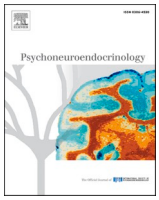
Psychoneuroendocrinology 172 (2025) 107276

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



# Linking childhood allostatic load, early adversity and the emergence of mental health symptoms in early adulthood: Analysis of the ALSPAC longitudinal birth cohort

Sabine Finlay [a,b], Oyelola Adegboye [c], Brett McDermott [d,e], Donna Rudd [b], Zoltán Sarnyai [a,b,*]

[a] Laboratory of Psychiatric Neuroscience, Australian Institute of Tropical Health and Medicine, James Cook University, Townsville, Queensland, Australia
[b] College of Medicine and Dentistry, James Cook University, Queensland, Australia
[c] Menzies, School of Health Research, Charles Darwin University, Casuarina, Northern Territory, Australia
[d] Child and Adolescent Mental Health Service, Hobart, Tasmania, Australia
[e] Tasmanian Centre for Mental Health Service Innovation, Hobart, Tasmania, Australia

ARTICLE INFO

*Keywords:*
Allostatic load
Psychiatric symptoms
Adverse childhood experiences
ALSPAC

ABSTRACT

*Background:* It has been well-established that the allostatic load (AL) index, a cumulative score of multi-system dysregulation in response to chronic stress, is significantly increased at the time of a psychiatric diagnosis. However, no studies have investigated if there is an association between the AL index in childhood and the later development of mental health symptoms in young adults.

*Methods:* Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population cohort from Bristol, United Kingdom, we investigated the AL index at age 9 years and the risks for mental health symptoms at age 24 years. We used multinomial logistic regression analysis to investigate the association between AL threshold (categorised into bottom third: AL index $\leq 7$, middle third: AL index $= 7.1$–$9.9$, and top third: AL index $\geq 10$) and mental health symptoms while adjusting for sex, the age of mother at delivery, and social class. We used a relative risk ratio (RRR) and 95 % confidence interval(CI) for each variable. We further investigated the association between adverse childhood experiences (ACEs) and mental health symptoms.

*Results:* We identified a significant association between sex and mental health symptoms, with more females (59 % vs 41 %) showing mental health symptoms than males. We found no direct association between the AL index at age 9 and the later development of mental health symptoms. However, an RRR analysis showed that individuals in the middle and the top third of the AL index had an RRR of 1.99 and 2.20, respectively, to develop mental health symptoms if they were females. We found that individuals who experienced ACE had a much higher risk of developing mental health symptoms as young adults, with the adjusted RRR of 5.39 (95 % CI: 3.00;9.67), 6.79 (95 % CI: 2.55; 18.1), and 2.10 (95 % CI: 0.37;11.8) for neglect, physical and sexual abuse, respectively, in individuals with mood disorder symptoms. The adjusted RRR for neglect and physical and sexual abuse in individuals with psychotic symptoms was 0.99 (95 % CI: 0.37; 2.59), 2.92 (95 % CI: 0.35; 24.4), and 10.5 (95 % CI: 0.99; 112), respectively.

*Conclusion:* Although the AL index in childhood was not directly associated with the later development of psychotic and mood disorder symptoms in this cohort, females in the higher tertiles of the AL index measured at 9 years of age had an elevated risk of mental health symptoms as young adults. In line with previous work, a strong association was identified between childhood adversity and mental health symptoms in young adulthood. These results highlight the importance of considering the impact of early stress on biological embedding and the later emergence of mental health problems, especially in females.

## 1. Introduction

Recent evidence indicates the decline of mental health in young adults in many countries over the past two decades (McGorry et al., 2024). The median age of onset of mental health disorders is around the time of adolescence and early adulthood (Solmi et al., 2022). A

* Correspondence to: College of Medicine and Dentistry, James Cook University, 1 James Cook Drive, Townsville, Queensland 4811, Australia.
*E-mail address:* zoltan.sarnyai@jcu.edu.au (Z. Sarnyai).

https://doi.org/10.1016/j.psyneuen.2024.107276
Received 15 October 2024; Received in revised form 28 November 2024; Accepted 29 December 2024
Available online 31 December 2024

considerable two to three-fold rise in mental health disorders was found in adolescents in the U.S. over the last twenty years (Merikangas et al., 2010). The role of chronic stress and trauma as contributing factors in the pathophysiology of psychiatric disorders has been a focus in recent years (Nugent et al., 2015). Exposure to chronic stress precedes disease onset, exacerbates symptoms, and results in poorer treatment response (Garner et al., 2011; Nugent et al., 2015). Proposed antecedent events and contributing factors to the increased rates of mental health disorders in children and young adults include trauma, discrimination, financial burden, adverse childhood experiences, and other environmental factors (McEwen, 2003; Varese et al., 2012), all resulting in acute and subsequent chronic, toxic stress resulting in multi-system physiological changes systemically and in the brain (McEwen, 2017).

In 1988, Sterling introduced the term *allostasis* referring to "maintaining stability (or homeostasis) through change" (Sterling, 1988). It was originally used to explain how the cardiovascular system adjusts to different states of the body (rest or active), but later, this adjustment was applied to other physiological mediators, such as the neuroendocrine system secreting cortisol and catecholamines, resulting in the concept of "allostatic load" (AL). The AL concept explains the chronic wear and tear that the body experiences due to repeated attempts to maintain allostasis (McEwen, 1998). A continuous activation (due to a stressful event or inability to shut off over-active physiological systems) of primary stress mediators with profound biological effects, such as cortisol, catecholamines, and interleukin-6 (IL-6) can result in the "secondary outcome", a process that reflects the cumulative outcome of the primary effect in the body, such as elevated blood pressure. These secondary mediators, such as C-reactive protein (CRP), fibrinogen, cholesterol, and insulin, contribute to the tertiary outcome, the development of physical disease or mental health disorder (McEwen, 1998). A quantitative measure of multi-system dysregulation, the AL index, was developed to capture the different biological responses related to stress exposure by giving each biomarker a score. It is a combined score across several biological measures and has been found to predict various health outcomes (Juster et al., 2010).

As the pathophysiology of mental health disorders (both psychotic and mood disorders) is complex and multisystemic (Pillinger et al., 2017), with the considerable contribution of chronic stress and trauma, the AL concept has gained increased attention in psychiatry in recent years. Several studies have used the AL index to investigate the links between this and psychotic disorders. The results from these studies indicated that patients with psychotic disorders, such as schizophrenia, psychosis, and bipolar disorder with psychotic features had elevated AL index at the time of the first symptom presentation or during the chronic illness (Greenhalgh et al., 2017; Miller et al., 2013). However, the AL index in childhood, before the emergence of mental health symptoms, and its relationship with the later development of mental health symptoms has not been studied.

