

Baseline Amyloid and Tau PET Characteristics in Early Stages of Alzheimer’s Disease: Data from the TRAILRUNNER-ALZ 3 PET Addendum

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OBJECTIVE

- To evaluate baseline amyloid and tau PET deposition in a subset of TRAILRUNNER-ALZ 3 participants enrolled in the PET addendum.

CONCLUSION

- TRAILRUNNER-ALZ 3 enrolled participants with cognitively unimpaired AD and AD with MCI based enrollment criteria.
- TRAILRUNNER-ALZ 3 PET addendum baseline characteristics were consistent with expectations based on other AD clinical trial populations.
- Global and regional tau deposition and amyloid levels in TRAILRUNNER-ALZ 3 CDR-GS=0.5 group were consistently lower than those in the CDR-GS=0.5 group of TRAILBLAZER-ALZ 2,⁵ indicating a less advanced pathological staging among TRAILRUNNER-ALZ 3 participants with MCI.
- Global and regional tau deposition in TRAILRUNNER-ALZ 3 CDR-GS=0 group was consistent with the A4 study.
- The slightly higher tau deposition observed in the Diversity addendum subgroup may indicate more advanced AD pathology of enrolled participants due to broader entry criteria.



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BACKGROUND

- Amyloid-targeting therapies are likely to offer greater benefit when treatment is initiated earlier in the AD continuum.^{1–3}
 - Studies have shown greater clinical benefit in those treated earlier in their disease.^{4,5}
- Remternetug is an immunoglobulin G1 monoclonal antibody directed at the pyroglutamate modification of the deposited amyloid plaque.
- TRAILRUNNER-ALZ 3 (NCT06653153) is a multi-center, randomized, double blind, placebo-controlled, ongoing phase 3 study evaluating remternetug in participants with cognitively unimpaired AD or AD with MCI (stages 1–3⁶) and with evidence of AD pathology by plasma P-tau217 levels.

STUDY

- The study includes a subset of TRAILRUNNER-ALZ 3 participants enrolled in the PET and Diversity addenda.
 - The PET addendum is being conducted in a subset of TRAILRUNNER-ALZ 3 participants to evaluate longitudinal amyloid and tau PET imaging data.
 - The Diversity addendum enrolled participants in racial and ethnic populations traditionally underrepresented in AD clinical trials using broadened entry criteria to reduce potential bias associated with standard cognitive assessments.

METHODS

- Baseline amyloid and tau PET scans were acquired to characterize the associations among plasma P-tau217 levels, clinical characteristics, amyloid plaque burden, and tau deposition.
- Tau PET scans were categorized using groups defined by global SUVr and visual read.¹⁰
 - Visual read categories consistent with AD (cAD+ or cAD++) associates with worse disease progression in all SUVr groups.¹¹
- Regional tau SUVr was estimated from 4 previously defined composite regions—medial temporal, lateral temporal, parietal, and frontal—using the cerebellar gray reference.⁷
- Separate analyses were conducted for participants enrolled in both PET and Diversity addenda.
- Baseline characteristics and imaging data from the LEARN, A4 (solanezumab trial in cognitively unimpaired AD), and TRAILBLAZER-ALZ 2 (CDR-GS=0.5 group) studies were compared to TRAILRUNNER-ALZ 3 data.^{5,7–9}

