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Full Length Article

Exposure to adversity and inflammatory outcomes in mid and late childhood

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ABSTRACT

Background: We aimed to estimate the association between exposure to adversity and inflammatory markers in mid (4 years) and late (11–12 years) childhood, and whether effects differ by type and timing of exposure.
Methods: Data sources: Barwon Infant Study (BIS; N = 510 analyzed) and Longitudinal Study of Australian Children (LSAC; N = 1156 analyzed). *Exposures*: Adversity indicators assessed from 0 to 4 (BIS) and 0–11 years (LSAC): parent legal problems, mental illness and substance abuse, anger in parenting responses, separation/divorce, unsafe neighborhood, and family member death; a count of adversities; and, in LSAC only, early (0–3), middle (4–7), or later (10–11) initial exposure. *Outcomes:* Inflammation quantified by high sensitivity C-reactive protein (hsCRP, Log (ug/ml)) and glycoprotein acetyls (GlycA, Log (umol/L)). *Analyses:* Linear regression was used to estimate relative change in inflammatory markers, adjusted for sociodemographic characteristics, with exposure to adversity. Outcomes were log-transformed.
Results: Evidence of an association between adversity and hsCRP was weak and inconsistent (e.g., 3+ versus no adversity: BIS: 12% higher, 95%CI -49.4, 147.8; LSAC 4.6% lower, 95%CI: −36.6, 48.3). A small positive association between adversity and GlycA levels was observed at both 4 years (e.g., 3+ versus no adversity: 3.3% higher, 95%CI -3.0, 9.9) and 11–12 years (3.2% higher, 95%CI 0.8, 5.8). In LSAC, we did not find evidence that inflammatory outcomes differed by initial timing of adversity exposure.
Conclusions: Small positive associations between adversity and inflammation were consistently observed for GlycA, across two cohorts with differing ages. Further work is needed to understand mechanisms, clinical relevance, and to identify opportunities for early intervention.

1. Introduction

Exposure to childhood adversity, such as experiences of violence, parent imprisonment, mental illness, and substance use, has harmful effects on mental and physical health throughout life (Anda et al., 2010; Hughes et al., 2017). The long term health consequences of childhood adversity are estimated to cost the US and Canada $748 billion annually (Bellis et al., 2019). Children from disadvantaged and marginalized backgrounds are disproportionately exposed (O'Connor et al., 2020). Understanding the mechanisms by which childhood adversity impacts health, and how these consequences can be reduced, is therefore important for the prevention of adult disease and reduction of health inequities (Anda et al., 2010; Hughes et al., 2017; Boullier and Blair, 2018).

Specific types of adversity vary in qualities such as the context in which they arise (e.g., family versus neighborhood), severity, and

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chronicity (Baumeister et al., 2016). Beyond their individual effects, evidence suggests that cumulative exposure to adversity can have a negative health impact (Evans et al., 2013; Sameroff, 1998; Black et al., 2017). Early adversity studies showed a dose-response relationship between the number of retrospectively-reported adversities experienced and risk for conditions such as diabetes, cancer, and mental illness in adulthood (Felitti et al., 1998). Cumulative exposure to adversity may be particularly harmful in early life, when rapid physiological change and sensitivity to environmental exposures creates a window of heightened vulnerability (Black et al., 2017).

Inflammation is proposed as a central mechanism through which exposure to childhood adversity translates to disease risk (Boyce et al., 2012; Miller et al., 2009). Chronically activated stress responses may result in immune dysregulation, leading to chronic inflammation (Felitti et al., 1998), a key pathogenic mechanism in many of the non-communicable diseases examined in the early adversity studies (Felitti et al., 1998; Danesh et al., 2004; Danese and Baldwin, 2017). Associations between retrospectively reported experiences of childhood adversity and markers of inflammation in adulthood have been consistently observed, supporting this potential mediating role (Baumeister et al., 2016; Rasmussen et al., 2019; Danese et al., 2007; Chen and Lacey, 2018). The limitations of retrospective reports have tempered causal interpretations however (McEwen and Gregerson, 2019), and information on early life has not been readily available.