Adverse Childhood Experiences (ACEs) have been defined as potentially traumatic events, which include neglect and physical and sexual abuse, that are known to increase the risk of poor health outcomes later in life (Boullier and Blair, 2018; Finlay, Roth, et al., 2022). There is increasing evidence showing that chronic, toxic stress and ACEs can result in permanent damage to the developing brain and an increased risk for the development of mental health symptoms and disorders (Fuller-Thomson et al., 2016; Merrick et al., 2017).

To date, no studies have investigated the potential link between multi-system dysregulation as measured by the AL index in childhood and the development of mental health symptoms—both psychotic and mood disorders symptoms—individually and combined in young adulthood. Additionally, the association between ACEs, such as neglect, physical and sexual abuse, with mental health symptoms at age 24 years old and AL load at 9 years remains unexplored. To address this, we utilised the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, a unique longitudinal dataset containing data on AL biomarkers, ACEs in childhood, and mental health symptoms in young adulthood, to investigate the potential link between multi-system dysregulation, as measured by the AL index in childhood, and the development of mental health symptoms in young adulthood. Our analysis also considered the influence of factors such as social class (based on the mother's occupation), the mother's age at delivery, and sex.

## 2. Methods

### 2.1. Description of cohort and sample selection

The ALSPAC birth cohort consists of births from mothers residing in or around the City of Bristol, United Kingdom, with expected delivery dates from the 1st of April 1991 to the 31st of December 1992 (Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2019). The enrolled participants and their children have been followed continuously since the study's inception and continue to be monitored today. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bristol (Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. The full cohort details appear elsewhere (Finlay et al., 2023). Our sample consisted of participants with AL biomarkers at age nine and whether they developed psychotic and/or mood disorder symptoms at ages 17–24 years old or not. Our cohort included 593 participants who were grouped into the "healthy controls" (n = 490) for those without any psychiatric symptoms and the "cases" (n = 103) group for individuals who showed either psychotic or mood disorder symptoms, or both, as young adults.

### 2.2. Allostatic load

For this study, we utilised data from individuals with more than 16 biomarkers representing multiple biological systems, including cardiovascular, immune, neuroendocrine, and metabolic systems. For detailed information on biomarker measurements, collection, and assay procedures, please refer to Finlay et al. (2023). Briefly, to calculate the AL index, we considered systolic and diastolic blood pressure and heart rate for cardiovascular functioning. Immune system dysregulation was assessed using CRP, IL-6, and albumin. Indicators of neuroendocrine stress biology included cortisol and dehydroepiandrosterone sulfate (DHEA-S). Lastly, metabolic regulation was represented by cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, very-low-density lipoprotein (VLDL), glucose, glycosylated hemoglobin (HbA1c), insulin, adiponectin, and body mass index (BMI).

The AL index was calculated at the age of 9 years old using two different approaches: The first method scores each biomarker using quartiles (i.e., upper or lower quartiles depending on whether low or high values confer a greater risk for health). For all participants, each biomarker was then assigned a score of 0 (normal value) or 1 (either above the 75th percentile or below the 25th percentile), depending on the biomarker's risk ranking. The 25th and 75th percentile were determined based on the control data distribution (participants who did not display psychiatric symptoms). Scores were then summed together across all biomarkers for a total score ranging from 0 to 18. Higher AL total scores indicate more profound physiological dysregulation. The second method involves categorising participants into groups based on the sample distribution of the AL index. Participants are divided into tertile groups (top, middle, and bottom tertile) based on their scores, creating a distinct group based on the **sample** AL threshold.

### 2.3. Psychiatric assessment

#### 2.3.1. Psychotic symptoms

Psychotic symptoms were assessed using the survey item "met diagnosis for psychotic disorder" with a dichotomous answer (yes/no) at the age of 17 years old. Psychotic symptoms were assessed using the

survey item "psychotic symptoms (ever)" with a dichotomous answer (yes/no) at the age of 24 years old. Psychosis-Like Symptom Interview (PLIKSi)(Fonville et al., 2015) was conducted by trained psychology graduates in assessment clinics and was coded according to the definitions and rating rules for the Schedules for Clinical Assessment in Neuropsychiatry. Psychotic experiences (PEs) covered the three main domains of positive psychotic symptoms: hallucinations (visual and auditory), delusions (spied on, persecuted, thoughts read, reference, control, and grandiosity), and thought interference (insertion, withdrawal, and broadcasting). After cross-questioning, interviewers rated PEs as *not present*, *suspected*, or *definitely present*. Cases of PEs in this study were defined only as individuals with *definite* PEs. Schizophrenia were assessed using the survey item "ever been diagnosed with schizophrenia" with a dichotomous answer (yes/no) at age 22 years old.

#### 2.3.2. Mood disorder and symptoms

Mood disorder was assessed at the age of 17 years using The Clinical Interview Schedule-Revised (CIS-R). The CIS-R is a structured interview for the measurement and diagnosis of non-psychotic psychiatric morbidity (Lewis et al., 1992). The scale used by ALSPAC was from 0 to 4; 0 = not present, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe. Depression was assessed using the survey item "ever been diagnosed with depression" at the age of 22 years old, with a dichotomous (yes/no) answer. Bipolar disorder was assessed using the survey item "ever been diagnosed with bipolar disorder" with a dichotomous answer (yes/no) at age 22 years old.

Individuals were considered a "case" if they had any positive screen of the questionnaires mentioned above (both psychotic and mood disorder symptoms) before the age of 25 years old.

### 2.4. Adverse childhood experiences

Adverse childhood experiences were assessed at age 11 when the children were allowed to answer themselves. ACEs included childhood neglect, childhood physical abuse, and childhood sexual abuse (Finlay et al., 2023). Childhood neglect was assessed with the questions: "*Frequency adults in the family shouted at the respondent before the age of 11*" and "*Frequency adults in the family said hurtful or insulting things to the respondent before the age of 11*". The answers were based on a scale of 1–5; 1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = very often. Childhood physical abuse was assessed with the questions: *"Frequency adults in the family actually kicked, punched, or hit respondent with something that could hurt respondent or physically attacked respondent in another way before age of 11"*, and "*frequency of adults in the family hit respondent so hard it left bruises or marks before the age of 11*". The answers were based on a scale of 1–5; 1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = very often. Childhood sexual abuse was assessed with the questions: "*Respondent was touched in a sexual way by an adult or older child or was forced to touch adult or older child in a sexual way, before age of 11*" and "*adult or older child forced or attempted to force, respondent into any sexual activity by threatening or holding respondent down or hurting respondent in some way, before the age of 11*", rated on the scale 1–3; 1 = no, this did not happen before 11, 2 = yes, this happened once, 3 = yes, this happened more than once.

