Appendices

Appendix 1: Supplemental Methods and Analyses

Methods

Standard meta-analysis methods cannot be applied to the typical intent-to-treat effect estimates here as we are estimating the effect of change in amyloid on change in cognition across heterogeneous drug treatments, while the intent-to-treat estimate corresponds with the effect of randomization on change in cognition. We derived a maximum-likelihood estimator to estimate the effect of amyloid reduction on cognitive change. Instrumental variable analyses are based on the following conditions ((14)): randomization to drug treatment plausibly affected the change in amyloid; randomization is independent of plausible confounders such as APOE-ε4; and randomization to drug treatment does not affect cognition through mechanisms other than amyloid reduction. Additionally, we assumed that change in cognition due to drug treatment to be proportional to the change in amyloid resulting from drug treatment, following a linear dose-response association with change in amyloid. This approach allowed us to combine results for trials with different durations of follow-up. In pooling results across trials, we assume that the effect of reducing amyloid on cognition does not vary with mechanism by which amyloid-β is targeted, i.e. by drug. We did not account for the covariance between measured mean change in cognition and measured mean change in SUVr as this information was not reported.

Since randomization depended on APOE-ε4 carrier status in the trial of BAN2401 (adaptive randomization altered mid-trial to exclude carriers from the highest treatment group), we required a second estimator for the effect of change in amyloid adjusting for the proportion of APOE-ε4 carriers in each group, because APOE-ε4 carrier status is known to affect change in cognition. For this trial, since data were collected at two time points, we additionally assumed that mean change in amyloid was linear with respect to time. See the directed acyclic graphs ((26)) in Appendix 3 for further details.

All statistical analysis was performed in `R` version `3.6.1`. The likelihood for each trial was the product of probabilities of the observed the change in cognition for each arm conditional on an intercept (the change in cognition associated with no change in SUVr) and a slope (the effect of change in SUVr on cognition). To obtain pooled estimates, these likelihoods were then multiplied assuming one common slope and a trial-specific intercept. Minimization of the negative log-likelihood was performed to obtain maximum-likelihood estimates for slopes and intercepts. Standard errors were obtained using observed Fisher information ((27)). Derivations of the maximum likelihood estimators are given in the Appendix 3.

We obtained estimates pooled by drug and overall of the effect of change in amyloid on change in cognition. Because the populations enrolled and time in followup in each trial may differ, we allowed each trial to have

its own intercept, which gives the expected change in cognition with no change in SUVr for participants in that trial over the followup period. We performed sensitivity analyses restricting to antibody drugs and with and without the unpublished trials of BAN2401 and Aducanumab. For the sake of comparison, we use a similar maximum-likelihood estimation procedure to estimate the effect of APOE-ε4 carriage on annual change in cognition.

We did not account for the covariance between measured cognition and measured SUVr since this information was not reported. This covariance is negligible if error in measured SUVr is large compared to the variance in true SUVr and predictors of cognition that do not also affect amyloid (e.g. education, vascular risk factors, and other non-amyloid pathologies such as TDP-43) account for the majority of the variance in cognition, then this covariance term is negligible. Both of these are plausible assumptions because amyloid-PET produces noisy measurements in SUVr ((28)) and variance in amyloid most plausibly accounts for only a minority of the variance in cognition across individuals (e.g. (29), (30)). More details are given in Appendix 3. If estimated covariances between measured SUVr and measured cognition become available, such information could be easily incorporated into the proposed estimation procedure.

Analysis of the BAN2401 trial

Note: For this trial, we did not use data from the AAIC presentation, but data emailed directly to us from Eisai pharmaceuticals.

BAN2401 targets protofibrils of amyloid-β and, in an ongoing trial, has produced statistically significant reductions in both amyloid-β in the brain as well as reductions in cognitive decline, according to a recent press release (AAIC 2018). However, there is a highly variable proportion of APOE-ε4 carriers across treatment arms, ranging from 30% to 91%. After the start of the trial it was determined that APOE-ε4 carriers had an unacceptably high risk of amyloid-related imaging abnormalities, specifically edema (ARIA-E). As a result, no additional APOE-ε4 carriers were assigned to this group. This prompted concerns that differences in cognitive outcomes between groups is due depletion of APOE-ε4 carriers in the highest treatment group and not drug efficacy. In a recent press release, Eisai pharmaceuticals stated their results were robust to adjustment for differences in APOE-ε4 carrier status across treatment arms. They additionally stated that this trial was the first of its kind to provide evidence for the amyloid cascade hypothesis since BAN2401 reduced-β amyloid and was associated with slower cognitive decline.

It was assumed that changes in ADCOMS in the BAN2401 trial were linear with respect to changes in MMSE and a conversion was derived using the following data (derived from table 4 in (31)). Differential weights are used to account for differences in sample size.

Change in ADCOMS	Change in MMSE	Weight
0.027	0.51	276.40
0.057	1.58	102.60
0.082	1.24	90.43
0.002	0.12	294.20

Supplemental Results

Effect of a 0.1 decrease in SUVr on the CDR-SB

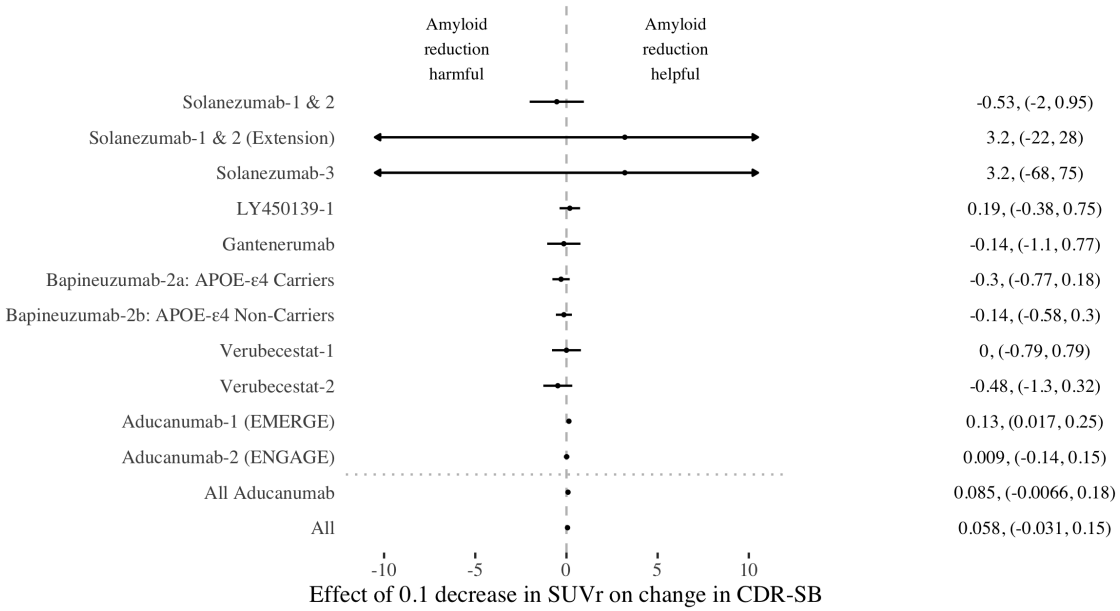


Figure S1: Forest plot of the estimated effects (95% confidence intervals) of an 0.1 decrease in SUVr on CDR-SB for each trial and drug. Change is signed such that positive change represents increased cognitive performance relative to no change in SUVr. A numbered key is given for multiple trials of the same drug (see *Table S2* for clinical trial numbers). We removed the trial LY450139-2 because the corresponding estimate was uninformative (i.e. all slopes were plausible) .