More recent prospective data suggests that the effects of adversity on inflammatory responses can be detected in childhood and adolescence, well before overt manifestations of disease. A meta-analysis of the limited available evidence found that associations between adversity exposure and inflammation in children and adolescents are comparable in magnitude to those in adults (Kuhlman et al., 2019). Interpretation of current evidence is difficult, however, as various biomarkers have been used to assess inflammation (Kuhlman et al., 2019). C-reactive protein (hsCRP) and interleukin-6 (IL-6) have been the most commonly examined markers (Kuhlman et al., 2019), but in children these are predominantly considered as acute phase reactants and levels drop quickly when the inflammatory stimulus (usually infection) is no longer present (Del Giudice and Gangestad, 2018).

A recently described biomarker is a composite NMR measure of circulating glycosylated acute phase proteins; glycoprotein acetyls (GlycA), which is suggested to reflect cumulative inflammation (Ritchie et al., 2015; Fischer et al., 2014). Adults with elevated baseline levels of GlycA are at increased risk for severe infection for up to 14 years into the future (Ritchie et al., 2015), and each standard deviation increase in GlycA above the population mean confers a 55–67% increase in all-cause mortality risk over a 5-year follow-up period (Fischer et al., 2014). It was recently shown that GlycA is associated with hsCRP and early life inflammatory immune measures at 12 months of age (Collier et al., 2019), suggesting that it may offer a useful marker for understanding persistent effects of adversity on chronic inflammation in early life.

Better understanding the early inflammatory pathway for childhood adversity can inform the potential benefits of prevention approaches, and opportunities to attenuate the impact of adversity for those who are exposed (Baumeister et al., 2016; Park and Kobor, 2015; Danese, 2018; Raison et al., 2013). We drew on longitudinal data from two prospective Australian cohorts to examine the effect of exposure to adversity on inflammatory biomarkers in mid and late childhood: the Barwon Infant Study (BIS, inflammation measured at 4 years of age) and the Longitudinal Study of Australian Children (LSAC, inflammation measured at 11–12 years of age). We examine both hsCRP (allowing comparison with existing studies) and GlycA. We hypothesized that while effects may vary across specific types of adversity, greater overall exposure to adversity, and initial exposure earlier in life (i.e. 0-3 years), would be associated with higher inflammation. We also hypothesized that stronger effects would be observed for GlycA than for hsCRP, reflective of chronic inflammation.

2. Methods

2.1. Data sources

Data were analyzed from two Australian cohorts with measures of exposure to childhood adversity from birth and inflammation in middle (4 years) and late childhood (11–12 years) (Fig. 1).

Barwon Infant Study (BIS) is a population-derived birth cohort study (N = 1074 infants) with antenatal recruitment during 2010–2013, conducted in the south-east of Australia (the Barwon region of Victoria) (Vuillermin et al., 2015). Participants have been reviewed at birth and at 1, 6, 9 and 12 months, and 2- and 4-years, with a primary school (8–10 years) review under way. Pregnant women attending an antenatal appointment at approximately 15 weeks of pregnancy were invited to participate. Ethical approval for this methodology was gained from the Barwon Health Human Research Ethics Committee. Characteristics of the cohort are similar to the Australian population, with the exception of a smaller proportion of families from non-English-speaking backgrounds (Vuillermin et al., 2015). Adversity was measured from 0 to 4 years, and inflammatory biomarkers were available for N = 510 children at 4 years (the analyzed sample herein; Fig. 1).

