Effect of Reduction in Brain β-Amyloid Levels on Cognitive Decline in Randomized Clinical Trials: An Updated Instrumental Variable Meta-Analysis

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Disclosures

- Changyu Shen, Menglan Pang, Ling Zhu, Audrey Gabelle, Arie Gafson, Ivana Rubino, Shibeshih Belachew and Carl de Moor are employees and shareholders of Biogen inc.
- Jim E. Galvin MD, MPH is a Professor of Neurology at University of Miami, consultant for Biogen, Alpha Cognition, Eisai, and Cognivue, and has research funding from NIH, and clinical income from patient care.
- Robert W. Platt, PhD, has an ongoing consulting arrangement with Biogen.
- Aducanumab is approved for use in the following markets: the United States, the United Arab Emirates, and Qatar. In the rest of the world, it is an investigational drug. Its efficacy and safety have not been established in Spain.

Background

- Brain β-amyloid plaque deposits are one of the defining pathological hallmarks of Alzheimer's disease (AD)
- Basic science, pre-clinical models and clinical studies have highlighted that removal of β-amyloid plaque is a relevant target for slowing AD disease progression
- Randomized clinical trials (RCTs) of therapeutic agents targeting β-amyloid (directly or indirectly) have yielded inconsistent results on the relationship between β-amyloid reduction and slowing of cognitive decline

Goate A et al. *Nature* 1991, 349:704-6. Karran E et al. *Nat Rev Drug Discov* 2011, 10:698-712. Thal DR et al. *Neurology* 2002, 58:1791-800. Ingelsson M et al. *Neurology* 2004, 62:925-31. Karlawish J and Grill JD. *Nat Rev Neurol* 2021 Sep;17(9):523-524.

Instrumental variable meta-analysis

thebmj

Research

Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis

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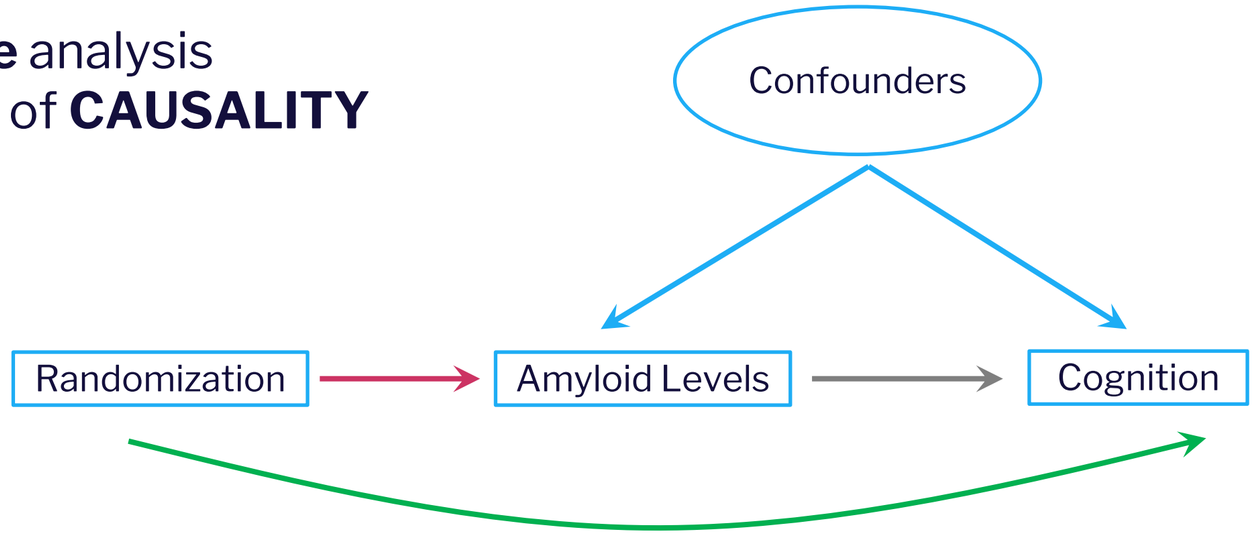
Instrumental-variable ↓ confounding bias

