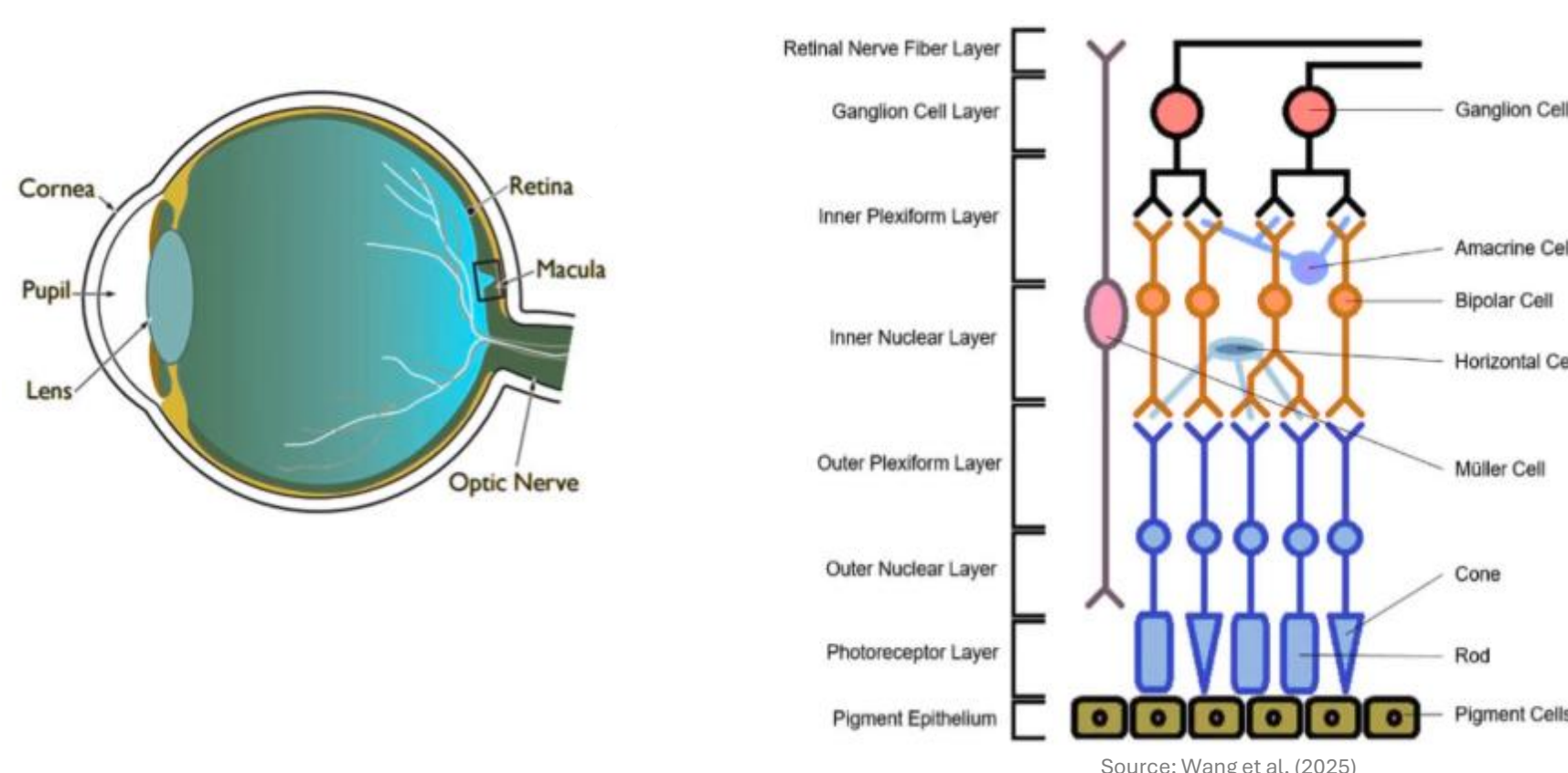


INTRODUCTION

- Preclinical Alzheimer's disease (AD) is an asymptomatic stage characterized by accumulation of cerebral beta-amyloid (A β) plaques, followed by hyperphosphorylated tau tangles.
- Current tools to detect these pathologies, like PET, can measure A β plaque burden. A β PET results can be standardized by a centiloid scale.
- These methods are highly sensitive and specific but are costly and invasive.
- The retina is an extension of the central nervous system (CNS), and retinal layers serve as promising sites for biomarkers.
- The ganglion cell inner plexiform layer (GC-IPL) may reflect early AD pathology due to housing retinal ganglion cells (RGCs).



