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Pathways to inflammation in adolescence through early adversity, childhood depressive symptoms, and body mass index: A prospective longitudinal study of Chilean infants

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ABSTRACT

Early adversity, depression, and obesity are associated with increases in low-grade inflammation. However, there are few prospective and longitudinal studies to elucidate how these associations unfold in children. The present study used latent growth curve models to examine pathways between family adversity in infancy, depressive symptoms in childhood, body mass index (BMI) in childhood, and inflammation in adolescence (age = 16–18). The study is an adolescent follow-up of infants from working-class communities around Santiago, Chile, who participated in a preventive trial of iron supplementation at 6 months of age. Anthropometrics, stressful life events, maternal depression, socioeconomic status, and developmental assessments were measured at 12 months, 5 years, 10 years, and adolescence. In adolescence, participants provided blood samples for high-sensitivity C-reactive protein (hsCRP) assessment. Greater exposure to early adversity in the form of interpersonal conflict stress in infancy indirectly associated with increased hsCRP through its association to increased intercept and slope of childhood BMI. Depressive symptoms at any time were not directly or indirectly associated with increased hsCRP. These findings contribute to our understanding of how early family adversity and its associations with obesity and depressive symptoms across childhood are linked to low-grade, chronic inflammation in adolescence. The model identified as best capturing the data supported the pivotal role of childhood BMI in explaining how early-life adversity is associated with inflammation in adolescence.

1. Introduction

Systemic inflammation is considered the “common soil” in the development of metabolic syndrome, cardiovascular disease, neurodegenerative diseases, cancer, asthma, and aging (Scrivo et al., 2011). In all of these conditions, health disparities are disproportionally evident in groups with higher experiences of childhood adversity (Miller et al., 2011). Stress engendered by adversity in childhood – e.g. poverty, conflict, maltreatment – may play a causal role in the development of physical and mental health problems via impacts on the immune system, particularly increases in circulating inflammatory factors (Miller et al., 2011; Nusslock and Miller, 2016; Scrivo et al., 2011). Adversity in infancy and toddlerhood may dysregulate stress-mediating systems during sensitive periods of brain and immune system development. This dysregulation can lead to persisting effects on the immune system regardless of current health behaviors (Miller et al., 2011). Early life adversity (ELA) in the form of maltreatment, neglect, and harsh family environments is associated with elevated, low-grade inflammation and proinflammatory cytokine gene expression in adults, with mixed evidence in adolescents (Danese et al., 2011; Kiecolt-Glaser et al., 2011; Pace et al., 2012; Slopen et al., 2012; Taylor et al., 2006). Elucidating the pathways of how inflammation develops early in life – before the onset of disease – may provide targets for interventions that prevent later mental and physical health problems. Though few prospective studies have examined the sequelae of early life adversity and inflammation as early as adolescence, studying this time point may be

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especially important as adolescence sets the stage for future adult health.

The Neuroimmmune Network Hypothesis, proposed by Nusslock and Miller (2016), provides a theoretical and mechanistic framework to understand how early life adversity becomes biologically embedded to disrupt immune functioning and increase risk for inflammation later in life. This hypothesis suggests that ELA programs the immune system to become pro-inflammatory by becoming hyper-responsive to inflammatory signals while downregulation inhibitory signals. Exposures like family instability, insensitive caregiving, and financial disadvantage can prime immune cells such as monocytes and macrophages to respond aggressively to pathogen- or danger-associated molecular signals, leading to a higher risk of increased inflammation (Nusslock and Miller, 2016). For example, adolescents reared in harsher family environments exhibit a proinflammatory phenotype (Miller and Chen, 2010). This pro-inflammatory phenotype is then exacerbated by health behaviors as well as hormonal dysregulation of stress-mediating systems, including the hypothalamic-pituitaryadrenal (HPA) axis (Miller et al., 2011). Chronic, mild inflammation could be the common pathway for stress-related diseases in individuals with histories of early adversity (Liu et al., 2017).

1.1. Infancy and relevant forms of early life adversity

Infancy is considered an especially salient time for the early programming of the immune system, due to its rapid development during this time (McDade et al., 2016). Exposures to ELA in infancy could have ramifications for inflammation later in childhood, adolescence, and adulthood. Family-level adversity such as family stress, socioeconomic disadvantage, and maternal depression in infancy have all been associated with higher levels of inflammation (David et al., 2017; Measelle and Ablow, 2017; Measelle et al., 2017; Nelson et al., 2019). This is consistent with literature in older children, where low socioeconomic status (SES) (Broyles et al., 2012; Howe et al., 2010; Miller and Chen, 2013) and maternal depression (Riis et al., 2016) have been associated with increases in inflammatory cytokines. One study in infants found that socioeconomic disadvantage and maternal psychosocial stress were independently associated with higher levels of salivary C-reactive protein (CRP), an inflammatory marker (David et al., 2017). This study did not find an interaction between maternal stress and SES disadvantage, suggesting that different forms of adversity may exert independent influences on inflammation. In the present study, financial hardship, interpersonal hardship, and maternal depressive symptoms are used to characterize adversity in the family environment that would be most relevant to infants and their subsequent risk for later inflammation. As these different forms may exert independent effects on later inflammation, they will be examined independently from each other.

1.2. Depression and obesity: possible mediating pathways between inflammation and early life adversity

Early immune and neuroendocrine programming is thought to exert influence on multiple pathways, with many mediators between early adversity exposures and later inflammation. Two mediators of interest between early life adversity and later inflammation are depression and body mass index (BMI). There is growing interest in the relationships between depression, early life adversity, and later inflammation, as early life adversity increases the risk of developing depression later in life (Nusslock and Miller, 2016). Cross-sectional and prospective studies show that depressed individuals who have experienced early adversity have subclinical and chronically elevated markers of inflammation (Chiang et al., 2017; Howren et al., 2009; Lacey et al., 2014; Liu et al., 2012; Slopen et al., 2013; Taylor et al., 2006). Mechanistically, childhood adversity could promote amplified inflammatory signaling between the brain and body's periphery and could lead to a tight coupling of depression and inflammation (Miller and Cole, 2012; Nusslock and Miller, 2016). A prospective study supports this hypothesis: adolescents with a history of childhood adversity were more likely to have higher levels of inflammation, even compared to adolescents with depression and no history of childhood adversity (Miller and Cole, 2012). In this sample, depression and inflammation were bidirectional: the transition to depression was coupled with increases in CRP and CRP remained higher in the adolescents months later even after depressive symptoms had lessened (Miller and Cole, 2012). Thus, depressive symptoms in children and adolescents with a history of early adversity could be an important risk factor for inflammation later in life.