We created a binary score (yes/no) across the ACE questionnaires based on whether an individual scored ≥ 2 (yes) on any of the questions mentioned above at the age of 11 years old or if an individual scored 1 (no) on all the questions.

### 2.5. Confounders

The sex of the participants, the mother's age at delivery, and the mother's occupation (or social class) were identified as possible confounders. Sex was recorded at birth and treated as a binary variable (male or female). The mother's occupation was recorded at birth using the UK Office of National Statistics' socioeconomic classification system (Class I = professional; Class II = managerial and technical workers; IIIa = skilled non-manual occupations; IIIb = skilled manual occupations; IV = partly skilled occupations; V = unskilled occupations). This will be referred to as "social class" from this point.

### 2.6. Statistical analysis

All analyses were performed using SPSS v23 and *R version 4.0.3*. Descriptive analysis was performed and stratified by "mental health symptoms". The differences in prevalence between categorical variables were tested using chi-square tests. In contrast, differences in prevalence between several independent groups were tested appropriately using analysis of variance (ANOVA) or the Kruskal-Wallis test. The sample was divided into thirds according to tertiles of AL distribution in the entire sample group at age 9. The participants were categorised into groups based on the AL threshold: bottom third (AL index ≤ 7), middle third (AL index = 7.1 – 9.9) and top third (AL index: ≥ 10). Imputation was performed using the package MICE in *R,* indicating no difference in results after imputation.

We employed multinomial log-linear models to investigate the risk of different thresholds of AL. The results were presented as relative risk ratios (RRR) and corresponding 95 % confidence intervals (CIs). The models were adjusted for potential confounders, including sex and social class. To calculate RRR, the reference category was defined as participants within the bottom third of the distribution, representing the lowest AL.

## 3. Results

### 3.1. Allostatic load index at age 9 and mental health symptoms at age 24

#### 3.1.1. Descriptive statistics

Of the 593 individuals that were included in this analysis, 103 individuals had mental health symptoms at the age of 24 years old (17.3 %). A summary of participants' descriptive statistics for both

**Table 1**
Participants' descriptive statistics for the total sample and stratified by outcome (controls and cases). Pearson's Chi-squared test was used to calculate the p-value for the number of biomarkers in healthy controls vs. cases. Significance (p-value <=0.05) was highlighted. The exact numbers (and percentages) for Class I and V are not presented due to small sample sizes. Missing sex data = 2.

| | Total sample | Controls | Cases | *p-value* |
|---|---|---|---|---|
| **Total number, n** | 593 | 490 | 103 | |
| **Sex** | | | | **0.004** |
| Male, n (%) | 316 | 274 (56) | 42 (41) | |
| Female, n (%) | 275 | 214 (44) | 61 (59) | |
| **Age of mother at delivery** | | | | > 0.9 |
| Mean | | 29.77 | 29.72 | |
| Standard Error | | 0.21 | 0.41 | |
| **AL index** | | | | 0.87 |
| Mean | | 4.84 | 4.83 | |
| Standard Error | | 0.11 | 0.22 | |
| **Allostatic load Group, n (%)** | | | | > 0.99 |
| Lower (<=5.2) | 359 | 299 (84) | 60 (85) | |
| Middle (5.3 – 13) | 51 | 43 (12) | 8 (11) | |
| Upper (>=13.1) | 19 | 16 (4.5) | 3 (4.2) | |
| **Social Class, n (%)** | | | | 0.26 |
| Class I (professional) | 22 | 19 (4.6) | < 5 (<5) | |
| Class II (managerial/ technical) | 179 | 142 (34) | 37 (40) | |
| Class IIIa (skilled non-manual) | 228 | 193 (47) | 35 (38) | |
| Class IIIb (skilled manual) | 31 | 26 (6.3) | 5 (5.4) | |
| Class IV (partly skilled) | 10 | 30 (7.3) | 10 (11) | |
| Class V (unskilled) | < 5 | < 5 | < 5 | |

controls and individuals with mental health symptoms (cases) is shown in Table 1. There were significantly ($p = 0.004$) more females in the "cases" group than in the control group. There is no significant difference between the groups on the mother's occupation or maternal age at delivery.

### 3.1.2. Nominal allostatic load grouping

The "nominal AL grouping" was calculated to investigate if there were any significant differences when dividing the individuals into tertiles based on their AL index. Table 2 shows no significant difference in individuals in the three groups when looking at mental health symptoms, the age of the mother at delivery, or social class. A significant difference was found in "sex" with more females (76 %) in the top third (higher AL).

### 3.1.3. Association between allostatic load grouping and mental health symptoms

Using the results of the nominal AL grouping above, the RRR was calculated for "Sex". The prevalence of mental health symptoms for individuals in the three AL index subgroups is presented in Table 3. The unadjusted RRR for mental health symptoms for participants in the upper third and the middle third compared with the bottom third of AL distribution was 1.43 (95 % CI, 0.84 – 2.43) and 1.51 (95 % CI, 0.89 – 2.58), respectively (Table 3). The adjusted RRR for sex (Model 1) in the top third compared with the bottom third of AL distribution was 2.20 (95 % CI, 0.84 – 5.77).

### 3.1.4. Mood disorder and psychotic symptoms

Previously, we combined the mood and psychotic disorder symptoms into one group, "mental health symptoms". Of the 103 individuals with mental health symptoms, 19 participants (18.4 %) reported psychotic symptoms at age 24, 79 participants (76.6 %) reported mood disorder symptoms at age 24, and 5 participants (4.8 %) had both psychotic and mood disorder symptoms. There were significantly more females than males that developed mood disorder symptoms at age 24 years old (Table 4). The mother's age at delivery, the AL index, and the mother's occupation (social class) did not show any significant effect in the three groups. RRR and 95 % CI were calculated for the variables: "sex", "age of mother at delivery", "total AL", "AL grouping" and "social class". The AL index at age nine was not associated with an increased risk of either psychotic or mood disorder symptoms.