Objective

Examine whether GC-IPL structure is associated with amyloid burden in preclinical older adults.

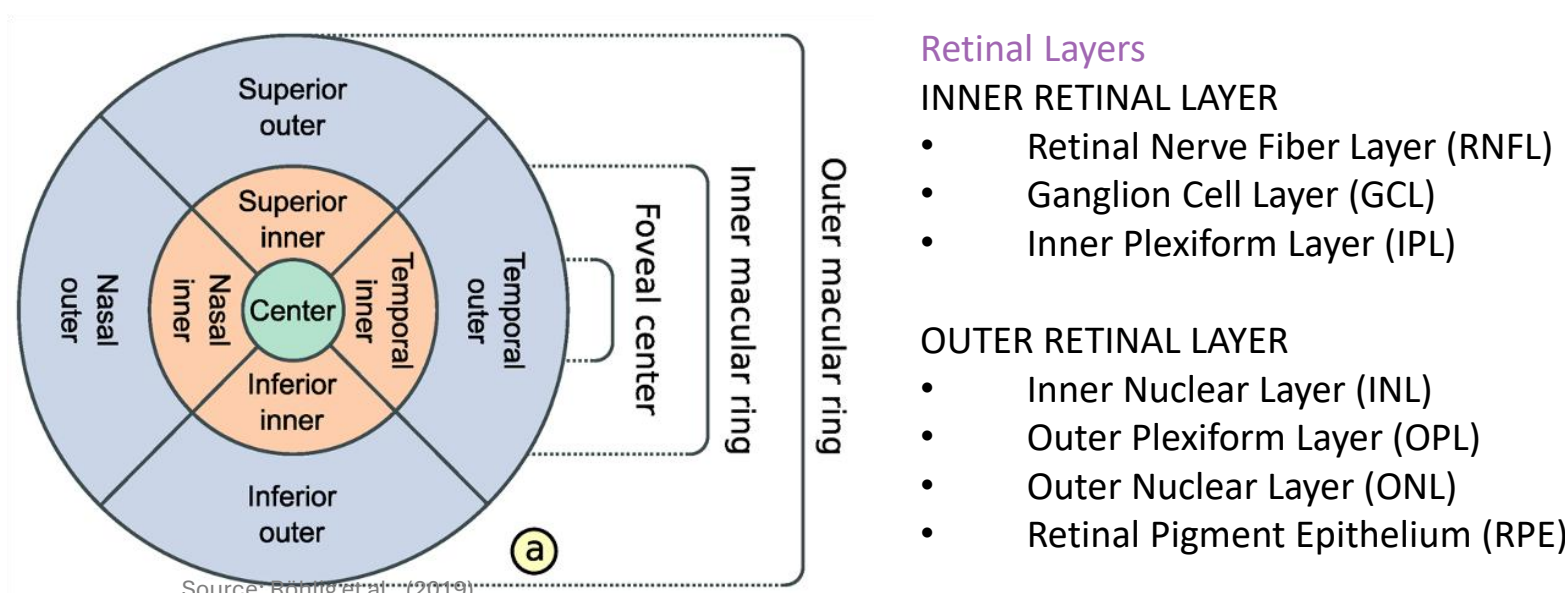
METHODS

Cognitive assessments:

- Montreal Cognitive Assessment (MoCA)
- Clinical Dementia Rating (CDR)
- Participants were either cognitively unimpaired (CU) (MoCA ≥ 26 , CDR=0) or cognitively impaired (CI) (MoCA ≥ 25 , CDR=0.5)

Retinal imaging:

- Spectral-domain optical coherence tomography (SD-OCT) using the Heidelberg SPECTRALIS
- ETDRS thickness maps of GCL and IPL were combined to form GC-IPL averaged metrics for inner, outer, central, and total thickness.



Amyloid burden:

- Florbetaben PET was quantified by centiloid scale as a continuous variable.

Statistical analysis:

- Linear regression model to examine associations between GC-IPL metrics and centiloid, adjusted for age and sex.

RESULTS

- 68 CU and 26 CI participants
- 6 of the 7 GC-IPL measures were positively associated with A β burden (Figure 2A-F).
- Greater GC-IPL thickness and volume corresponded to higher A β burden.
- Total thickness and volume showed similar effect sizes ($\beta=0.35$, 0.37).
- Central retinal measures showed no association with A β burden.