RESULTS

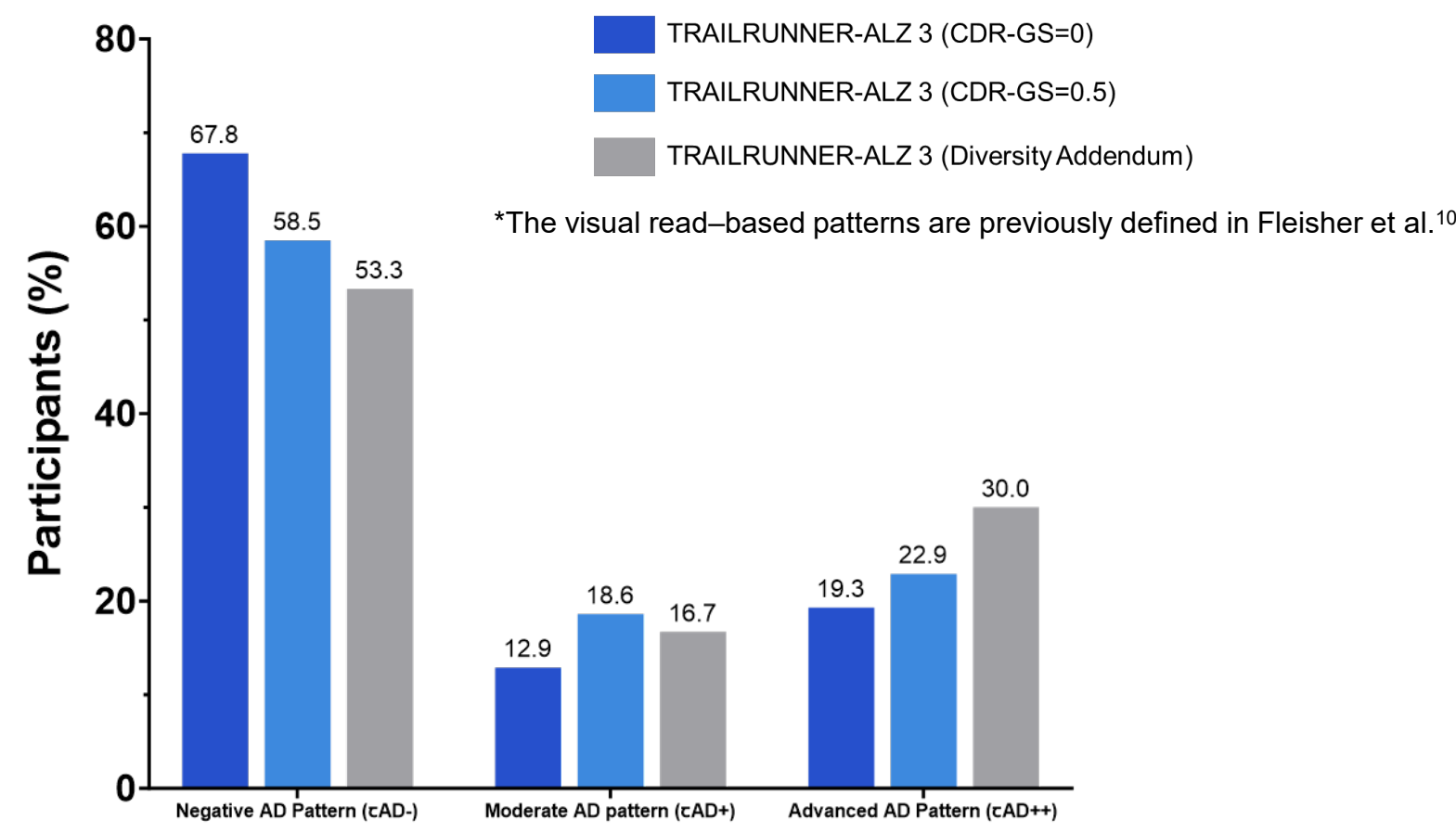
Demographics and baseline clinical characteristics

	LEARN ⁷ (CDR-GS=0) N=469	A4 ⁷ (CDR-GS=0) N=1169	TRAILRUNNER-ALZ 3 (CDR-GS=0) N=283	TRAILRUNNER-ALZ 3 (CDR-GS=0.5) N=127	TRAILRUNNER-ALZ 3 [†] (all in main study) N=411	TRAILRUNNER-ALZ 3 (Diversity addendum) [‡] N=33	TRAILBLAZER-ALZ 2 [†] (CDR-GS=0.5) N=1046
Age, years	70.5 (4.3)	71.9 (4.8)	72.0 (4.6)	71.8 (5.1)	71.9 (4.8)	71.5 (5.3)	72.5 (6.0)
Female, n (%)	289 (61.6)	694 (59.4)	170 (60.1)	67 (52.8)	238 (57.9)	21 (63.6)	586 (56.0)
Race, n (%)							
American Indian/Alaska Native	5 (1.1)	2 (0.2)	0	0	0	1 (3.4)	1 (0.1)
Asian	9 (1.9)	24 (2.1)	16 (5.7)	5 (4.0)	21 (5.2)	4 (13.8)	71 (6.8)
White	440 (93.8)	1100 (94.1)	254 (90.4)	119 (95.2)	374 (91.9)	13 (44.8)	948 (90.7)
Black/African American	10 (2.1)	28 (2.4)	10 (3.6)	1 (0.8)	11 (2.7)	10 (34.5)	25 (2.4)
Multiple	5 (1.1)	8 (0.7)	1 (0.4)	0	1 (0.2)	1 (3.4)	0
Ethnicity, n (%)							
Hispanic/Latino	15 (3.2)	34 (2.9)	18 (6.4)	14 (11.0)	32 (7.8)	17 (51.5)	40 (5.2)
Not Hispanic/Latino	450 (95.9)	1124 (96.2)	264 (93.3)	113 (89.0)	378 (92.0)	15 (45.5)	726 (94.8)
Not reported	4 (0.9)	11 (0.9)	1 (0.4)	0	1 (0.2)	1 (3.0)	1 (0.1)
APOE ε4 carrier, n (%)	104 (22.2)	689 (58.9)	162 (57.2)	70 (55.1)	233 (56.7)	19 (57.6)	756 (72.4)
AD signature-weighted neocortical SUVr [‡]	—	1.03 (0.1)	1.02 (0.10)	1.05 (0.14)	1.03 (0.11)	1.13 (0.22)	1.31 (0.24) [‡]
CDR-SB score	0.0 (0.1)	0.1 (0.2)	0.07 (0.2)	1.43 (0.8)	0.49 (0.8)	1.44 (1.2)	2.7 (1.0)