Meta-analysis ↑ statistical power

Ackley SF et al. *BMJ* 2021;372:n156

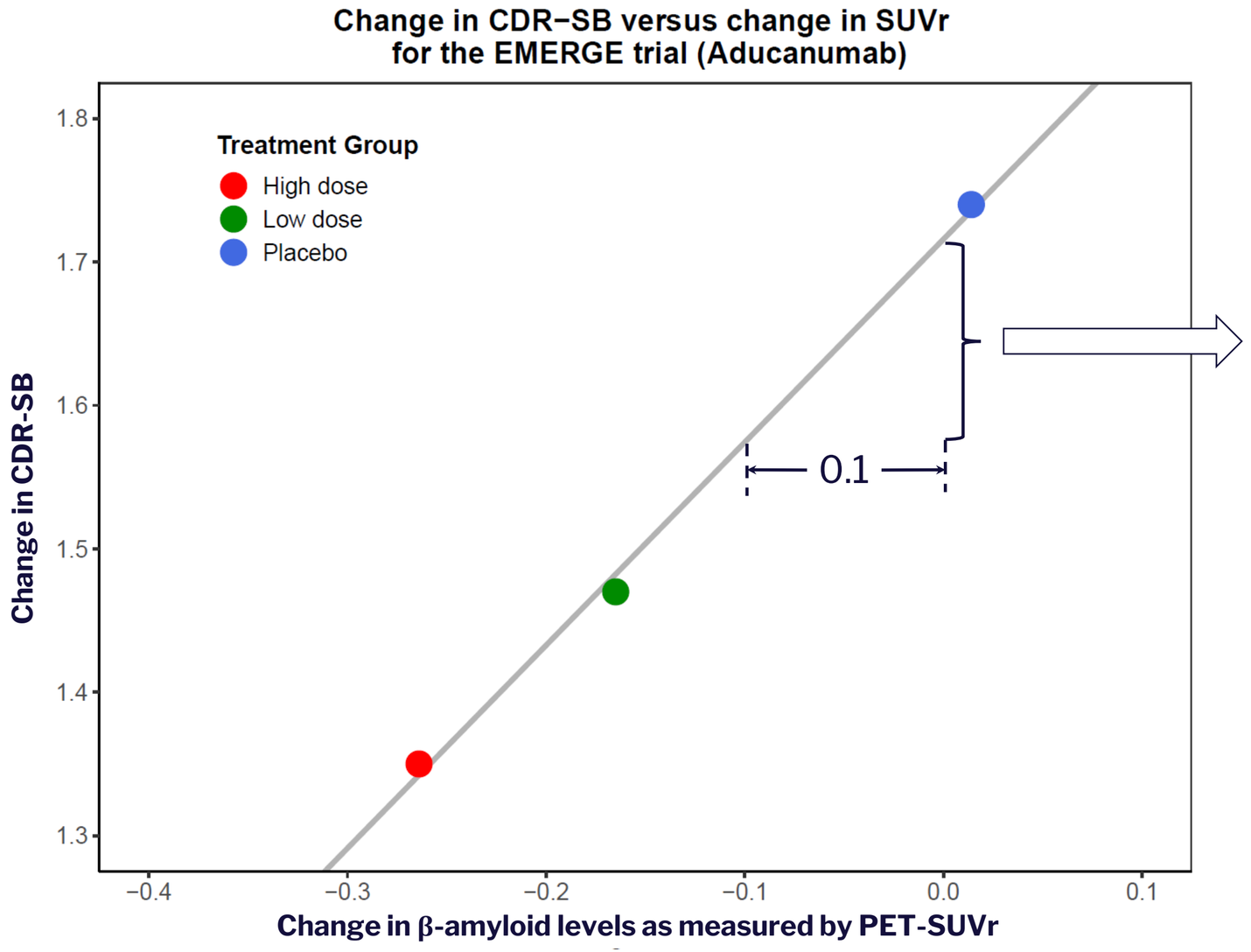
How does an instrumental variable work ?