Childhood adversity within the family environment, including financial strain, maternal depression, and distress or neglect, is also a risk factor for childhood obesity (Bzostek and Beck, 2011; Gundersen et al., 2011; Jelleyman and Spencer, 2008; Weinberg et al., 2013; Wells et al., 2010; Yannakoulia et al., 2008). Adversity in childhood could lead to childhood obesity as it is associated with physiological changes that result in increased activation of neurobiological stress-mediating systems (Danese and McEwen, 2012; McCrory et al., 2010). In adults, the activation of such systems leads to a cascade of physiological processes that are associated with the development of increased adiposity, especially central adiposity (Danese and McEwen, 2012). Aside from physiological cascades, psychosocial stress has been found to promote adiposity-inducing behaviors such as the preferential eating of foods high in fats and sugars especially in response to stressful tasks (Dallman, 2010; Dallman et al., 2005; Danese and McEwen, 2012). Obesity at any age is an inherently inflammatory condition (Galcheva et al., 2011; Himmerich et al., 2006; Panagiotakos et al., 2005; Steene-Johannessen et al., 2010). Adipose tissue generates and regulates a large proportion of circulating inflammatory markers (Black, 2003), and obesity in childhood is associated with low-grade inflammation (Visser et al., 2001). However, few studies focus on the links between early adversity and inflammation (Chiang et al., 2017; Hostinar et al., 2015).

Though higher levels of adiposity and depression are both associated with inflammation, the interrelationships between early life adversity, depression, and adiposity over time are not well understood, as studies in this area are often cross-sectional (Copeland et al., 2012; Dowlati et al., 2010; Haapakoski et al., 2015; Himmerich et al., 2006; Panagiotakos et al., 2005). In healthy adults, depressive symptoms can promote weight accumulation and activate an inflammatory response through adipose tissue release and leptin-induced upregulation of pro-inflammatory cytokines (Miller et al., 2003). Mechanistically, this suggests that depression influences a proinflammatory phenotype through increased adiposity, though whether this holds true in younger populations remains unclear. Across development, childhood obesity and depressive symptoms are related in what appears to be a reciprocal relationship: depression in childhood is associated with obesity in adulthood and obesity in youth is associated with increased risk for depression in adulthood (Puder and Munsch, 2010). Either of these pathways could influence the development of increased inflammation. In young adults, depressive symptoms have been found to contribute to increased adiposity and later inflammation (Miller et al., 2003) and, in adolescents, higher body mass index (BMI) at 14 years was associated with higher BMI, inflammation, depressive symptoms, and mental health problems at 17 years. However, exposure to early adversity was not measured (Oddy et al., 2018). As risk for obesity and depressive symptoms are increased in individuals experiencing early adversity, longitudinal analyses could help explain the relative contribution of increased BMI and depressive symptoms to the relationship between early adversity and inflammation.

1.3. The present study and hypotheses

As a number of co-occurring risk factors associated with early adversity have been identified, prospective and longitudinal studies are needed to understand whether adiposity and depressive symptoms

contribute to inflammation following early adversity. Many of the referenced studies have been conducted in adults with retrospective reports of early adversity and without longitudinal measures of body composition. In this sample of adolescents followed prospectively from infancy, we hypothesize that 1) family-level adversity in infancy, including financial stress, interpersonal conflict stress, and maternal depression, will each be independently associated with inflammation in adolescence. We hypothesize that 2) these forms of adversity in infancy will also be associated with increased adiposity early in childhood as well as positive growth in adiposity across childhood. Accordingly, we hypothesize that 3) the increased growth of adiposity across childhood will be associated with increased inflammation in adolescence, suggesting a mediating pathway between adversity in infancy and inflammation in adolescence. With regards to depressive symptoms, we hypothesize that 4) all measures of early life adversity will be associated with both the intercept and growth trajectory of depressive symptoms, and that the growth in depressive symptoms will predict inflammation in adolescence. Finally, we hypothesize that 5) growth in depressive symptoms will predict growth in adiposity, which will mediate the relationship between depressive symptoms and adolescent inflammation. This prospective, longitudinal study investigates how inflammation in adolescence is predicted by early life adversity, depressive symptoms, and BMI at multiple time points between infancy and adolescence.

2. Methods

2.1. Participants

The current study is drawn from an adolescent follow-up of an infancy iron deficiency anemia preventive trial and neuromaturation study for those infants who were already anemic. From 1991 to 1996, 1657 infants were enrolled at clinics in four working-class communities in Santiago. Inclusion and exclusion criteria were chosen to enroll healthy infants without common risk factors for developmental or behavioral problems (Lozoff et al., 2003). Inclusion criteria for the infancy study included birth weight ≥3.0 kg, singleton term birth, stable caregiver, vaginal delivery, and residence in the selected communities. Exclusion criteria included birth complications, major congenital anomaly, phototherapy, illness, hospitalization longer than five days, iron therapy, another infant less than 12 months old in the household, infant enrolled in day care, or a caregiver who was illiterate or psychotic as reported by the caregiver and/or family members on a recruitment questionnaire (Lozoff et al., 2003). Children who did not have iron deficiency anemia at six months were randomized to high-iron, low-iron, or no-iron supplementation for six months.

Follow-up assessments were completed at 5 years, 10 years, and in adolescence. At 5 years, hose in the no-added iron and high-iron supplementation groups were invited back for an assessment that included measurement of anthropometry (height and weight), socioeconomic status (SES), stressful life events in the past year, and a developmental assessment. At 16 years, those assessed at 5 years, drawn from the no-added iron and high-iron supplementation (n = 888), were invited to participate in a study of obesity and cardiovascular/metabolic health. Of this group, 679 participants were assessed (76%). For this analysis, we included adolescents who had measured serum markers of inflammation (n = 622, M age = 16.8 y, SD = 0.26). The Institutional Review Boards at the Institute of Nutrition and Food Technology (INTA), at the University of Chile, Santiago, the University of Michigan, and the University of California, San Diego approved the study.