**Table 2**
Descriptive summary of participants grouped by nominal AL. Significance (p-value <=0.05) was highlighted.

| | Distribution of AL index at age 9 years | | | *p-value* |
|---|---|---|---|---|
| | **Bottom Third (<=7)** | **Middle Third (7.1 – 9.9)** | **Top Third (>=10)** | |
| **Total number, n** | 517 | 59 | 17 | |
| **AL index** | | | | **< 0.001** |
| Mean | 3.80 | 8.36 | 11.00 | |
| Standard Error | 0.09 | 0.06 | 0.18 | |
| **Sex** | | | | **0.004** |
| Male, n (%) | 288 (56) | 24 (41) | 4 (24) | |
| Female, n (%) | 227 (44) | 35 (59) | 13 (76) | |
| **Age of Mother at delivery** | | | | 0.2 |
| Mean | 29.90 | 28.85 | 28.82 | |
| Standard Error | 0.23 | 0.69 | 0.99 | |
| **Mental health symptoms, n (%)** | 89 (17) | 11 (19) | 3 (18) | 0.9 |
| **Social Class, n (%)** | | | | 0.2 |
| Class I (professional) | 20 (4.6) | 2 (3.6) | 0 (0) | |
| Class II (managerial/ technical) | 161 (37) | 17 (31) | 1 (6.7) | |
| Class IIIa (skilled non-manual) | 191 (44) | 26 (47) | 11 (73) | |
| Class IIIb (skilled manual) | 25 (5.8) | 6 (11) | 0 (0) | |
| Class IV (partly skilled) | 34 (7.8) | 3 (5.5) | 3 (20) | |
| Class V (unskilled) | 3 (0.7) | 1 (1.8) | 0 (0) | |

**Table 3**
Relative risk ratios for mental health symptoms at age 24 for participants in top and middle tertiles of AL distribution compared with bottom third (reference) at age 9. Model 1: adjusted for sex.

| | | | ***RRR (95 % CI)*** | |
|---|---|---|---|---|
| AL tertiles | No. of observations | Mental health symptoms, no. (%) | Unadjusted | Model 1 |
| Bottom third | 359 | 89 (17) | 1 [reference] | 1 [reference] |
| Middle third | 51 | 11 (19) | 1.10 [0.55; 2.21] | 1.85 [1.07;3.21] |
| Top third | 19 | 3 (18) | 1.03 [0.29; 3.66] | 4.18 [1.34;13.0] |

### 3.1.5. Mental health symptoms, allostatic load index, and adverse childhood experiences

Past exposure to ACEs did not significantly affect the AL index. In the controls (individuals without mental health symptoms in young adulthood), the AL index for individuals who did not experience ACEs was 4.37 (SD= 2.49) vs 4.45 (SD 2.44) for individuals who did experience one or more ACEs ($p = 0.5$). For the individuals with mental health symptoms ($n = 103$), a similar trend was observed. The AL index for individuals with mental health symptoms who did not experience ACEs was 4.40 (SD 2.50) vs 4.53 (SD 2.44) for individuals who did experience one or more ACEs ($p = 0.3$).

In the second part of this manuscript, we investigated the role of ACEs on mental health symptoms.

## 3.2. Adverse childhood experiences and mental health symptoms

### 3.2.1. Neglect, physical and sexual abuse in controls vs. cases

Individuals who developed mental health symptoms at age 24 were almost seven times more likely to have experienced physical abuse than the controls (12 % vs 1.8 %)(Fig. 1). Individuals who developed mental health symptoms at age 24 were significantly more likely ($p = 0.034$) to have experienced sexual abuse than the controls and almost twice as likely to have experienced neglect (72 % vs 39 %). A significant difference between the number of children that did and did not develop mental health symptoms at age 24 was found in all categories of adverse childhood experiences: neglect = <0.001, physical abuse = <0.001, and sexual abuse = 0.034.

### 3.2.2. Relative risk ratio for ACEs in psychotic symptoms and mood disorder symptoms

The unadjusted RRR for mood disorder symptoms for female participants compared to male participants was 1.91 (95 % CI, 1.14; 3.20) (Table 5). The adjusted RRR for neglect (Model 1) for females was 5.45 (95 % CI, 3.04; 9.78), while for physical abuse (Model 2), this was 7.43 (95 % CI, 2.85; 19.4) for females and sexual abuse (Model 3) this was 2.06 (95 % CI, 0.37; 11.6).

The unadjusted RRR for psychotic symptoms for female participants compared to male participants was 0.59 (95 % CI, 0.22; 1.58)(Table 5). The adjusted RRR for neglect (Model 1) for females was 0.99 (95 % CI, 0.37; 2.59), while for physical abuse (Model 2), this was 2.92 (95 % CI, 0.35; 24.4) for females and sexual abuse (Model 3) this was 10.5 (95 % CI, 0.99; 112). These results indicate that being female is a significant risk factor for mood disorder symptoms but not psychotic symptoms. The ACEs, neglect, and physical abuse increase this risk further for mood

**Table 4**
Descriptive statistics of individuals with psychotic symptoms and mood disorder symptoms compared with controls. The relative risk ratio was calculated and reported. Significance (p-value <=0.05) was highlighted.

| | Controls | Psychotic symptoms | *RRR (95 % CI)* | *p-value* | Controls | Mood disorder symptoms | *RRR (95 % CI)* | *p-value* |
|---|---|---|---|---|---|---|---|---|
| **Total number, n (%)** | 490 | 19 | | | 490 | 80 | | |
| **Sex** | | | 0.59 (0.22 1.58) | 0.3 | | | 2.51 (1.53;4.13) | **< 0.001** |
| Male, n (%) | 274 (56) | 13 (68) | | | 274 (56) | 27 (34) | | |
| Female, n (%) | 214 (44) | 6 (32) | | | 214 (44) | 53 (66) | | |
| **Age mother** | | | 0.96 (0.87; 1.06) | 0.4 | | | 1.01 (0.96; 1.07) | 0.6 |
| Mean | 29.77 | 28.95 | | | 29.77 | 30.04 | | |
| Standard Error | 0.21 | 0.90 | | | 0.21 | 0.46 | | |
| **Allostatic load index** | | | 1.08 (0.91; 1.29) | 0.4 | | | 1.05 (0.96; 1.15) | 0.3 |
| Mean | 4.40 | 4.89 | | | 4.40 | 4.70 | | |
| Standard Error | 0.11 | 0.47 | | | 0.11 | 0.24 | | |
| **Allostatic load Group, n (%)** | | | | | | | | |
| Lower (<=5.2) | 428 (87) | 16 (84) | 1 [reference] | | 428 (87) | 70 (88) | 1 [reference] | |
| Middle (5.3 – 13) | 48 (9.8) | 2 (11) | 1.01 (0.23; 4.51) | > 0.9 | 48 (9.8) | 8 (10) | 1.02 (0.46; 2.25) | > 0.9 |
| Upper (>=13) | 14 (2.9) | 1 (5.3) | 2.97 (0.35; 24.9) | 0.3 | 14 (2.9) | 2 (2.5) | 0.87 (0.19; 3.93) | 0.9 |
| **Social Class, n (%)** | | | 1.46 (0.93; 2.28) | 0.1 | | | 1.00 (0.77; 1.30) | > 0.9 |