Instrumental variable analysis allows the estimation of **CAUSALITY** instead of correlation



$$\text{Causal effect of amyloid on cognition} = \frac{\text{Causal effect of randomization on cognition}}{\text{Causal effect of the randomization on amyloid}}$$

How does an instrumental variable work ?

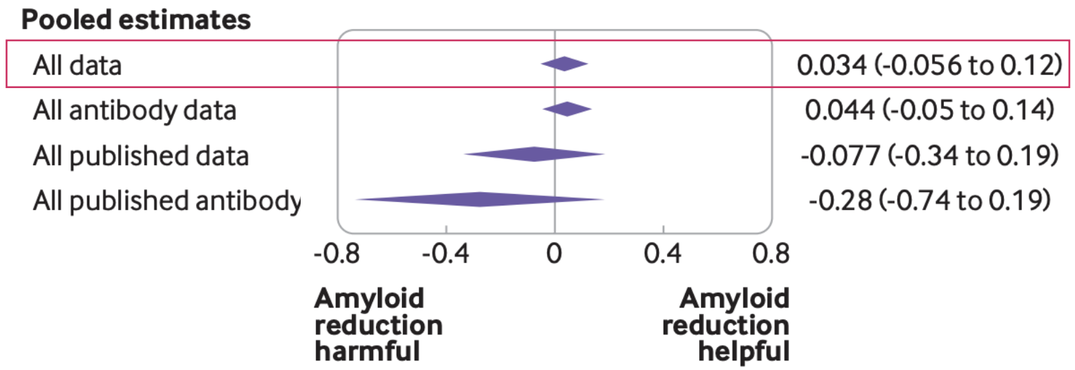


CDR-SB change for each 0.1 unit reduction of β-amyloid PET-SUVr

Summary of Ackley *et al.* study

- **Trials**: 14 randomized controlled trials of 8 drugs that target an amyloid mechanism
- **Population**: AD dementia or mild cognitive impairment due to AD
- **Clinical endpoints:**
  - Mini-Mental State Examination (MMSE)
  - Clinical Dementia Rating-Sum of Boxes (CDR-SB)
  - Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)

Primary analysis was on MMSE endpoint



- In their original work, **Ackley *et al*. provided a publicly available web interface** containing an interactive version of their analytic approach **to encourage recalculation of their results when updated or new data are available**

Figure adapted from Ackley SF et al. *BMJ* 2021;372:n156

Assessment of Ackley *et al.* 2021 identified 3 main areas for data updates

ORIGINAL Analysis

Limitations in data access

- MMSE data used for the Lecanemab trial [NCT01767311] included in the original analysis were computed using an algorithm that converts ADCOMS to MMSE
- MMSE data for Verubecestat-2 [NCT01953601] trial were derived by conversion of CDR-SB into MMSE in the original analysis

Data inconsistencies

- In the original analysis, the values used for standard error were inconsistent with the source for 4 trials
  - For example, the standard deviation (SD) was used as the standard error (SE) for some trials
  - A total of 11 figures of SE affected
- In the original analysis, point estimates were incorrect in two cognitive endpoints (CDR-SB & ADAS-Cog) in 1 trial.