Total Sample (n=94)	
	mean $\pm$ SD
Age (years)	71.8 $\pm$ 4
Education (years)	16 $\pm$ 2
Sex, n (%)	
Male	32 (34%)
Female	62 (66%)
MoCA	26.9 $\pm$ 2.3
CDR, n (%)	
0 (CU)	80 (85%)
0.5 (CI)	12 (13%)
APOE E4, n (%)	
Carrier	25 (27%)
Non-carrier	69 (73%)
Centiloid	40.8 $\pm$ 41.1

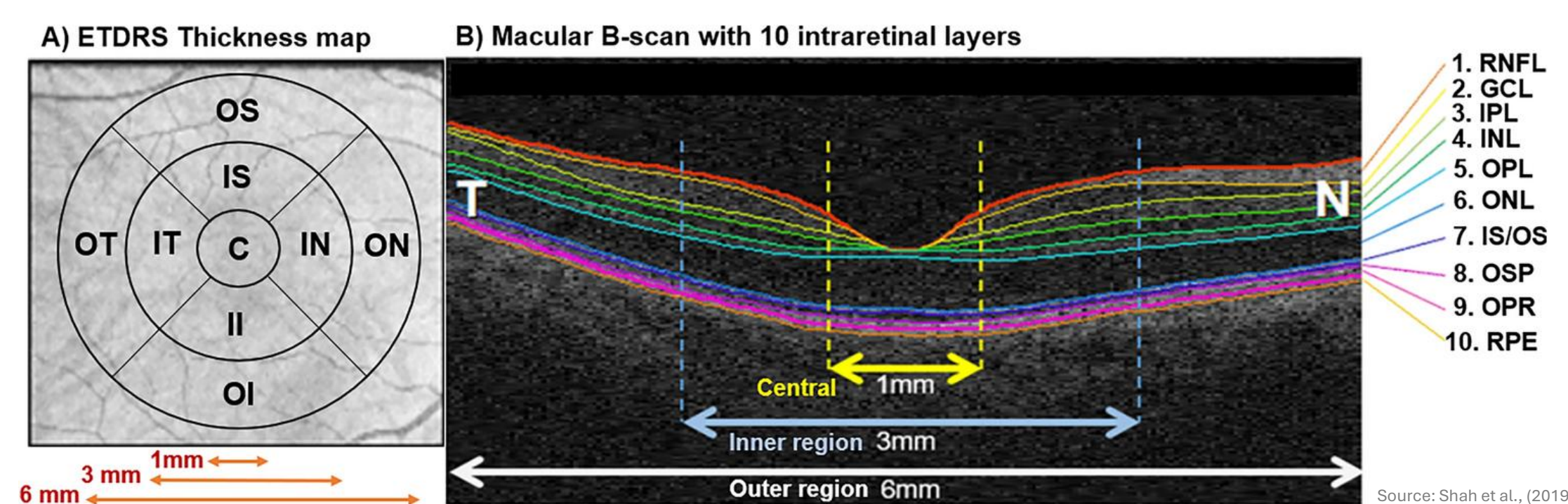


Figure 1. (A) ETDRS thickness map overlap with macula. (B) Retinal image of macular B-scan showing cross-sectional review of retinal layers.