disorder symptoms, while physical and sexual abuse increases the risk for psychotic symptoms.

## 4. Discussion

To our knowledge, this is the first longitudinal study of the AL index measured in childhood covering the four major biological systems and subsequent psychotic and mood disorder symptoms in young adulthood. Our results indicate that females were more likely to develop mental health disorder symptoms than males, which was strongly driven by the higher incidence of mood disorder symptoms (almost twofold more in females than in males). At 9 years of age, more females appeared in the top tertile of the AL grouping, which indicates a higher AL index in the females compared to the males at that age. The results of the RRR analysis also supported this. Despite our study not finding an overall significant association between the AL index in childhood and later development of psychotic or mood disorder symptoms, a higher AL index showed an increased risk of developing psychotic disorder symptoms, as indicated by the RRR result in the individuals in the middle AL grouping. Unfortunately, due to the small number of cases in the upper AL group with psychotic disorder symptoms, we were unable to calculate an RRR in this group. Results from other studies have indicated that higher levels of AL during childhood are likely to be related to poorer physical health in later life (Calcaterra et al., 2019; Cedillo et al., 2019; Finlay, Rudd, et al., 2022); however, the potential link between increased AL in childhood and poorer mental health outcomes in adulthood has not yet been previously investigated. We further conducted an exploratory analysis with participants who had both mood disorder and psychotic symptoms, which showed that these had a higher AL index of 5.75 vs 4.84 for controls. As only five participants met the criteria for having both mood disorder symptoms and psychotic symptoms, no statistical significance can be established. To our knowledge, no other study has looked at the childhood AL index in individuals with both mood disorder symptoms and psychotic symptoms. Therefore, despite the preliminary nature of our results due to the small sample size, we suggest that elevated childhood AL may precede and possibly contribute to the later development of more complex and severe mental illness symptoms.

Previous studies using the same cohort have investigated the association between the often used AL biomarkers CRP (an inflammatory marker) and IL-6 (an immune marker) at age 9 and depression and psychotic symptoms in adulthood using the ALSPAC dataset and found that higher IL-6 (but not CRP) in childhood was associated with an increased risk of depression and psychotic symptoms in adulthood (Chu et al., 2019; Khandaker et al., 2014; Perry et al., 2021). Another study by Lamers et al. (2019) utilized data from the Netherlands Study of Depression and Anxiety and likewise found that IL-6 was associated with depressive disorders, whereas CRP was not (Lamers et al., 2019). An exploratory analysis of our data, a much more limited sub-sample of the ALSPAC cohort due to the constraints driven by the fact that a considerably smaller section of the ALSPAC cohort had all AL biomarkers available, also showed that IL-6 at age 9 was significantly associated with psychotic disorder symptoms, whereas CRP was not. However, we did not find an association between IL-6 at age 9 and mood disorder symptoms ($p = 0.5$) (Supplementary 8.1). These findings, in combination with the lack of significance between the AL index and mental health symptoms, may indicate that hints of allostasis can be observed early. However, the multi-system effects captured by the AL index have yet to manifest at this relatively early age.

The confounding factor "sex" was identified as a risk factor for mood disorder symptoms with significantly more females than males (59 % vs. 41 %) developing mental health symptoms, which were strongly driven by mood disorder symptoms (66 % vs. 34 %). This tendency is well-described in the literature (Kessler et al., 2005; Parker and Brotchie, 2010).

In addition, we found that more females were in the top tertile (upper) AL group (63 %) compared to males (37 %), which is a new finding. Several studies have investigated AL in adulthood and looked at the role of sex, finding that females have either lower AL than males (Juster et al., 2016; Kinnunen et al., 2005) or found no difference (Brody et al., 2013; Westerlund et al., 2012). Our findings contrast this, as females were found to have higher AL than males, though it is important to note that our study population included children aged 9, whereas most studies looking at AL have been in adults. Our RRR analysis established that the risk for mental health symptoms increased for the individuals who were females and in the highest AL tertile (upper third). These findings further underline that being female and having higher AL increases the risk of developing mental health symptoms in later life (Australian Bureau of Statistics, 2022).

In the second half of this paper, we looked at how ACEs influence the AL index and how ACEs increase the risk of mental health disorder symptoms. Our results indicated that ACEs increase the AL index at age 9