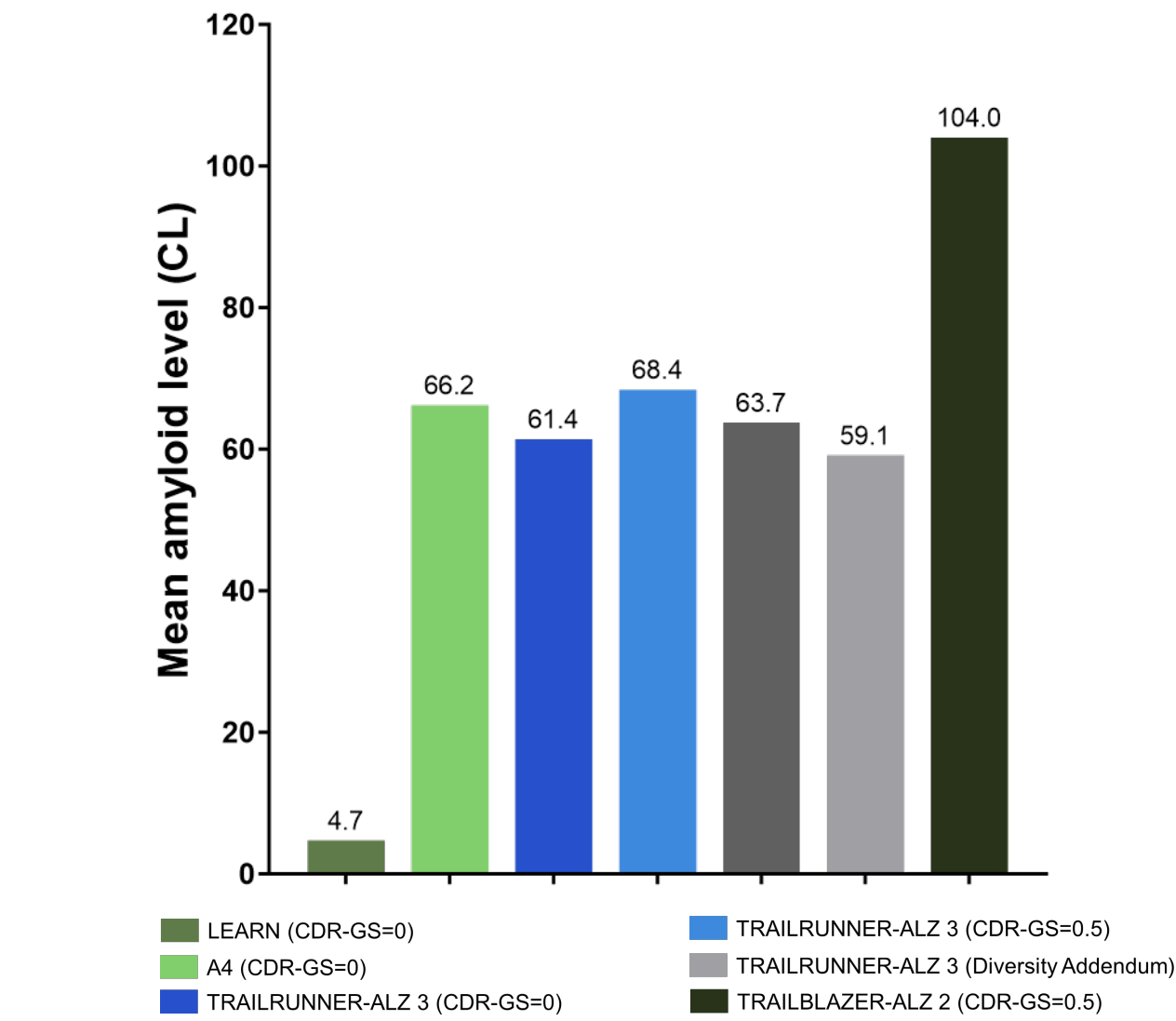
Data are reported as mean (SD) unless otherwise stated.