Longitudinal Study of Australian Children (LSAC) is a nationally representative birth cohort of 5107 infants, overseen by the Australian Institute of Family Studies human ethics review board. A complex survey design was used to select a sample that is broadly representative of all Australian children, with the exception of children living in highly remote geographic areas (Soloff et al., 2005). In 2015, a comprehensive, one-off physical health and biomarker module, known as the Child Health CheckPoint, was conducted for the birth cohort between LSAC Waves 6 and 7, when children were 11–12 years of age (Clifford et al., 2018). Approximately half (53%, N = 1874 families) of the Wave 6 sample participated in the Child Health CheckPoint, with these families more socioeconomically advantaged than the original cohort (Clifford et al., 2019). Adversity was measured from 0 to 11 years, and inflammatory biomarkers were available for N = 1156 children, who form the analysis sample herein (Fig. 1).

2.2. Measures

2.2.1. Adverse experiences in childhood

Following our previously detailed measurement framework (O'Connor et al., 2020), we examined adversities that 1) have been consistently measured in the childhood adversity literature, and 2) had assessments available during the relevant age periods in both cohorts. Seven types of adverse experiences met these criteria: parent legal problems, mental illness and substance abuse; anger in parenting responses; separation/divorce; unsafe neighborhood; and family member death. See Supplementary Table 1 for details of how each adversity was measured in each cohort. Some were measured directly (e.g., parents' self-report of psychological distress for parent mental illness), and proxy measures were used where direct indicators were not available. For example, high levels of anger in parenting responses were used as a correlate for child maltreatment (Rodriguez, 2010). Indicators were measured repeatedly in each wave of LSAC, and were measured at least once across the relevant waves of BIS (Supplementary Table 1).

Exposure to types of adversity. From these data, we generated indicators of whether the child was exposed versus unexposed to each type of adversity over the full childhood period (0 = never exposed to that adversity over childhood, 1 = exposed to that adversity at any measured time point/s).

Count of adversity types. In addition, we examined a count of the types of adversities experienced (i.e., summing the adversity type indicators described above). Due to low numbers at higher values, counts were truncated resulting in values of 0, 1, 2 and 3+.

Initial timing of exposure to adversity (LSAC only). Timing of initial exposure to adversity was examined in LSAC, where repeated

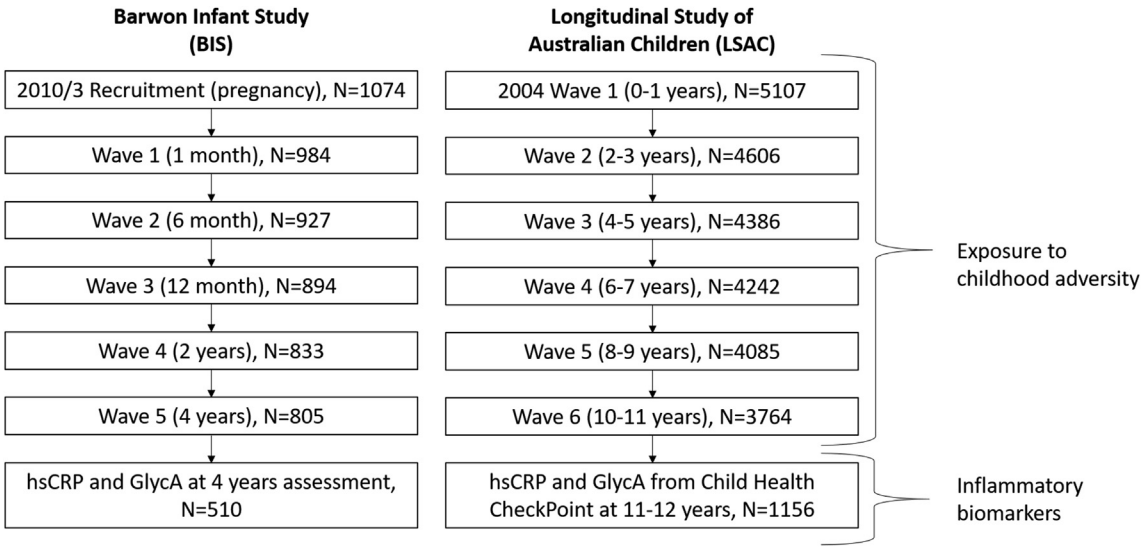


Fig. 1. Analyzed waves of the Barwon Infant Study (BIS) and Longitudinal Study of Australian Children (LSAC) cohorts providing data on adversity and inflammation.

assessments of adversities were consistently available. First, we categorized whether children were exposed versus unexposed to any type of adversity during three periods: 0–3, 4–7, and 8–11 years. We then created a composite variable categorizing children's first exposure to adversity as occurring never, early (0–3 years), middle (4–7 years), or later (8–11 years).

