Childhood Social Isolation as a Predictor of Retinal Neuronal Thickness in Middle Age: A Lifecourse Birth Cohort Study

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ABSTRACT

Objective: We investigated whether childhood social isolation was associated with retinal neural layer changes in adulthood, and whether this association was independent of other childhood or adulthood risk factors, including adult social isolation.

Methods: Participants were members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal population-based birth cohort from Aotearoa New Zealand ($n = 1037$), born 1972 to 1973 and followed until age 45 years, with 94% of the living cohort still participating. Social isolation was recorded prospectively at ages 5, 7, 9, and 11 years, from teacher and parent report. Retinal nerve fiber layer (RNFL) and ganglion cell–inner plexiform layer thicknesses were measured via optical coherence tomography at age 45 years.

Results: Childhood social isolation was associated with thinner average RNFL ($B = -0.739$, $p = .02$), nasal RNFL ($B = -1.118$, $p = .005$), and inferior RNFL ($B = -1.524$, $p = .007$), although only nasal RNFL remained significant after adjustment. These associations were not fully explained by other psychosocial or physical health risk factors in childhood or adulthood, nor were they mediated by adult loneliness or social support.

Conclusions: Childhood social isolation was an independent predictor of RNFL thickness in middle age. Highlighting prospective links between childhood psychosocial adversity and retinal neuronal measures will help to inform future research into the utility of retinal neuronal thickness as a biomarker for neurodegeneration.

Key words: social isolation, child adversity, retina, retinal nerve fiber layer, optical coherence tomography.

INTRODUCTION

Social isolation has long been recognized as a risk factor for morbidity and mortality (1–3), perhaps on par with traditional clinical risk factors (4). However, social isolation often co-occurs with other risk factors for poor health; for example, socially isolated adults are less likely to own their own homes or be employed (5), and socially isolated young people are more likely to have experienced adverse childhood experiences or live in poverty (6). Moreover, the direction of causality is unclear, as social isolation could be either a risk factor for or a consequence of poor health (7). Thus, there is a need to establish whether social isolation is an independent risk factor for poorer health across the lifecourse, or whether it is part of a more general constellation of adversities that tend to co-occur.

Social Isolation, Psychosocial Adversity, and Health

Social isolation is broadly defined as lacking in close social relationships (8). Social interactions are a necessary part of the human experience, and people without close social relationships experience a number of poorer health and well-being outcomes (9). Subjective measures of social isolation tend to measure perceived social isolation, which is considered synonymous with loneliness (10). Objective measures of social isolation, such as quantifications of a person's social network, tend to show weaker associations with poorer outcomes compared with subjective measures, suggesting that a person's emotional reaction to a lack of social

AD = Alzheimer disease, **GC-IPL** = ganglion cell–inner plexiform layer, **OCT** = optical coherence tomography, **RNFL** = retinal nerve fiber layer, **SEP** = socioeconomic position

SDC Supplemental Digital Content

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connections could be the driving force underlying observed associations with health outcomes (8).

Although there is much research linking social isolation and poorer health, most of this research is cross-sectional and focused on adults. Thus, it does not necessarily indicate that social isolation leads to poor health. For example, greater social support may enable better adherence to treatment plans, or poorer social networks may be a consequence, rather than a cause, of poor health. The effects of social isolation in childhood may be even greater than at any other point during the lifecourse because of accumulating damage over the lifetime (2). Social isolation is closely related to loneliness in childhood, which is a predictor of poorer health in adolescence (11). Young children who are rejected by their peers often experience feelings of loneliness (12), and child-centered research suggests that children have an understanding of the concept of loneliness from as young as 5 or 6 years, so they may suffer the effects of perceived social isolation from early in life (13). Social isolation is a form of psychosocial adversity, as children are negatively affected by feeling socially isolated from their peers, leading to a chronic stress response that may have long-term adverse effects (14). Psychosocial adversity is known to affect the development of biological systems, with variation in individual responses to adversity likely partly due to genetic risk and the developmental period in which adversity is experienced (15). Childhood is thought to be a sensitive period when psychosocial adversity becomes biologically embedded, as chronic activation of the physiological stress response influences physical and psychological development (16–18). Biological systems, including the central nervous system, are particularly vulnerable to the stress response during development and particularly in the childhood period (15,17,19). Chronic activation of the stress response leads to suboptimal neurobiological development, in turn leading to poorer brain and physical health throughout the lifecourse (20). Thus, the effects of psychosocial adversity in childhood may continue to reverberate well into adulthood (21,22).

Childhood social isolation has been associated with a number of poorer health outcomes in adulthood, including cardiovascular risk (2), clustering of metabolic risk factors (23), decreased brain and neural volume (24), and all-cause mortality (25). Childhood psychosocial adversity is particularly harmful for neurobiological development, affecting cognitive function (20) and the structural integrity of the brain (26). Moreover, childhood psychosocial adversity tends to cluster with other risk factors, and the cumulative effect may lead to greater deficits over the lifecourse (23,27). Chronic stress has been associated with poorer cognitive functioning (28,29) and Alzheimer disease (AD) (30–34), as well as heightened risk for age-related diseases (18) and accelerated cellular aging (35).