Effect of a 0.1 decrease in SUVr on the ADAS-Cog

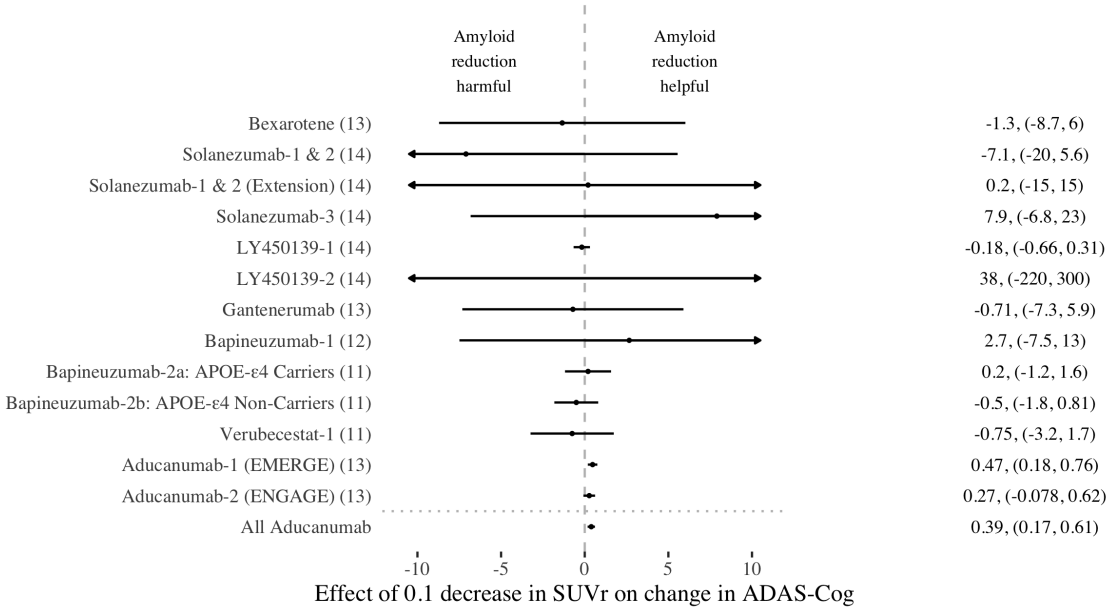


Figure S2: Forest plot of the estimated effects (95% confidence intervals) of an 0.1 decrease in SUVr on ADAS-Cog for each trial and drug. Change is signed such that positive change represents increased cognitive performance relative to no change in SUVr. A numbered key is given for multiple trials of the same drug (see *Table S2* for clinical trial numbers). The version of the ADAS-Cog is given in parentheses.

Change in SUVr Stratified by Tracer

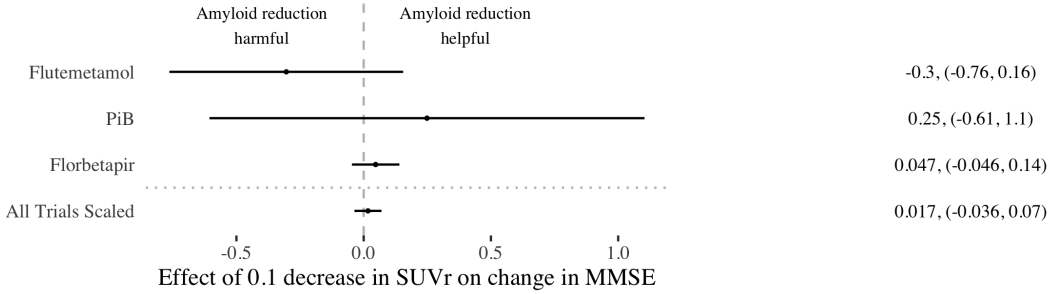


Figure S3: Forest plot of the estimated effects (95% confidence intervals) of an 0.1 decrease in SUVr on MMSE stratified by radiotracer. The *all trials scaled* estimate scales the SUVrs so that each tracer is approximately on same scale (1/100th of the centiloid transformation).

Effect of APOE-$\varepsilon 4$

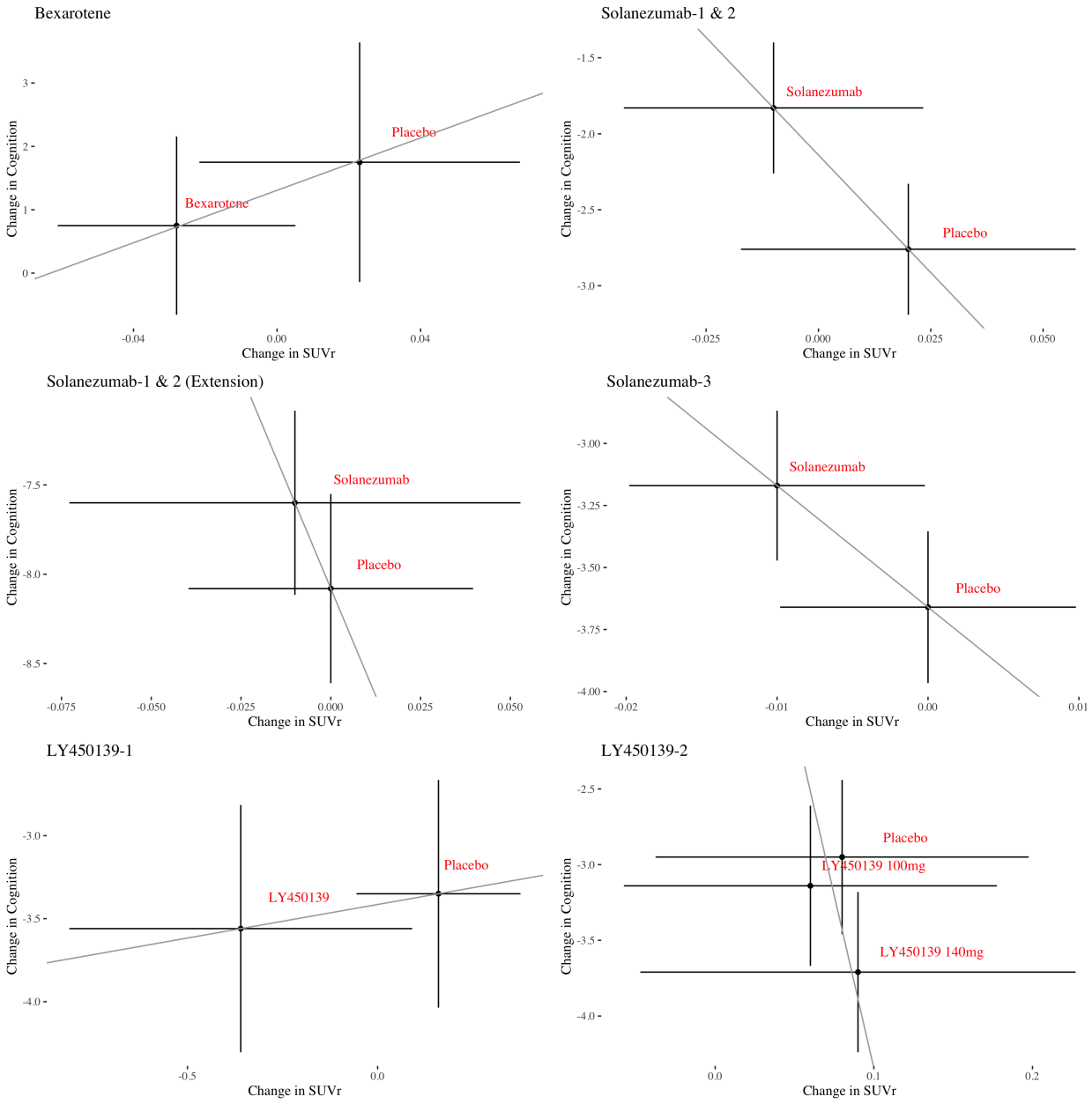
Drug	Effect of APOE-ε4 on MMSE Change per Year, 95% CI
BAN2401	-1.33, (-1.99, -0.67)
Bapineuzumab	-0.70, (-1.09, -0.31)

Table S1: The estimated effect of APOE-ε4 on annual change in MMSE. All values are reported to two decimal places.