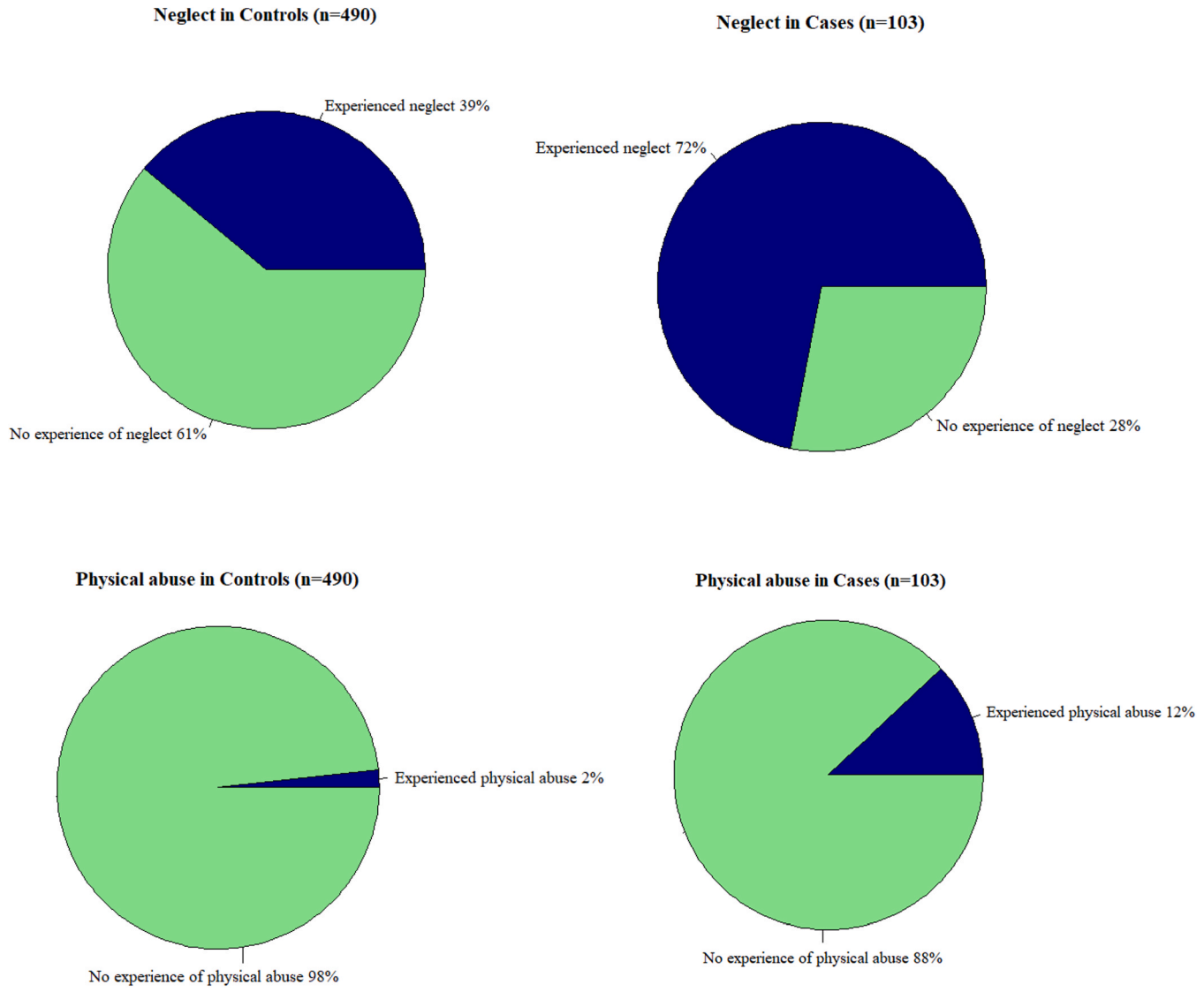



**Fig. 1.** Participants' adverse childhood experience statistics stratified by outcome (controls and cases). Pearson's Chi-squared test was used to calculate the p-value for the number of biomarkers in healthy controls vs. cases.

**Table 5**
Relative risk ratios for mood disorder symptoms and psychotic symptoms at age 24 for females compared to male participants (reference) at age 9 when adjusting for ACEs. Model 1: adjusted for neglect. Model 2: adjusted for physical abuse. Model 3: adjusted for sexual abuse. P-value 0.05 = *, p-value 0.005 = ** , p-value < 0.001 = ** *.

| | | | *RRR (95 % CI)* | | | |
|---|---|---|---|---|---|---|
| | No. | Mood disorder symptoms, no. (%) | Unadjusted | Model 1 | Model 2 | Model 3 |
| Male | 316 | 27 (34) | [reference] | [reference] | [reference] | [reference] |
| Female | 275 | 53 (66) | 1.91 * | 5.45 * ** | 7.43 * ** | 2.06 |
| | | | (1.14; 3.20) | (3.04; 9.78) | (2.85; 19.4) | (0.37; 11.6) |
| | | Psychotic symptoms, no. (%) | | | | |
| Male | 316 | 13 (68) | [reference] | [reference] | [reference] | [reference] |
| Female | 275 | 6 (32) | 0.59 | 0.99 | 2.92 | 10.5 * |
| | | | (0.22; 1.58) | (0.37; 2.59) | (0.35; 24.4) | (0.99; 112) |

in both healthy controls and individuals who developed mental health symptoms in young adulthood; however, this increase was not statistically significant. It is known that there are critical childhood brain development periods characterized by increased neuroplasticity and sensitivity to epigenetic effects (Cisneros-Franco et al., 2020). Long-term exposure to AL may have long-lasting effects on specific neuronal networks that lead to permanent neuroendocrine alterations, such as impairment of learning processes, suppression of synaptic transmission, and neurogenesis (McEwen, 2007; McEwen et al., 2016). Exposure to ACEs (early-life stress) during critical periods of development is likely to influence the epigenome, causing epigenetic alterations that may help explain the long-term effect of childhood trauma and toxic stress on later mental and physical health. A study found that ACEs increased pro-inflammatory cytokines, accelerated cellular aging, and elevated adult blood pressure (Carroll et al., 2011). More importantly, these findings are also reported in children currently going through ACEs

(Drury et al., 2012; Evans, 2003; Finlay, Roth, et al., 2022), indicating that the increase may persist from childhood until adulthood.

We found that individuals who developed mental health symptoms before the age of 25 were much more likely to have experiences of neglect and physical and/or sexual abuse. This relationship is well-established and has also been shown by other studies (Iob et al., 2022; Martín-Higarza et al., 2020). Lastly, we performed an RRR analysis for mood disorder and psychotic symptoms separately, investigating how the risk for mental health symptoms increased for females compared to males when adjusting for neglect and physical and sexual abuse. These findings highlight that sex is a significant risk factor for mood disorder symptoms but not psychotic symptoms. Furthermore, adjusting for ACEs, the female sex further increases the risk up to almost sevenfold.

Interestingly, physical abuse had the most considerable effect on the risk of mood disorder, while sexual abuse was the most significant risk factor for psychotic disorders. Another group investigated the association between ACEs (neglect, physical and sexual abuse) and major depressive disorder (MDD), finding that physical abuse and neglect were significantly associated with the risk of developing MDD in adulthood (Widom et al., 2007). Interestingly, they did not find an association between sexual abuse and the risk of MDD (similar to ours). In contrast, another study found that sexual abuse was more strongly associated with any psychiatric condition than any other category of abuse (Dube et al., 2005). There is a possibility that the AL index (at age 9) serves as a mediating factor between ACEs and mental health symptoms. However, this possible connection could not be investigated because the AL index was reported at age 9, and ACEs were reported at age 11.

