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Research paper

Emotional symptoms and inflammatory biomarkers in childhood: Associations in two Australian birth cohorts

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ABSTRACT

Background: An increasing body of evidence supports associations between inflammation and mental health difficulties, but the onset and directionality of these relationships are unclear.
Methods: Data sources: Barwon Infant Study (BIS; n = 500 4-year-olds) and Longitudinal Study of Australian Children (LSAC; n = 1099 10–13-year-olds). *Measures:* Strengths and Difficulties Questionnaire emotional symptoms at 4, 10–11 and 12–13 years, and circulating levels of two inflammatory biomarkers, high-sensitivity C-reactive protein (hsCRP) and glycoprotein acetyls (GlycA), at 4 and 11–12 years. *Analysis:* Adjusted quantile regression models examining cross-sectional associations between emotional symptoms and inflammation in 4-year-olds (BIS), and cross-lagged associations in 10–13-year-olds (LSAC).
Results: We identified a small association between higher emotional symptoms at 10–11 years and higher GlycA levels a year later (standardised coefficient β = 0.09; 95%CI: 0.02 to 0.15). Sex-stratified analyses revealed this association was stronger for boys (β = 0.13; 95%CI: 0.04 to 0.21) than girls (β = 0.01; 95%CI: −0.09 to 0.11). These associations were not observed for hsCRP. There was little evidence of an association between higher GlycA or hsCRP at 11–12 years and emotional symptoms a year later, or cross-sectional associations between emotional symptoms and hsCRP or GlycA at 4 years.
Limitations: A single time-point of biomarker collection in late childhood precluded adjustment for baseline inflammatory biomarkers.

Abbreviations: 95%CI, 95 % Confidence interval; BIS, Barwon Infant Study; BMI, Body mass index; CDC, Centers for Disease Control and Prevention; EPDS, Edinburgh Post-natal Depression Scale; ELISA, Enzyme-linked immunosorbent assay; GlycA, Glycoprotein acetyls; hsCRP, High-sensitivity C-reactive protein; LSAC, Longitudinal Study of Australian Children; LSAC-CP, Longitudinal Study of Australian Children with Child Health CheckPoint wave; PSS, Perceived Stress Scale; SD, Standard deviation/s; SDQ, Strengths and Difficulties Questionnaire; SEP, Socioeconomic position.

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Conclusions: Our results support the direction of association from emotional symptoms to inflammation in late childhood, with potential sex differences. This adds to the body of evidence that addressing emotional symptoms in childhood is a major priority in optimising overall health throughout the life course.

1. Introduction

Emotional symptoms, such as depression and anxiety, are expected to be a leading cause of disease burden globally by 2030 (WHO Executive Board, 2012), even prior to the exacerbation of mental health difficulties observed during the COVID-19 pandemic (Cénat et al., 2022). Emotional symptoms often first emerge in childhood (Kessler et al., 2007; Kessler et al., 2005), with national Australian data from 2015 estimating nearly 14 % of primary school-aged children are affected (Lawrence et al., 2015), and approximately half of these children are likely to experience persistent emotional symptoms into adulthood (Dunn and Goodyer, 2018). Targeting interventions to children with early signs of emotional symptoms is therefore a key public health and clinical priority for preventing the entrenchment of long-term mental health challenges later in life (WHO, 2014), and particularly timely during the recovery period of the COVID-19 pandemic.

Systemic inflammation could play a role in the etiology of emotional symptoms across childhood (Eisenberger and Moieni, 2020). Inflammation is a natural defense mechanism of body tissues in response to injury and infection, but may subsequently be harmful to the body if inflammation does not resolve and becomes chronic (Esteban-Cornejo et al., 2016; Tyrka et al., 2016). Inflammation is suggested to impact brain morphology and connectivity, which may, in turn, contribute to impairments in mood, cognition and perception (Marsland et al., 2015). Inflammatory processes may also signal the brain to initiate somatic symptoms of depression, such as loss of appetite and fatigue, as well as behavioral responses like social withdrawal (Eisenberger and Moieni, 2020). A previous randomised controlled trial has shown that an induced acute inflammatory response can increase self-reported feelings of social disconnection and depressed mood in adults (Eisenberger et al., 2010).

In epidemiological studies, systemic inflammation can be measured by circulating levels of inflammatory biomarkers, such as high-sensitivity C-reactive protein (hsCRP) and glycoprotein acetyls (GlycA). Generally, higher levels of hsCRP reflect an acute inflammatory response to exogenous stimuli such as infection, whereas lower hsCRP levels are commonly used to assess cardiovascular and metabolic disease risk (Yeh, 2005). GlycA is a newly-described inflammatory biomarker that may reflect chronic inflammation, and has been associated with cardiometabolic risk, disease severity and mortality for a range of non-communicable diseases (Brunoni et al., 2020; Connelly et al., 2017).