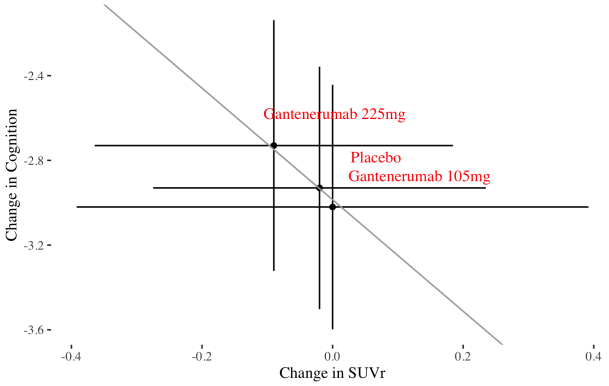
Plots of Data and Fits

Each point represents one randomization arm in the trial. The larger the horizontal distance between points, the larger the effect of the drug on amyloid. The larger the vertical distance between points, the larger the effect of the drug on cognition. Changes in the ADAS-Cog and CDR-SB are signed such that, as with the MMSE, negative slopes indicate reduction in amyloid reduces cognitive decline.

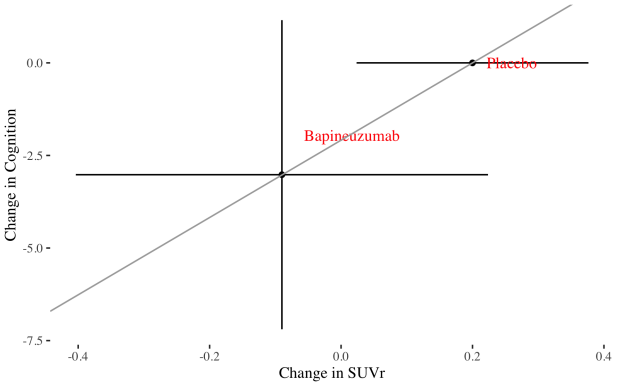
MMSE



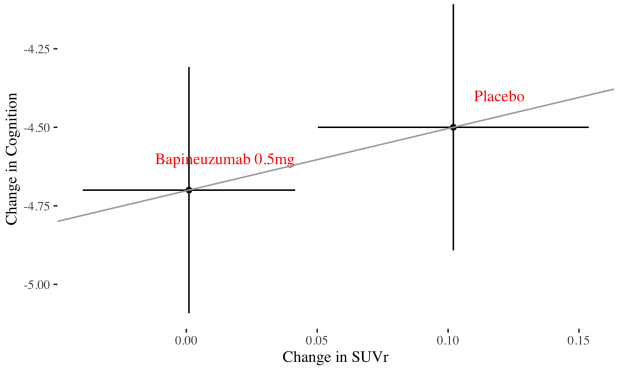
Gantenerumab



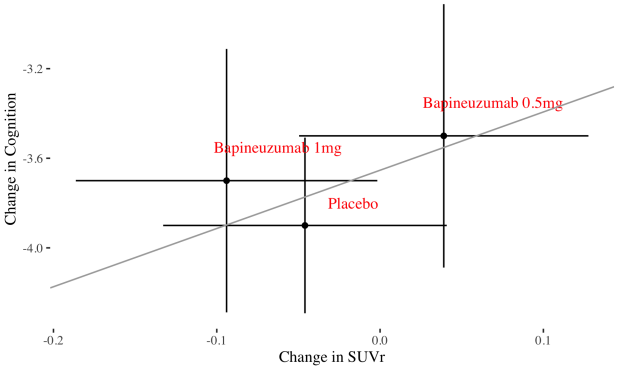
Bapineuzumab-1: Change in Cognition Relative to Placebo Group



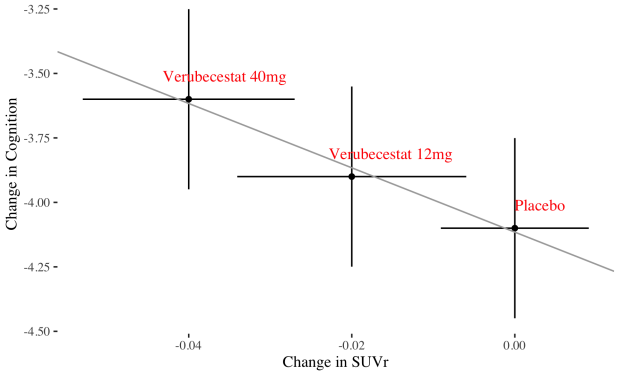
Bapineuzumab-2a: APOE-ε4 Carriers



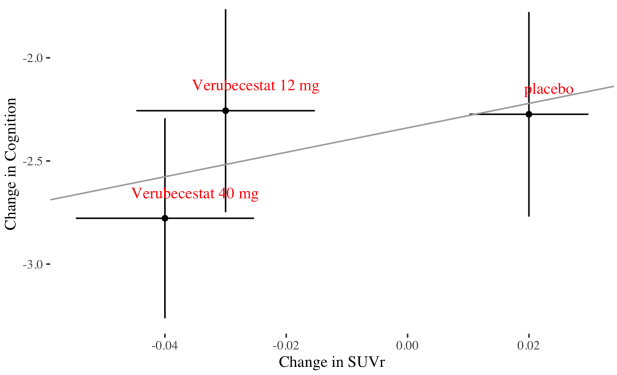
Bapineuzumab-2b: APOE-ε4 Non-Carriers



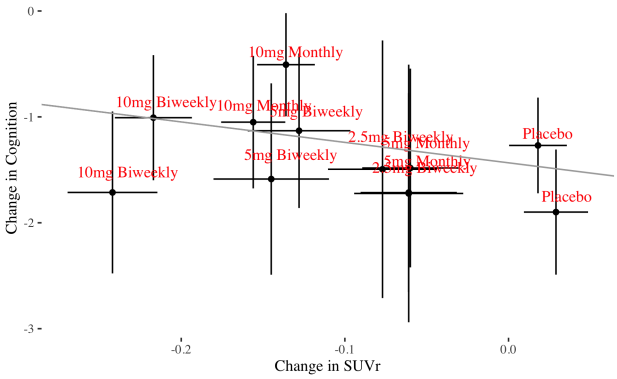
Verubecestat-1



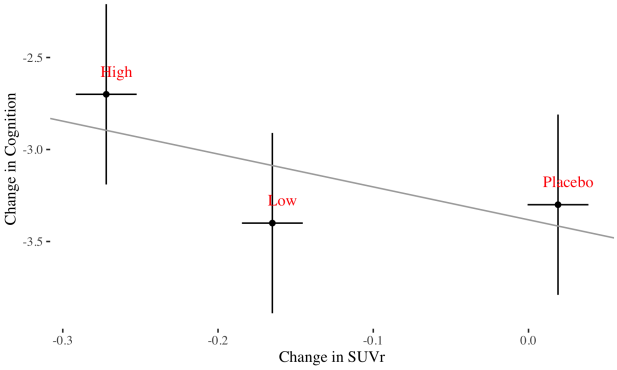
Verubecestat-2



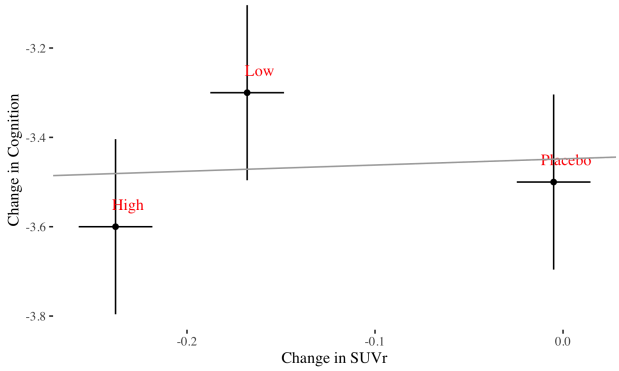
BAN2401, Adjusted for Fraction APOE-ε4+ & Time