Trials not included

- The original analysis included 14 trials based on available data on 30 April 2020
  - e.g. PRIME [NCT01677572] and Donanemab [NCT03367403] (published in May 2021) trials were not included

UPDATED Analysis

- We **used direct source data** for Lecanemab [NCT01767311] and Verubecestat-2 [NCT01953601] trials
- We **corrected data inconsistencies** where applicable (SE, point estimates)
- We **augmented** the set of trials with inclusion of PRIME [NCT01677572], and TRAILBLAZER/donanemab [NCT03367403] (May 2021) clinical trials
- The same instrumental-variable-based meta-analysis was then repeated using the updated data from 16 trials

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16 Trials included in the updated instrumental variable meta-analysis

Trial	Trial number	Data Updates
Bexarotene (BEAT-AD)	NCT01782742	
Solanezumab-1 & 2 Extension (EXPEDITION EXT)	NCT01127633	
Solanezumab-3 (EXPEDITION 3)	NCT01900665	
LY450139-1 [Semagacestat]	NCT00762411	
LY450139-2 [Semagacestat]	NCT00594568	
Gantenerumab	NCT01224106	Correct inconsistency
Bapineuzumab-1	2004-004120-12 (EudraCT)	Correct inconsistency
Bapineuzumab-2a (APOE-e4 Carrier)	NCT00575055	

Trial	Trial number	Data Updates
Bapineuzumab-2b (APOE-e4 Non-Carrier)	NCT00574132	
Verubecestat-1 (EPOCH)	NCT01739348	
Verubecestat-2 (APECS)	NCT01953601	Correct inconsistency Use source data
Lecanemab	NCT01767311	Use source data
Aducanumab-1 (EMERGE)	NCT02484547	
Aducanumab-2 (ENGAGE)	NCT02477800	Correct inconsistency
Aducanumab-3 (PRIME)	NCT01677572	Added trial
Donanemab (TRAILBLAZER-ALZ)	NCT03367403	Added trial

Results of the updated meta-analysis – Pooled estimates

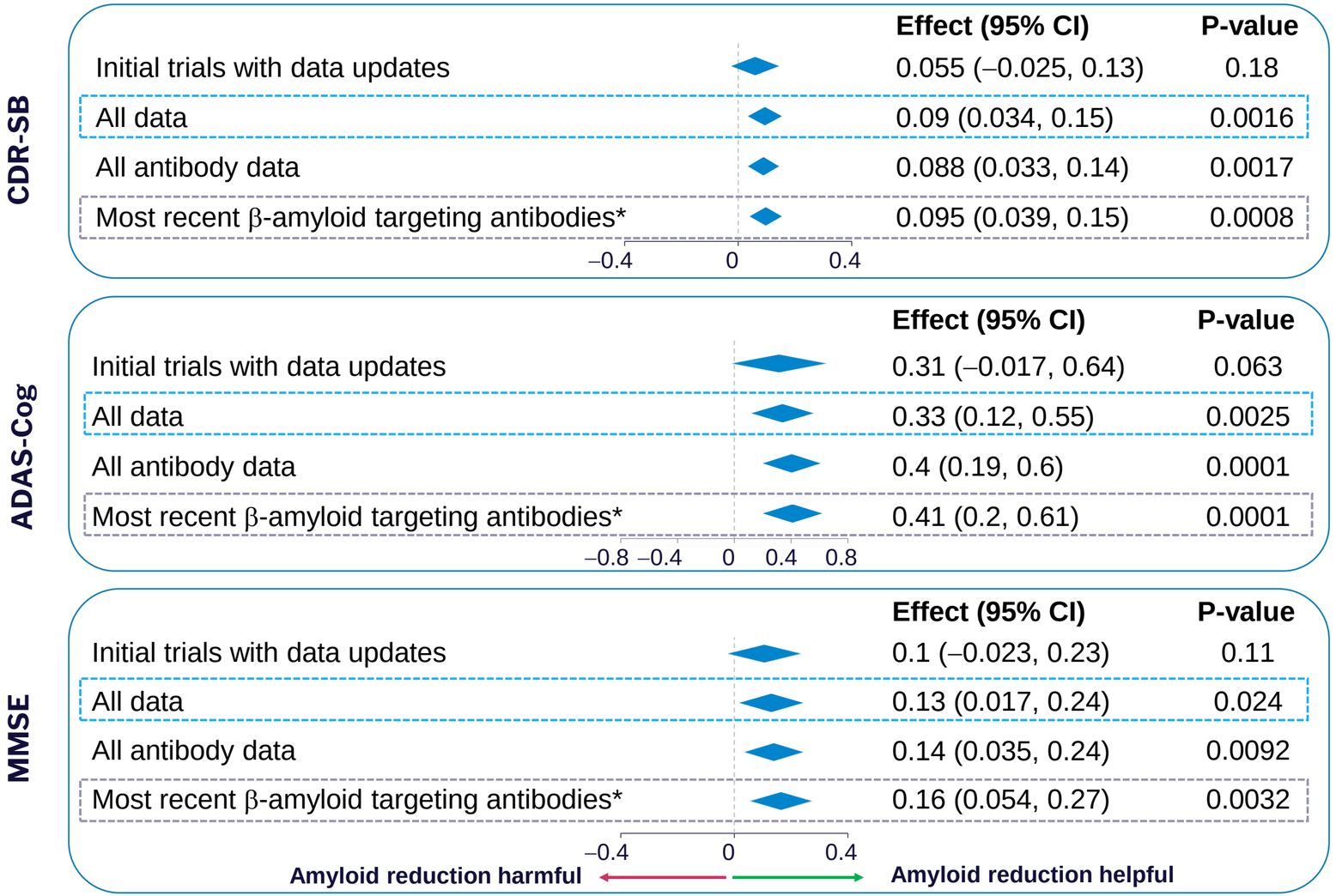
Effect of the reduction in β-amyloid SUVr on change in cognitive endpoints