2.2. Measures

2.2.1. Adversity measures

Adversity was quantified in three family-level dimensions: serious interpersonal conflict stress, serious financial stress, and maternal depressive symptoms. Each measure was assessed at infancy (12 months), 5 years, 10 years, and adolescence. Serious interpersonal conflict stress and serious financial stress were reported by the mother using a modified Social Readjustment Rating Scale (Holmes and Rahe, 1967). The items used for interpersonal conflict were serious spousal conflict, serious family conflict, serious neighbor conflict, serious conflict with others, and marital separation. The items used for financial conflict were unstable employment by the head of the household, an unemployed head of the household, serious debts, and serious financial hardship. All items were coded as 0 if the event did not happen in the past year and 1 if the event did happen within the past year. The sum score of items were then used for each adversity scale and the sum scores were standardized (z-scores). Maternal depressive symptoms were assessed via the Center for Epidemiological Studies Depression scale (CES-D) (Radloff, 1977, 1991) at 12 months, 5 years, 10 years, and adolescence. The raw sum score of maternal depressive symptoms were used in this analysis, with higher scores indicating a higher number of depressive symptoms.

2.2.2. Anthropometric measures

At each time point, a research nurse at INTA, University of Chile, took measurements of participants in underwear and without shoes. A Holtain stadiometer was used to measure height to the nearest 0.1 cm and a SECA scale was used to measure weight to the nearest 0.1 kg. All participants were assessed using standard protocols on the same scale, which was calibrated every other day. BMI z-scores were calculated using World Health Organization (WHO) standards adjusted for age and sex.

2.2.3. Adolescent inflammation

After a 12 h overnight fast, inflammation was measured in serum with high sensitive C-reactive protein (hsCRP), a widely used biomarker of systemic inflammation (Steptoe et al., 2007). The hsCRP was assessed by immunoturbidimetry (QCA S.A. Amposta, Tarragona, Spain, 0.02 mg/L sensitivity). Values of hsCRP greater than 10 mg/L are indicative of infection, trauma, or disease (Yeh, 2003) and were excluded from analyses (n = 22). Therefore, hsCRP was analyzed as a continuous measure of inflammation with values that ranged from 0 to 10 mg/L.

2.2.4. Child depressive symptoms

Depressive symptoms in the child were measured at 5 years using the parent-report of the Children's Adaptive Behavior Inventory (CABI) (Cowan and Cowan, 1990). The child's depressive symptoms were measured at the 10 years and early adolescence by parent-report using the Child Behavior Checklist (CBCL) (Achenbach and Edelbrock, 1991). At 5 and 10 years, the CABI and the CBCL were administered simultaneously to the anthropometric assessment. In late adolescence, parents completed the CBCL during an assessment prior to the blood draw for hsCRP (M age depressive symptoms = 14.0 y, SD = 1.63, M age blood assessment = 16.8 y, SD = 0.26). Questionnaires at all time points were administered in Spanish. Raw scores were used in analyses for the CABI and CBCL.

2.2.5. Potential confounders

We considered the following as potential confounders in the relationship between early life adversity and inflammation in adolescence: age, sex, iron supplementation in infancy trial, maternal BMI, serious interpersonal conflict stress, serious financial stress, SES, maternal depressive symptoms, adolescent diet quality, adolescent alcohol use, and adolescent tobacco use. Socioeconomic status (SES) was measured using a modified Graffar Index (higher scores indicate lower SES) in infancy, 5 years, 10 years, and adolescence (Alvarez et al., 1985). The Graffar takes into account number of people in the home, head of household educational attainment, employment status, home ownership, ownership of major material goods (e.g., home appliances, car), housing type and size, running water, and crowding. Maternal

depressive symptoms, serious interpersonal conflict stress, and serious financial stress were calculated for each time point using the scales described in Section 2.2.1. Alcohol and tobacco use were assessed in a self-report questionnaire. Alcohol use was defined as "1" for alcohol use in the past 30 days and "0" for no alcohol use in the past 30 days. Tobacco use was defined as "1" for tobacco use in the past 30 days and "0" for no tobacco use in the past 30 days. Adolescent diet quality was used as a covariate for hsCRP and assessed through a self-report food frequency questionnaire. Computerized software based on the Chilean Food Composition Tables (2010) calculated nutrient intakes. Depending on the amounts of saturated fat, fiber, sugar, and salt in the foods, diet was classified as unhealthy (items of poor nutritional value and high in fat, sugar, salt, and energy), poor-to-fair (highly processed items although low in fat), and healthy (nutrient-rich items and protective foods) on a scale of 0 to 6, with higher scores indicating higher diet quality (Correa-Burrows et al., 2015). Tanner staging for puberty, assessed by a pediatrician, was also included as a covariate for hsCRP. Physical activity was also used as a covariate, and was defined as the average moderate to vigorous physical activity (MVPA) per day in minutes was also used as a covariate, calculated from a subset of the full sample with accelerometer data (described in Wang et al., 2016). Iron supplementation in infancy trial was defined as 1 = received iron supplements and 0 = did not receive iron supplements.

In all path analyses to participant BMI measures, we controlled for maternal BMI, which was calculated using measured maternal height and weight at 10 years (BMI = kg/m^2). We also controlled for concurrent SES, concurrent adversity measures, and iron supplementation in infancy. In all path analyses to hsCRP, we controlled for age in adolescence, sex, concurrent SES, concurrent maternal depressive symptoms, concurrent serious financial stress, and concurrent serious interpersonal stress, alcohol use, tobacco use, diet quality, and iron supplementation in infancy. In all path analyses to depressive symptoms, we controlled for sex, iron supplementation in infancy, concurrent maternal depressive symptoms, concurrent SES, and concurrent adversity measures.

2.3. Data preparation and analysis

Variables were examined for outliers and their approximation of the normal distribution before analyses. The final analytical sample included 600 participants. hsCRP in late adolescence was log-transformed to normalize the distribution of the right skewed variables. Little's Missing Completely at Random (MCAR) Test indicated that the BMI, depressive symptoms, sources of psychosocial stress, and background variables were missing at random. As more than 5% of data was missing for key variables, multiple imputation by chained equations (MICE) was used with R software (version 3.4.3, 2017) to create imputed values for missing data across all variables. MICE is robust, able to impute data with large amounts of missingness, and is appropriate for use in large datasets in epidemiological and medical data (White et al., 2011). The imputation model included all the variables in the growth curve model. The R package "semTools" was used to pool point and standard error (SE) estimates across 20 imputed data sets.