The Retina as a Model of Brain Health

The long-term effects of psychosocial adversity and chronic stress on the retina across the lifecourse have been largely unexplored, despite the wide use of retinal biomarkers in neuro-ophthalmological research. The retina is homologous with the brain because of their shared embryological and developmental origins and similarities in neural structure and vasculature (36). The retina can be easily and noninvasively imaged using widely available technologies, such as optical coherence tomography (OCT), giving it practical advantages over brain imaging technologies such as magnetic resonance imaging (36). The retina has been proposed as a biomarker for AD, as the retinal nerve fiber layer (RNFL) and ganglion cell–inner plexiform layer (GC-IPL) are subject to the same neurodegenerative processes as in AD (37–41). RNFL and GC-IPL thickness are associated with cognitive decline, AD (42–47), and Parkinson disease (48), diseases for which chronic stress is a risk factor (49,50). One of the mechanisms by which psychosocial adversity is thought to affect biological systems is through chronic inflammation (51,52), which has been linked to retinal aging and many retinal diseases (53–55). Thus, given the increased interest in the retina as a biomarker of nonophthalmological disease, particularly preclinical AD (37), it is important to understand the determinants of retinal thickness.

Building on research showing that psychosocial stress in childhood was associated with cardiovascular dysfunction, some studies have investigated the effects of psychosocial stress on the retinal microvasculature. Altered retinal microvasculature has been associated with depression and anxiety in adolescents and adults (56–61), lower quality of life (62), and vital exhaustion (63). However, some studies have found either a weak association or no association between psychosocial stress and retinal microvasculature (64,65). A small number of longitudinal studies involving assessment of psychological stress over a number of years have also revealed associations between altered retinal microvasculature and internalizing disorders (61), persistent depression in adults (66), and high stress in children (67). In addition, overactivation of the sympathetic nervous system, which occurs in chronic stress, has been associated with altered retinal microvasculature (68). These studies indicate that the retinal microvascular system may be negatively affected by psychosocial stress from early life.

No studies, to our knowledge, have investigated whether chronic stress is associated with RNFL or GC-IPL, which are measures of cell density in the retina. One study found a weak association between a biomarker of the acute stress response (endogenous plasma adrenocorticotropic hormone) and RNFL thickness after acute laboratory-induced stress (69). However, the effects of chronic stress in response to psychosocial adversity in childhood are likely to be more damaging than for acute stress; in addition, it is thought that retinal thinning occurs over an expanded time frame rather than as an immediate response to an acute stressor.

The Present Study

Given the increased interest in the retina as a biomarker of nonophthalmological disease, particularly preclinical AD (37), it is important to understand the determinants of retinal thickness. The objective of our study was to investigate whether childhood social isolation was associated with RNFL and GC-IPL thickness, potential biomarkers of neurodegeneration, in midlife. To test the strength of any observed association, we also included a number of possible co-occurring risk factors in subsequent models that could explain or alter the relationship. The relationship between childhood psychosocial adversity and physical health outcomes is not straightforward and there are a number of potential risk factors that may influence the extent to which a person is affected by their childhood situation. Childhood risk factors tend to cluster and likely have a cumulative effect on physical health outcomes (70,71). Thus, psychosocial adversity variables (child maltreatment and socioeconomic position [SEP]) were added to a model including known risk factors present from early life, such as perinatal complications, childhood health, and childhood IQ.

Childhood psychosocial adversity may set up individuals for accumulating further risk factors in adulthood, which cumulatively drive an association with poorer physical health in midlife. Thus, mean arterial blood pressure, cannabis use, tobacco use, and adult SEP were included as potential physical health and lifestyle variables that may influence any association between social isolation and retinal thickness. It was hypothesized that childhood social isolation would be associated with RNFL and GC-IPL thickness in middle age, and that these associations would persist when possible other risk factors from childhood and adulthood were added to the model. To better understand whether childhood social isolation was an independent predictor of retinal thickness, we also examined if other psychosocial risk factors in adulthood, that is, adult loneliness or social support, mediated this association. Thus, our final hypothesis was that childhood social isolation would exert its effects on the retina independently of adult loneliness or social support.

METHODS

Participants

Participants were members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behavior in a representative birth cohort. Study members (n = 1037; 91% of eligible births, 51.6% male) were born between April 1972 and March 1973 in Ōtepoti/Dunedin, Aotearoa New Zealand. The cohort represents the full range of SEP in the general population of New Zealand and is predominantly New Zealand European/Pākehā (93%) and underrepresentative of Māori or Pacific Island participants. The study design and participant characteristics have been described extensively elsewhere (72,73). Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years, and most recently at age 45 years, when 94% of the living Study members participated. At each assessment, Dunedin Study members were brought to the research unit for a full day of interviews and examinations. The relevant ethics committees approved each phase of the study, and informed consent was obtained from all Study members. Study members were offered a small reimbursement for their time and travel expenses.

Childhood Measures

Childhood Social Isolation

Study members' parents and teachers were asked to complete the Rutter Child Scale, of which two items assessed peer problems: (*a*) "tends to do things on his/her own; is rather solitary" and (*b*) "not liked much by other children" (74). Response scales for both items were coded 0 = "doesn't apply," 1 = "applies somewhat," and 2 = "certainly applies." This scale was completed when the Study members were 5, 7, 9, and 11 years old, and a measure of social isolation was derived by averaging these two items across the two reporters (parents and teachers) and the four time points (Cronbach $\alpha = 0.77$) (2). A cumulative score was chosen because there is evidence that the duration of social isolation may be a better predictor of poorer outcomes than intensity of social isolation (75). The child social isolation variable is a normalized z score, where a higher score reflects increased social isolation. We also analyzed these items separately in post hoc analyses, using the mean across the same ages and raters as for the cumulative social isolation measure; the mean of item *a* was labeled "solitary," and the mean of item *b* was labeled "rejected by peers." Childhood social isolation data were available for 98.4% of the sample (n = 1020). Characteristics of social isolation across the lifecourse in this cohort have been previously described (76). Child social isolation groups used in supplementary analysis were formed from social isolation data across the lifecourse, as described previously (76).