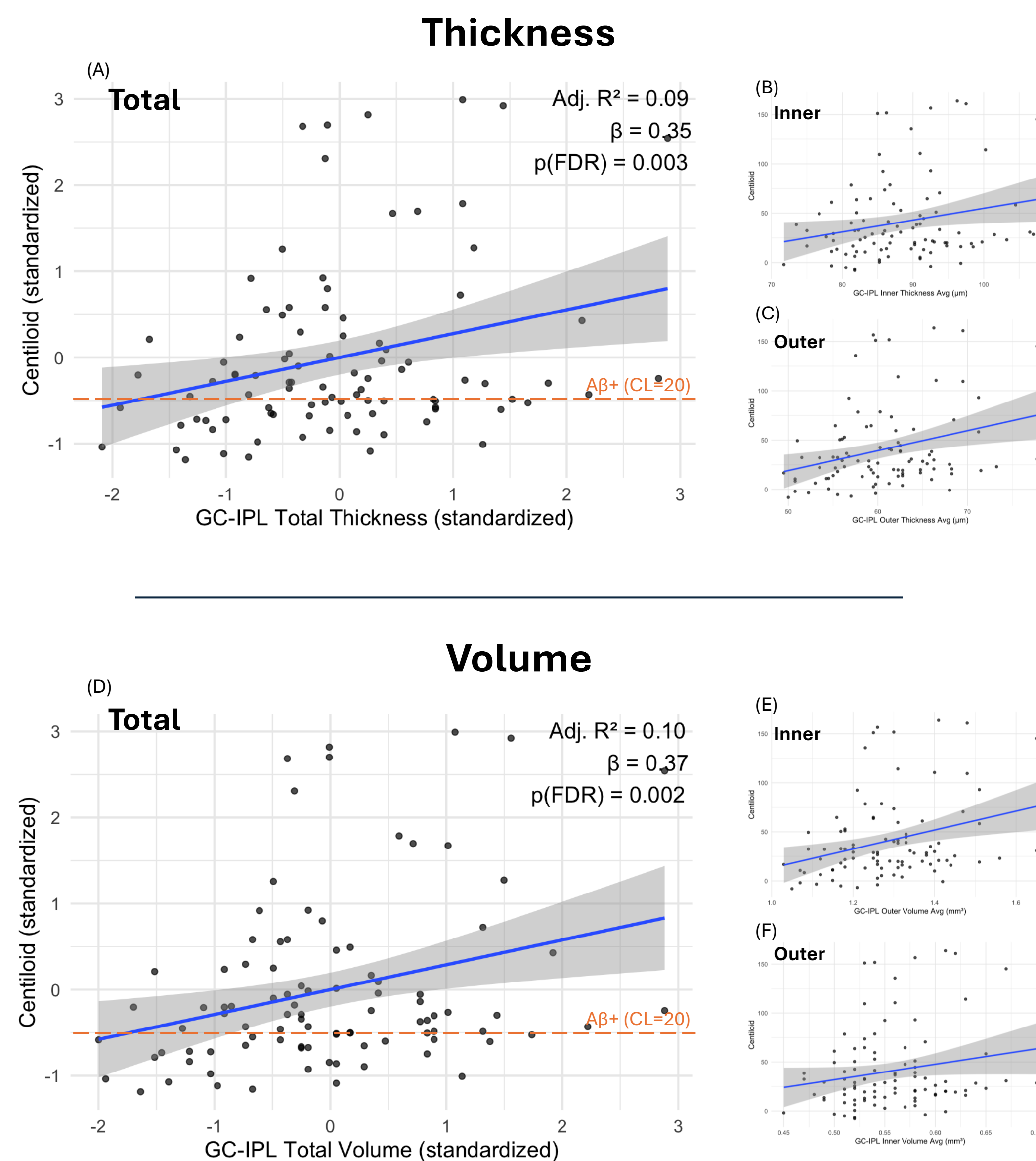


Figure 2A-F. Scatterplots of GC-IPL thickness (A-C) and volume (D-F) versus standardized Centiloid. Lines represent age- and sex-adjusted linear models; β values are standardized and p-values are FDR-corrected.

DISCUSSION

- GC-IPL thickness and volume showed overlapping changes and may represent the early changes associated with A β pathology.
- In contrast with previous findings of retinal thinning in clinical AD, increased retinal thickening may occur at preclinical and prodromal stages, suggesting that the retina has a stage-dependent response to amyloid.
- This may indicate early inflammation in response to amyloid deposits within RGC layers.
- These findings support retinal imaging as a noninvasive biomarker for early AD risk assessment.
- This replicates early studies in our lab demonstrating increased thickness/volume in the IPL in preclinical AD.

FUTURE DIRECTIONS

- Longitudinal studies will determine whether retinal imaging can serve as a tool to assess disease progression.
- Future studies should account for tau pathology, considering its central role in AD continuum, to determine its relationship with retinal biomarkers in early-stage AD.
- Additional retinal imaging metrics, such as OCTA, may offer further insight into retinal changes in preclinical and prodromal stages.
- This non-invasive, cost-effective biomarker has potential to be implemented as a wide-scale screening tool in primary care settings.

CONCLUSION

Retinal structural imaging, specifically of GC-IPL thickness and volume, is associated with cerebral amyloid burden. These findings support the promise of SD-OCT imaging, a widely accessible tool in primary care settings, for identifying early AD-related pathology.

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