Aducanumab-1



Aducanumab-2



ADAS-Cog

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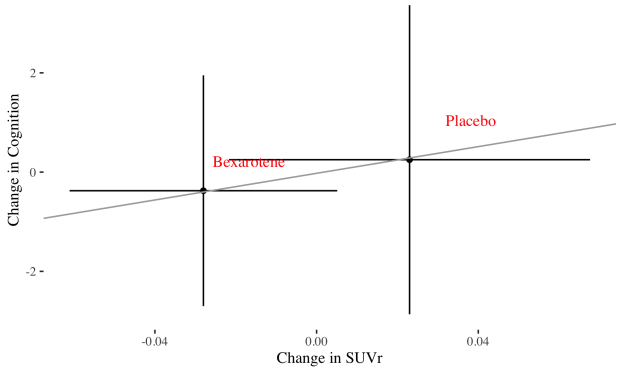
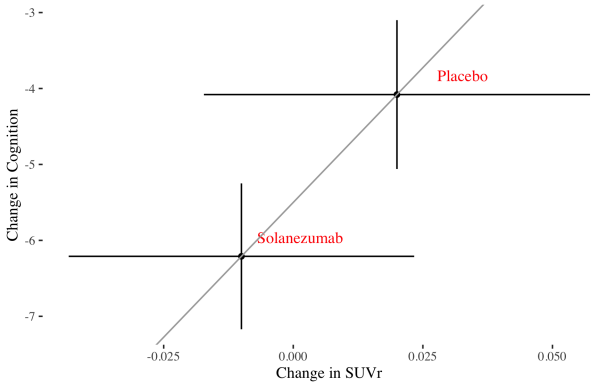


Solanezumab-1 & 2



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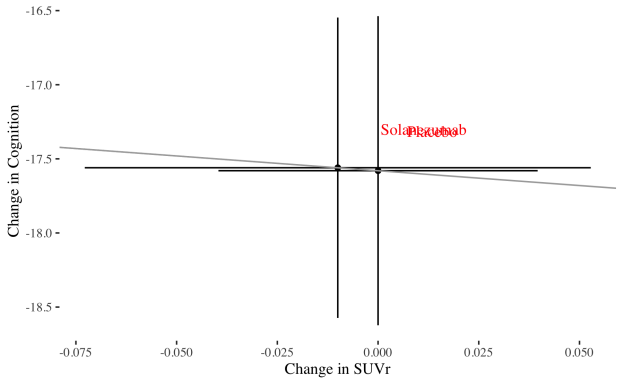

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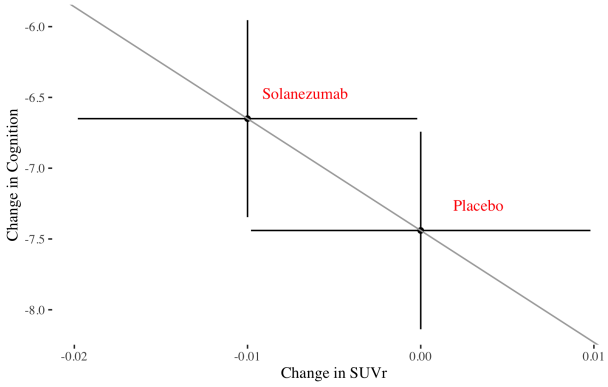

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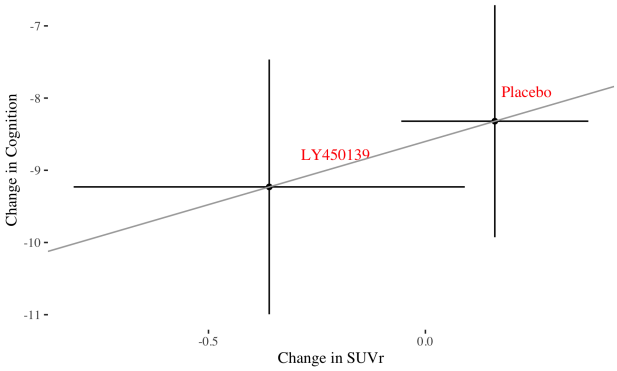

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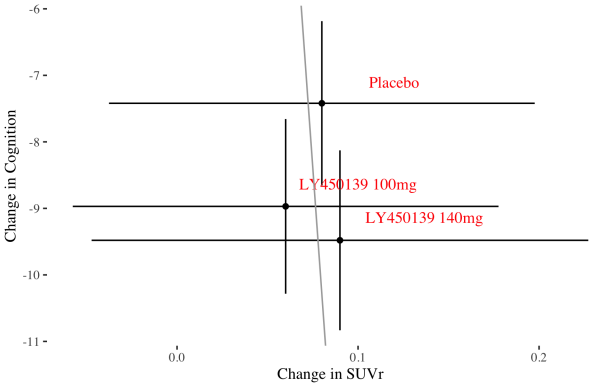
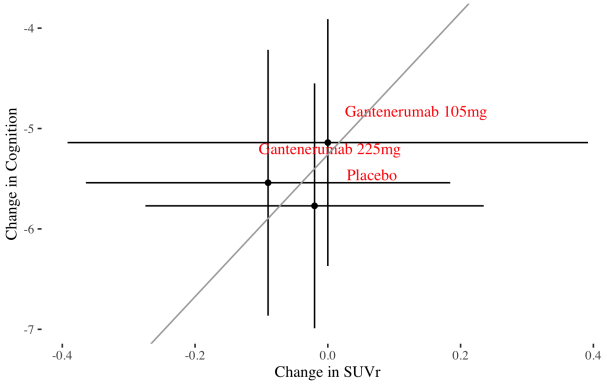
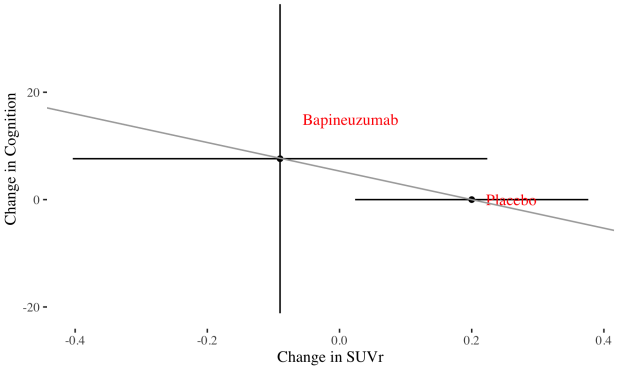