The proposed model was tested using growth curve modeling, implemented with the "lavaan" and "semTools" packages and R Software (version 3.4.3, 2017) to estimate the strength of both direct and indirect pathways between variables (Rosseel, 2012). First, we tested a model of linear growth of BMI z-score, constructed using BMI at 5y, 10y, and 16y, using the latent intercept and slope of BMI to predict hsCRP and using the early life adversity variables to assess the direct and indirect paths between early life adversity, BMI growth, and hsCRP. Then, we tested models adding depressive symptoms to the previous model. Reported model estimates were all standardized across the 20 imputed datasets.

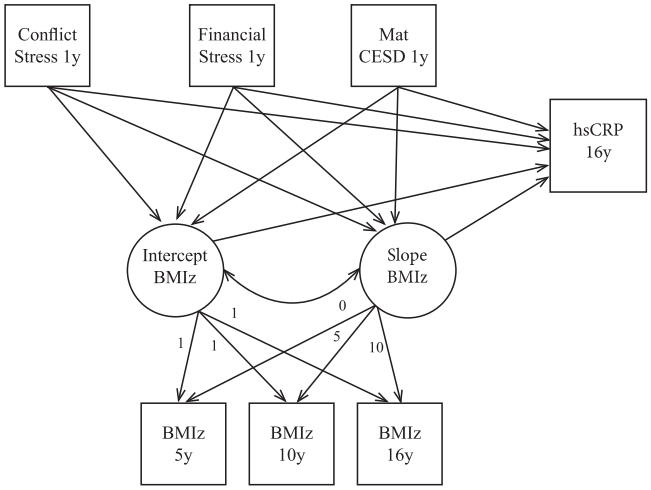

Fig. 1A. Growth curve model tested. Latent variables are represented by circles and observed variables by rectangles. Indicators for each latent factor and paths from covariates to the endogenous variables in the structural models were included but not shown here for visual clarity.

3. Results

We began by testing the model of early life adversity, hsCRP, and the growth curve of BMI (ELA-BMI model, depicted in Fig. 1A). In this model, indices of early life adversity (severe interpersonal conflict stress, severe financial stress, and maternal depression in infancy) were allowed to predict hsCRP in adolescence as well as the intercept and slope of BMI. Covariates included age, gender, and current life stress sum scores and current SES at each time point. Alcohol use, tobacco use, diet, and physical activity were not associated with hsCRP and thus were not included in the model. Results indicated that this model was an acceptable overall fit to the data (CFI = 0.91, RMSEA = 0.058, SRMR = 0.017). In the next step, we constructed a series of models that added youth depressive symptoms to the ELA-BMI model. In the ELA-BMI-DEP models, we examined the following additions to the ELA-BMI model: (a) are depressive symptoms at any time point associated with hsCRP in adolescence, (b) do depressive symptoms at any time (5y, 10, 14y) predict the slope of BMI or do depressive symptoms at 5y predict the intercept of BMI. Results indicated that depressive symptoms at any time point were not associated with hsCRP and model fit was unacceptable (CFI = 0.88, RMSEA = 0.055, SRMR = 0.019). Furthermore, depressive symptoms did not predict the latent intercept or slope of BMI and model fit was again unacceptable (model fit: CFI = 0.89, RMSEA = 0.055, SRMR = 0.019). As a result, the ELS-BMI model without depressive symptoms was retained (Fig. 1B). Table 1 displays observed sample characteristics on major constructs. Table 2 displays zero-order correlations among the measured variables (see supplemental material for full model paths). All results presented are standardized estimates.

Inflammation (hsCRP) in late adolescence was directly and positively predicted by the latent slope and intercept of BMI ($p < .001$ for both). However, hsCRP was not directly predicted by maternal depression in infancy, serious interpersonal conflict stress in infancy, or serious financial stress in infancy. Serious interpersonal conflict stress in infancy was indirectly and positively associated with inflammation in late adolescence through positive associations with both the latent intercept and the latent slope of BMI (indirect path for intercept: standardized estimate = 0.048, SE = 0.010 $p = .002$; indirect path for slope: standardized estimate = 0.043, SE = 0.024 $p = .004$). Additionally, and contrary to our hypotheses, maternal depressive symptoms in infancy were indirectly associated with inflammation in late adolescence, as maternal depressive symptoms in infancy was negatively associated with the latent slope of BMI, which in turn was

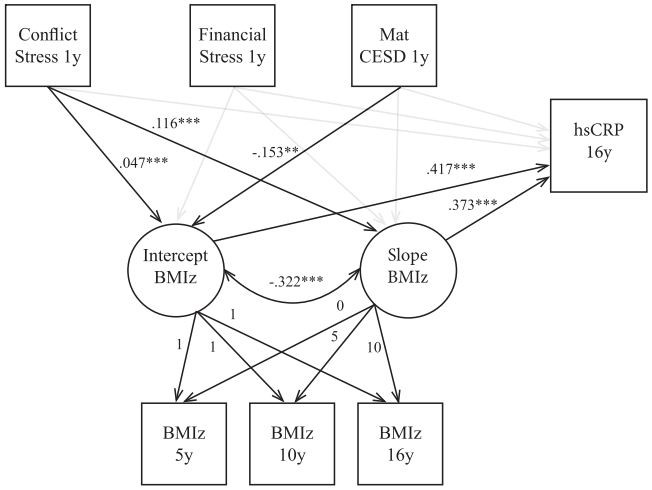

Fig. 1B. Significant standardized paths are displayed in black, nonsignificant in gray. The model was an acceptable fit to the data (CFI = 0.91, RMSEA = 0.058, SRMR = 0.017). Serious interpersonal conflict stress in infancy was positively associated with the latent intercept and latent slope of BMI, which in turn was related to hsCRP (indirect path for intercept: standardized estimate = 0.048, SE = 0.010 p = .002; indirect path for slope: standardized estimate = 0.043, SE = 0.024 p = .004). Maternal depressive symptoms in infancy were indirectly associated with inflammation in late adolescence through a negative association with the latent slope of BMI (indirect path: standardized estimate = −0.064, SE = 0.001 p = .010). Abbreviations: Body mass index (z-score), BMIz; High sensitivity c-reactive protein, hsCRP; Mat CESD, maternal score on Center for Epidemiological Studies Depression scale. *** p < .001; ** p < .01; * p < .0.

related to hsCRP (indirect path: standardized estimate = −0.064, SE = 0.001 p = .010).[1]

