



Estimating Clinical Trial Eligibility for Anti-Amyloid Therapies in Down Syndrome: The Role of Amyloid Positivity and Cerebral Microhemorrhage Frequency Across Age

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OBJECTIVE

The goal of this work was to perform a retrospective assessment of two cohort studies of people with DS to assess potential eligibility for AAT clinical trials. This study addressed three questions:

1. What is the frequency of amyloid positivity across age groups in adults with DS?
2. How frequent are MRI biomarkers predictive of ARIA risk?
3. What proportion of individuals would meet radiographic and early clinical eligibility criteria for AAT trials based on strict selection criteria of one mH or less and low WMH burden.

BACKGROUND

- AD is the leading cause of death in adults with DS over age 35^{1,2}.
- Amyloid accumulation begins the 30s, followed by a ~15–20 year preclinical window before dementia, during which anti-amyloid therapies could potentially delay cognitive decline³.
- Individuals with DS have been excluded from anti-amyloid therapy (AAT) trials, due to concerns about increased microhemorrhages (mHs), raising risk for amyloid-related imaging abnormalities (ARIA)^{4,5}.
- DS patients show increasing cerebrovascular changes (mHs, WMH, enlarged perivascular spaces) from their late 30s, often independent of traditional risk factors; although mHs correlate with age and APOE4 (not amyloid/tau), autopsy data show high CAA prevalence, suggesting elevated ARIA risk, but longitudinal mH burden and safe inclusion thresholds (e.g., ≤1 mH in ALADDIN trial) remain poorly studied^{6,7}

METHODS

- Participants enrolled in ABC-DS and/or TRC-DS had a karyotype-confirmed trisomy 21, brain MRI with T2* GRE for mH assessment and FLAIR for white matter hyperintensity (WMH) burden quantification, and amyloid PET.
- We estimated the proportion of participants who were amyloid-positive (centiloid value > 18), who had ≤1 mH on MRI, and had low burden of WMH (WMH/TIV<1.15%).

RESULTS

- We evaluated 303 participants (age 38.2 ± 8.4 years, 41.3% women. Nine participants (3.0%) had one mH, 11 (3.6%) had 2–4 mH, and seven participants (2.3%) had >4 mH.
- In a subset of 133 participants with amyloid PET, 31 (23.3%) of them were amyloid-positive. Of 114 participants with complete multimodal imaging, 25 participants were amyloid PET positive and 20 of them (80%) would be eligible for anti-amyloid therapies by radiographic criteria.
- In 88 participants with cognitive status available, there were no participants with a clinical diagnosis of dementia, with 14 of 18 (77.8%) amyloid PET positive individuals eligible for asymptomatic and early symptomatic intervention trials.

