DUNEDIN STUDY CONCEPT PAPER FORM

Provisional Paper Title: Retinal-based biomarkers and midlife ADRD risk

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Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

The retina has been proposed as a biomarker for Alzheimer's disease and related dementias (ADRD) as it is the only part of the central nervous system that can be observed directly.[1] It is also readily imaged using non-invasive, cost-effective, and widely available technology; thus there is a lot of interest in understanding how the retina reflects brain health, particularly neurodegeneration.[2]

While retina-based biomarkers have been associated with mild cognitive decline, as well as mild to severe Alzheimer's disease,[3–5] their utility as pre-morbid biomarkers remains under characterized. Principally, it is not clear to what extent variation in these measures in midlife characterizes individuals known to be at higher or lower risk for later ADRD.

Furthermore, investigating both neuronal and microvascular measures may provide insight into the mechanisms by which the retina reflects the brain. There is evidence that the neuronal layers (RNFL and GC-IPL) experience the same pathology as Alzheimer's-affected neurons in the brain (i.e., amyloid plaques, tau neurofibrillary tangles), so that the thinning of retinal neuronal layers is thought to reflect apoptosis elsewhere in the brain.[2,6] However, the retinal microvasculature reflects the overall cardiovascular system (including the cerebrovasculature), which is also implicated in the pathology of ADRD.[7,8] Clarity on the associations of these various measures with known ADRD risk factors (e.g., hypertension, depression, smoking) will aide in our understanding of the interplay of retinal biomarkers with mechanistic risk factors.

We propose to investigate whether measures of retinal neuronal thickness (RNFL and GC-IPL) and retinal microvasculature (CRAE/CRVE) identify individuals at higher ADRD risk as indexed by existing ADRD risk indexes (the CAIDE, LIBRA, Lancet, and ANU-ADRI) or with

comprehensive midlife ADRD risk, as indexed by the DunedinARB and its 10 domains of ADRD risk.[9]

Data analysis methods:

Using multiple linear regression techniques appropriate to the data, we will test whether each retinal measure is associated with each of the 5 indices of ADRD risk. In follow up analyses, we will describe mean retinal scores for high, medium, and low ADRD risk individuals, and test for statistically significant differences between groups. Tests will be adjusted for sex. Follow-up sensitivity tests may examine the 10 domains of risk comprising the overall DunedinARB as well potential early life factors that may influence both later ADRD risk and retinal health (e.g., early life brain health).

Variables needed at which ages:

All at/up to phase 45:

- ADRD Risk Indexes
  - DunedinARB and its 10 constituent risk domains
  - CAIDE
  - LIBRA
  - LANCET
  - ANU-ADRI
- Retinal Measures
  - RNFL (average and quadrants, average of both eyes)
  - GC-IPL (average and segments, average of both eyes)
  - Axial length (average of both eyes—control for RNFL and GC-IPL)
  - CRAE
  - CRVE
- Covariates / early life factors
  - Sex

Significance of the Study (for theory, research methods or clinical practice):

This project will be of interest to many researchers and clinicians in the areas of ophthalmology and neurology. If we find that retinal measures are associated with premorbid ADRD risk, it would add further evidence that these measures may be useful in identifying individuals at risk well before clinical symptoms emerge, a key goal of preventive medicine. If we fail to find significant associations it will bookend the age points / clinical timeline during which retinal measures may be useful in characterizing ADRD risk and disease.

References:

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