In our paper, the lack of significance in the psychotic disorder group is likely due to limited case numbers. For the females with psychotic symptoms, we had a very small case number (n = 6), resulting in a lack of significance for the adjusted models. The significance of the RRR model is consistent with the meta-analysis by Varese et al. (2012), who identified that childhood adversities were overall associated with a 2.78-fold increased risk of psychosis. Separating each ACE and its risk, they found that sexual abuse had an OR of 2.38, physical abuse had an OR of 2.95, and neglect had an OR of 2.90. Additional studies have reported similar evidence (Addington et al., 2013; Holshausen et al., 2016).

A limitation of the present study is the nature of the prevalence of these disorders. The prevalence of mood disorder symptoms is approximately 6–10 % (Australian Bureau of Statistics, 2022) and 2–3.5 % (Sullivan et al., 2020) for psychotic symptoms at age 24. In this study, 13.3 % of the individuals had mood disorder symptoms, while 3.2 % had psychotic symptoms, which is clearly in line with more extensive population prevalence data. However, the small sample size due to missing biomarker and confounder data did not result in significant differences despite high RRR. Another limitation of the study is the issue of missing data, a common challenge for prospective cohort studies (Shortreed and Forbes, 2010). However, we assessed our findings using sensitivity analysis, including imputation for missing data, and the patterns remained similar. This suggests that missing data were unlikely to impact our findings significantly. In addition, the study only included biomarkers measured at a single time-point, so it is unclear to what extent they reflect persistent trends. Finally, as the AL index was measured at 9 years old and ACEs were reported at 11 years old, there is a possibility that ACE was not reflected in the AL if this was experienced between the ages of 9 and 11 years old.

## 5. Conclusion

In conclusion, we report evidence for a longitudinal association between increased childhood AL index in females and the increased risk of mood disorder, but not psychotic, symptoms. Furthermore, we provide evidence that ACEs increase the risk for these disorders. The combination of being female and having experienced an ACE increases the risk of mood disorder symptoms almost sevenfold and the risk of psychotic symptoms tenfold. Our findings suggest that elevated AL in childhood may contribute to a developmental trajectory that raises the risk for mental health disorders in later life, especially among women.

## Ethics approval and consent to participate

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. Children were invited to give assent where appropriate. Study participants have the right to withdraw their consent for elements of the study or from the study entirely at any time. Full details of the ALSPAC consent procedures are available on the study website (http://www.bristol.ac.uk/alspac/researchers/research-ethics/). Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and local research ethics committees (NHS Haydock REC: 10/H1010/70). Consent for biological samples has been collected in accordance with the Human Tissue Act (2004).

Further ethics approval was obtained from the Human Research Ethics Committee at James Cook University, Australia (H8535).

## Consent for publication

Participants have been provided with fair processing materials describing the studies' use of the data they have provided or those collected through record linkage and about the legal basis under which the study operates including the sharing of de-identified data with researchers and the publishing of research findings. Study members have the right to withdraw from elements of the study or from the study entirely at any time. Full details of the ALSPAC consent procedures are available from the study website.

## Avail ability of data and materials

No specific data are associated with this protocol.

ALSPAC data access is through a system of managed open access. The steps below highlight how to apply for access to the data referred to in this article and all other ALSPAC data. The datasets presented in this article are linked to ALSPAC project number B3847. The ALSPAC variable codes highlighted in the dataset descriptions can be used to specify the required variables.

- 1. Please read the ALSPAC access policy (https://www.bristol.ac.uk/media-library/sites/alspac/documents/researchers/data-access/ALSPAC_Access_Policy.pdf) which describes the process of accessing the data and samples in detail, and outlines the costs associated with doing so.
- 2. You may also find it useful to browse our fully searchable research proposals database (https://proposals.epi.bristol.ac.uk/), which lists all research projects that have been approved since April 2011.
- 3. Please submit your research proposal for consideration by the ALSPAC Executive Committee. You will receive a response within 10 working days to advise you whether your proposal has been approved.

The study website also contains details of all the data that is available through a fully searchable data dictionary and variable search tool: http://www.bristol.ac.uk/alspac/researchers/our-data/

## Funding

The UK Medical Research Council and Wellcome (Grant ref: 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and Sabine Finlay will serve

as guarantor for the contents of this paper.

A comprehensive list of grant funding is available on the ALSPAC website (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf). This research was specifically funded by Wellcome Trust and MRC (core) (Grant ref: 076467/Z/05/Z), British Heart Foundation (Grant ref: CS/15/6/31468), and NIH (Grant ref: PD301198-SC101645), MRC (Grant ref: MR/M006727/1).

This work was funded as a whole by the Australian Institute of Medical Scientists (Grant ref: REGS-29277–2021).

## CRediT authorship contribution statement

**Zoltan Sarnyai:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization. **Donna Rudd:** Writing – review & editing, Supervision, Conceptualization. **Brett McDermott:** Writing – review & editing, Supervision, Conceptualization. **Oyelola Adegboye:** Writing – review & editing, Formal analysis. **Sabine Finlay:** Writing – original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization.

## Declaration of Competing Interest

No competing interests.

## Acknowledgments

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2024.107276.

## References

Addington, J., Stowkowy, J., Cadenhead, K.S., Cornblatt, B.A., McGlashan, T.H., Perkins, D.O., Seidman, L.J., Tsuang, M.T., Walker, E.F., Woods, S.W., 2013. Early traumatic experiences in those at clinical high risk for psychosis. Early Interv. Psychiatry 7 (3), 300–305.

Australian Bureau of Statistics, 2022. National Study of Mental Health and Wellbeing. Australian Bureau of Statistics. ⟨https://www.abs.gov.au/statistics/health/mental-health/national-study-mental-health-and-wellbeing/latest-release⟩. Retrieved 12.02 from.

Boullier, M., Blair, M., 2018. Adverse childhood experiences. Paediatr. Child Health (U. Kingd. ) 28 (3), 132–137. https://doi.org/10.1016/j.paed.2017.12.008.

Boyd, A., Golding, J., Macleod, J., Lawlor, D.A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S., Davey Smith, G., 2013. Cohort profile: the 'children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. Int. J. Epidemiol. 42 (1), 111–127.