4. Discussion

Despite well-documented associations between early life adversity and later inflammation, much less is known about how early life adversity exerts effects on inflammation in adolescence through longitudinal pathways of increased BMI and depressive symptoms. The present study focused on three types of early life adversity exposures (maternal depression, serious financial stress, and serious interpersonal conflict stress) and their relationships to BMI and depressive symptoms across childhood to investigate the links between adversity in infancy and low-grade, chronic inflammation in adolescence. In a sample of biologically low-risk infants (normal birth weight and no perinatal complications) followed to adolescence, the model identified as best capturing the data showed that childhood BMI played a pivotal role in the pathway from early-life adversity to later inflammation. This pathway was specific to serious interpersonal conflict stress, but not to serious financial stress or maternal depression. It was associated with the latent intercept and slope of BMI, and indirectly associated with adolescent inflammation through the latent intercept and slope of BMI. These associations were independent of participants' current SES, current stress, age, and gender. Depressive symptoms were not found to be associated with increased inflammation in adolescence either directly or indirectly through BMI in adolescence. This study adds to the current literature with a large longitudinal cohort of low- and middle-income Chilean adolescents with repeated measures of adversity, adiposity, and depressive symptoms from infancy to late adolescence. The use of longitudinal modeling permitted us to examine early life course trajectories of BMI regardless of missing data, varying ages at measurement, and numbers of measurements in children.

[1] As the temporal association between hsCRP and concurrent BMI at 16y was strong, we conducted a follow-up linear regression analysis, with hsCRP predicted by change in BMI and BMI at 16. This analysis found that BMI at 16y (Beta = −0.462, $P < .001$), not the change of BMI over childhood (Beta = −0.023, n.s.), was significantly associated with hsCRP ($R^2 = 0.10$). However, as both the slope and the intercept of BMI were associated with increased hsCRP, and BMI at 16y is a function of BMI at 5y and 10y, we have kept the linear growth curve model in our discussion of results.

Table 1
Sample Characteristics. Mean (SD) Is Presented, Unless Noted.

	N	Mean or *n*	SD or %
Sex, female, *n* (%)	600	289	48.2%
Maternal education (years)	567	9.58	2.507
Paternal education (years)	567	9.84	2.618
Maternal age (years)	566	26.2789	6.06074
Maternal BMI	503	29.10	5.2
Iron supplemented status, *n* (%)	500	331	55.2%
Infancy Wave			
Age at assessment (months)	598	12.25	0.4
BMI for age, z-score	526	0.79	0.9
SES[1]	598	27.02	6.3
Maternal CES-D score	329	15.52	12.2
Interpersonal conflict stress sum score	307	0.60	0.8
Financial stress sum score	308	1.55	1.3
Five Year Wave			
Age at assessment (years)	597	5.51	0.0
BMI for age, z-score	599	1.02	1.2
SES	594	35.98	7.7
Maternal CES-D score	595	19.40	13.4
Interpersonal conflict stress sum score	447	0.71	0.8
Financial stress sum score	447	1.99	1.4
CABI depressive symptoms score	592	9.53	2.7
Ten Year Wave			
Age at assessment (years)	528	10.03	0.1
BMI for age, z-score	529	1.09	1.2
SES	514	33.91	7.3
Maternal CES-D score	524	17.41	13.0
Interpersonal conflict stress sum score	522	0.61	0.8
Financial stress sum score	522	1.84	1.5
CBCL depressive symptoms total score	527	1.94	1.6
Adolescent Wave			
Age at assessment (years)	600	16.83	0.3
BMI for age, z-score	600	0.65	1.2
SES	537	33.49	6.8
Maternal CES-D score	461	18.95	14.2
Interpersonal conflict stress sum score	470	0.56	0.8
Financial stress sum score	472	1.82	1.4
Used tobacco in the past 30 days, *n* (%)	563	105	18.7%
Used alcohol in the past 30 days, *n* (%)	561	117	20.9%
Diet quality	599	5.22	1.2
CBCL depressive symptoms total score (YSR)	567	6.07	3.7
CBCL depressive symptoms total score (parent report)	475	4.69	3.7
hsCRP	600	1.02	1.6
Average MVPA per day (minutes)	183	50.9	24.9
Pubertal Stage	252		
Tanner Stage 3		17	6.7%
Tanner Stage 4		133	52.8%
Tanner Stage 5		102	17%

[1]SES indexed by Graffar.
[2]Z-score calculated with CDC references for age and sex.
Abbreviations: Body mass index, BMI; socioeconomic status, SES; center for epidemiological studies depression scale, CES-D; children's adaptive behavior inventory, CABI; child behavior checklist, CBCL; youth self-report, YSR; High sensitivity c-reactive protein, hsCRP; MVPA, moderate to vigorous physical activity.

4.1. Early high BMI and inflammation

Our findings of pathways from both early BMI and the growth trajectory of BMI to inflammation are consistent with a number of health

Table 2
Zero-Order Correlations Among Observed Variables.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Ln CRP	–	0.02	−0.025	0.014	0.016	0.044	0.02	0.053	0.029	0.069	0.028	0.027	0.039	−0.038	0.012	0.001
2	CABI depressed − 5y		–	0.319**	0.046	0.263**	0.037	0.034	0.049	0.037	0.114*	0.183**	0.102*	0.153**	0.114*	0.300**	0.232**
3	CBCL Depressive Problems − 10y			–	0.153**	0.352**	0.071	−0.002	0.099*	0.105*	0.083	0.190**	0.167**	0.132**	0.087	0.224**	0.347**
4	Adol. Depressive Problems (YSR)				–	0.311**	0.107	0.107*	0.139**	0.112*	0.056	0.111*	0.126**	0.100*	0.182**	0.144**	0.186**
5	Adol. Depressive Problems (Parent)					–	0.015	0.094	0.170**	0.163**	0.09	0.319**	0.197**	0.306**	0.259**	0.337**	0.391**
6	Financial Stress − 1y						–	0.290**	0.230**	0.187**	0.231**	0.256**	0.102	0.051	0.141*	0.114*	0.022
7	Financial Stress − 5y							–	0.290**	0.316**	0.109	0.253**	0.132**	0.027	0.133	0.290**	0.141**
8	Financial Stress − 10y								–	0.341**	0.181**	0.135**	0.093*	0.116*	0.097	0.179**	0.244**
9	Financial Stress - Adol.									–	0.028	0.158**	0.175**	0.198**	0.138*	0.134**	0.213**
10	Interpersonal Conflict Stress − 1y										–	0.279**	0.234**	0.230**	0.242**	0.227**	0.203**
11	Interpersonal Conflict Stress − 5y											–	0.309**	0.275**	0.229**	0.453**	0.331**
12	Interpersonal Conflict Stress − 10y												–	0.214**	0.181**	0.235**	0.371**
13	Interpersonal Conflict Stress - Adol.													–	0.153*	0.221**	0.266**
14	CESD − 1y														–	0.352**	0.417**
15	CESD − 5y															–	0.462**
16	CESD − 10y																–
17	CESD - Adol.																
18	SES Graffar − 1y																
19	SES Graffar − 5y																
20	SES Graffar − 10y																
21	SES Graffar - Adol.																
22	BMI z-score − 5y																
23	BMI z-score − 10y																
24	BMI z-score - Adol.																
25	Maternal BMI − 1y																
26	Sex																
27	Age at Adolescent Blood Draw																
28	Diet Quality																
29	Cigarette use - Adol.																
30	Alcohol Use - Adol.																
31	Tanner Stage - Adol.																
32	Physical Acitivty (MVPA/day) - Adol																