Childhood SEP

The occupations of Study members' parents were measured on a 6-point scale based on typical educational levels and income associated with that occupation (1 = unskilled laborer; 6 = professional). These categories were derived from data from the New Zealand Census (77). Parents' SEP was recorded at the Study members' birth and at ages 3, 5, 7, 9, 11, 13, and 15 years. When SEP data were available for both parents, the highest score at each time point was included in the calculation of the overall measure. This was considered a suitable measure of family SEP because of the high number of stay-at-home mothers in the cohort at the time. A mean was calculated across all time points to give a single variable of SEP across childhood. This cumulative measure was selected because it accounts for SEP change across the childhood years and gives an overall reflection of the socioeconomic conditions experienced by the Study members during childhood (78). Childhood SEP was available for 99.4% of the full sample (n = 1031).

Childhood Maltreatment

The measure of childhood maltreatment is a cumulative index of five maltreatment indicators during childhood (from ages 3 to 11 years; see also Methods, Supplemental Digital Content [SDC], http://links.lww.com/PSYMED/A904, for details) (79). Childhood maltreatment data were available for all Study members except one (n = 1036). "Severe" maltreatment was categorized if Study members experienced two or more indicators (9.2%), "probable" maltreatment for one indicator (26.6%), and no maltreatment for zero indicators (64.1%).

Adult Measures

All adult measures were recorded at age 45 years.

Optical Coherence Tomography

OCT scans were performed in the morning by one of two trained technicians using a spectral domain OCT machine (Cirrus HD-OCT, model 5000, software version 10.0.1; Carl Zeiss Meditec, Dublin, California). All scans were checked by trained graders for quality. Scans were removed from the final data set because of OCT machine problems (e.g., signal strength <6, scan not correctly positioned, scan inverted, or image artifacts). In addition, seven Study members were removed because of diseases affecting the retina (two with multiple sclerosis, one with retinitis pigmentosa, two with brain tumors, one with diabetic laser pan-retinal photocoagulation, and one with an anomalous optic disc). All Study members were reviewed by two ophthalmologists for glaucoma; three Study members were categorized as having glaucoma in both eyes and were removed from the data set. Three further Study members had glaucoma in one eye each; because glaucoma is an asymmetrical disease, the healthy eye was retained. When data from one eye were available, that eye was used; when both eyes were available, an average of the measurements from both eyes was used.

Adult Loneliness

Four items from the UCLA Loneliness Scale (80) ("how often do you feel you lack companionship?" "how often do you feel left out?" "how often do you feel isolated from others?" and "how often do you feel alone?") and one item adapted from the Center for Epidemiological Studies Depression Scale (81) ("how often have you felt lonely in the past week?") were summed to form a loneliness scale. Responses were coded as follows: "hardly ever" = 0, "some of the time" = 1, and "often" = 2. The scale range was 0 to 10, with higher scores indicating higher levels of loneliness.

Adult Social Support

Twelve items from the Multidimensional Scale of Perceived Social Support (82) were summed to form a social support scale. Responses were coded as follows: "not true" = 0, "somewhat true" = 1, and "very true" = 2. The scale range was 0 to 24, with higher scores indicating higher levels of social support.

Covariates used in the regression models are described in Supplemental Methods (SDC, http://links.lww.com/PSYMED/A904).

Data Analysis

Analyses were conducted in SPSS version 26 (IBM Corp, 2019). Hierarchical linear regression was used to assess the relationship between social isolation in childhood and retinal measures in adulthood. All models were adjusted for sex, intraocular pressure, axial length, and optic disc size (see Supplemental Methods for details of these variables, SDC, http://links.lww.com/PSYMED/A904). All participants were chronologically the same age, and thus, age was not included as a covariate in any models. To test whether social isolation was a unique predictor of retinal thickness, or simply co-occurred with other risk factors, three models with possible confounding or mediating variables were subsequently tested. In model 1, childhood social isolation was the independent variable, adjusted for sex and ocular covariates. In model 2, other indicators of childhood psychosocial adversity were added to the model (childhood SEP and maltreatment). In model 3, possible co-occurring childhood risk factors were entered (childhood health score, childhood IQ, and perinatal complications; see Supplemental Methods for details of these variables, SDC, http://links.lww.com/PSYMED/A904). In model 4, possible co-occurring risk factors from adulthood were entered (mean arterial blood pressure, cannabis use, tobacco use, and adult SEP; see Supplemental Methods for details of these variables, SDC, http://links.lww.com/PSYMED/A904). The approach to regression analysis is illustrated in Figure 1, which illustrates the hypothesized relationships between the included variables.

Loneliness and social isolation are well recognized as cross-sectional correlates of physical health, especially in older people (9). Thus, it is conceivable that any association observed with childhood social isolation is an artifact of the relationship between adult loneliness or social isolation and the retina, measured at the same time point. Therefore, mediation analyses including adult loneliness and social support were conducted for retinal variables demonstrating statistically significant associations in the previous analyses. Mediation analyses were conducted using the PROCESS tool, a macro for mediation analysis of observed variables using ordinary least squares regression (83). To further test these associations, we used analysis of variance to test for group differences between three groups: participants who experienced childhood social isolation, participants who experienced isolation in adulthood only, and those who were never reported as experiencing isolation. The formation of these groups has been described previously (76).

