

# Do CSF A $\beta$ 42 Increases Predict Cognitive Benefit? Evidence from Alzheimer's Disease Trials

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Anti-amyloid therapy significantly increased CSF A $\beta$ 42 levels, but the increase showed only modest correlation with cognitive improvement, suggesting CSF A $\beta$ 42 alone is not a reliable surrogate marker of clinical benefit.

## Background

- Anti-amyloid therapies aim to modify Alzheimer's disease pathology by reducing amyloid burden, and CSF A $\beta$ 42 is a key biomarker of target engagement
- However, its relationship with cognitive and behavioral outcomes remains uncertain, which is critical for validating surrogate endpoints and guiding trial design.
- Objective:** evaluate whether changes in CSF A $\beta$ 42 correlate with clinical outcomes measured by Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), and Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) in anti-amyloid trials.

## Methodology

- We conducted a meta-analysis of **6 randomized controlled trials** (EXPEDITION 1 & 2, CREAD 1 & 2, GRADUATE I & II) identified via PubMed.
- Total Participants:** 3,071 (1,517 experimental, 1,554 control)
- Mean differences** in CSF A $\beta$ 42 between treatment and placebo groups were pooled using inverse variance weighting under fixed- and random-effects models.
- Heterogeneity** was quantified using  $\tau^2$ ,  $I^2$ , and Q statistics.
- Correlations between **A $\beta$ 42 changes** and MMSE, NPI, and CDR-SB score changes were assessed using  $R^2$ , with confidence intervals estimated via bootstrap resampling.