2.2.2. Inflammatory markers

We examined markers of inflammation (hsCRP and GlycA), in plasma samples from blood collected in sodium heparin tubes at 4 years and 11–12 years, in BIS and LSAC, respectively. High sensitivity CRP (ug/ml) was determined using ELISA Human C-Reactive Protein/hsCRP assay DY1707 in BIS samples (Collier et al., 2019), and Roche/Hitachi Cobas c311 in the LSAC samples. The hsCRP measurements equal to zero (BIS: n = 66; LSAC: n = 261) were assigned a value equal to 50% of the lowest measure (BIS: 0.001 μg/ml; LSAC: 0.01 μg/ml). High-throughput proton NMR metabolomics (Nightingale Health, Helsinki, Finland) quantified GlycA (mmol/L) (Collier et al., 2019; Ellul et al., 2019). Both measures were natural log-transformed for all analyses (see Supplementary Figures 1 to 4 for raw and log transformed distributions).

2.2.3. Potential confounders

Confounders included child age at the outcome assessment and the following parent-reported measures in infancy: child sex, family socioeconomic position (BIS: composite of education and income; LSAC: composite of education, occupation, and income (Blakemore et al., 2006); dichotomized at bottom third versus higher (O'Connor et al., 2020)), young maternal age (below or above 23 years (Goldfeld et al., 2018)), indoor smoking (BIS: same room as baby; LSAC: any indoor smoking), and ethnicity/ancestry (BIS: derived from response to "ancestry/ethnic origin"; LSAC: derived from language and country of birth; categorized as Anglo/European and ethnic minority due to small numbers of any one group). BMI (continuous score) was measured at 4–5 years.

2.3. Analytic approach

A directed acyclic graph (DAG) was used to specify proposed causal relationships and covariates a priori (Williams et al., 2018) (Fig. 2). This was used to inform the selection of measures, including potential confounders.

First, descriptive data on study measures was examined. Linear regression was then used to estimate associations between childhood adversity and inflammatory markers. Separate models were constructed to estimate the effects of adversity according to type, cumulative adversity, and earlier versus later initial exposure. Following our conceptual model (Fig. 2) and recommendations for confounder selection (VanderWeele, 2019), estimates were adjusted for child sex, family socioeconomic position, young maternal age, indoor smoking, and ethnicity. Unadjusted estimates are provided in Supplementary Tables 3 and 4. We further adjusted for BMI in sensitivity analyses, while recognizing that this is likely to be on the causal pathway and require formal mediation analysis in future research (Ikram, 2019). All estimates are expressed as percentage difference between mean outcome at each exposure to aid interpretation of the log-transformed inflammatory markers (Cole and Altman, 2017). For hsCRP in BIS, outliers were evident (n = 66 reflecting those hsCRP values originally below the lower limit of detection). Supplementary Table 3 provides estimates with and without their inclusion; results excluding