In adults, depression has been associated with heightened innate and adaptive immune activation (Beurel et al., 2020), including increased levels of hsCRP (Tayefi et al., 2017) and GlycA (Bot et al., 2020). A similar cross-sectional association has been observed between hsCRP and depressive symptoms in adolescent girls (Tabatabaeizadeh et al., 2018), and between GlycA and a range of psychosocial health and wellbeing measures in 11–12 year olds (Lange et al., 2020). GlycA levels at birth has also recently been associated with internalizing and externalizing problems at 2 years of age (Pham et al., 2022).

It is also plausible that emotional symptoms could lead to elevated inflammation (Copeland et al., 2012), or that there is a potential bi-directional relationship (Colasanto et al., 2020). Previous epidemiological studies have demonstrated children with increasing internalizing problems from age 4 to 9 years have higher levels of inflammatory biomarkers, hsCRP and interleukin-6, at 9 years of age (Flouri et al., 2020). Physiological changes in response to chronic stressor load, such as dysregulation of the hypothalamic-pituitary-adrenal axis, are suggested to increase inflammatory responses (Danese and Baldwin, 2017; Nusslock and Miller, 2016). In addition, increased inflammation may be further exacerbated by behavioral responses to emotional dysregulation, such as poorer diet and lower levels of physical activity (Haapala et al., 2022).

To date, there has been a paucity of data suitable for teasing out the age of onset or directionality of associations between emotional symptoms and inflammation in childhood. In this study, we aimed to: 1) test if previously observed cross-sectional associations between emotional symptoms and inflammatory biomarkers are apparent in early life (age 4 years), and 2) examine longitudinal effects of emotional symptoms on inflammatory biomarkers, and vice versa, in late childhood (age 10–13 years).

2. Methods

2.1. Data sources

We drew on data from two high-quality prospective Australian birth cohorts collaborating through the LifeCourse initiative (O'Connor et al., 2022a): the Barwon Infant Study (BIS) at age 4 years, and the Longitudinal Study of Australian Children (LSAC) and its interpolated Child Health CheckPoint wave (LSAC-CP) at ages 10–13 years.

2.2. Barwon Infant Study (BIS)

BIS is a population-derived birth cohort study (n = 1074 infants) with antenatal recruitment in the south-east of Australia (the Barwon region of Victoria) during 2010–2013 (Vuillermin et al., 2015). Participants completed parent-reported structured questionnaires, and clinical and biological measurements were collected in multiple waves from birth (2010−13) to 4 years of age (2014–16). Data on emotional symptoms and inflammatory biomarkers at 4 years were available for 506 children (Supplementary Fig. S1). Ethical approval was provided by the Barwon Health Human Research Ethics Committee (#10/24), and parents/guardians provided written informed consent.

2.3. Longitudinal Study of Australian Children and Child Health CheckPoint (LSAC-CP)

LSAC recruited a nationally representative birth cohort of 5107 infants in 2004. A complex clustered random sampling survey design based on postcode was used to select a sample that is broadly representative of Australian children, except children living in very remote geographic areas (Soloff et al., 2005). Health and environmental data were collected at in-home assessments every 2 years, with 74 % retention (n = 3764) of the original sample in wave 6 (2014, 10–11 years) and 66 % (n = 3381) in wave 7 (2016, 12–13 years). The Child Health CheckPoint (CheckPoint) was a one-off comprehensive physical health and biomarker module for approximately half (n = 1874) of the birth cohort families retained to wave 6, conducted between LSAC waves 6 and 7 (2015, 11–12 years) (Clifford et al., 2018). Data for emotional symptoms at both 10–11 and 12–13 years, and inflammatory biomarkers at 11–12 years, were available for 1105 children (referred to as LSAC-CP) (Supplementary Fig. S2). Ethical approval was provided by the Australian Institute of Family Studies Human Ethics Review Board for each wave of LSAC and CheckPoint (#14–26), and by the Royal Children's Hospital Melbourne Human Research Ethics Committee for CheckPoint (#33225D), and parents/guardians provided written informed consent for both studies.

2.4. Measures

2.4.1. Emotional symptoms

We used parent reports on their child's emotional symptoms from the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 2001). The SDQ measures emotional and behavioral symptoms across a range, from normative to highly elevated (Stone et al., 2010). The SDQ is used extensively, and shows robust psychometric properties (e.g. α = 0.8 across six waves of LSAC in 4–12 year olds (Stone et al., 2010)). The SDQ comprises a number of subscales focussed on different aspects of social, emotional and behavioral development. Our focus here is specifically on emotional symptoms that reflect the potential for later internalizing disorders, such as depression and anxiety, which are among the most costly (Trautmann et al., 2016). In line with this focus, and following the approach of Bayer et al (Bayer et al., 2011) and O'Connor et al (O'Connor et al., 2021), we analysed the parent-reported emotional subscale of the SDQ, which is strongly correlated with clinical diagnosis of internalizing disorders in Australian children (odds ratio 11.9; 95%CI 3.6, 39.6) (Hawes and Dadds, 2004). The emotional subscale includes five items (unhappy/depressed/tearful, worried, many fears, nervous/easily lose confidence, and complain of headaches) reported on a three-point Likert scale ("Not true", "Somewhat true", "Certainly true"); scores were summed across the five items and re-scaled to create a continuous emotional score from 0 to 10 (higher value indicates greater symptoms) (Muris et al., 2003). The SDQ was collected at the four-year review in BIS, and at waves 6 (10–11 years) and 7 (12–13 years) in LSAC.

