



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

Proposing Author: Ashleigh Barrett-Young

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P.I. Sponsor: Richie Poulton
(if the proposing author is a student or colleague of an original PI)

Today's Date: 23 June 2021

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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DATA SECURITY AGREEMENT

Provisional Paper Title	Childhood social isolation as a predictor of retinal nerve fibre layer and ganglion cell layer in middle age
Proposing Author	Ashleigh Barrett-Young
Today's Date	23 June 2021

Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement: (customize as necessary)

Y	I am current on Human Subjects Training [CITI www.citiprogram.org] or equivalent.
Y	My project is covered by the Dunedin Study's ethics approval OR I have /will obtain ethical approval from my home institution (please specify).
Y	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: <ul style="list-style-type: none"> • encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) • password-protected • configured to lock-out after 15 minutes of inactivity AND • has an antivirus client installed as well as being patched regularly.
Y	I will not "sync" the data to a mobile device.
Y	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact my PI Sponsor or Study Director, Richie Poulton (richie.poulton@otago.ac.nz).
Y	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
Y	I will not post data online or submit the data file to a journal for them to post. <i>Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to your PI Sponsor or Richie Poulton for strategies for achieving compliance with data-sharing policies of journals.</i>
Y	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: Ashleigh Barrett-Young

CONCEPT PAPER RESPONSE FORM

A To be completed by the proposing author:

Provisional Paper Title	Childhood social isolation as a predictor of retinal nerve fibre layer and ganglion cell layer in middle age
Proposing Author	Ashleigh Barrett-Young
Other Contributors	Antony Ambler, Avshalom Caspi, Kirsten Cheyne, Hayley Guiney, Jesse Kokaua, Terrie Moffitt, Barbara Steptoe, Yih Chung Tham, Mike Williams, Graham Wilson, Tien Yin Wong, Richie Poulton
Potential Journals	
Today's Date	23 June 2021
Intended Submission Date	

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B. To be completed by potential co-authors:

Approved
 Not Approved
 Let's discuss, I have concerns

Comments: _____

Please check your contribution(s) for authorship:

<input type="checkbox"/>	Conceptualizing and designing the longitudinal study
<input type="checkbox"/>	Conceptualizing data collection protocols and creating variables
<input type="checkbox"/>	Data collection
<input type="checkbox"/>	Conceptualizing and designing this specific paper project
<input type="checkbox"/>	Statistical analyses and interpretation (or reproducibility check)
<input type="checkbox"/>	Writing
<input type="checkbox"/>	Reviewing manuscript drafts
<input type="checkbox"/>	Final approval before submission for publication
<input type="checkbox"/>	Agreement to be accountable for the work
<input type="checkbox"/>	Acknowledgment only, I will not be a co-author

Signature: _____