[†]CDR-GS data were missing for 1 participant. [‡]Includes participants enrolled in both PET and Diversity addenda. In this group, 11 participants had a CDR-GS of 0, and 22 had a CDR-GS of 0.5. Participants in the Diversity addendum met all main study eligibility criteria, except for MMSE (≥27) and/or FAQ (≤6) thresholds. [‡]Tau PET data are based on 264 participants with CDR-GS=0, 118 participants with CDR-GS=0.5, 383 main study participants, and 30 Diversity addendum participants. [§]Data based on n=988 from TRAILRUNNER-ALZ 3.

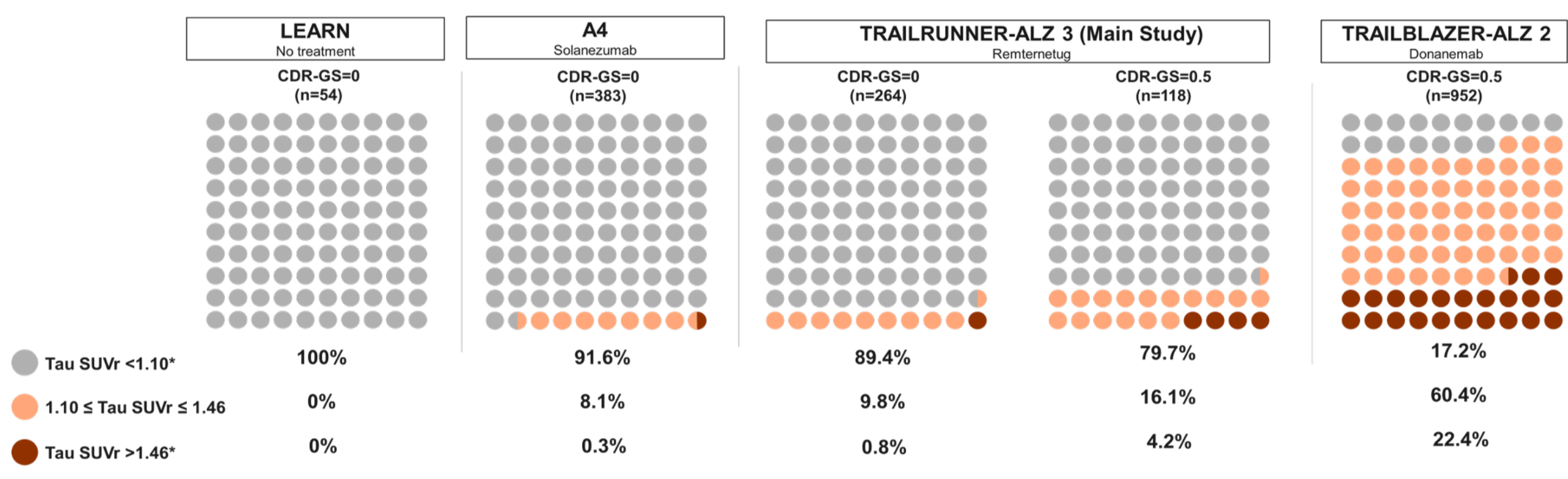
Tau PET visual read patterns among TRAILRUNNER-ALZ 3 participants