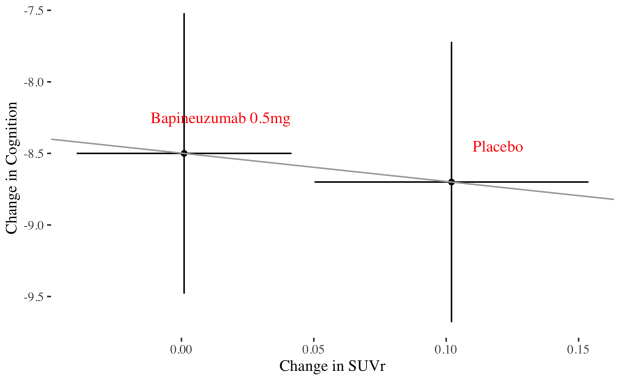
Gantenerumab



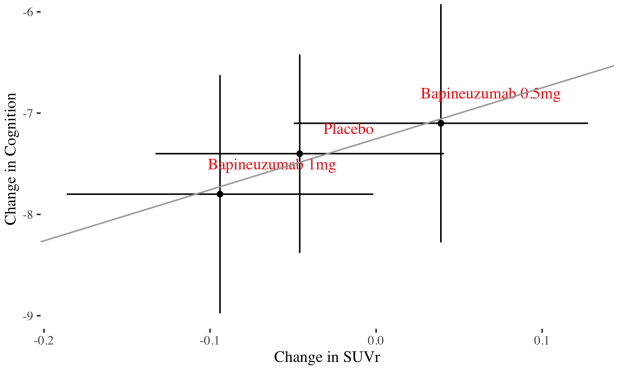
Bapineuzumab-1: Change in Cognition Relative to Placebo Group



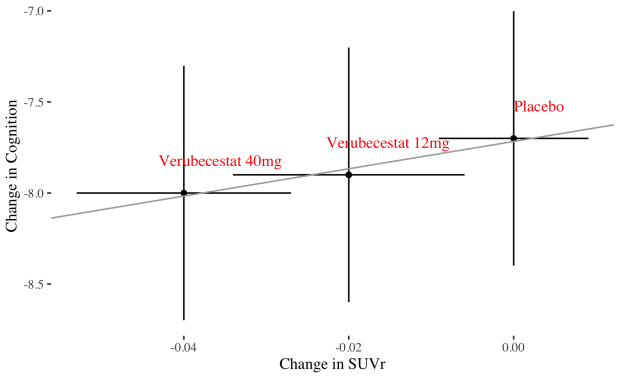
Bapineuzumab-2a: APOE-ε4 Carriers



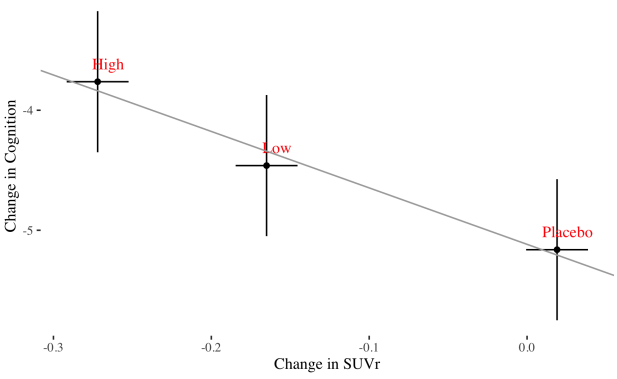
Bapineuzumab-2b: APOE-ε4 Non-Carriers



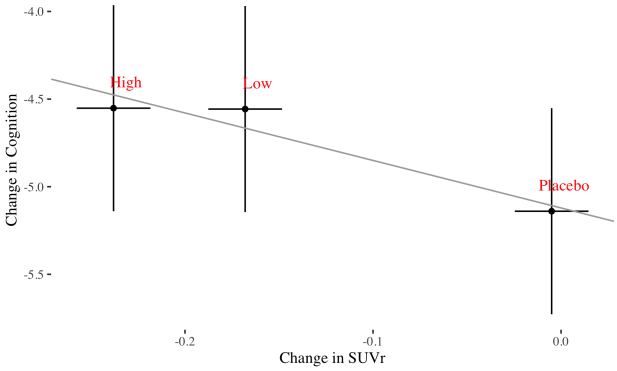
Verubecestat-1



Aducanumab-1

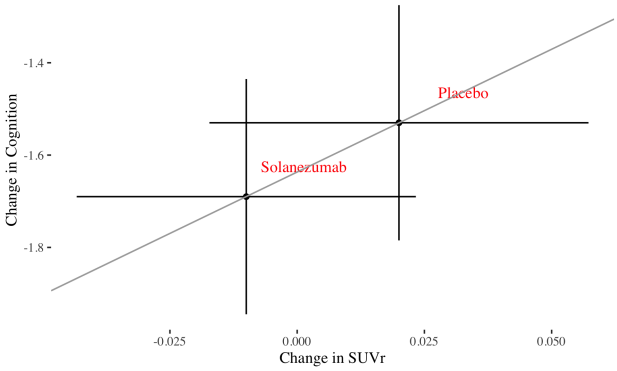


Aducanumab-2

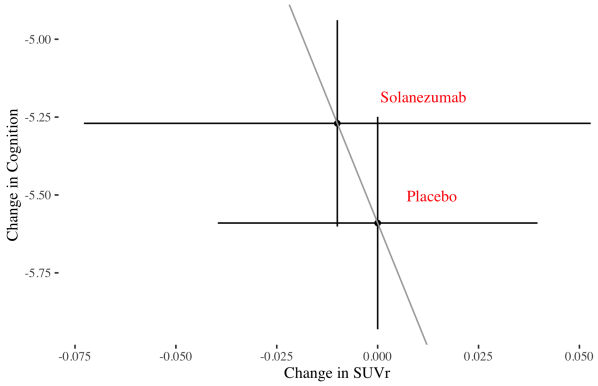


CDR-SB

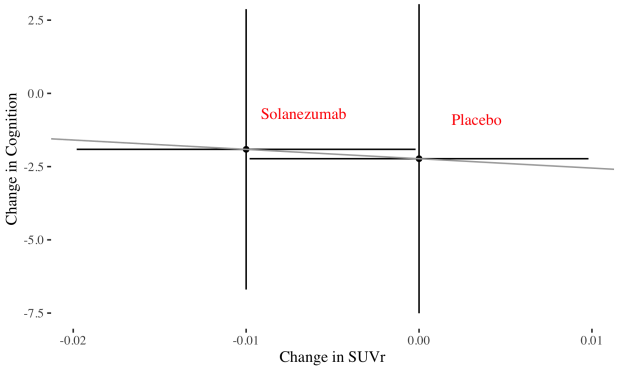
Solanezumab-1 & 2



Solanezumab-1 & 2 (Extension)



