified coverage gates are met (≥ 10 studies for GMV, ≥ 5 studies for arm-level means/SD); otherwise they will be reported descriptively only.

Language restriction Searches will be limited to English and Chinese. Records in these two languages will be screened and extracted. Non-English and non-Chinese records will be excluded at the screening stage due.

Country(ies) involved China.

Other relevant information This protocol was pre-registered on OSF (<https://osf.io/4ejzh>) on 2026-10-15. The full Statistical Analysis Plan (SAP v1.2) and the extraction template codebook are provided as supplementary files. The search is limited to English and Chinese records.

Keywords brain age gap; BAG; lifespan; developmental; aging; neuroimaging; meta-analysis; systematic review; machine learning; brain age prediction.

Dissemination plans The findings will be submitted for publication in a peer-reviewed journal focused on neuroscience, neuroimaging, or psychiatry. The full protocol, extracted data, and R analysis code will be made publicly available on OSF upon submission. We will also present the results at relevant national and international conferences. Any deviations from the pre-registered protocol will be reported as dated amendments in the final publication.

Contributions of each author

Author 1 - Zifeng Zhou - Conceptualization, methodology, literature screening, data extraction, formal analysis, and drafting the original manuscript.

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Author 2 - Shuyu Xu - Independent literature screening (title/abstract and full-text), data extraction, and cross-checking of the primary effect sizes.

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