2.4.2. Inflammatory biomarkers

Two inflammatory biomarkers, hsCRP and GlycA, were measured at age 4 years in BIS and 11–12 years in LSAC-CP. Non-fasted (BIS) or semi-fasted (LSAC-CP, median fast 4.1 h) venous blood was collected in sodium heparin tubes (BIS) or serum gel tubes (LSAC-CP), and inflammatory biomarkers were measured in derived plasma (BIS) or serum (LSAC-CP). hsCRP (mg/L) was determined using enzyme-linked immunosorbent assay (ELISA) hsCRP DuoSet ELISA (DY1707; R&D Systems, Minneapolis, USA) in BIS samples and Roche/Hitachi Cobas c311 in the LSAC-CP samples (O'Connor et al., 2020). High-throughput proton nuclear magnetic resonance metabolomics (Nightingale Health, Helsinki, Finland) quantified GlycA (mmol/L) in both cohorts (Ellul et al., 2019; O'Connor et al., 2020). We excluded participants with hsCRP>10 mg/L (BIS n = 6, LSAC-CP n = 6), as these were likely indicative of acute infection (Pearson et al., 2003).

2.4.3. Covariates

Details of covariate collection and coding, measure references, and published evidence of their associations with children's emotional symptoms and inflammatory biomarkers, are described in Supplementary Tables S1 (BIS) and S2 (LSAC-CP). Child factors included age (years to nearest week), sex at birth, socioeconomic position (SEP; z-score combining household income, education and occupational status from both parents; see Supplementary Table S3), ethnic minority group (either parent born in non-English speaking country (BIS and LSAC-CP), or Indigenous or Torres Strait Islander (LSAC-CP only)), body mass index (BMI) US Centres for Disease Control (CDC) z-score, inflammatory diet score (weighted sum of estimated weekly intake for inflammatory diet groups; see Supplementary Table S4), total circulating triglycerides (mmol/L), physical activity (BIS average daily hours reported; LSAC-CP average daily moderate-to-vigorous activity measured via wrist accelerometer, hours to nearest minute), screen time (average daily hours reported) and sleep problems (four-point Likert from "Not a problem at all" to "A large problem"). Maternal factors included age at birth (whole years) and emotional symptoms (BIS mean of Edinburgh Post-natal Depression Scale (EPDS) and Perceived Stress Scale (PSS); LSAC-CP Kessler-6) at baseline. Household factors included smoke exposure (binary, anyone in household), substance and alcohol problems (binary, anyone in household), and stressful life events in the past year (sum of 16 possible items). Additional covariates for LSAC-CP children included pubertal development score (Tanner score), household chronic medical condition or disability (binary, anyone in household), and bullying (binary, experienced any bullying behavior), which were not available in the BIS cohort.

2.4.4. Statistical analyses

Our analysis sample was defined by complete data for the exposure/s and outcome/s for all waves of interest (BIS n = 500 children at 4 years and LSAC-CP n = 1099 at 10–13 years), excluding participants with hsCRP>10 mg/L (BIS n = 6, LSAC-CP n = 6). To address aim 1, we examined the association between emotional symptoms and inflammatory biomarkers in BIS using models defining alternative exposures and outcomes: emotional symptoms (SDQ emotional score) at 4 years as the exposure and inflammatory biomarkers (hsCRP and GlycA) at 4 years as the outcome, and then conversely inflammatory biomarkers at 4 years as the exposure and emotional symptoms at 4 years as the outcome. To address aim 2, we examined the potential directionality of association at 10–13 years in LSAC-CP using a cross-lag analysis: emotional symptoms (SDQ emotional score) at 10–11 years as the exposure and inflammatory biomarkers (hsCRP and GlycA) at 11–12 years as the outcome, and then conversely inflammatory biomarkers at 11–12 years as the exposure and emotional symptoms at 12–13 years as the outcome (Fig. 1).

Associations between emotional symptoms and each inflammatory biomarker were analysed using multivariable quantile regression models (for the median), as measures of interest were right skewed and to adjust for potential confounders. Covariates were selected based on published evidence of their associations with both children's emotional symptoms and inflammatory biomarkers (see references in Supplementary Tables S1 and S2), and by constructing directed acyclic graphs for each research question of interest (Supplementary Figs. S3-S6). Associations were estimated 1) unadjusted, and 2) adjusted for baseline covariates (age, sex, SEP, ethnic minority group, maternal age at birth, maternal emotional symptoms, smoke exposure, household substance and alcohol problems, stressful life events, household chronic medical conditions (LSAC-CP only), and puberty (LSAC-CP only)). Exposures and outcomes were internally standardised (mean 0, standard deviation (SD) 1) to allow direct comparison of the magnitude of associations using standardised coefficients (β) with a 95 % confidence interval (95%CI). Statistical analyses were conducted using Stata version 17 (StataCorp, College Station, TX) (StataCorp, 2021).