## Results

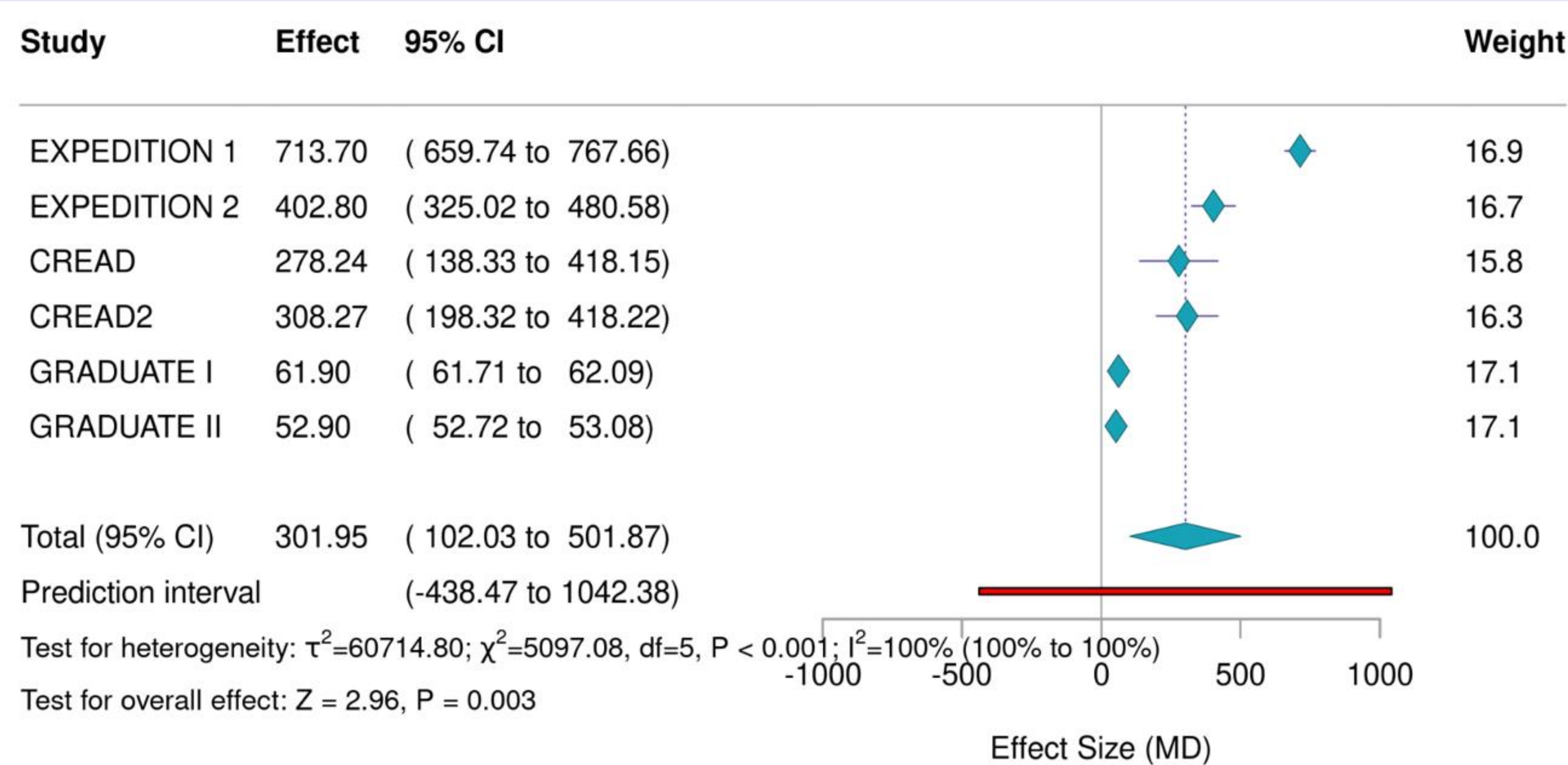


Figure 1. Forest plot of mean differences in CSF A $\beta$ 42 between treatment and placebo across six trials, pooled estimate with 95% CI, prediction interval, and heterogeneity metrics.