A priori α level of .05 and two-tailed hypothesis testing were used. Listwise deletion was used for missing data. Analyses were

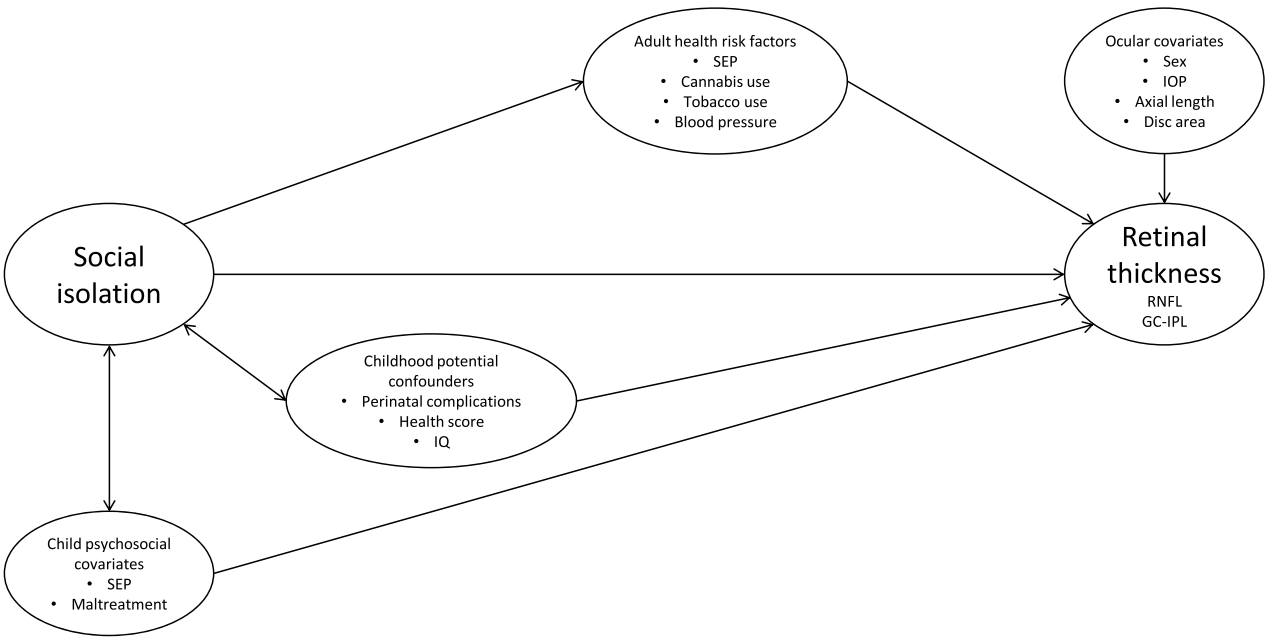


FIGURE 1. Diagram representing analytic assumptions of regression analysis. Note: This diagram illustrates the hypothesized relationships between the variables included in regression analysis. It does not preclude other confounding or mediating variables, nor does it hypothesize the mechanisms of action underlying any observed associations. SEP = socioeconomic position; RNFL = retinal nerve fiber layer; GC-IPL = ganglion cell–inner plexiform layer; IOP = intraocular pressure.

TABLE 1. Descriptive Statistics for Participants With OCT Scans

	Participants With RNFL Data			Participants With GC-IPL Data		
	n	M (SD)	Range	*n*	M (SD)	Range
Male, *n* (%)	431 (49.8)			430 (49.9)		
Female, *n* (%)	434 (50.2)			431 (50.1)		
Chiildhood variables						
Childhood social isolation (*z* score)	859	−0.029 (0.99)	−1.25 to 4.61	855	−0.034 (0.99)	−1.25 to 4.61
Child socioeconomic position	860	3.77 (1.13)	1.0 to 6.0	857	3.78 (1.13)	1.0 to 6.0
Child maltreatment						
None	559 (64.6%)			558 (64.8%)		
Probable	226 (26.1%)			223 (25.9%)		
Severe	80 (9.2%)			80 (9.3%)		
Perinatal complications						
None	550 (63.6%)			555 (64.5%)		
1 complication	217 (25.1%)			211 (24.5%)		
≥2 complications	98 (11.3%)			95 (11.0%)		
Childhood IQ	855	101.34 (13.79)	47.34 to 141.10	851	101.43 (13.70)	47.34 to 141.10
Childhood health (*z* score)	815	−0.026 (0.94)	−2.50 to 2.50	812	−0.029 (0.94)	−2.50 to 2.50
Age 45 variables						
Mean arterial blood pressure	863	93.93 (11.33)	65.0 to 140.0	859	93.88 (11.39)	65.0 to 140.0
Cumulative cannabis consumption, joint years	849	2.51 (5.60)	0.0 to 28.0	847	2.49 (5.57)	0.0 to 28.0
Cumulative tobacco consumption, pack-years	864	7.27 (10.60)	0.0 to 51.03	860	7.27 (10.61)	0.0 to 51.03
Adult socioeconomic position	865	3.73 (1.48)	1.0 to 6.0	861	3.75 (1.48)	1.0 to 6.0
Loneliness scale	863	1.29 (1.98)	0.0 to 10.0	859	1.27 (1.96)	0.0 to 10.0
Social support scale	862	20.11 (4.82)	0.0 to 24.0	857	20.12 (4.82)	0.0 to 24.0
Average RNFL, µm	865	92.78 (9.35)	63.0 to 126.0			
Temporal RNFL, µm	865	63.79 (10.21)	40.0 to 105.0			
Superior RNFL, µm	865	114.25 (14.89)	68.0 to 166.0			
Nasal RNFL, µm	865	72.44 (11.21)	42.0 to 128.0			
Inferior RNFL, µm	865	120.62 (16.04)	77.0 to 178.5			
Average GC-IPL, µm				861	82.85 (5.87)	62.0 to 103.0
Temporal-superior GC-IPL, µm				861	81.79 (5.97)	51.0 to 100.0
Superior GC-IPL, µm				861	83.42 (6.17)	67.0 to 104.5
Nasal-superior GC-IPL, µm				861	84.77 (6.32)	65.0 to 107.5
Nasal-inferior GC-IPL, µm				861	83.12 (6.29)	64.0 to 108.0
Inferior GC-IPL, µm				861	81.06 (6.38)	62.0–101.0
Temporal-inferior GC-IPL, µm				861	82.98 (6.09)	61.5 to 100.5

OCT = optical coherence tomography; RNFL = retinal nerve fiber layer; GC-IPL = ganglion cell–inner plexiform layer; M (SD) = mean (standard deviation).

checked for reproducibility by an independent statistician, who recreated the code and output using the manuscript and an unaltered copy of the data set. STROBE reporting guidelines were followed.