Baseline Amyloid PET results across studies

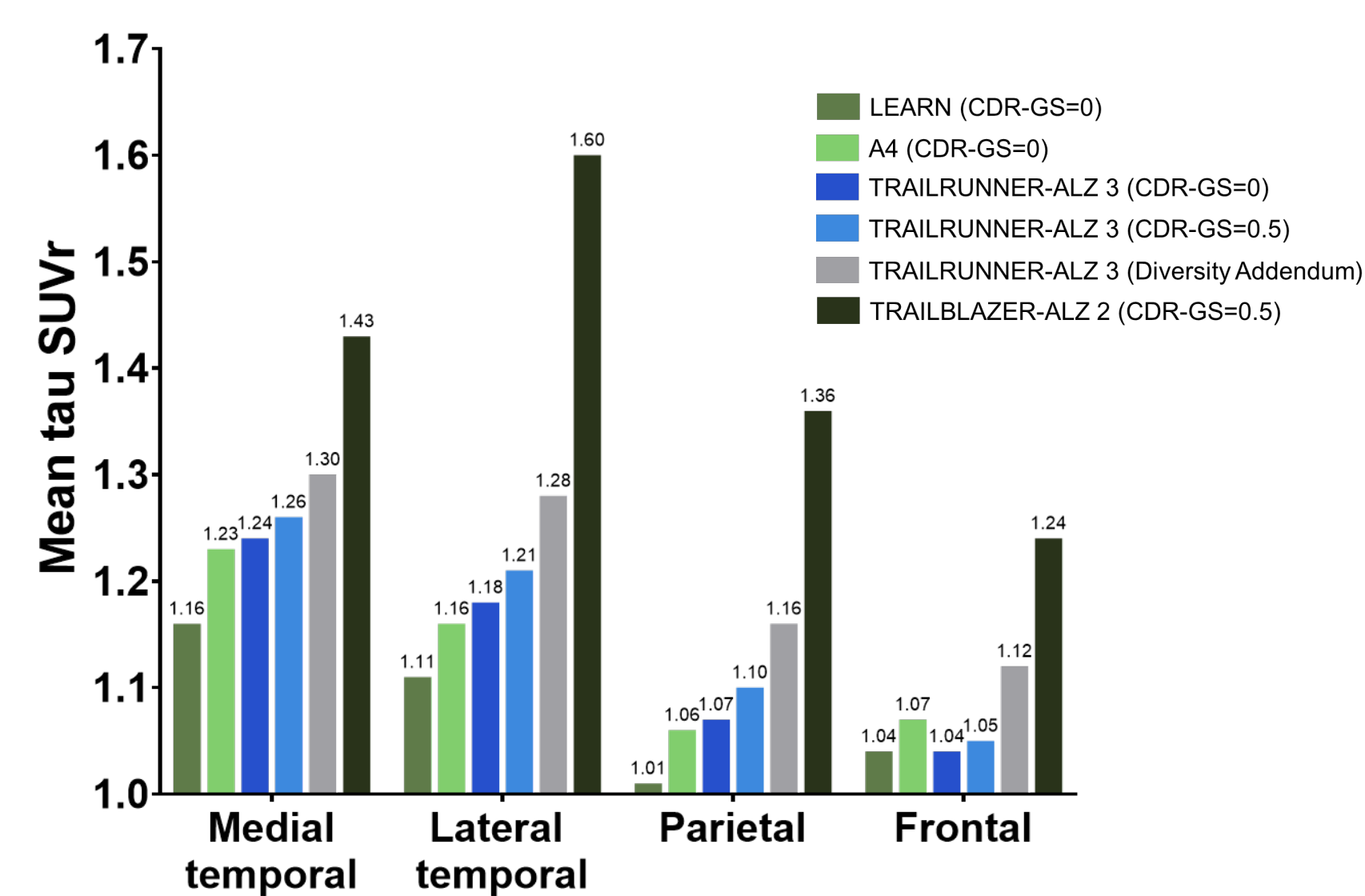


Baseline global tau SUVr-based stratification across studies



*Tau cutoffs were derived from Mintun et al.⁴ Quantitation were based on AD-signature weighted neocortical SUVr. TRAILRUNNER-ALZ 3 data excludes diversity addendum.

Baseline regional tau PET SUVr for 4 composite regions



The 4 composite regions were previously defined in Yaari et al.⁷ Refinement of optimal regional ROI definitions may be warranted. All images were analyzed using consistent methodologies.

Abbreviations: AD, Alzheimer’s disease; APOE, apolipoprotein E; CL, centiloid; CDR-GS; Clinical Dementia Rating-Global Score; CDR-SB, CDR-Sum of Boxes; FAQ, Functional Activities Questionnaire; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; N, number; PET, positron emission tomography; P-tau217, phosphorylated tau217; ROI, region of interest; SD, standard deviation; SUVr, standardized uptake value ratio.