Solanezumab-3



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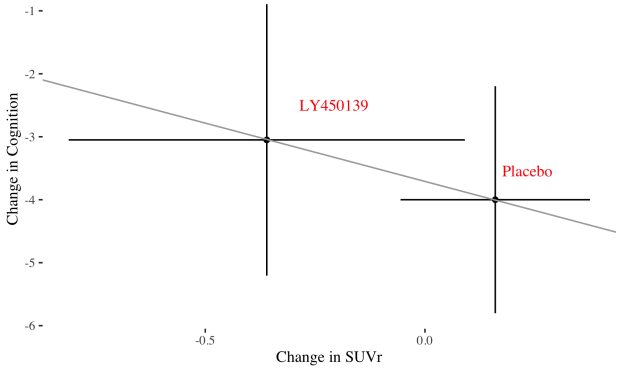
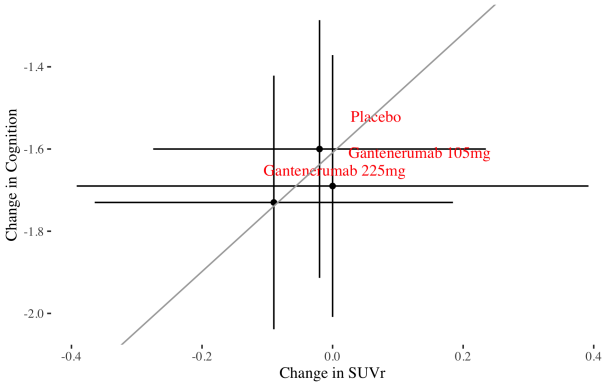
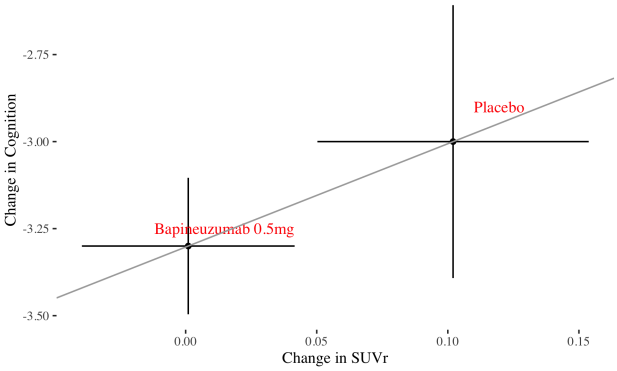


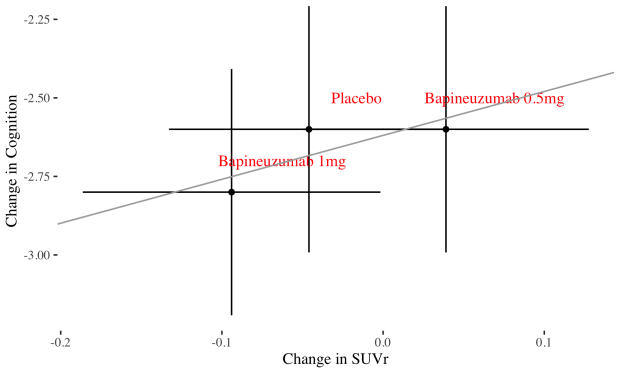
Gantenerumab



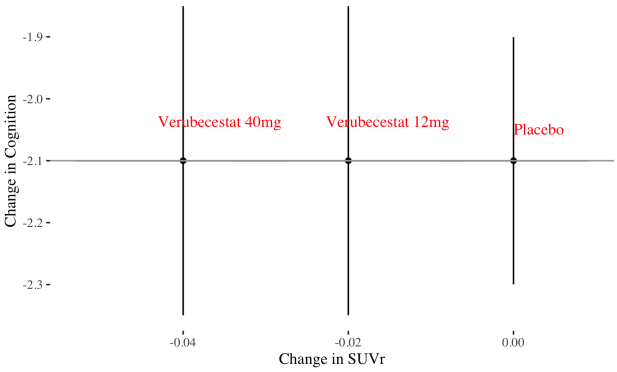
Bapineuzumab-2a: APOE-ε4 Carriers



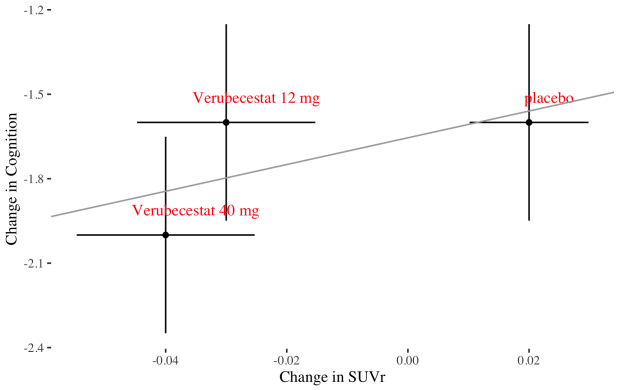
Bapineuzumab-2b: APOE-ε4 Non-Carriers



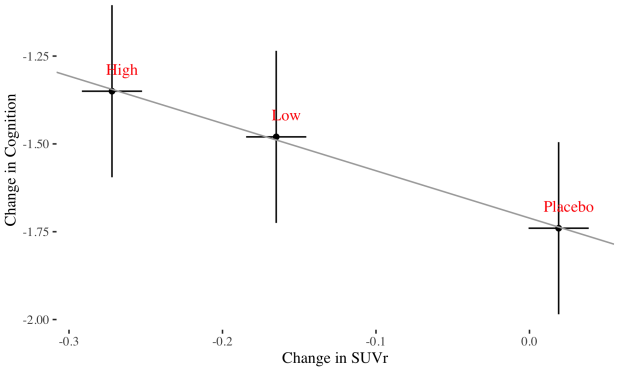
Verubecestat-1



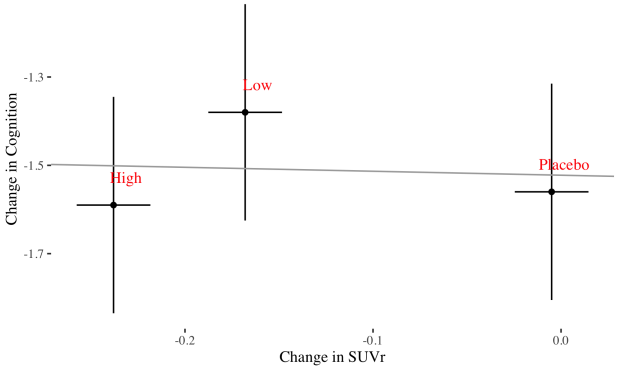
Verubecestat-2



Aducanumab-1



Aducanumab-2



Appendix 2: Data Sources

1. Bexarotene NCT01782742: (32)
2. Solanezumab NCT00904683 & NCT01127633: (33)
3. Solanezumab NCT00904683 & NCT01127633 (Extension):

https://clinicaltrials.gov/ct2/show/results/NCT01127633

4. Solanezumab NCT01900665: https://www.clinicaltrials.gov/ct2/show/results/NCT01900665
5. LY450139 NCT00762411: https://clinicaltrials.gov/ct2/show/results/NCT00762411
6. LY450139 NCT00594568: https://clinicaltrials.gov/ct2/show/results/NCT00594568
7. Gantenerumab NCT01224106: (34)
8. Bapineuzumab NCT00575055: (20)

9-10. Bapineuzumab NCT00676143, NCT00667810: (18)

11. Verubecestat (MK-8931) NCT01739348: https://clinicaltrials.gov/ct2/show/results/NCT01739348
12. Verubecestat (MK-8931) NCT01953601: https://clinicaltrials.gov/ct2/show/results/NCT01953601
13. BAN2401 (NCT01767311): presented at the Alzheimer's Association International Conference, 2018; summary data from Eisai pharmaceuticals
14. Aducanumab (EMERGE) NCT02484547: Press Release
15. Aducanumab (ENGAGE) NCT02477800: Press Release