RESULTS

In the regression analyses, the data set was determined from those Study members with available data for all variables (analysis with RNFL as outcome variable: $n = 783$; analysis with GC-IPL as outcome variable: $n = 765$; see Table 1 for descriptive statistics). One-way analyses of variance were used to compare participants who had all data available and were therefore included in the regression analysis with those who had retinal data available but were not included in the regression analysis because of missing data (attrition analysis can be found in the SDC, http://links.lww.com/PSYMED/A904). Of the participants who had RNFL data available, participants who were included in the regression analysis were significantly less socially isolated as children ($F(1,857) = 17.587$, $p < .001$; M $[SD]_{included} = -0.073$ [0.949], M $[SD]_{excluded} = 0.421$ [1.261]) and less likely to have been maltreated ($F(1,863) = 4.068$, $p = .044$; M $[SD]_{included} = 0.43$ [0.652], M $[SD]_{excluded} = 0.59$ [0.702]) than those who were not included in the regression analysis. Of the participants who had GC-IPL data available, participants who were included in the regression analysis were significantly less socially isolated as children ($F(1,853) = 17.80$, $p < .001$; M $[SD]_{included} = -0.081$ [0.944], M $[SD]_{excluded} = 0.391$ [1.250]) than those who were not included in the regression analysis. No group differences were found for any other variables included in the regression analyses. For mediation analysis, those who were included were not significantly different on childhood social isolation than those who were not included; however, included

TABLE 2. Childhood Social Isolation and Psychosocial Adversity as Predictors of RNFL Thickness (μm), With Potential Co-occurring Risk Factors From Childhood and Adulthood ($n = 783$)

	Average RNFL		Temporal		Superior		Nasal		Inferior	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Model 1 (sex and ocular covariates)										
Social isolation	−0.739 (−1.376 to −0.102)	.023*	0.114 (−0.631 to 0.859)	.76	−0.466 (−1.497 to 0.564)	.38	−1.118 (−1.895 to −0.341)	.005**	−1.524 (−2.637 to −0.411)	.007**
Model 2 (+ psychosocial)										
Social isolation	−0.766 (−1.414 to −0.119)	.020*	0.111 (−0.647 to 0.869)	.77	−0.620 (−1.666 to 0.426)	.25	−1.059 (−1.849 to −0.269)	.009**	−1.543 (−2.674 to −0.411)	.008**
SEP	−0.052 (−0.616 to 0.511)	.86	−0.043 (−0.702 to 0.616)	.90	−0.383 (−1.293 to 0.527)	.41	0.280 (−0.407 to 0.967)	.42	−0.068 (−1.052 to 0.917)	.89
Maltreatment	0.193 (−0.762 to 1.149)	.69	−0.012 (−1.130 to 1.105)	.98	1.012 (−0.532 to 2.555)	.20	−0.271 (−1.436 to 0.894)	.65	0.104 (−1.566 to 1.773)	.90
Model 3 (+ childhood risk factors)[a]										
Social isolation	−0.558 (−1.206 to 0.090)	.091	0.150 (−0.616 to 0.917)	.70	−0.468 (−1.527 to 0.590)	.39	−0.880 (−1.675 to −0.086)	.030*	−1.078 (−2.203 to 0.047)	.060
SEP	−0.421 (−1.014 to 0.172)	.16	−0.198 (−0.899 to 0.504)	.58	−0.669 (−1.638 to 0.300)	.18	0.027 (−0.700 to 0.754)	.94	−0.846 (−1.877 to 0.184)	.11
Maltreatment	0.320 (−0.625 to 1.266)	.51	0.035 (−1.084 to 1.154)	.95	1.108 (−0.437 to 2.653)	.16	−0.171 (−1.330 to 0.989)	.77	0.368 (−1.275 to 2.010)	.66
Model 4 (+ adulthood risk factors)[b]										
Social isolation	−0.536 (−1.188 to 0.115)	.11	0.153 (−0.618 to 0.923)	.70	−0.473 (−1.538 to 0.592)	.38	−0.863 (−1.661 to −0.065)	.034*	−1.004 (−2.135 to 0.127)	.082
SEP	−0.479 (−1.086 to 0.127)	.12	−0.243 (−0.960 to 0.475)	.51	−0.672 (−1.663 to 0.320)	.18	−0.077 (−0.820 to 0.666)	.84	−0.934 (−1.987 to 0.119)	.082
Maltreatment	0.370 (−0.590 to 1.331)	.45	0.063 (−1.074 to 1.200)	.91	1.185 (−0.386 to 2.755)	.14	−0.125 (−1.302 to 1.052)	.84	0.427 (−1.241 to 2.095)	.62

RNFL = retinal nerve fiber layer; CI = confidence interval; SEP = socioeconomic position.

All models were adjusted for sex, intraocular pressure, axial length, and optic disc area.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

[a] Model 3: In addition to previous covariates, adjusted for child health score, childhood IQ, and perinatal complications.