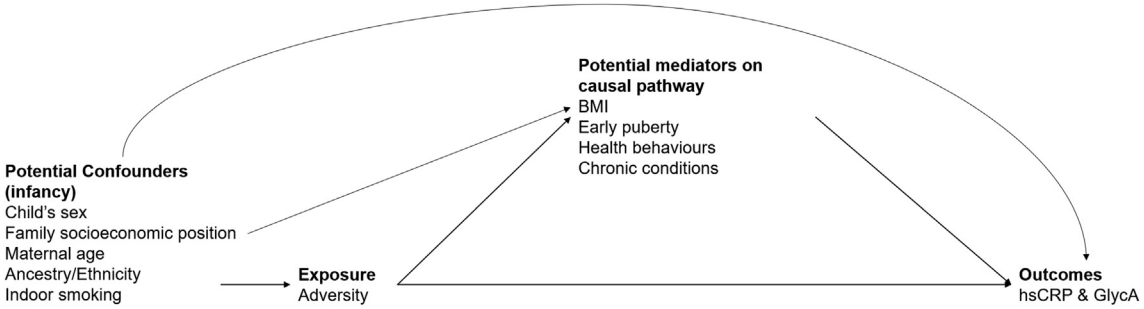


Fig. 2. Directed acyclic graph (DAG) showing the assumed relationship between adversity and inflammation, simplified for clarity.

these outliers are provided in the main text.

Missing data in study variables (Supplementary Table 2) was handled using multiple imputation by chained equations in all analyses, under the missing at random assumption (White et al., 2010). The imputation model included all study variables, and fifty data sets were generated with results combined using Rubin's rules (Rubin, 1987). LSAC analyses also accounted for the sample design whereby clustering occurred via residential post codes (Clifford et al., 2018). Analyses were conducted using Stata/SE V.16.1 for Windows.

3. Results

3.1. Sample characteristics

In both cohorts, there was an even distribution of child sex (BIS: 53% male; LSAC: 49% male; Table 1). There was a similar proportion of families from ethnic minority backgrounds (BIS: 8%; LSAC: 11%) across cohorts, and a low proportion of families with young maternal age (BIS: 1%; LSAC: 4%).

Table 1
Participant characteristics on study variables.

Variable	BIS (N = 510)			LSAC (N = 1156)		
	%	95% CI		%	95% CI	
Adverse experiences						
Type of adversity						
Parent legal problems	7.2	4.4	10.0	13.6	11.1	16.0
Parent mental illness	24.1	19.8	28.4	14.3	11.9	16.7
Parent substance abuse	10.1	7.0	13.3	13.4	11.0	15.8
Anger in parental responses	5.2	2.7	7.6	23.8	20.7	26.9
Separation/divorce	9.7	6.6	12.8	16.9	14.6	19.3
Unsafe neighborhood	8.0	4.2	11.8	22.2	19.3	25.0
Family member death	10.6	7.5	13.8	29.4	26.5	32.2
Count of adversity types						
0	60.4	55.8	65.0	35.3	32.4	38.3
1	25.6	21.3	30.0	31.1	28.0	34.1
2	7.6	4.6	10.5	16.1	13.5	18.8
3+	6.4	3.6	9.2	17.5	14.9	20.1
Timing of initial exposure						
None	–	–	–	35.1	32.2	38.1
Early (0–3 years)	–	–	–	33.9	30.9	36.9
Mid (4–7 years)	–	–	–	16.3	14.1	18.6
Late (8–11 years)	–	–	–	14.7	12.5	16.8
Inflammatory outcomes						
hsCRP (ug/ml) – log transformed						
Mean, SD	−2.2 (2.6)			−2.2 (2.1)		
Median (IQR)	−1.8 (−3.2, −0.3)			−1.9 (−3.9, −0.7)		
hsCRP (ug/ml) – raw						
Mean, SD	.8 (1.8)			.6 (1.4)		
Median (IQR)	.2 (.04, .7)			.2 (.02, .5)		
GlycA (mmol/L) – log transformed						
Mean, SD	0.1 (0.1)			−0.02 (0.1)		
Median (IQR)	0.1 (0.04, 0.2)			-.04 (−.1, 0.04)		
GlycA (mmol/L) – raw						
Mean, SD	1.1 (0.1)			.99 (0.1)		
Median (IQR)	1.1 (1.0, 1.2)			.96 (.9, 1.0)		
Sociodemographic characteristics						
Sex						
Female	46.9	42.5	51.2	51.4	48.5	54.3
Male	53.1	48.8	57.5	48.6	45.7	51.5
Composite socioeconomic position						
Higher	72.8	68.9	76.6	83.1	80.7	85.5
Low/disadvantaged	27.3	23.4	31.1	16.9	14.5	19.3
Maternal age						
Over 23 years of age	98.8	97.9	99.8	95.9	94.6	97.1
Equal to or less than 23 years	1.2	0.2	2.1	4.2	2.9	5.4
Ethnicity						
Anglo/Euro	92.4	90.0	94.7	89.0	87.0	91.0
Ethnic minority	7.6	5.3	10.0	11.0	9.0	13.0
Smoking in the home						
No	97.6	96.2	99.0	93.9	92.3	95.6
Yes	2.5	1.1	3.9	6.1	4.5	7.7
Age at outcome assessment (M, SE)	4.1 (.01)			11.9 (.01)		
BMI (M, SE)	15.6 (.07)			16.3 (.05)		