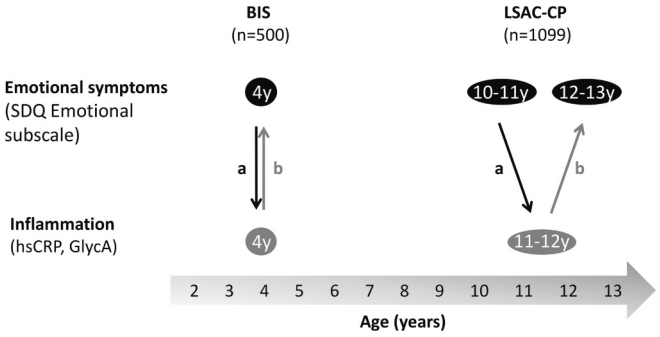

Fig. 1. This study included data from two Australian cohorts, examining cross-sectional associations in BIS children at 4 years (n = 500) and longitudinal associations in LSAC-CP children at 10–13 years (n = 1099). Associations were examined from emotional symptoms (black circles; SDQ emotional score) to inflammatory biomarkers (gray circles; hsCRP and GlycA), shown as path (a), and vice versa from inflammatory biomarkers to emotional symptoms, shown as path (b). BIS, Barwon Infant Study; LSAC-CP, Longitudinal Study of Australian Children with Child Health CheckPoint wave; SDQ, Strengths and difficulties questionnaire; hsCRP, High-sensitivity C-reactive protein; GlycA, Glycoprotein acetyls.

Table 1
Sample characteristics for BIS and LSAC-CP analysis samples with imputed covariates, showing mean and standard deviation (SD) for continuous variables (prior to standardisation), or number (n) and percentage [%] for binary variables. Recruitment is during pregnancy or birth for BIS and during infancy (child aged 0–1 year) for LSAC-CP; baseline for these analyses is 4 year assessment in BIS and 10–11 year assessment in LSAC-CP.

	Mean (SD) or n [%]	
	BIS (n = 500)	*LSAC-CP (n = 1099)*
Emotional symptoms:		
SDQ emotional score at 4 years	1.52 (1.57)	–
SDQ emotional score at 10–11 years	–	1.67 (1.90)
SDQ emotional score at 12–13 years	–	1.73 (1.89)
Inflammatory biomarkers:		
hsCRP (mg/L) at 4 years	0.63 (1.25)	–
hsCRP (mg/L) at 11–12 years	–	0.49 (1.00)
GlycA (mmol/L) at 4 years	1.14 (0.14)	–
GlycA (mmol/L) at 11–12 years	–	0.99 (0.13)
Main covariates:		
Age (years) at baseline	4.14 (0.25)	10.95 (0.33)
Female sex at recruitment	235 [47.00]	565 [51.41]
Male sex at recruitment	265 [53.00]	534 [48.59]
Socioeconomic position (z-score) at baseline	0.77 (0.85)	0.29 (0.90)
Ethnic minority at recruitment	28 [5.60]	148 [13.47]
Maternal age (years) at recruitment	32.01 (4.35)	32.38 (4.73)
Maternal emotional symptoms score (0−100) at baseline[a]	27.32 (13.73)	12.27 (13.29)
Tobacco smoke exposure at baseline	66 [13.20]	152 [13.83]
Household alcohol or substance problem at baseline	13 [2.60]	18 [1.64]
Stressful life events in the last 12 months (0–16) at baseline	1.05 (1.38)	2.43 (2.19)
Household chronic medical condition at baseline	–	386 [35.12]
Puberty development score (1–4) at baseline	–	1.66 (0.50)
Covariates examined in sensitivity analyses:		
BMI (CDC z-score) at baseline	−0.05 (1.16)	0.25 (1.01)
Inflammatory diet score (−6 to 29) at baseline	3.53 (3.41)	–
Inflammatory diet score (−6 to 29) at 11–12 years	–	2.31 (3.03)
Triglycerides	0.89 (0.29)	1.19 (0.56)
Daily physical activity (hours) at baseline	6.43 (2.44)	–
Daily physical activity (hours) at 11–12 years	–	1.05 (0.58)
Daily screen time (hours) at baseline	2.35 (1.18)	–
Daily screen time (hours) at 11–12 years	–	3.42 (1.99)
Any sleep problems at baseline	196 [39.20]	280 [25.45]
Bullying at baseline	–	707 [64.33]
Other demographics:		
Reside outside of major cities at baseline	133 [26.68]	298 [27.12]
Household income less than AUD50,000pa at baseline	42 [8.46]	102 [9.38]
Mother had completed school (year 12) at baseline	472 [94.34]	875 [79.84]

