

INTRODUCTION

- Autosomal dominant Alzheimer's disease (ADAD) is a rare, genetic form of early-onset Alzheimer's with nearly 100% penetrance.
- Eligibility for ADAD trials typically relies on estimated years to expected onset (EYO), but this does not guarantee presence of AD-related pathology.
- Could biomarker-based eligibility improve the efficiency of clinical trials?**

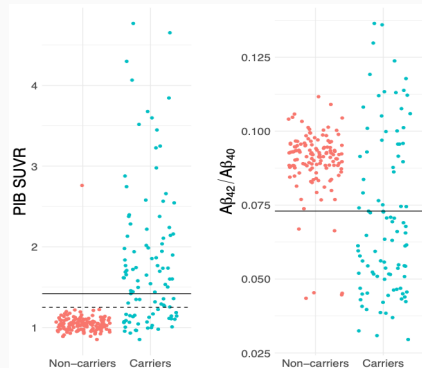


Figure 1 – Amyloid levels using PIB PET (left) and CSF (right) by mutation status. Horizontal lines represent cutpoints for amyloid positivity

Table 1 – Study demographics. Categorical values listed as number (%) of carrier/non-carrier subgroup and continuous variables are provided as mean (standard deviation)

	Non-carriers	Carriers
N	160	138
Age, years	36.6 (10.7)	36.5 (8.7)
Family Mutation		
APP	36 (22.5%)	25 (18.1%)
PSEN1	111 (69.4%)	103 (74.6%)
PSEN2	13 (8.1%)	10 (7.2%)
Parental EYO, years	-10.2 (11.8)	-10.0 (7.3)
Mutation EYO, years	-12.0 (10.4)	-10.4 (6.8)
Cortical PIB SUVR	1.05 (0.16), n=146	1.78 (0.83), n=122
CSF Lumipulse Aβ 42/40	0.090 (0.011), n=132	0.073 (0.029), n=118

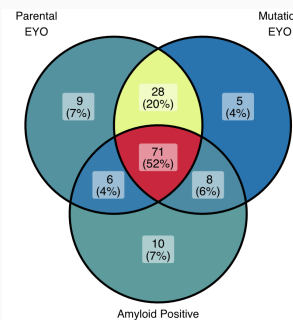


Figure 2 – Venn diagram indicating overlap of the participants and which eligibility criteria that they fulfilled. 71 (52%) were eligible in all three. Approximately 25–30% of EYO-eligible carriers were amyloid-negative, while 17–20% of amyloid-positive participants were ineligible by EYO

METHODS

Cognitive, biomarker data from DIAN (Table)

- Asymptomatic participants (CDR=0), data freeze 17
- Non-carriers used to establish treatment effects

Eligibility criteria scenarios

- Parental age-based EYO ($-15 < \text{EYO} < 10$),
- Mutation mean-based EYO ($-15 < \text{EYO} < 10$)
- Amyloid positive cutpoints: Cortical PIB SUVR > 1.42 (original DIAN-OBS), PIB SUVR > 1.25 (more recent DIAN-TU), CSF Aβ42/40 Lumipulse < 0.073 (FDA approved)

Sample size estimates:

- Assuming future trial analysed using ANCOVA model
- Parameter estimates needed for sample size calculations obtained from linear mixed effects model
- Target treatment effect: 50% slowing (cognitive, MRI, FDG) or 25% reduction in biomarker levels (CSF, PIB) over four years, relative to non-carriers
- Detecting target treatment effect with 95% significance, 80% power, assuming 40% dropout
- Uncertainty quantified through bootstrapping

CONCLUSIONS

Amyloid-based (CSF, PIB PET) eligibility provided comparable sample sizes to conventional EYO-based eligibility while ensuring presence of AD pathology.

However, we would not recommend doing trials with as few participants as some estimates provide, as assumptions behind the sample size calculation may not hold in these settings

If plasma-based biomarker produce similar estimates, this could represent a feasible and potentially more efficient strategy for future ADAD trials.

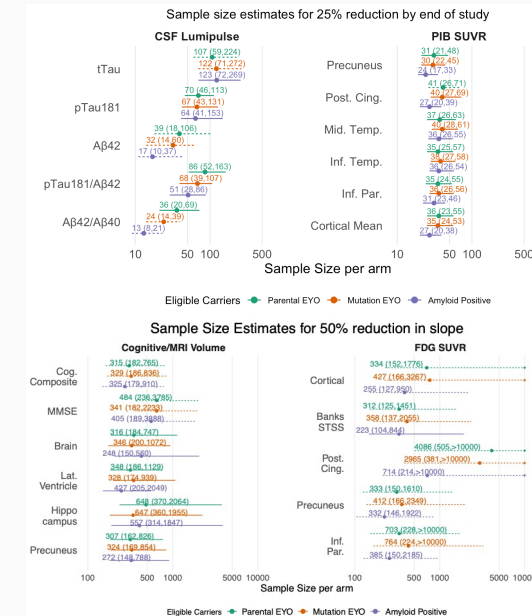


Figure 3 – Sample size estimates (mean and 95% bootstrapped confidence intervals) needed to detect 25% absolute reduction (top) or a 50% slowing (bottom) in a four-year trial Dashed intervals indicate that the number of bootstrap samples where the model failed to converge was $>1\%$, and thus the confidence intervals should be treated with caution.