3.2. Exposure to childhood adversity

Parental mental illness (24%) was the most common type of adversity children were exposed to in BIS, while family member death (e.g., of grandparent; 29%) was most common for LSAC (Table 1). A larger proportion of children (18%) had been exposed to three or more types of adversity in LSAC as compared to BIS (6%), reflecting the longer period captured. In LSAC, 34% of children were initially exposed to adversity in the early years, while 15% were initially exposed in late childhood.

3.3. Associations between adversity exposure and inflammatory outcomes

While greater adversity was associated with hsCRP levels at 4 years in the expected direction, confidence intervals were wide (e.g., 3+ types of adversity versus no adversity: 12% higher, 95% CI -49.4, 147.8). Hypothesized differences in hsCRP were not observed at 11–12 years (e.g., 3+ types of adversity versus no adversity: LSAC 4.6% lower, 95% CI: −38.6, 48.3; Fig. 3, Supplementary Table 3).

There was more consistent evidence of an association between exposure to adversity and GlycA at 4 years (e.g., 3+ adversities: 3.3% higher, 95% CI -3.0, 9.9) and at 11–12 years (e.g., 3+ adversities: 3.2% higher, 95% CI 0.8, 5.8; Fig. 4; Supplementary Table 4). Associations were in the expected direction for all types of adversity, across both samples. The magnitude of these differences was small. Sensitivity analyses showed that estimates were reduced further when adjusting for BMI, consistent with its potential mediating role (Supplementary Table 5).

In LSAC, we did not find evidence that inflammatory outcomes differed for those with earlier as compared to later initial timing of adversity exposure (hsCRP: 16.5% lower, 95%CI -44.3, 25.2; GlycA: 0.4% lower, 95%CI -2.6, 1.9).

4. Discussion

We found evidence that greater exposure to adversity was longitudinally associated with increased inflammation. Small associations between adversity and inflammation were consistently observed for GlycA, across two childhood cohorts with differing ages. Given that chronic inflammation is considered a common underlying factor in the development of a range of non-communicable diseases (Boyce et al., 2012; Miller et al., 2009; Danesh et al., 2004; Danese and Baldwin, 2017), results reinforce the potential role of childhood adversity in contributing to this burden.

The associations observed between exposure to adverse experiences and higher GlycA levels align with findings from retrospective reports by adults (Baumeister et al., 2016; Rasmussen et al., 2019; Danese et al., 2007; Chen and Lacey, 2018), and a small but growing body of prospective evidence on the link between cumulative adversity and inflammation (Kuhlman et al., 2019). Some types of adversity appeared to be more strongly associated than others, with the largest effects observed for exposure to an unsafe neighborhood and parental separation. Adversities differ along a range of dimensions, such as duration of exposure and perceived severity (Baumeister et al., 2016). The magnitude of the differences observed in GlycA were small, however, and their clinical relevance is not yet known.