[a] Maternal emotional symptoms were measured using the Kessler-6 Psychological Distress scale (Kessler et al., 2003) in LSAC-CP, or the sum of the Edinburgh Postnatal Depression Scale (Cox et al., 1987) and Perceived Stress Scale (Cohen et al., 1994) in BIS, scaled to a total 0–100 scale for cross-cohort comparison. Abbreviations: BIS, Barwon Infant Study; LSAC-CP, Longitudinal Study of Australian Children with Child Health CheckPoint wave; SDQ, Strengths and Difficulties Questionnaire; hsCRP, high-sensitivity C-reactive protein; GlycA, glycoprotein acetyls; BMI, body mass index; CDC, Centres for Disease Control and Prevention; AUD, Australian dollars.

2.4.5. Sensitivity analyses

We included a sensitivity analysis additionally adjusted for covariates with inconsistent evidence on potential for confounding (BMI z-score, inflammatory diet score, triglycerides, physical activity, screen time, sleep problems, and bullying (LSAC-CP only)), as some of these factors may have mediation effects in the relationships of interest (see discussion). For longitudinal analysis in LSAC-CP, we examined models additionally adjusting for baseline emotional symptoms at 10–11 years when examining the association between 11–12 year inflammatory biomarkers and 12–13 year emotional symptoms. However, as inflammatory biomarkers were only collected at one time-point in LSAC-CP, we could not conduct a similar sensitivity analysis when examining the association between 10–11 year emotional symptoms and 11–12 year inflammatory biomarkers. Post-hoc analyses stratified by sex were examined in light of evidence for sex differences in emotional symptoms (Seedat et al., 2009), and inflammatory biomarkers hsCRP (Khera et al., 2005) and GlycA (Ellul et al., 2020). Except where specified, we present results of unstratified models adjusted for baseline covariates, but include all results in supplementary data for completeness.

2.4.6. Missing data

Missing covariate data within the analysis sample were imputed using multiple imputation by chained equations (Lee and Carlin, 2010) (Supplementary Tables S5 and S6). We specified 40 imputations, with linear regression for continuous variables and logistic regression for binary variables, and pooled model estimates via Rubin's rules.

3. Results

3.1. Sample characteristics

Table 1 describes characteristics of BIS and LSAC-CP analysis samples. Compared with Australian population statistics, both cohorts had lower proportions of families with low income (BIS 8 %, LSAC-CP 9 %), living outside of major cities (BIS and LSAC-CP 27 %), and ethnic minority groups (BIS 6 %, LSAC-CP 13 %); higher proportions of mothers completing year 12 (BIS 94 %, LSAC-CP 80 %); and older maternal age at birth (mean age BIS and LSAC-CP 32 years) (Australian Bureau of Statistics, 2016). Both cohorts were more socio-economically advantaged (composite socioeconomic position: BIS 0.8 and LSAC-CP 0.3SD higher) than the general Australian population (Australian Bureau of Statistics, 2016; Blakemore et al., 2009). LSAC-CP had a slightly higher proportion of female children (51 %), while BIS had a slightly lower proportion of female children (47 %), than their respective national age groups