Summary of Trials Included

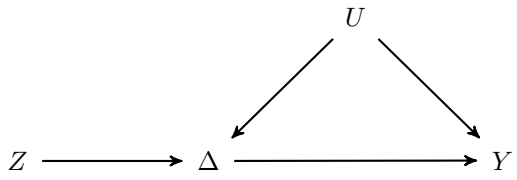
Clinical Trial Number	Drug(-key)	Drug Classification	Number of Treatment Arms	Number with Cognitive Assessment	Number with Amyloid PET	Length of Followup
NCT 01782742	Bexarotene	Small molecule	2	20	20	4 weeks
NCT 00904683	Solanezumab-1 & 2	Antibody	2	1322	251	80 weeks
NCT 01127633	Solanezumab-1 & 2 (Extension)	Antibody	2	860	90	104 weeks
NCT 01900665	Solanezumab-3 (Expedition 3)	Antibody	2	1769	1596	80 weeks
NCT 00762411	LY450139-1	Small molecule	2	1108	1108	76 weeks
NCT 00594568	LY450139-2	Small molecule	3	939	125	76 weeks
NCT 01224106	Gantenerumab	Antibody	3	797	55	104 weeks
NCT 00575055	Bapineuzumab-1	Antibody	2	26	26	78 weeks
NCT 00676143	Bapineuzumab-2a	Antibody	2	1090	115	71 weeks
NCT 00667810	Bapineuzumab-2b	Antibody	3	1114	39	71 weeks
NCT 01739348	Verubecestat-1	Small molecule	3	1838	44	78 weeks

Clinical Trial Number	Drug(-key)	Drug Classification	Number of Treatment Arms	Number with Cognitive Assessment	Number with Amyloid PET	Length of Followup
NCT 01953601	Verubecestat-2	Small molecule	3	1392	187	104 weeks
NCT 01767311	BAN2401	Antibody	5	854	306	79 weeks
NCT 02484547	Aducanumab-1	Antibody	3	879	317	78 weeks
NCT 01953601	Aducanumab-2	Antibody	3	923	317	78 weeks

Table S2: Description of trials included in the aggregated analysis. A numbered key is given for multiple trials of the same drug.

Appendix 3: Derivation of the Maximum Likelihood Estimator

A



B

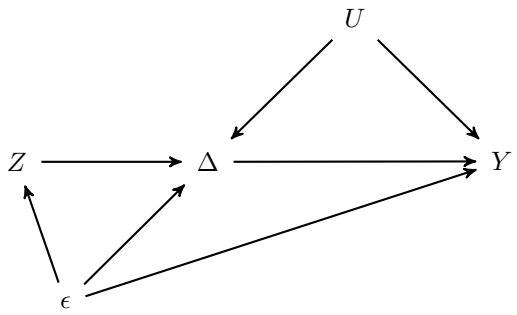


Figure S4: DAGs representing experimental design for all trials except the trial of BAN2401 (**A**) and the BAN2401 trial (NCT01767311) (**B**). **A**: Nodes represent the following variables: Z: randomization arm ; Δ: amyloid change; Y: cognitive change; U: disease severity or other shared causes of amyloid and cognition change. **B**: Nodes represent the following variables: Z: randomization arm (one of 6 possible groups); Δ: amyloid change; Y: cognitive change; U: disease severity or other shared causes of amyloid and cognition change; ϵ: APOE-ε4 status, positive or negative.

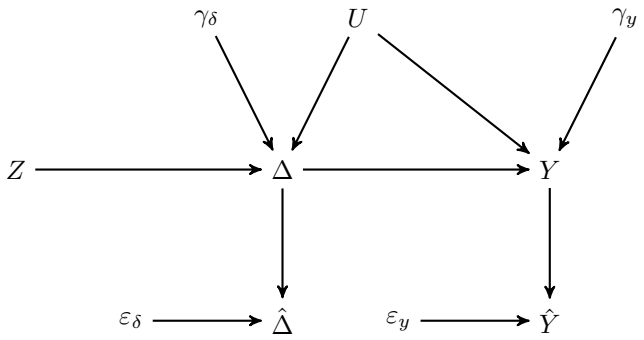


Figure S5: DAGs representing experimental design for non-BAN2401 trials with other sources of variance for amyloid reduction (γ_δ) and cognition (γ_y), as well as measurement error for amyloid (ε_δ) and cognition (ε_y)

We assume the causal structure in *figure S4*, with the following random variables: Z is the instrumental variable, Δ is the endogenous variable, U is an unmeasured confounder of amyloid accumulation and cognition, and Y is the outcome. Lowercase z, δ, u, and y are used to represent specific values these random variables. We assume the Y , Δ, and U are continuous random variables. Similar results can be obtained assuming discrete random variables by replacing integrals with sums over the support of these variables. While we assume only one unmeasured confounder U, these results can easily be extended for multiple unmeasured confounders. We consider the possibility that measures of the endogenous and outcome variables are only available for a subsample of individuals within each study arm $N_{z,\delta}$ and $N_{z,y}$ (as is often the case when the endogenous variable is an expensive biomarker).

We begin with a standard IV linearity assumption: we assume $\mathrm{E}[Y|\Delta = \delta, U = u] = \alpha\delta + \beta u$, where α is the parameter of interest, giving the effect of Δ on Y. Since treatment z is randomly assigned and only affects Y through Δ, we can write:

$$\mathrm{E}[Y|\Delta = \delta, U = u, Z = z] = \alpha\delta + \beta u. \tag{1}$$

We obtain the unconditional expectation for a given treatment arm z by integrating the conditional expectation over the support of u and δ, multiplied by the probability densities of u and δ:

$$\mathrm{E}[Y|Z = z] = \int_{u,\delta} (\alpha\delta + \beta u) \Pr(U = u) \Pr(\Delta = \delta|Z = z, U = u) d\delta du \tag{2}$$

Integrating, we can write this as follows:

$$\mathrm{E}[Y|Z = z] = \alpha\mathrm{E}[\Delta|Z = z] + b_0, \tag{3}$$

where b_0 is a study dependent constant (since the distribution of confounders may vary with study population). Therefore, the expected value of Y changes linearly with the expected value of Δ within randomization arms z of a study.

Let

$$\mu_z = \mathrm{E}[Y|Z = z]$$

and

$$\theta_z = \mathrm{E}[\Delta|Z = z].$$

We measure sample means $\hat{\mu}_z$ and $\hat{\theta}_z$, with sample standard errors $\hat{\sigma}_z$ and $\hat{\rho}_z$, respectively. As sample size

increases, the distributions of $\hat{\mu}_z$ and $\hat{\theta}_z$ approach normal distributions with standard deviations given by the unmeasured population standard errors σ_z and ρ_z. If Y and Δ are normally distributed, we do not have to consider this a large-sample approximation. Therefore, $\alpha\hat{\theta}_z + b_0$, the value of $\hat{\mu}_z$ we would predict based on $\hat{\theta}_z$, also approaches a normal distribution with mean $\alpha\hat{\theta}_z + b_0$ and standard deviation $\alpha\rho_z$. The discrepancy between $\hat{\mu}_z$ and $\alpha\hat{\theta}_z + b_0$ is a measure of how far values of $\hat{\mu}_z$ based on $\hat{\theta_z}$ are from $\hat{\mu}_z$, and this discrepancy will be expected to be smaller the better estimates of the parameters α and b_0. Therefore, based on a Welch's two-sample t-test, we can write the likelihood function of the parameters α and b_0 given the observed data D ($\hat{\theta}_z$, $\hat{\mu}_z$, $\hat{\sigma}_z$, and $\hat{\rho_z}$ for each treatment level z) as:

$$\mathcal{L}(\alpha; b_0|D) = \prod_z f\left(\frac{\alpha\hat{\theta}_z + b_0 - \hat{\mu}_z}{\sqrt{\sigma_z^2 + \alpha^2\rho_z^2}}\right) \tag{4}$$

where f is a t-distribution with mean zero and standard deviation 1, with degrees of freedom given by:

$$\frac{(\sigma_z^2 + \alpha^2\rho_z^2)^2}{\frac{\sigma_z^4}{N_{z,y}-1} + \frac{\alpha^4\rho_z^4}{N_{z,\delta}-1}}. \tag{5}$$

The correct variance of

$$\alpha\hat{\theta}_z + b_0 - \hat{\mu}_z$$

is obtained from the variance of the difference of two non-independent random variables multiplied by constant coefficients and is given by:

$$\mathrm{Var}[\alpha\hat{\theta}_z + b_0 - \hat{\mu}_z] = \sigma_z^2 + \alpha^2\rho_z^2 - 2\alpha\mathrm{Cov}(\hat{\theta}_z, \hat{\mu}_z) \tag{6}$$

With only aggregated data, we do not know, nor can we estimate, the value of

$$\mathrm{Cov}(\hat{\theta}_z, \hat{\mu}_z).$$

However, we explore some plausible scenarios to determine the effect of this unmeasured covariance. See **Simulation Results**.