Evidence of an effect of cumulative adversity, or of specific types of adversity, on hsCRP was weaker and inconsistent. While estimates of the association between adversity and hsCRP were in the expected direction at 4 years, this association was slightly negative at 11–12 years. There was also little consistent patterning by adversity types. There is less evidence in children than adults that hsCRP is an informative marker of chronic inflammation, especially outside the setting of infectious,

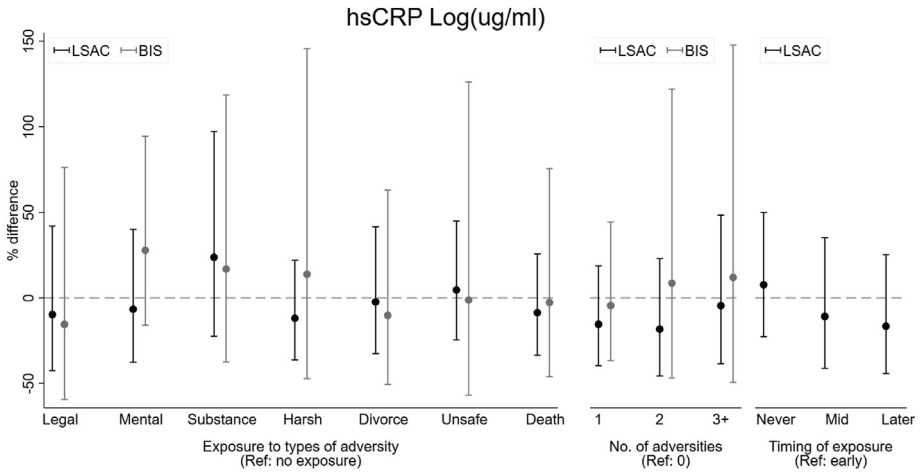


Fig. 3. Association between adversity and hsCRP in the Barwon Infant Study (BIS) and Longitudinal Study of Australian Children (LSAC). Estimates adjusted for sex, child age at outcome, ethnicity, socioeconomic position, smoking in the home, and young maternal age.

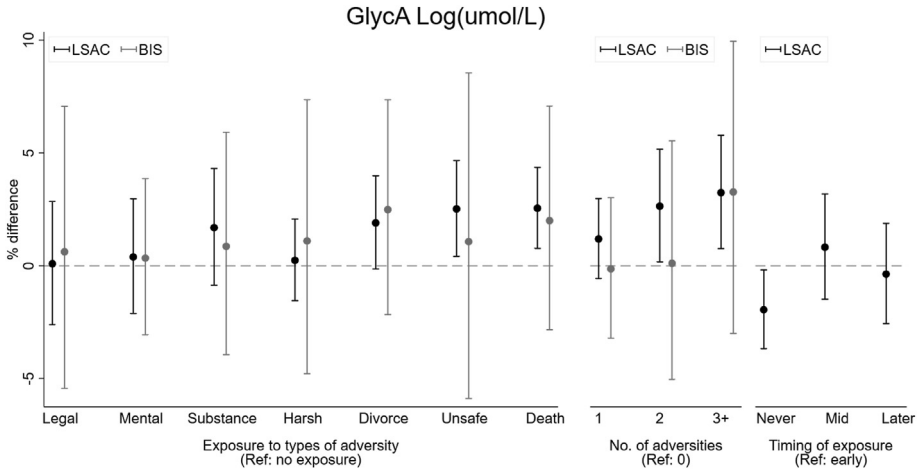


Fig. 4. Associations between adversity and GlycA in the Barwon Infant Study (BIS) and Longitudinal Study of Australian Children (LSAC). Estimates adjusted for sex, child age at outcome, ethnicity, socioeconomic position, smoking in the home, and young maternal age.

rheumatologic and autoimmune diseases. In the context of acute inflammation, such as infection, hsCRP returns to normal if the inflammatory stimulus attenuates. In contrast, GlycA is suggested to capture chronic inflammation (Collier et al., 2019), and may therefore reveal effects of even temporally distal exposures.

Notably, children who initially experienced adversity in the early years had similar outcomes across these inflammatory biomarkers to those who first experienced adversity in mid or later childhood, contrary to our hypothesis. While we cannot discern the reasons for this with the current data, one potential explanation is that the inflammatory system is still resilient in the early years, able to adapt to the environment and maintain homeostasis (Chiang et al., 2019; Miller and Chen, 2010). It is also possible that inflammatory responses to frequent infections in childhood may mask more subtle contributions, such as that of timing of adversity exposure, while the blunter impact of presence/absence of adversities can still be discerned.