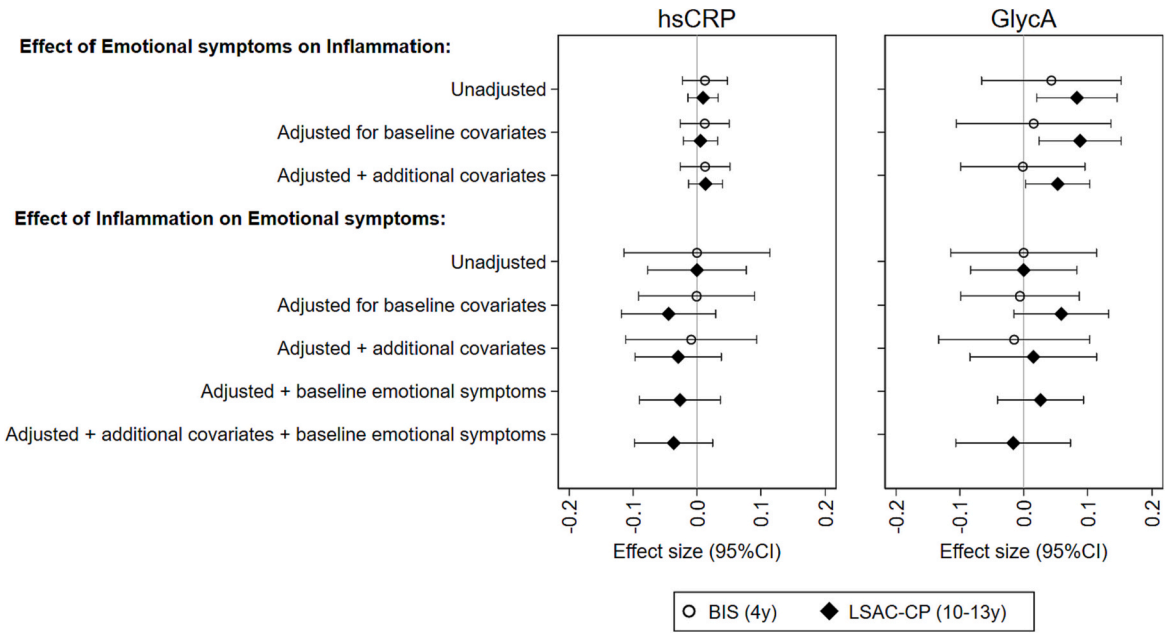

Fig. 2. Associations between emotional symptoms (SDQ emotional score) and inflammatory biomarkers (hsCRP and GlycA) in BIS (4y, n = 500) and LSAC-CP (10-13y, n = 1099), unadjusted and adjusted for baseline covariates (age, sex, SEP, ethnic minority group, maternal age at birth, maternal emotional symptoms, smoke exposure, household substance and alcohol problems, stressful life events, household chronic medical conditions (LSAC-CP only), and puberty (LSAC-CP only)). We also included sensitivity analyses adjusting for additional covariates (BMI z-score, inflammatory diet score, physical activity, screen time, sleep problems, and bullying (LSAC-CP only)), and, for LSAC-CP children with inflammatory biomarker (11–12y) as the exposure and emotional symptoms (12-13y) as the outcome, additionally adjusted for baseline emotional symptoms (10-11y SDQ). See Supplementary Table S7 for further detail. BIS, Barwon Infant Study; LSAC-CP, Longitudinal Study of Australian Children with Child Health CheckPoint wave; hsCRP, High-sensitivity C-reactive protein; GlycA, Glycoprotein acetyls.

(Australian Bureau of Statistics, 2016). Mean emotional symptoms (range 1.52–1.73) were lower in both cohorts compared with Australian population's normative values for their respective age groups (Hawes and Dadds, 2004; Mellor, 2005).

Aim 1: Cross-sectional relationship between emotional symptoms and inflammatory biomarkers at 4 years.

Using SDQ emotional score as the exposure, there was little evidence of a cross-sectional association between 4 year SDQ emotional score and 4 year hsCRP (standardised coefficient β = 0.01; 95%CI: −0.03 to 0.05) or 4 year GlycA (β = 0.02; 95%CI: −0.11 to 0.14) in BIS children. Similarly, using inflammatory biomarkers as the exposure, there was little evidence of a cross-sectional association between 4 year hsCRP (β = 0.001; 95%CI: −0.09 to 0.09) or 4 year GlycA (β = −0.006; 95%CI: −0.10 to 0.09) and 4 year SDQ emotional score in BIS children (Fig. 2).

Aim 2: Longitudinal relationship between emotional symptoms and inflammatory biomarkers at 10–13 years.

Using SDQ emotional score as the exposure, there was a small association between higher 10–11 year SDQ emotional score and higher 11–12 year GlycA (β = 0.09; 95%CI: 0.02 to 0.15) in LSAC-CP children. However, there was little evidence of an association between 10–11 year SDQ emotional score and 11–12 year hsCRP (β = 0.006; 95%CI: −0.02 to 0.03). Using inflammatory biomarkers as the exposure, there was little evidence of an association between 11–12 year hsCRP (β = −0.04; 95%CI: −0.12 to 0.03) or 11–12 year GlycA (β = 0.06; 95%CI: −0.02 to 0.13) and 12–13 year SDQ emotional score in LSAC-CP children (Fig. 2).

3.2. Sensitivity analyses

The association seen between 10–11 year SDQ emotional score and higher 11–12 year GlycA persisted but was attenuated after adjusting for additional covariates (β = 0.05; 95%CI: 0.003 to 0.10); this attenuation was primarily after adjustment for triglycerides, which partially overlaps NMR signals from GlycA (Connelly et al., 2017). Other analyses described above continued to demonstrate little evidence of an association when adjusted for additional covariates, and/or baseline emotional symptoms (Fig. 2).

When stratified by sex (Supplementary Figs. S7 and S8), the observed association between higher 10–11 year SDQ emotional score and higher 11–12 year GlycA was more apparent in boys (β = 0.13; 95%CI: 0.04 to 0.21) than girls (β = 0.01; 95%CI: −0.09 to 0.11). We did not observe any other meaningful sex differences in the relationships analysed.

4. Discussion

We investigated the age of onset and directionality of associations between emotional symptoms and inflammation in childhood. Our first aim was to examine whether previously observed cross-sectional associations between emotional symptoms and inflammatory biomarkers are evident in early childhood (age 4 years), for which we found little evidence. Our second aim was to examine longitudinal effects of emotional symptoms on inflammatory biomarkers, and vice versa, in late childhood (age 10–13 years). We found a small association between higher emotional symptoms at 10–11 years and higher levels of GlycA at 11–12 years, and sensitivity analyses revealed that this association was stronger in boys than in girls. There was little evidence of an association between 10–11 year emotional symptoms and 11–12 year hsCRP, or for a reverse direction of association between 11–12 year GlycA or hsCRP and 12–13 year emotional symptoms.