[b] Model 4: In additional to previous covariates, adjusted for age 45 years mean arterial pressure, lifetime tobacco use, cumulative cannabis use, and adult SEP.

participants scored significantly lower on adult loneliness ($F(1,861) = 6.319$, $p = .012$; M $[SD]_{included} = 1.26$ [1.957], M $[SD]_{excluded} = 2.30$ [2.439]). Childhood social isolation was correlated with lower childhood SEP ($R = -0.107$, $p = .001$; Table S1, SDC, http://links.lww.com/PSYMED/A904) and childhood maltreatment ($R = 0.188$, $p < .001$).

Childhood social isolation was associated with thinner average RNFL ($B = -0.739$, $p = .02$; Table 2), as well as thinner RNFL in the nasal quadrant ($B = -1.118$, $p = .005$) and inferior quadrant ($B = -1.524$, $p = .007$), after adjustment for sex and ocular covariates (model 1, Table 2). These associations persisted with the inclusion of other childhood psychosocial adversities in the model: average RNFL ($B = -0.766$, $p = .02$), nasal quadrant ($B = -1.059$, $p = .009$), and inferior quadrant ($B = -1.543$, $p = .008$; model 2, Table 2).

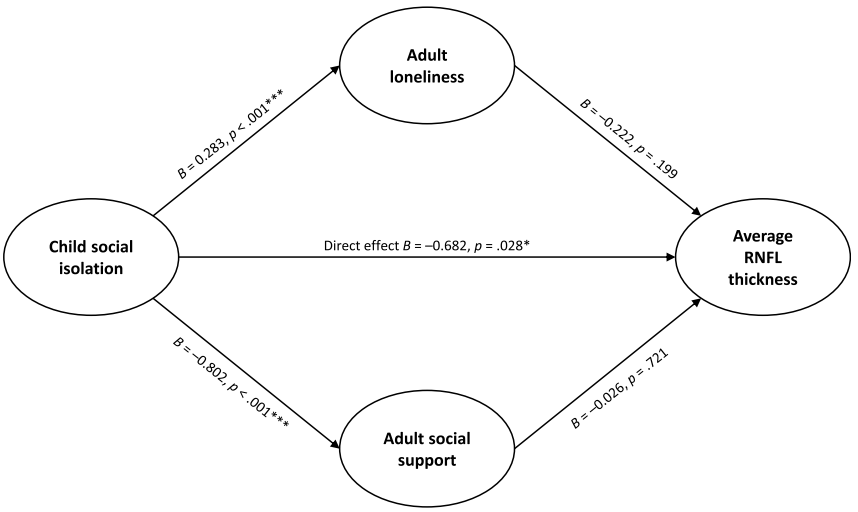
In model 3, co-occurring risk factors from childhood were added; childhood social isolation was associated with thinner RNFL in the nasal quadrant only ($B = -0.880$, $p = .03$). In model 4, co-occurring adult risk factors were added, and the association with thinner RNFL in the nasal quadrant persisted ($B = -0.863$, $p = .03$). This indicates that other risk factors across the lifecourse may account for some, but not all, of the observed association between childhood social isolation and RNFL thickness.

The same models were used with GC-IPL measurements as the dependent variables. No associations were found between social isolation or other measures of childhood psychosocial adversity and any GC-IPL measurement (Table S2, SDC, http://links.lww.com/PSYMED/A904).

Because the two items in our cumulative variable could be measuring different constructs, we used the same regression models to examine whether being rejected by peers or being rather solitary was primarily responsible for the observed association with social isolation. The results are presented in Tables S3 and S4, SDC, http://links.lww.com/PSYMED/A904. Being rejected by peers was associated with average RNFL thickness ($B = -2.818$, $p = .037$), nasal RNFL ($B = -4.774$, $p = .004$), and inferior RNFL ($B = -4.733$, $p = .045$; Table S3, SDC, http://links.lww.com/PSYMED/A904) after adjustment for sex and ocular covariates, whereas being solitary was associated with nasal RNFL ($B = -2.591$, $p = .034$) and inferior RNFL ($B = -4.274$, $p = .014$; Table S4, SDC, http://links.lww.com/PSYMED/A904). Being rejected by peers seemed to be more strongly associated with RNFL, with associations with nasal RNFL remaining significant in models 2, 3, and 4, and both average RNFL and inferior RNFL remaining significant in model 2 only (see Tables S3 and S4 for test statistics, SDC, http://links.lww.com/PSYMED/A904). Being solitary was more weakly associated with RNFL thickness, with both nasal RNFL and inferior RNFL significantly associated with solitary status in models 1 and 2, and no associations observed across models 3 and 4.

Adult Loneliness and Social Support as Potential Mediators

Cross-sectional associations have been observed between social isolation and a number of markers of morbidity and mortality, particularly in later life (9). To test whether childhood social isolation independently predicted retinal thickness or was primarily due to cross-sectional associations between adult social isolation and RNFL thickness in middle age, mediation analyses were conducted. Mediation models were tested where adult loneliness and adult social support were included as potential mediators of the association between childhood social isolation and RNFL thickness. Because the effects of chronic stress are known to exert their effects through multiple pathways, including cardiovascular and behavioral changes, some of the covariates included in models 3 and 4 could be controlling for the effects of the pathways themselves. Thus, in the mediation model, these variables were excluded.



Total effect	$B = -0.724$ (-1.323, -0.125), $p = .018$*
Total indirect effect	$B = -0.042$ (-0.177, 0.080)
Percentage mediated	0.06%

* $p < .05$; ** $p < .01$; *** $p < .001$

FIGURE 2. Child social isolation as a predictor of average RNFL thickness, with adult loneliness and social support as potential mediators (adjusted for sex, optic disc area, intraocular pressure, and axial length; $n = 840$). RNFL = retinal nerve fiber layer.