		17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
1	Ln CRP	0.086	−0.021	−0.006	−0.056	0.019	0.187**	0.216**	0.317**	0.052	0.071	0.088*	0.002	0.03	−0.029	0.033	−0.148*
2	CABI depressed − 5y	0.253**	0.125**	0.159**	0.137**	0.094*	−0.014	−0.014	0.022	−0.041	−0.013	0.03	−0.064	−0.096*	−0.064	−0.128*	−0.072
3	CBCL Depressive Problems − 10y	0.281**	0.023	0.097*	0.108*	0.062	0.121**	0.077	0.076	−0.099*	0.033	0.058	−0.028	0.007	−0.034	−0.099	0.038
4	Adol. Depressive Problems (YSR)	0.219**	0.062	0.129**	0.110*	0.132**	0.019	0.02	0.111**	0.098*	0.216**	0.114**	−0.160**	0.178**	0.086*	0.042	−0.11
5	Adol. Depressive Problems (Parent)	0.451**	0.048	0.079	0.131**	0.148**	0.086	0.037	0.126**	0.094	0.069	0.047	−0.152**	0.156**	0.119**	0.041	−0.061
6	Financial Stress − 1y	0.105	0.185**	0.270**	0.253**	0.172**	0	0.026	0.075	0.074	−0.086	−0.085	−0.169**	0.092	0.077	−0.114	0.09
7	Financial Stress − 5y	0.136*	0.116*	0.210**	0.241**	0.169**	−0.012	−0.036	0.116*	0.114*	0.052	0.022	−0.138**	0.103*	0.038	−0.072	0.029
8	Financial Stress − 10y	0.199**	0.068	0.191**	0.259**	0.214**	0.046	−0.009	0.036	0.034	0.021	0.009	−0.142**	0.048	0.01	−0.007	0.108
9	Financial Stress - Adol.	0.247**	0.013	0.178**	0.216**	0.157**	0.058	0.051	0.093*	0.095	0.064	0.008	−0.009	0.029	0.059	−0.027	−0.053
10	Interpersonal Conflict Stress − 1y	0.228**	0.118*	0.032	0.001	−0.055	0.073	0.136*	0.155**	−0.028	0.008	−0.044	−0.077	0.131*	0.001	−0.009	0.122
11	Interpersonal Conflict Stress − 5y	0.290**	−0.025	0.123**	0.117*	0.141**	0.043	0.028	0.104*	0.054	−0.017	0.082	−0.059	0.041	0.058	−0.118	0.019

(*continued on next page*)

Table 2 (*continued*)

		17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
12	Interpersonal Conflict Stress − 10y	0.229**	−0.057	0.054	0.092*	0.100*	0.051	0.081	0.095*	−0.049	−0.056	0.012	−0.036	−0.018	−0.011	0.095	0.028
13	Interpersonal Conflict Stress - Adol.	0.389**	−0.026	0.031	0.062	0.082	−0.012	−0.035	0.042	−0.064	−0.053	0.04	−0.077	−0.009	0.028	0.054	−0.017
14	CESD − 1y	0.348**	0.102	0.044	0.133*	0.153**	0.041	0.007	−0.006	−0.075	−0.038	0.048	−0.186**	0.196**	0.031	−0.033	0.211*
15	CESD − 5y	0.451**	−0.012	0.077	0.088*	0.098*	−0.027	−0.056	0.014	−0.003	0.002	−0.013	−0.112**	0.03	−0.001	−0.032	−0.065
16	CESD − 10y	0.506**	−0.038	0.099*	0.175**	0.160**	−0.013	−0.014	0.011	−0.077	−0.025	0.075	−0.101*	0.053	0.041	−0.001	0.039
17	CESD - Adol.	_	0.057	0.118*	0.111*	0.138**	−0.019	−0.061	0.071	−0.023	0.05	0.038	−0.177**	0.099*	0.03	−0.065	−0.177*
18	SES Graffar − 1y		_	0.242**	0.237**	0.200**	0.003	0.007	−0.022	0.096*	0.009	−0.047	−0.087*	0.011	−0.048	−0.130*	−0.044
19	SES Graffar − 5y			_	0.608**	0.546**	−0.01	0.019	−0.029	0.037	0.082*	0	−0.156**	0.031	−0.079	−0.059	−0.094
20	SES Graffar − 10y				_	0.667**	−0.019	−0.029	−0.021	0.044	0.015	−0.043	−0.113*	0.015	−0.04	−0.027	−0.065
21	SES Graffar - Adol.					_	−0.051	−0.039	−0.04	0.04	−0.004	−0.019	−0.078	0.027	−0.099*	0.043	0.064
22	BMI z-score − 5y						_	0.792**	0.547**	0.205**	0.012	−0.006	0.036	0.093*	0.001	0.128*	−0.1
23	BMI z-score − 10y							_	0.641**	0.217**	−0.053	−0.014	0.006	0.062	0.06	0.191**	−0.03
24	BMI z-score - Adol.								_	0.293**	0.081*	0.026	−0.019	0.032	0.001	0.181**	−0.075
25	Maternal BMI − 1y									_	0.025	0.011	0.03	0.056	0.03	−0.005	−0.018
26	Sex										_	0.080*	0.036	0.086*	−0.141**	.c	−0.502**
27	Age at Adolescent Blood Draw											_	0.011	0.085*	0.095*	0.07	−0.154*
28	Diet Quality												_	−0.125**	−0.015	0.1	−0.091
29	Cigarette use - Adol.													_	0.421**	−0.068	0.142**
30	Alcohol Use - Adol.														_	−0.003	0.192**
31	Tanner Stage - Adol.															_	0.084
32	Physical Acitivty (MVPA/day) - Adol																_