Our results did not support the usual conceptualisation of a direction of effect from inflammation to emotional health in late childhood. Although inflammation has been suggested to impact emotional symptoms through changes in brain morphology and connectivity (Marsland et al., 2015), there has been a lack of robust longitudinal evidence to demonstrate a causal link to changes in emotional symptoms (Byrne et al., 2016), particularly in children and adolescents (Colasanto et al., 2020). Our analysis used prospective longitudinal data and careful adjustment for potential confounders and baseline emotional symptoms to assess evidence for directionality of this relationship, strengthening confidence in these findings within the childhood period.

Our results supported a small prospective association in the opposite

direction, from emotional symptoms to levels of GlycA a year later, in late childhood. GlycA is a reliable biomarker of cardiometabolic risk in adults (Connelly et al., 2017), and higher rates of co-morbid cardiovascular disease are well-documented for adults with mental health challenges (Prince et al., 2007). Inflammation is likely to be a mediator in the relationship between mental health challenges and increased incidence of cardiovascular events in adults (Wirtz and von Känel, 2017), given that psychological conditions such as depression and anxiety in adults are associated with increased numbers of pro-inflammatory immune cells (Foley, 2023) and increased expression of inflammatory mediators (Debnath et al., 2021). Our results raise the possibility that such pathways can have origins in childhood.

Emotional symptoms may influence inflammation through chronic activation of the stress response, such as through dysregulation of cortisol (Knight et al., 2021) or oxidative stress pathways (Salim, 2016). Emotional symptoms may also indirectly influence inflammatory pathways. For instance, poorer emotional functioning is likely to impact health behaviors, such as diet, exercise, screen time and sleep (Gialluisi et al., 2020), and can influence social stressors such as bullying (Soares et al., 2022). As some of these factors could act as mediators on this causal pathway between emotional symptoms and inflammation, we adjusted for BMI, diet, triglycerides, physical activity, screen time, sleep, and bullying in sensitivity analyses only. This reinforces the complexity of the causal pathway between emotional symptoms and inflammation, and the need for formal mediation analyses to clarify these pathways in future research (Ikram, 2019).

Sensitivity analyses revealed that the association between emotional symptoms and GlycA levels during late childhood was stronger in boys than girls. Following well established gender differences (Seedat et al., 2009), mean emotional symptoms in our cohorts was higher in girls than boys. GlycA was also higher in girls than boys in early childhood, as previously reported for this cohort in infancy (Ellul et al., 2020), but in late childhood GlycA levels for boys and girls were similar (Ellul et al., 2019). Our analysis assumes a linear relationship across the entire range of values of emotional symptoms and GlycA, but an association in girls may be more relevant at more extreme values.

Our results did not provide evidence of a cross-sectional association between emotional symptoms and inflammatory biomarkers during the early childhood period (4 years). This contrasts our previous work in BIS suggesting an association between GlycA levels in cord blood and internalizing problems at 2 years (Pham et al., 2022). One possible explanation is the use of a different emotional and behavioral assessment in this previous study (the Child Behavior Checklist), which may capture different symptomology profiles in younger children (Goodman and Scott, 1999). Alternatively, inflammation may influence emotional and behavioral symptoms during periods of significant development, such as gestation (Gustafsson et al., 2018; Mac Giollabhui et al., 2019), but not in later childhood. This may also explain the attenuated association found between GlycA levels at 12 months and internalizing problems at 2 years in the above previous work (Pham et al., 2022).

Additionally, previous studies in children have focussed on inflammatory responses to longer term stressors or severe adversity (Flouri et al., 2020; O'Connor et al., 2020). We did not examine chronicity of emotional symptoms herein, but given the well-documented persistence of emotional symptoms over time (Seedat et al., 2009), the small differences in inflammatory biomarkers we observed in later childhood may reflect the impact of chronic and sustained emotional symptoms, while our early childhood timepoint may be too soon to see an association on a population scale. Early and mid-childhood may present a window of opportunity for intervention in children with greater emotional symptoms, to prevent mental health disorders and other noncommunicable diseases later in life.

Our results did not provide evidence of an association between hsCRP and emotional symptoms in early or late childhood, similar to our previous findings for childhood adversity (O'Connor et al., 2020) and child internalizing and externalizing problems (Pham et al., 2022). In BIS, a preliminary study demonstrated that GlycA correlated better than hsCRP with parent-reported cumulative early childhood infections, and other measures of inflammation such as granulocyte proportions (Collier et al., 2019). GlycA has also been shown more stable over time in adults than hsCRP (Connelly et al., 2016; Ritchie et al., 2015). Thus, GlycA may be a better biomarker of chronic inflammation than hsCRP. GlycA may also contribute additional information about inflammation above that from CRP, and likely act through different but potentially partially overlapping biological pathways (Duprez et al., 2016; Muhlestein et al., 2018).