Childhood social isolation was associated with both adult loneliness ($B = 0.283$, $p < .001$) and adult social support ($B = -0.802$, $p < .001$). However, neither adult loneliness nor social support mediated the association between childhood social isolation and average RNFL (direct effect: $B = -0.682$, $p = .028$; total indirect effect: $B = -0.042$ [95% confidence interval {CI} = −0.177 to 0.080]; Figure 2), nasal RNFL (direct effect: $B = -1.045$, $p = .006$; total indirect effect: $B = -0.044$ [95% CI = −0.201 to 0.106]; Figure S1, SDC, http://links.lww.com/PSYMED/A904), or inferior RNFL (direct effect: $B = -1.453$, $p = .007$; total indirect effect: $B = -0.098$ [95% CI = −0.332 to 0.128]; Figure S2, SDC, http://links.lww.com/PSYMED/A904).

In addition, to test whether childhood social isolation uniquely predicted RNFL thickness in midlife, we tested for group differences between participants who experienced childhood social isolation, those who experienced social isolation in adulthood only, and those who were never isolated. RNFL differences among groups were apparent for average RNFL ($F(2) = 3.041$, $p = .048$) and inferior RNFL (F 2) = 3.859, $p = .021$; Table S5, SDC, http://links.lww.com/PSYMED/A904). Pairwise comparisons revealed statistically significant differences in inferior RNFL thickness between participants who experienced social isolation in childhood and those who had never experienced social isolation at any point (M $[SD]_{child}$ = 117.29 [16.21] μm, M $[SD]_{never}$ = 121.31 [15.76] μm; $p = .023$).

DISCUSSION

We demonstrated that childhood social isolation was associated with thinner RNFL (average, nasal, and inferior) at age 45 years in a basic model, although childhood social isolation remained associated with only nasal RNFL after adjustment for potential co-occurring risk factors. The association was generally independent of other psychosocial or physical health risk factors in childhood or adulthood and was not mediated by adult loneliness or social support. This suggests that childhood social isolation may be an independent predictor of RNFL thickness in midlife. These findings provide some support for the hypothesis that RNFL thickness in midlife is influenced by childhood social isolation independent of co-occurring risk factors from across the lifecourse.

The relationship between childhood psychosocial adversity and physical health outcomes is not straightforward, and there are a number of potential risk factors across the lifecourse that may influence the extent to which a person is affected by their childhood situation. Childhood risk factors tend to cluster and likely have a cumulative effect on physical health outcomes (27,70), making it difficult to determine how much childhood social isolation contributes to outcomes. Thus, we assessed the relationship between childhood social isolation and retinal measures before and after adjusting for other childhood risk factors, such as maltreatment, SEP, perinatal complications, childhood health, and childhood IQ. Childhood psychosocial adversity may also set up individuals for accumulating further risk factors in adulthood, which cumulatively drive an association with poorer physical health in midlife (23). Thus, mean arterial blood pressure, cannabis use, tobacco use, and adult SEP were subsequently adjusted for as possible physical health and lifestyle variables that may influence retinal thickness. Although the observed associations were attenuated, neither childhood nor adult risk factors fully explained the association between RNFL and childhood social isolation.

Determining the mechanisms underlying the observed associations was beyond the scope of this study, as the mechanisms by which social isolation affects physical health are likely to be multifaceted. Covariates included in our analyses were chosen for one of two reasons: either they were known to directly influence the retina (e.g., sex, ocular measures, perinatal complications) or they were thought to be associated with social isolation, agnostic to the direction of that relationship (e.g., maltreatment, cannabis use, SEP). This is the first time that an association between childhood social isolation and adult retinal thickness has been reported, to our knowledge; thus, replication of the findings should occur before in-depth investigations of the mechanisms of the association.

There are several potential mechanisms that warrant future investigation. One pathway through which social isolation is thought to affect physical health is via chronic activation of the stress response leading to chronic inflammation. Childhood social isolation is a predictor of higher levels of C-reactive protein, a marker of chronic inflammation, later in life; this association was mediated by psychological distress, educational attainment, and adult SEP, suggesting that there may be multiple pathways from childhood social isolation to adult health (84). Another biomarker of chronic stress, the proinflammatory cytokine interleukin-6, has been proposed as a pathogenic pathway of retinal ganglion cell death (85). Dysfunctional levels of interleukin-6 lead to a reduction in RNFL thickness and have been implicated in normal-tension glaucoma, a disease where retinal thinning is the hallmark pathology (86). This suggests that chronic stress may lead to retinal thinning. However, there are a number of other potential mechanisms (e.g., increased oxidative stress, altered autoimmune processes, or altered expression of genes that regulate glucocorticoid responses) that could also be involved (8). Further research is needed to determine which, if any, of these mechanisms are implicated in the pathway from childhood social isolation to adult retinal thickness.

The variable used in the primary analysis comprised two items from the Rutter scale. It is possible that these items measure different constructs, so we conducted additional analyses to better understand the nature of the relationship between social isolation in childhood and retinal thickness in midlife. We found stronger associations with retinal measures for being "rejected by peers" than for children who were identified as being "rather solitary." However, it is notable that associations with RNFL were observed with both component variables, and the combined variable (childhood social isolation) was the strongest predictor.

There are few studies with which to compare these findings. Previous studies examining the effects of psychosocial adversity and chronic stress on the retina have examined effects on retinal fundus photographs and used microvascular end points (e.g., retinal vascular caliber) rather than OCT-assessed neuronal layer measures (61–64,66–68). Our findings are consistent with the only other study, to our knowledge, to investigate the effects of stress on RNFL, which found a weak association between increased stress reactivity and thinner RNFL in a laboratory-based task (69).