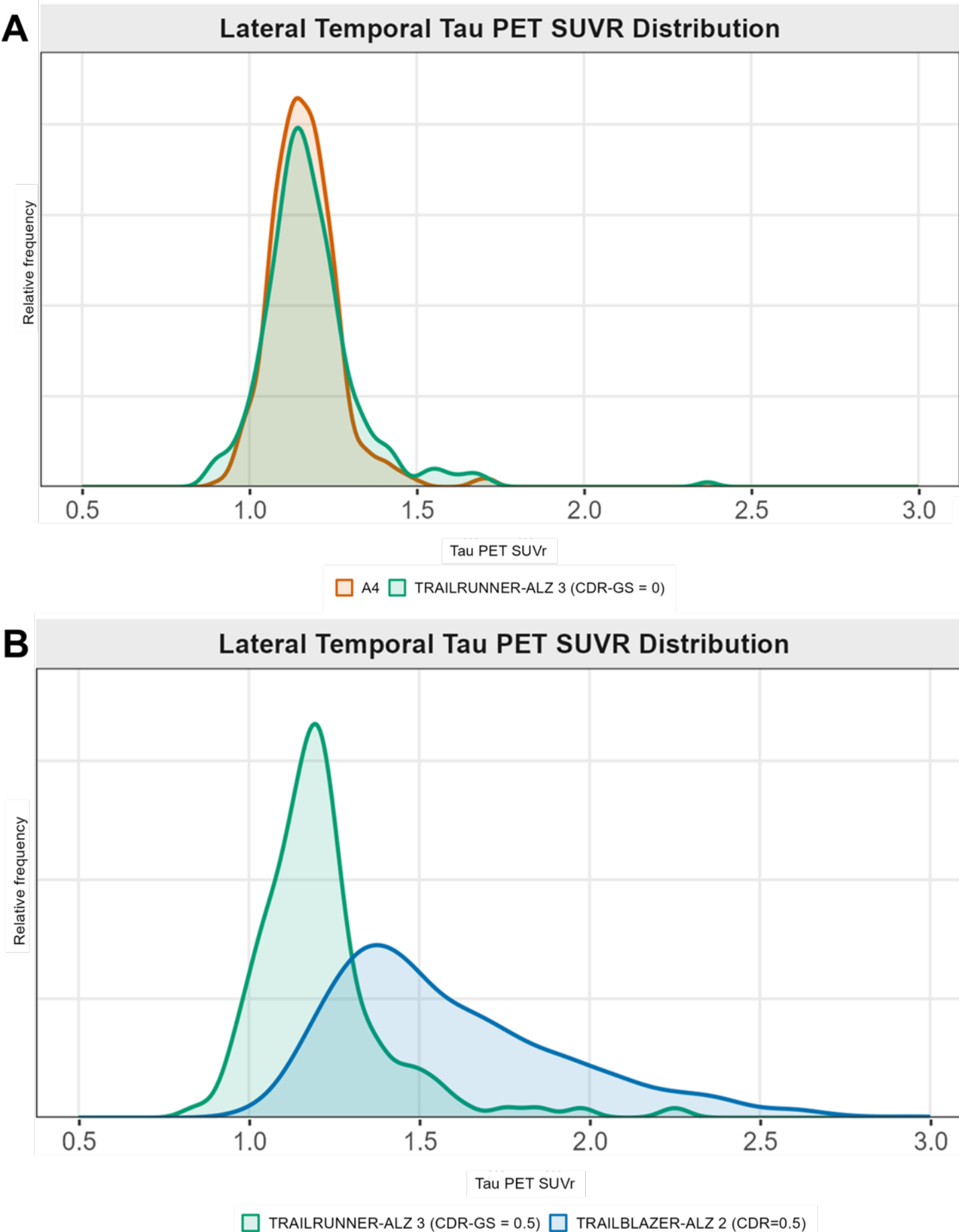
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Baseline lateral temporal SUVr distributions in (A) TRAILRUNNER-ALZ 3 (CDR-GS=0) vs A4 and (B) TRAILRUNNER-ALZ 3 (CDR-GS=0.5) vs TRAILBLAZER-ALZ 2 (CDR-GS=0.5)



Tau PET SUVr distributions are shown as kernel density estimates. Each curve integrates to ~1 within its trial. Intensity distributions are capped from 0.5 to 3.0 SUVr. All images were analyzed using consistent methodologies. Refinement of optimal regional ROI definitions may be warranted.