4.1. Strengths and limitations

We examined two Australian prospective population-based cohorts at different stages of childhood, to expand the developmental scope of our investigation beyond what would be possible within each cohort alone (O'Connor et al., 2022b). Both the LSAC-CP sub-cohort and BIS cohort used here are of slightly higher socioeconomic standing than the general Australian population. Our analysis sample, which was defined by complete data for the exposure/s and outcome/s, may also have some additional selection bias. Given that emotional symptoms are higher among more disadvantaged children (Reiss, 2013), and lower SEP is also associated with higher markers of inflammation (Ranjit et al., 2007), the generally higher SEP in our cohorts may underestimate the effect in more disadvantaged families in Australia.

Our study also utilized longitudinal evidence with careful and comprehensive consideration of potential confounding, to examine the evidence of directional relationships. However, the longitudinal data used here was only available for late childhood, while early childhood analyses were cross-sectional and thus could not inform the direction of relationships at that age. Additionally, due to a single time-point of biomarker collection in the late childhood cohort, we could not adjust for baseline inflammatory biomarkers in relevant analysis models.

Analyses were conducted using the continuous emotional symptoms score, rather than imposing cut-points, to provide greater resolution to detect associations with inflammatory biomarkers across the full spectrum of difficulty levels. However, the parent-reported SDQ emotional subscale is a brief and non-specific measure of emotional symptoms. Our analysis assumes a linear relationship between the exposure and outcome across the entire range of values of each variable, but the relationship may differ at more extreme values of emotional symptoms. A preliminary analysis suggests the association between emotional symptoms and levels of GlycA may be stronger ($\beta = 0.18$; 95%CI: −0.15 to 0.50) for children with clinically relevant emotional symptoms (score 5 or higher). However, the limited number of children meeting this criterion in our population-based samples ($n = 27$ in BIS and $n = 107$ in LSAC-CP) limits our confidence in this conclusion.

Additionally, while we have focussed on emotional symptoms, psychosocial functioning as a whole is complex and multi-faceted, and future research would be valuable to explore the correlation between inflammatory biomarkers and other mental health challenges such as externalizing behavior problems. We also examined two different biomarkers of inflammation that provided insight into different molecular pathways through which emotional symptoms may impact inflammation, but inflammatory biomarkers, such as cytokines and interleukin-6, may also be important.

4.2. Implications

Our findings suggest that emotional symptoms in late childhood may contribute to increased inflammation, adding to the body of evidence of how unaddressed emotional symptoms may contribute to a range of noncommunicable diseases and reduced life expectancy. In the context of the COVID-19 recovery period, this raises an important consideration of how reported exacerbation of mental health difficulties observed during the COVID-19 pandemic may have influenced immune function

during a critical health crisis.

In clinical terms, the change in GlycA reported here represented approximately 0.006 mmol/L (6 μmol/L) increase in GlycA concentration per 10 % increase in emotional symptoms (e.g. the difference between borderline and clinically relevant emotional symptoms). This is similar to reported effects of regular exercise on GlycA concentration in a population-based adult sample (Barber et al., 2018). Even small increases in GlycA levels have been associated with significant differences in risk of certain diseases (Chandler et al., 2016; Ormseth et al., 2015), suggesting that the prevention and treatment of emotional symptoms may be an important target alongside other lifestyle changes for reducing inflammation and long term disease risk.

5. Conclusion

Our results suggest that emotional symptoms may have a small effect on GlycA levels in late childhood, particularly in boys. This contradicts the usual conceptualisation of a direction of effect from inflammation to emotional health. We did not find evidence that a similar relationship existed in preschool-aged children, or for hsCRP. This adds to the body of evidence that addressing emotional symptoms in childhood is a major priority in optimising overall health throughout the life course. Future studies prioritising longitudinal data analysis are warranted to further elucidate the mechanisms through which emotional symptoms may impact inflammation in children.

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Data sharing statement

LSAC and CheckPoint data are available at no cost from the National Centre for Longitudinal Data (dataverse.ada.edu.au/dataverse/lsac). BIS data are available by application through the MCRI LifeCourse initiative (lifecourse.melbournechildrens.com/data-access).

Contributors

DB, CO, MT, ALP, CS, PV, LG, PS, JC, RS and MW designed the cohort studies. DB, CO, MT, ALP, CS, AL, PV, JK, LG, PS, KLy, JC, RS and MW directed the cohort studies' implementation. KLa, CP and TM were involved in data acquisition and preparation. KLa, CP, IF, FC, DB, CO, MD, NP, KLy and MOC were involved in the initial manuscript planning. KLa, CP, IF, FC and MOC conducted the literature review and drafted the manuscript. KLa conducted the analyses. MD provided statistical input on the analyses. MOC provided oversight for the study as senior author. All authors provided critical review of the manuscript, and have reviewed and approved the final article.

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None.

Declaration of competing interest

All authors declare no conflict of interest.

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Appendix A. Supplementary data

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