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Note: Ln = natural log.

studies on childhood obesity. Many studies have found that obesity early in childhood is linked to obesity later in childhood, adolescence, and adulthood (de Onis et al., 2010; Evensen et al., 2016; Han et al., 2010; Kumar and Kelly, 2017). As noted above, obesity is a known inflammatory condition and adipose tissue is a key regulator of circulating inflammatory markers in the body (Tilg and Moschen, 2006). In this study, the intercept and slope of the BMI trajectory throughout childhood and adolescence was the sole mediator of relationships between early life adversity and inflammation. Importantly, we also found that the intercept of BMI (measured at 5y) was positively associated with hsCRP in adolescence in addition to the slope of BMI over childhood, suggesting that both early BMI and growth of BMI (which is more temporally relevant) play important roles in the relationship between BMI and inflammation.

4.2. Interpersonal conflict stress, BMI, and inflammation

This study found that interpersonal conflict stress – but not financial stress - in infancy was indirectly associated with increased CRP through the growth of BMI over the course of childhood and adolescence. Our finding that early life interpersonal stress was related to inflammation through the pathway of BMI is similar to other papers that found that BMI was a critical mediating pathway from early life adversity to later inflammation (Chiang et al., 2017; Hostinar et al., 2015). In a cross-sectional study of adults aged 32 to 47 years, BMI was found to partially mediate the relationship between a harsh early childhood environment, psychological functioning and hsCRP (Taylor et al., 2006). As in that study, we found that the pathway from BMI to hsCRP was stronger than the pathways from psychosocial functioning to hsCRP.

Why interpersonal conflict stress and not other forms of early adversity was related to increased BMI and inflammation remains an open question. One explanation might be due to the measure itself: the social nature of interpersonal conflict stress might be especially potent as a psychosocial stressor in the family environment. In a systematic review, multiple studies showed that high levels of family conflict were associated with an increased risk obesity in adolescence and childhood (Halliday et al., 2014). Households with more family conflict were found to increase a child's risk of being overweight (Kitzmann et al., 2008). Previous research has found that infants are attuned and responsive to their mothers' stress response and cortisol levels (Laurent et al., 2011, 2012). Given the close relationship between infants and mothers, this context of family conflict and psychosocial stress may be especially important for how stress acts on the infant's physiology to impact inflammation. Chronic activations of the HPA-axis and the resulting physiological reactions are associated with metabolic changes that are linked to weight gain in children (Maiemi et al., 2002; Siervo et al., 2009). Additional contributing factors to the pathway between early life adversity and BMI include stress-mediating epigenetic and inflammatory processes that become dysregulated after early life adversity. For example, epigenetic changes such as DNA methylation at the glucocorticoid receptor gene promotor in the hippocampus are proposed as a mechanism for how early life adversity can become biologically "embedded" to influence behaviors, endocrine responses to stress, and the development of obesity (Meaney and Szyf, 2005; Szyf and Bick, 2013). Alternatively, the neuroimmune network hypothesis proposes that early-life stress instigates crosstalk between the neural and immune systems to create a loop of elevated threat sensitivity, inflammation, and unhealthy behaviors that result in increased risk for obesity (Nusslock and Miller, 2016). Any of these processes may have latent impacts on a developing individual.

Behaviorally, stress-induced over-eating behavior over the course of childhood might also be a contributing factor to the pathway between early life adversity and BMI. Children's stress has been linked with emotional eating and unhealthy dietary patterns (Michels et al., 2012), and early adversity could increase the risk for school-aged children to engage in stress-induced eating behaviors that contribute to increased

BMI and ultimately increased inflammation in adolescence. Stress-induced over-eating has been experimentally manipulated in animal models of early life adversity and observed in adults (Dallman, 2010; Dallman et al., 2005; Michopoulos et al., 2012). However, it is important to note that stress can influence eating behavior by contributing to both under-eating and over-eating (Stone and Brownell, 1994; Dallman et al., 2003). Research on the relations between childhood adversity and decreased levels of self-control could explain why our study found an association between early life interpersonal conflict stress and the increased trajectory of BMI over childhood and adolescence (Evans et al., 2012; Hostinar et al., 2015). As children age, food choices could become more dependent on the child's own self-control and impulsivity. A study about food advertisement and preferences in Chile showed that French fries, sweet and salty snacks, soft drinks and fast foods were the products most often remembered and purchased by school-aged children (Olivares et al., 2004). These results suggest that once children have more control over their food choices, they might be more likely to choose unhealthy foods and this choice could be especially impactful for children with a history of early life adversity.

4.3. Severe financial stress, BMI, and inflammation

Severe financial stress in this context was not associated with either increased childhood BMI or increased CRP. This was surprising, as socioeconomic disadvantage has been found to be associated with CRP levels and increased BMI as discussed previously. Although we hypothesized that financial stress in the family would be associated with both BMI and inflammation, perhaps financial stress was not as proximal of a stressor in these participants in infancy. One study did find that family financial stress was positively associated with overweight and obesity status in older children (12–17 years), but not younger children (Garasky et al., 2009), supporting the idea that, for certain populations, financial stress might be less salient for younger children and infants. In this study, financial stress was used as an indicator of socioeconomic disadvantage in order to increase sample variability as all participants were recruited from low- and middle-income families. Therefore, without high-income families, the surprising lack of association could be due to an absence of enough variability in socioeconomic status in the sample. Finally, this study has the strength of longitudinal measures of both interpersonal and financial stress. In studies that have found the association between financial stress and child adiposity, interpersonal stress could have driven some of the associations as interpersonal and financial stress are likely correlated but, unlike the current study, are infrequently measured together.