FIGURE

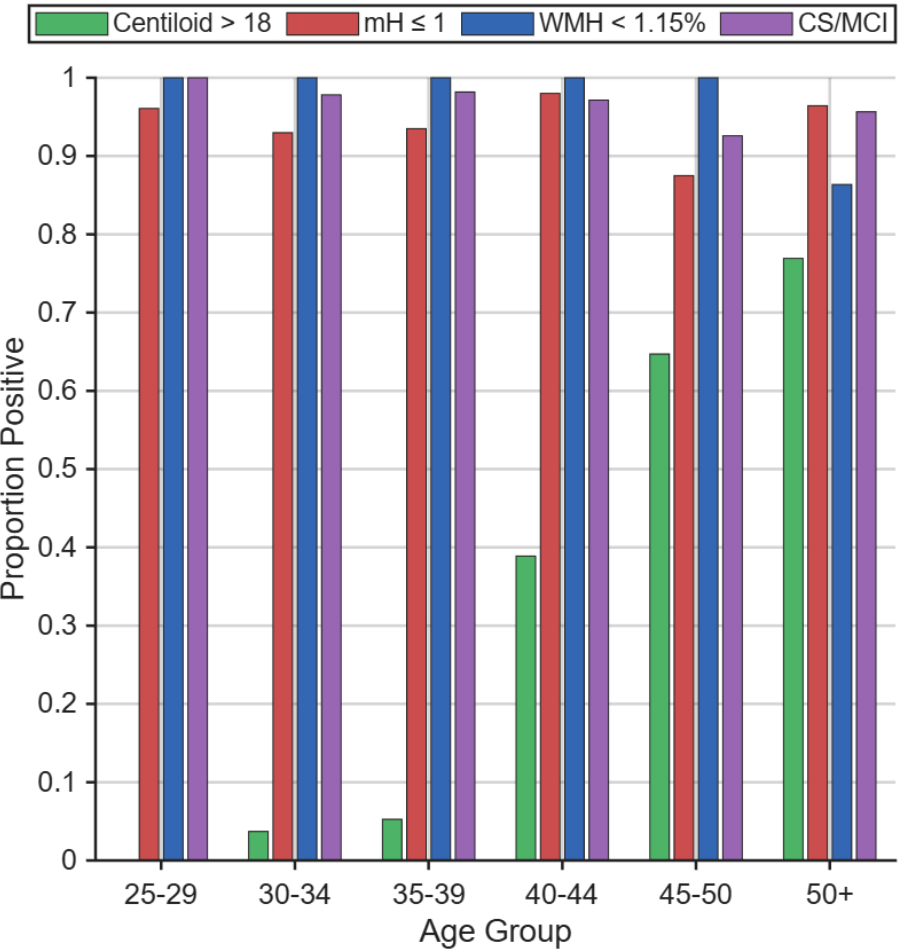


Figure. Percent of participants with amyloid PET positivity (green), ≤1 microhemorrhage (mH) (red), %WMH ≤ 1.15% (blue), and CS/MCI clinical diagnosis (purple).

TABLE

	Age at Visit					
	25-29 (N = 18)	30-34 (N = 23)	35-39 (N = 32)	40-44 (N = 15)	45-50 (N = 15)	Over 50 (N = 11)
Positive Amyloid PET (Centiloid >18)	0	1	2	5	9	8
MRI with ≤ 1 mH	17	21	29	15	14	11
Mild WMH burden(WMH/TIV < 1.15%)	18	23	32	15	15	9
Cognitive Diagnosis (CS/MCI/Dementia)	13/0/0	19/0/1	23/0/0	13/1/0	8/2/0	6/2/0
Total Eligible by radiographic criteria only (N = 114)	0 (0%)	1 (4.4%)	2 (6.3%)	5 (33.3%)	8 (53.3%)	6 (54.6%)
Total eligible by radiographic and clinical criteria (N = 88)	0/13 (0%)	0/20 (0%)	0/23 (0%)	5/14 (35.7%)	7/10 (70%)	4/8 (50%)

Table 2. Radiographic eligibility for all participants with complete multimodal imaging available (N = 114). We also include radiographic and cognitive eligibility in participants with a cognitive diagnosis available (N = 88).

DISCUSSION

- Most amyloid-positive adults with DS meet baseline radiographic eligibility for anti-amyloid trials, with low rates of exclusion markers like mH.
- mH burden was generally low, even among amyloid-positive individuals, suggesting a potential window in midlife for trial eligibility before cerebrovascular changes increase. However, ARIA risk, treatment safety, and efficacy were not assessed.
- Limitations include young cohort bias able to participate in observational studies. Further studies are needed to evaluate safety, scalability, and inclusion of more symptomatic individuals.

REFERENCES

1. Fortea J, Zaman SH, Hartley S, Rafii MS, Head E, Carmona-Iragui M. Alzheimer's disease associated with Down syndrome: a genetic form of dementia. *Lancet Neurol* 2021;20:930-942.
2. Hithersay R, Startin CM, Hamburg S, et al. Association of Dementia With Mortality Among Adults With Down Syndrome Older Than 35 Years. *JAMA Neurol* 2019;76:152-160.
3. Fortea J, Vilaplana E, Carmona-Iragui M, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. *Lancet* 2020;395:1988-1997.
4. Barroeta I, Videla L, Carmona-Iragui M, Fortea J, Rafii MS. Current advances and unmet needs in Alzheimer's disease trials for individuals with Down syndrome: Navigating new therapeutic frontiers. *Alzheimers Dement* 2025;21:e70258.
5. Helman AM, Siever M, McCarty KL, et al. Microbleeds and Cerebral Amyloid Angiopathy in the Brains of People with Down Syndrome with Alzheimer's Disease. *J Alzheimers Dis* 2019;67:103-112.
6. Lao P, Edwards N, Flores-Aguilar L, et al. Cerebrovascular disease emerges with age and Alzheimer's disease in adults with Down syndrome. *Sci Rep* 2024;14:12334.
7. Head E, Phelan MJ, Doran E, et al. Cerebrovascular pathology in Down syndrome and Alzheimer disease. *Acta Neuropathol Commun* 2017;5:93.