Simulation Results

To determine the potential effect of not including the unmeasured covariance in our estimation procedure, we performed simulations under 4 scenarios, described below. The simulation is based on the DAG in *Figure S5*, and incorporates variation across individuals (terms labeled SD for standard deviation in the table below) and measurement error (terms labeled error in the table below). In all four scenarios there are three treatment levels–placebo, low-dose, and high-dose groups. The low dose group has a decrease in SUVr of 0.05 relative to the placebo group, and the high dose group has a decrease in SUVr of 0.1 relative to the placebo group. 1000 simulations were run for each scenario. Bias is reported as the absolute error in the effect of a 0.1 decrease in SUVr on MMSE score. All scenarios are not significantly biased and the coverage of the 95% confidence interval is close to 95%.

1. Amyloid Mediates All Cognitive Change

This scenario reflects a parameterization of the amyloid cascade hypothesis. In this scenario, there are no common causes of change in amyloid and cognition. That is, amyloid mediates all cognitive change. In this scenario, each 0.1 unit increase in SUVr, results in an expected 1 point decline in MMSE score.

2. No Confounding, No Effect of Amyloid

This scenario is identical to scenario 1, except that there is no effect of amyloid on cognition.

3. Confounding, An Effect of Amyloid

This scenario is similar to scenario 1, except that in addition to an effect of amyloid on cognition, there are common causes of change in amyloid and change in cognition.

4. Confounding, No Effect of Amyloid

This scenario is identical to scenario 3, except that there is no effect of amyloid on cognition.

	1. Amyloid Mediates All Cognitive Change	2. No Confounding, No Effect of Amyloid	3. Confounding, Effect of Amyloid	4. Confounding, No Effect of Amyloid
Number of Treatment Groups	3	3	3	3
Number with Cognitive Test	879	879	879	879
Number with PET	317	317	317	317
Effect of Treatment on Change in SUVr	-0.05	-0.05	-0.05	-0.05
SD of Change in SUVr within Treatment Arm	0.15	0.15	0.15	0.15
Error in Change in SUVr Measurement	0.05	0.05	0.05	0.05
SD in Unmeasured Confounder	1	1	1	1
Effect of U on Change in SUVr	0	0	0.09	0.09
Effect of U on Change in Cognition	0	0	-10	-10
Effect of Change in SUVr on Change in Cognition	-10	0	-10	0
Error in Cognition Measurement	1	1	1	1
SD of Cognition	3	3	3	3
Change in Cognition in Placebo Group	-3	-3	-3	-3
95% CI Coverage (%)	94.3	96.5	97.9	96.4
Bias	0.013, (-0.0085, 0.035)	-0.00093, (-0.019, 0.017)	0.009, (-0.054, 0.072)	-0.025, (-0.086, 0.035)

Appendix 4: Conversion of CDR-SB to MMSE

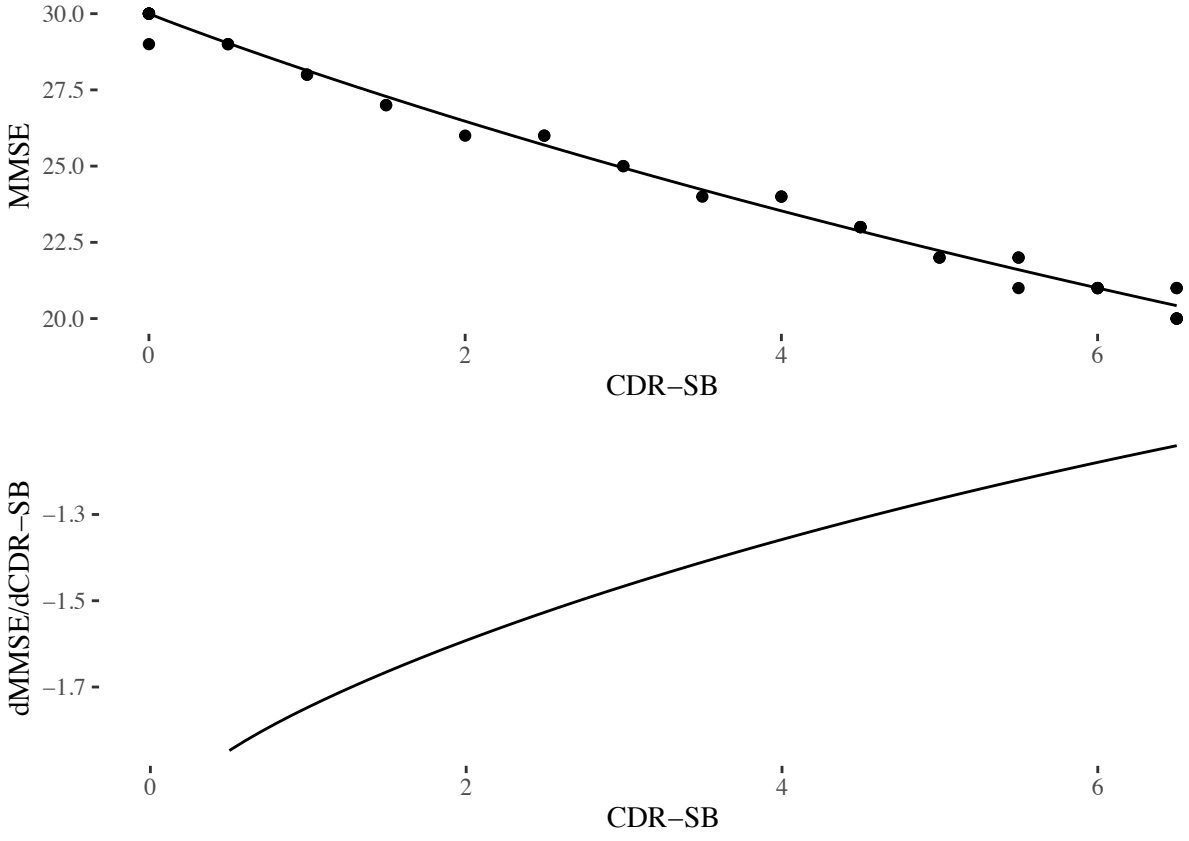
ClinicalTrials.gov Identifier: NCT01953601

CDR-SB to MMSE

We use the crosswalk between the CDR-SB and MMSE in *table 1* of (23). We fit a logistic curve with an upper bound at 30 to obtain a function that predicts a mean MMSE score as function of mean ADAS-Cog score. We then calculate the derivative of this function. We use the following midpoint approximation to calculate how the change in CDR-SB with respect to changing amyloid is related to the change in MMSE with respect to changing amyloid:

$$\text{Mean change in MMSE} = \left(\frac{d\text{MMSE}}{d\text{CDR-SB}} \Big|_{(\text{Starting CDR-SB}+\text{Change in CDR-SB})/2} \right) \text{Mean change in CDR-SB}$$

We plot the crosswalk between between CDR-SB and MMSE (*table 1* of (23)) and the fitted model (top) and the derivative of the fitted model (bottom).



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