4.4. Maternal depressive symptoms, BMI, and inflammation

Interestingly, and contrary to our hypotheses, maternal depressive symptoms in infancy were also not associated with increased CRP or increased BMI growth over time. Instead, maternal depressive symptoms in infancy were negatively associated with BMI growth over time. In this context, interpersonal conflict stress might be more salient in terms of activating an infant's stress response and influencing later adiposity and inflammation. Though a systematic review of maternal depression and child BMI found that only half of the studies found a positive association between maternal depression and increased BMI (Lampard et al., 2014), there studies in Latino-American and South American populations, find no link between maternal depression in infancy and increased risk for overweight. Similar to our results, a study in Latino mothers and infants found that chronic maternal depression was actually associated with a decreased risk for overweight in the child's first two years of life (Wojcicki et al., 2011). Another study in Brazil found that maternal depression in infancy (12 and 24 months) was also not associated with increased risk for overweight when the children were 4 years old (Santos et al., 2010).

The measure of maternal depressive symptoms might also not adequately capture levels of family stress that would be proximal and relevant for infants in our study. First, many women (43%) met the cutoff for the CES-D depressive symptoms when their child was an infant and therefore this measure might differentiate adverse caregiving in this sample. This prevalence of depressive symptoms has been documented before among lower SES mothers in Chile: prevalence rates of up to 50% have been reported in mothers with infants aged 3 to 6 months (Póo et al., 2008; Wolf et al., 2002). Relatedly, maternal depressive symptoms were collected only a few years after the fall of the Chilean military junta regime, where government-enforced violence reached high levels (National Research Council, 1985). To our knowledge, no studies have examined how this time period impacted prevalence rates of maternal depression, though one empirical study found that the sociopolitical violence experienced by pregnant women during this time was associated with a five-fold increase in pregnancy complications (Zapata et al., 1992). Given the widespread sociopolitical violence in Santiago in the years immediately preceding the start of this study, perhaps a measure of maternal depressive symptoms does not adequately capture psychosocial adversity that would be relevant to increasing levels of later BMI and inflammation. Alternatively, maternal depressive symptoms might be a more salient stressor and influence on child adiposity and inflammation later in childhood. In sum, interpersonal conflict stress in infancy might have been salient with regards to increasing BMI in this sample of infants than either financial stress or maternal depression.

4.5. Depressive symptoms and inflammation

We did not find an association between early life adversity or depressive symptoms and a marker of inflammation in adolescence. In contrast, studies of adults with retrospective reporting of early life adversity have found associations between early life adversity, depression and inflammation (Danese et al., 2008; Pace et al., 2012). It is possible that inflammation develops over a longer period of time (Slopen et al., 2012). Another possibility is that inflammation is related to more severe early life adversity. Prior adolescent studies that have found relationships between depression and inflammation in adolescence focused specifically on prior maltreatment or victimization as early life adversity (Miller and Cole, 2012; Slopen et al., 2013). We did not measure maltreatment, though family conflict is often related to maltreatment (Black et al., 2001; Pittman and Buckley, 2006). It is also possible that a growth curve model of depressive symptoms over childhood and early adolescence would lend more clarity to the associations between childhood depressive symptoms and inflammation in adolescence. However, as our measures of depressive symptoms changed over the course of the study, we were unable to test such a growth curve model. Additionally, our data included depressive symptoms in youth but not a clinical depression diagnosis. Severity or specific depressive etiology may be linked to inflammation (Danese et al., 2008). Though our study did not have diagnosis of clinical depression in youth, we controlled for maternal depressive symptoms in our examination of early life adversity and depression. Further, we used both youth self-report and parent-report measures of depressive symptoms in our model of depressive symptoms in adolescence to reduce reporter bias.

4.6. Limitations

The first study limitation is that inflammation was measured at only one time point in adolescence. Importantly, increased levels of hsCRP are not necessarily limited to adolescence, and may be present if inflammation was assessed at younger ages. Future studies would benefit from longitudinal measurements of inflammation and considerations of genetic factors. hsCRP is known to show genetic variability, estimated to account for 13% to 30% of the within-subjects variability (Pankow et al., 2001). While we were able to explain a statistically significant

proportion of variability in hsCRP, the residual variance suggested that other mediators (physical environment, air pollution) and moderators (genetic liabilities) should be considered in future research. Furthermore, hsCRP is one measure of inflammation, and both its relationship to disease and how it functions within a developing child are not fully understood. Furthermore, although this study demonstrates that BMI is a critical driver of increased hsCRP levels, the causal relationships between BMI, depression, and inflammation in adolescence still needs to be determined. Other inflammatory markers and indicators of immune system function could help future research elucidate the relationships between early life adversity, depression, and obesity.

While results in this cohort of Chilean youth from low- and middle-income families may not generalize to other populations, it is a strength that we see replicated pathways that have previously been reported in US or EU samples. This is noteworthy due to the special context in Chile between the beginning of the study in 1991 and adolescent assessments. During this time, Chile experienced a fast-growing economy and significant poverty reduction and moved from a low-income to a high-income country (Bank, 2018). The rapidly changing food and physical activity environment contributed to increasing overweight and obesity rates between 1987 and 2000 (Albala et al., 2001; Vio et al., 2008). During this nutrition transition across low- and middle-income countries, Chile and other Latin American countries have exhibited some of the highest prevalence of overweight in children under 5 years of age (de Onis et al., 2010). The study of a population affected by an economic transition provides a unique contribution in understanding pathways of early life adversity, obesity, and inflammation, as rapidly developing low- and middle-income countries are challenged with emerging epidemics of obesity and psychopathology (Black et al., 2017; de Onis et al., 2010; Kieling et al., 2011; Lund et al., 2010).

4.7. Conclusions

This study found that early life adversity in the form of interpersonal conflict stress in infancy was indirectly associated with inflammation in late adolescence (16–18 y) through the growth trajectory of childhood BMI. This study found that, in this cohort of Chilean adolescents, childhood depressive symptoms were not associated with inflammation in adolescence or through childhood BMI. This study also found that an increasing growth curve trajectory of childhood BMI and higher BMI at 5 years of age were both strongly associated with inflammation in adolescence. Understanding how early life adversity impacts later psychosocial and physical functioning through pathways of obesity is of critical importance, as estimates indicate that 43% of children under 5 years in low- and middle-income countries − 250 million children - are at risk of growing up with varying degrees of health problems due to a combination of psychosocial adversity and under- and over-nutrition (Black et al., 2017). This study provides preliminary evidence for the multiple pathways that must be studied when examining early life adversity and later inflammatory outcomes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2019.06.003.

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