Cognitive endpoints	Original analysis (All data)	Updated analysis (All data)	
	Effect (95% CI)	**Effect (95% CI)**	**P value**
CDR-SB	0.058 (-0.031, 0.15)	0.09 (0.034, 0.15)	**0.0016**
ADAS-Cog	N.A.	0.33 (0.12, 0.55)	**0.0025**
MMSE	0.034 (-0.056, 0.12)	0.13 (0.017, 0.24)	**0.024**

Positive values of the estimate – for each 0.1-unit reduction in SUVr – indicate β-amyloid reduction slows cognitive decline

- MMSE was the main clinical endpoint driving the conclusion in Ackley *et al.* study, while this updated analysis further suggested that it may lack sensitivity in capturing progression in cognitive decline as compared with CDR-SB and ADAS-Cog (i.e. higher p-values for MMSE)

Results of the updated meta-analysis – Sensitivity analyses



- Instrumental variable analysis requires the absence of off-target effect from a drug
- Hence, analyses based on antibodies are likely to be more accurate due to specificity of antibodies and their direct impact on β-amyloid plaques

Positive values of the effect estimate – for each 0.1-unit reduction in PET-SUVr – indicate β-amyloid reduction slows cognitive decline.
*The most recent β-amyloid targeting antibodies included Gantenerumab [NCT01224106], Aducanumab [NCT02484547, NCT02477800, NCT01677572], Lecanemab [NCT01767311] , and Donanemab [NCT03367403] trials.

Limitations

- Heterogeneous population: β-amyloid removal may have different effect on cognitive decline for different subjects
- Heterogeneity in radiotracers: PET SUVr may not be totally matched
- Impact of amyloid plaque removal on cognitive decline and functional activities may not be fully elucidated in the short-term setting of most clinical trials where a potentially delayed-onset effect cannot be captured
- **These limitations work against our ability to detect a causal relationship between β-amyloid removal and cognitive decline. That a statistically significant causal association is consistently demonstrated on all 3 cognitive endpoints despite those limitations highlights the potential of β-amyloid as a viable biological target in AD**

Conclusion

- After updating and augmenting this **instrumental variable** meta-analysis from Ackley *et al*., we demonstrate through combined results of 16 trials that there is a **consistent and statistically significant** beneficial and **causal** impact of PET β-amyloid SUVr change on 3 commonly used measures of cognitive decline

Ackley SF et al. *BMJ* 2021;372:n156

Thank you

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