Because this is the first study to investigate the influence of childhood social isolation on RNFL or GC-IPL thickness, replication is needed before firm conclusions can be drawn. However, two implications of this research should be considered. First, because retinal imaging with OCT holds much promise as a biomarker of AD (37,43–45), we suggest that the effects of childhood psychosocial adversity on the retina should be better understood. Childhood

psychosocial adversity and chronic stress are potential risk factors for AD and cognitive decline (29,30,34), so it is possible that there is a shared pathological pathway from childhood psychosocial adversity to retinal thinning and AD pathology. It is important to consider the influence of psychosocial risk factors on retinal neural layers when considering how the retina may be used as a biomarker for AD.

Second, these findings might have future implications for policy at national and school levels, as well as for parents and other people who interact with children. Childhood social isolation is an especially modifiable risk factor because it is more easily identified and less stigmatizing than other childhood psychosocial adversities, such as poverty or abuse. Moreover, it is particularly relevant because of the impact of the COVID-19 pandemic restrictions that may exacerbate social isolation (87). Social isolation may be identified by the child themselves, or by a parent, teacher, or other adult (13,88). Interventions have been shown to improve social isolation, often through teaching emotional management or social skills (89). The mechanisms by which social isolation exerts its effect are at least twofold: social isolation is associated with chronic inflammation (23,84,90) and higher-risk health behaviors, such as smoking, lack of physical exercise, or poor sleep (91–93). Thus, addressing social isolation may also help with other aspects of physical health. The present findings suggest that childhood social isolation may have long-term implications for retinal health and therefore brain health, thus providing an impetus for interventions targeting social isolation in childhood.

The main strength of this study was the use of a prospective longitudinal design to examine relationships between childhood social isolation and a potential biomarker of neurodegeneration. A limitation is that the measure of social isolation included in this study was an objective measure that was provided by parents and teachers, rather than a direct measurement of the child's subjective feelings of loneliness. This is largely a reflection of the era in which the data were collected, with loneliness not typically considered a concept that could be reliably measured in children at the time (1970s–early 1980s) (13,94). Thus, the variable used in our study is an indirect measure of a child's social isolation rather than a measure of the child's experience of loneliness. Objective social isolation is an imperfect correlate of loneliness, with perceived feelings of loneliness likely to be more highly associated with possible mechanistic pathways than objective social isolation, because perceived social isolation (or loneliness) is a better predictor of poor health outcomes than objective measures of social isolation (8,10). Thus, it is possible that our study, by including objective measures of social isolation, may present smaller associations than might be expected in a study on the effects of perceived loneliness on the retina. Nevertheless, social isolation as measured by the same items as the present study has been associated with chronic inflammation, cardiovascular disease, and metabolic risk (2,84), and rejection by peers is a close correlate of loneliness in children (12).

Attrition analysis indicated that those who were deceased by age 45 years tended to be higher on psychopathology risk and had lower childhood IQs. This may be a limitation of the study because both psychopathology and IQ are likely to be related to both social isolation and retinal thickness (47,95,96) and may be associated with mechanisms of biological embedding, such as oxidative stress or chronic inflammation, thus influencing retinal thickness. Recent research has begun to examine the associations between retinal measures and psychopathology, particularly depression (97,98). Future research with targeted sampling of children and young people who are high on psychopathology measures in particular may help elucidate the nature of the association between psychopathology, social isolation, and retinal outcomes. In addition, participants who did provide data at age 45 years but who were excluded from the main regression analyses were less likely to have been socially isolated or maltreated as children, so the effects of severe social isolation and maltreatment in childhood on later retinal outcomes should be explored further.

Furthermore, there are a number of other causes of psychosocial adversity that were not tested in our study. Parental mental health may lead to a chronic stress response in children, as may bullying victimization (99,100). In addition, there are also a number of protective factors that may attenuate or mitigate the negative effects of childhood psychosocial adversity, which were not examined in the present study. A supportive family environment is known to improve resilience after psychosocial adversity (101,102). Gene-environment interactions may also confer protective resilience factors, influencing the long-term effects of chronic stress exposure (20,102).

The sample in our study was primarily of White European descent and is underrepresentative of Māori, Pacific peoples, and Asians compared with New Zealand national norms. Ophthalmological research has largely been conducted in White and Asian populations, and although some ocular parameters are known to differ between ethnic groups, the nature and extent of ethnic differences in retinal parameters are unknown (103–105). In addition, most research in the psychological sciences, including social isolation research, has been conducted with White people (106), meaning that the findings of the current study cannot be generalized to non-White populations. This is an important area of future research, particularly because non-White children are more likely to experience psychosocial adversity as a result of racism and consequently its long-term effects on health (22).

CONCLUSIONS

Our study goes some way toward a better understanding of how chronic stress caused by psychosocial adversity affects the retina, and possibly neuronal structures and function in the brain. We showed that childhood social isolation was associated with RNFL thickness at age 45 years, measured over three decades after the exposure to psychosocial adversity. This association was not entirely accounted for by childhood or adulthood risk factors, or by adult loneliness or social support. These findings suggest that childhood social isolation, a form of psychosocial adversity, may exert long-term effects on the retina into adulthood. This finding is notable given the potential of the retina as a biomarker of neurodegenerative diseases.

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Data sharing statement: The Dunedin Study data sets reported in the current article are not publicly available because of a lack of informed consent and ethical approval for public data sharing. The Dunedin Study data sets are available on request by qualified scientists. Requests involve a concept paper describing the purpose of the data access, ethical approval at the applicant's institution, and provision for secure data access. We offer secure access on the Duke, Otago, and King's College campuses.

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