4.1. Limitations

A strength of this investigation is the use of two longitudinal cohorts with granular data on covariates and standardized data on exposures in the childhood years. Nevertheless, limitations should be considered in the interpretation of these findings and the extent to which they provide evidence for a causal effect of adversity on inflammation. Retention has been differentially higher for those most privileged, and higher socioeconomic position families from Anglo/European backgrounds experience lower levels of adversity (O'Connor et al., 2020). We have adjusted for key factors likely to be driving selective attrition to minimize the impact on estimates of association, but the prevalence of adversity in these samples is unlikely to be representative of the Australian child population. While there were no specific confounders that we were unable to adjust for, we are not able to rule out the potential for unmeasured confounding. Further, confidence intervals were wide around most estimates, particularly in BIS; further investigations are needed in large samples, although such data are currently rare.

Within the available data, not all types of adversity were captured (e.g., racial discrimination). Of those that were, a proxy indicator was sometimes used (e.g., anger in parental responses in the absence of direct indicators of child maltreatment). Indicators of adversity sometimes did not include the full interval between waves (with, for example, responses made in reference to the past 12 months), meaning that some adverse experiences could have been missed, and there was temporal overlap between the adversity measure and outcomes for BIS. Parental reports on questions about adversities can be influenced by feelings of guilt, shame and embarrassment, and the desire to portray oneself in a positive light (Loxton et al., 2017).

Conceptual clarity about the purpose of measuring adversity is critical to defining how best to summarize and analyze these data (Bethell et al.,

2017). Our approach is appropriate to the current research questions, but will not necessarily be informative for other aims. For example, our measure of cumulative adversity summed the types of adversities experienced but did not capture the number of time points in which each adversity was present. Similarly, our timing indicator captured initial exposure but not whether the adversity was experienced chronically thereafter.

4.2. Future directions

Most of our current understanding of the clinical and public health implications of inflammatory biomarkers comes from adult data. As a result, we have limited understanding of the clinical implications of the small differences observed here and the degree to which they translate to increased disease risk. Further research is needed to understand these markers in childhood and their long-term risk implications. In future studies, it will also be of value to explore potential mechanisms of influence. Results from sensitivity analyses herein were suggestive that BMI may play a mediating role, but this will require formal mediation analysis in future work. Additionally, the potential intermediary role of recurrent infections in the relationship between adversity and chronic inflammation, and the likely complex interrelationships with socioeconomic disadvantage, require further examination (Liu et al., 2017).

More broadly, our findings reinforce the need to address childhood adversity to reduce the burden of adult non-communicable diseases. Childhood adversity can be addressed through complementary strategies. This includes direct efforts aimed at the prevention of and early intervention on the occurrence of childhood adversity, such as through the provision of parent mental health and addiction services (Burke Harris et al., 2017). Many adversities are difficult to modify directly, however, and so finding opportunities to address the social and structural conditions that contribute to the risk of exposure is also critical (O'Connor et al., 2020). Indeed, attention to childhood adversity without addressing social and structural conditions is likely to produce fewer gains and may reinforce stigma for those experiencing high levels of adversity. This includes children who are socioeconomically disadvantaged, from Indigenous backgrounds, and from ethnic minorities, who are disproportionately exposed (O'Connor et al., 2020).

5. Conclusions

We found evidence of an association between adversity and chronic inflammation in mid and late childhood. This effect was consistently observed for GlycA, but not hsCRP, across 4 and 11–12 years. Reducing childhood adversity may have the potential to minimize later inflammation and downstream adult health outcomes, and reduce health disparities for marginalized groups of children. However, to fully understand this pathway we need further evidence of the long-term clinical outcomes associated with the small differences observed, replication with larger more diverse samples, and mechanistic studies.

Declaration of competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

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