DUNEDIN STUDY CONCEPT PAPER FORM

Provisional Paper Title: Childhood social isolation as a predictor of retinal nerve fibre layer and ganglion cell layer in middle age

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

Objective of the study:
The long-term effects of chronic stress on the retina across the lifetime have been largely unexplored, despite the wide use of retinal biomarkers in neuro-ophthalmological research. The retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) have been proposed as potential biomarkers for Alzheimer's disease, although the psychosocial determinants of RNFL and GCL are under researched.

Thus, the objective of this study is to investigate whether childhood social isolation or other markers of early psychosocial adversity (SES or maltreatment) are associated with RNFL and GCL, which are potential markers of neurodegeneration in the retina. Further, we aim to investigate whether any observed associations are attenuated by other risk factors from childhood or adulthood, or mediated by adult social isolation.

Data analysis methods:
Multiple regression and mediation analysis.

Variables needed at which ages:
Child psychosocial variables:

- Childhood social isolation (ages 5, 7, 9, and 11)
- Childhood SES (from birth to age 15)
- Childhood maltreatment (from age 3 to 11)

Vision variables (age 45):

- Retinal nerve fibre layer (RNFL) thickness—average & quadrants.
- Ganglion cell layer (GCL) thickness—average & quadrants.
- Intraocular pressure
- Axial length
- Optic disc area

Co-occurring risk factors:

- Perinatal complications
- Childhood health score (birth to age 11)
- Childhood IQ (ages 7, 9, and 11)
- Mean arterial blood pressure (age 45)
- Tobacco pack-years (to age 45)
- Cannabis joint-years (18 to 45)
- SES (age 45)
- Adult loneliness (age 45)
- Adult social support (age 45)

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

Psychosocial adversity in childhood is particularly harmful for neurobiological development, affecting diverse cognitive functions (Cross et al., 2017) as well as the structural integrity of the brain (Gehred et al., 2021). Childhood social isolation has been associated with cardiovascular risk (Caspi et al., 2006), clustering of metabolic risk factors (Danese et al., 2009), decreased brain and neural volume (Castillo-Gómez et al., 2017) and all-cause mortality (Calvin et al., 2015). Moreover, childhood psychosocial adversity tends to cluster with other risk factors, and the cumulative effect may lead to greater deficits over the lifecourse (Evans et al., 2013; Danese et al., 2016). Given the increased interest in the retina as a biomarker of non-ophthalmological disease, particularly preclinical Alzheimer's disease (Alber et al., 2020), it is important to understand the determinants of retinal thickness.

The retina is homologous with the brain, due to their shared embryological and developmental origins, as well as similarities in neural structure and vasculature (London et al., 2013; Patton et al., 2005). Moreover, the retina can be easily and non-

invasively imaged using widely available technology, such as optical coherence tomography (OCT), giving it practical advantages over brain imaging technologies such as magnetic resonance imaging (London et al., 2013). In particular, the retina has been proposed as a biomarker for AD, as the retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) are subject to the same neurodegenerative processes as in AD.

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