Dynamic PET imaging reduces sample sizes to detect longitudinal amyloid accumulation

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on behalf of the AMYPAD Consortium

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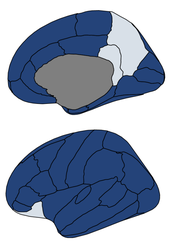
Background

Detecting subtle-to-moderate biomarker changes becomes increasingly relevant in the context of primary and secondary prevention of Alzheimer's disease (AD). However, a known bias associated with standardized uptake value ratios (SUVR) and the recent findings on the value of regional amyloid PET analyses in the early stages of AD suggest standard analyses of global SUVR might be sub-optimal in the context of anti-amyloid interventional trials.

Aim

To determine whether distribution volume ratio (DVR; derived from dynamic imaging) and regional quantification could improve statistical power in primary and secondary prevention trials using longitudinal PET imaging.

Material and Methods



Data: Tabulated [^{11}C]PIB quantitative data (SUVR, DVR and Centiloid (CL) values) was obtained from 237 cognitively healthy individuals from the OASIS-3 database. Baseline and annualized % change in SUVR and DVR were computed for a global cortical composite and an "early" region of interest (ROI) composed of **the isthmus cingulate, precuneus and lateral orbitofrontal regions** (light blue in Figure on the right) [1,2].

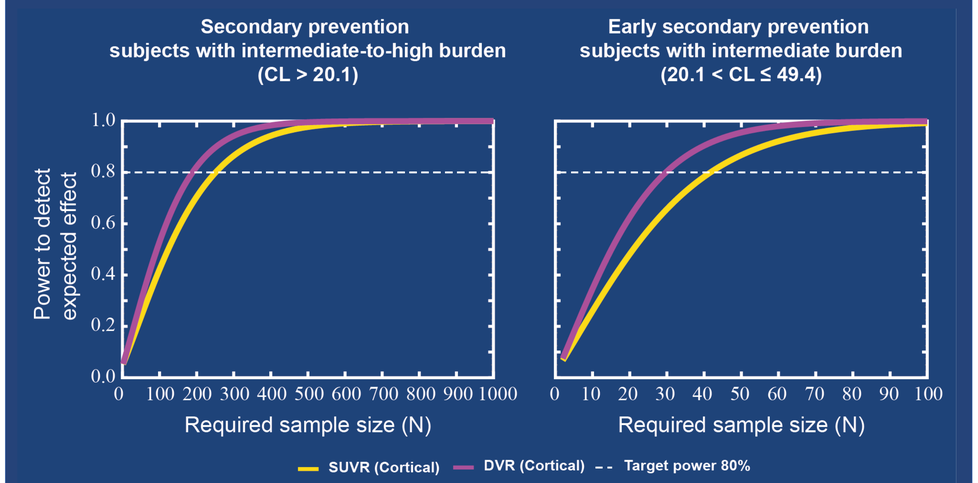
Descriptive analyses: Bland-Altman and correlation analyses were used to assess the relationship between SUVR and DVR. The level of amyloid burden at baseline was classified as **low** (CL ≤ 20.1), **intermediate** (20.1 < CL ≤ 49.4) or **high** (CL ≥ 49.4)[3].

Trial scenarios: We assessed differences between SUVR and DVR using a cortical or early composite ROI in their statistical power considering three anti-amyloid trial scenarios:

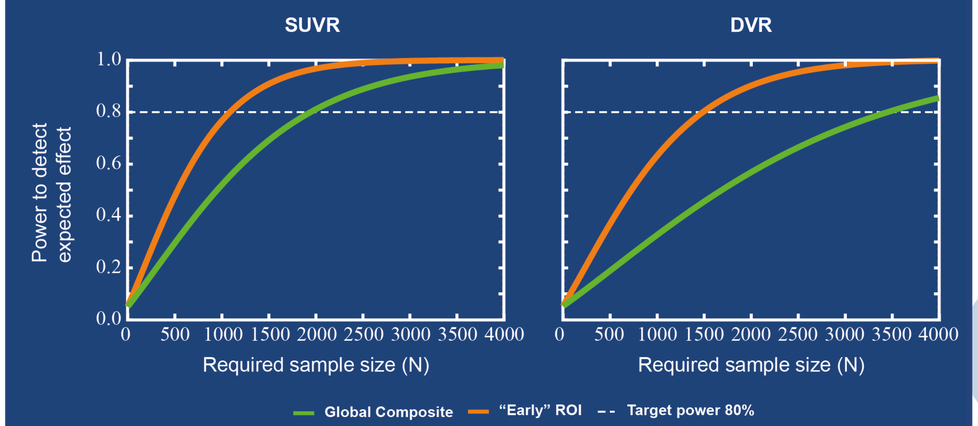
1) a ***secondary prevention trial*** including subjects with intermediate-to-high levels of amyloid (Centiloid > 20.1)
2) an ***"early" secondary prevention trial*** focusing on subjects with intermediate levels of amyloid, which displayed the highest amyloid accumulation rates (20.1 < Centiloid ≤ 49.4)
3) a ***primary prevention trial*** focusing on subjects with low levels of amyloid (Centiloid ≤ 20.1).

All trial scenarios were set to detect a 20% reduction in β-amyloid accumulation rates across the population, as well as restricted to APOE-ε4 carriers only.

DVR reduces sample sizes by 25-30% in secondary prevention trials



"Early" ROIs reduces sample sizes **only** in primary prevention trials



Results

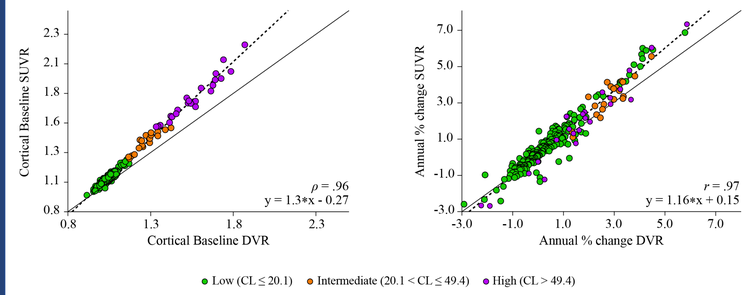


Figure 1. Although highly correlated to DVR (ρ=.96), cortical SUVR significantly overestimated DVR cross-sectionally and in annual % change. The SUVR **bias was not constant, but proportional to the underlying level of amyloid burden and accumulation rates** (slopes in Figure 1).

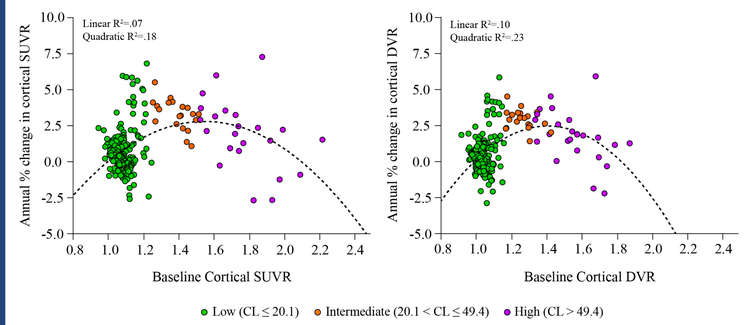


Figure 2. The relationship between baseline amyloid burden and annual % change was not linear, and **subjects in the intermediate amyloid burden group (orange) display the highest accumulation rates on average.**

Trial scenarios

	Whole population				APOE- ε4 carriers only			
	SUVR		DVR		SUVR		DVR	
	Cortical ROI	Early ROI	Cortical ROI	Early ROI	Cortical ROI	Early ROI	Cortical ROI	Early ROI
Secondary prevention (CL> 20.1)	252	296	189	220	81	96	57	63
Early secondary prevention (20.1 < CL ≤ 49.4)	42	64	30	40	46	64	35	39
Primary prevention (CL ≤ 20.1)	1951	1092	3479	1501	1364	811	2412	1270

Table 1. Secondary prevention trials can benefit from the use of DVR or focused selection on individuals with intermediate amyloid burden. Primary prevention trials can benefit from using an early ROI, and selecting APOE-ε4 carriers improves sample sizes across all scenarios.

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