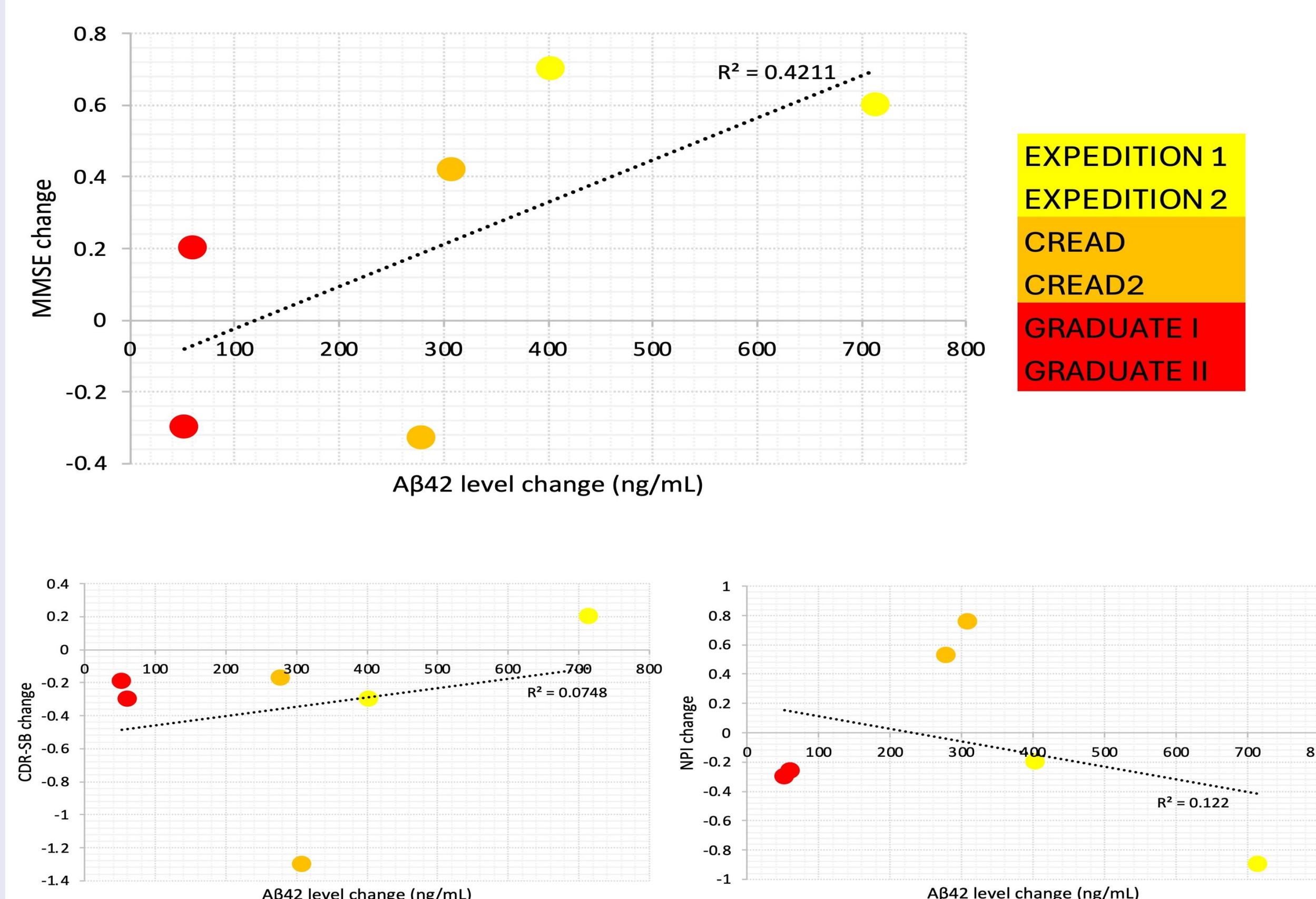


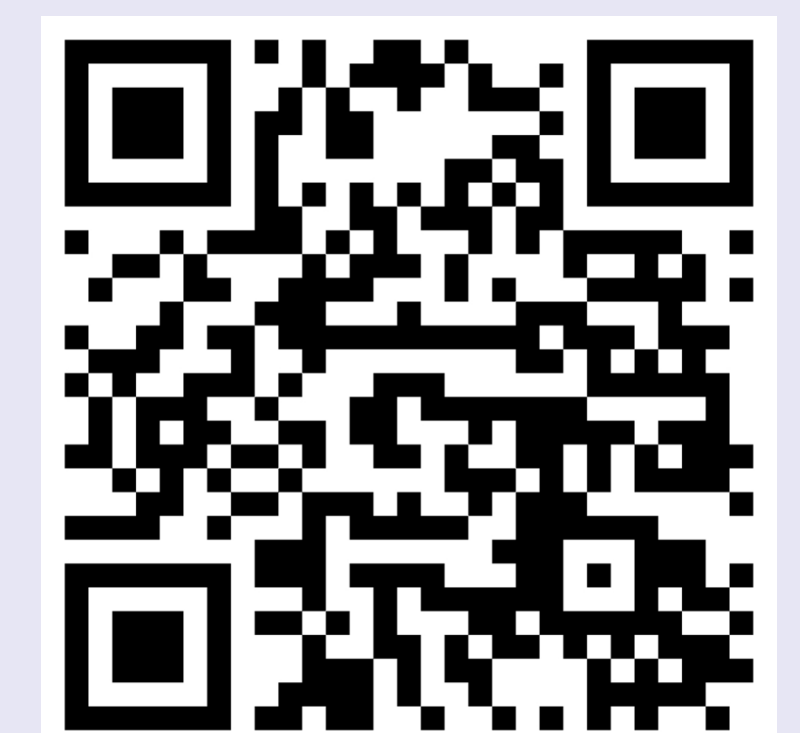
Figure2. Scatterplots showing associations between CSF A $\beta$ 42 changes and MMSE, CDR-SB, and NPI changes across six trials, with regression lines and  $R^2$  values indicating correlation strength.

- Pooled mean difference for CSF A $\beta$ 42 was **57.15 pg/mL** (95% CI: 57.01–57.28;  $p < 0.001$ ) under a fixed-effect model and **301.95 pg/mL** (95% CI: 102.03–501.87;  $p = 0.003$ ) under a random-effects model (Figure 1).
- Heterogeneity was substantial** ( $I^2 = 100\%$ ;  $Q = 5097.08$ ;  $p < 0.001$ ), and the prediction interval ranged from –438.47 to 1042.38 pg/mL.
- Correlation analysis revealed **modest associations** between A $\beta$ 42 changes and clinical outcomes

## Conclusion

- Anti-amyloid therapies **significantly increase CSF A $\beta$ 42**, indicating robust target engagement.
- Although correlations between A $\beta$ 42 changes and clinical outcomes were weak for NPI and moderate for MMSE, these associations suggest some link between biomarker shifts and cognition.
- However, the high heterogeneity and overall modest effect sizes indicate that CSF A $\beta$ 42 alone may not serve as a reliable surrogate for cognitive or functional benefit, underscoring the need for composite biomarkers and multimodal endpoints in Alzheimer's disease trials

## References



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