Brody, G.H., Yu, T., Chen, E., Miller, G.E., Kogan, S.M., Beach, S.R., 2013. Is resilience only skin deep?: rural African Americans' socioeconomic status-related risk and competence in preadolescence and psychological adjustment and allostatic load at age 19 [Research Support, N.I.H., Extramural]. Psychol. Sci. 24 (7), 1285–1293. https://doi.org/10.1177/0956797612471954.

Calcaterra, V., Vinci, F., Casari, G., Pelizzo, G., De Silvestri, A., De Amici, M., Albertini, R., Regalbuto, C., Montalbano, C., Larizza, D., 2019. Evaluation of allostatic load as a marker of chronic stress in children and the importance of excess weight. Front. Pediatr. 7, 335.

Carroll, J.E., Cohen, S., Marsland, A.L., 2011. Early childhood socioeconomic status is associated with circulating interleukin-6 among mid-life adults. Brain, Behav., Immun. 25 (7), 1468–1474.

Cedillo, Y.E., Murillo, A.L., Fernández, J.R., 2019. The association between allostatic load and anthropometric measurements among a multiethnic cohort of children. Pediatr. Obes. 14 (6), e12501.

Chu, A.L., Stochl, J., Lewis, G., Zammit, S., Jones, P.B., Khandaker, G.M., 2019. Longitudinal association between inflammatory markers and specific symptoms of depression in a prospective birth cohort. Brain, Behav., Immun. 76, 74–81.

Cisneros-Franco, J.M., Voss, P., Thomas, M.E., de Villers-Sidani, E., 2020. Chapter 8 - critical periods of brain development. In: Gallagher, A., Bulteau, C., Cohen, D., Michaud, J.L. (Eds.), Handbook of Clinical Neurology, 173. Elsevier, pp. 75–88. https://doi.org/10.1016/B978-0-444-64150-2.00009-5.

Drury, S.S., Theall, K., Gleason, M.M., Smyke, A.T., De Vivo, I., Wong, J., Fox, N.A., Zeanah, C.H., Nelson, C.A., 2012. Telomere length and early severe social deprivation: linking early adversity and cellular aging. Mol. Psychiatry 17 (7), 719–727.

Dube, S.R., Anda, R.F., Whitfield, C.L., Brown, D.W., Felitti, V.J., Dong, M., Giles, W.H., 2005. Long-term consequences of childhood sexual abuse by gender of victim. Am. J. Prev. Med. 28 (5), 430–438.

Evans, G.W., 2003. A multimethodological analysis of cumulative risk and allostatic load among rural children. Dev. Psychol. 39 (5), 924–933.

Finlay, S., Juster, R.-P., Adegboye, O., Rudd, D., McDermott, B., Sarnyai, Z., 2023. Childhood adversity, allostatic load, and adult mental health: study protocol using the avon longitudinal study of parents and children birth cohort. Front. Psychiatry 13, 976140.

Finlay, S., Roth, C., Zimsen, T., Bridson, T.L., Sarnyai, Z., McDermott, B., 2022. Adverse childhood experiences and allostatic load: a systematic review. Neurosci. Biobehav. Rev. 136, 104605. https://doi.org/10.1016/j.neubiorev.2022.104605.

Finlay, S., Rudd, D., McDermott, B., Sarnyai, Z., 2022. Allostatic load and systemic comorbidities in psychiatric disorders. Psychoneuroendocrinology 140, 105726.

Fonville, L., Zammit, S., Lewis, G., David, A.S., 2015. Review of assessment tools for psychotic-like experiences misses the psychosis-like symptoms semi-structured interview (PLIKSi) in ALSPAC. Early Interv. Psychiatry 11 (3), 269–270.

Fraser, A., Macdonald-Wallis, C., Tilling, K., Boyd, A., Golding, J., Davey Smith, G., Henderson, J., Macleod, J., Molloy, L., Ness, A., 2013. Cohort profile: the Avon longitudinal study of parents and children: ALSPAC mothers cohort. Int. J. Epidemiol. 42 (1), 97–110.

Fuller-Thomson, E., Baird, S., Dhrodia, R., Brennenstuhl, S., 2016. The association between adverse childhood experiences (ACEs) and suicide attempts in a population-based study. Child.: Care, Health Dev. 42 (5), 725–734.

Garner, B., Phassouliotis, C., Phillips, L.J., Markulev, C., Butselaar, F., Bendall, S., Yun, Y., McGorry, P.D., 2011. Cortisol and dehydroepiandrosterone-sulphate levels correlate with symptom severity in first-episode psychosis. J. Psychiatr. Res. 45 (2), 249–255.

Greenhalgh, A.M., Gonzalez-Blanco, L., Garcia-Rizo, C., Fernandez-Egea, E., Miller, B., Arroyo, M.B., Kirkpatrick, B., 2017. Meta-analysis of glucose tolerance, insulin, and insulin resistance in antipsychotic-naïve patients with nonaffective psychosis. Schizophr. Res. 179, 57–63.

Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inform. 42 (2), 377–381.

Holshausen, K., Bowie, C.R., Harkness, K.L., 2016. The relation of childhood maltreatment to psychotic symptoms in adolescents and young adults with depression. J. Clin. Child Adolesc. Psychol. 45 (3), 241–247.

Iob, E., Lacey, R., Giunchiglia, V., Steptoe, A., 2022. Adverse childhood experiences and severity levels of inflammation and depression from childhood to young adulthood: a longitudinal cohort study. Mol. Psychiatry 27 (4), 2255–2263. https://doi.org/10.1038/s41380-022-01478-x.

Juster, R.P., McEwen, B.S., Lupien, S.J., 2010. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci. Biobehav. Rev. 35 (1), 2–16. https://doi.org/10.1016/j.neubiorev.2009.10.002.

Juster, R.-P., Pruessner, J.C., Desrochers, A.B., Bourdon, O., Durand, N., Wan, N., Tourjman, V., Kouassi, E., Lesage, A., Lupien, S.J., 2016. Sex and gender roles in relation to mental health and allostatic load. Psychosom. Med. 78 (7), 788–804. https://doi.org/10.1097/PSY.0000000000000351.

Kessler, R.C., Demler, O., Frank, R.G., Olfson, M., Pincus, H.A., Walters, E.E., Wang, P., Wells, K.B., Zaslavsky, A.M., 2005. Prevalence and treatment of mental disorders, 1990 to 2003. N. Engl. J. Med. 352 (24), 2515–2523.

Khandaker, G.M., Pearson, R.M., Zammit, S., Lewis, G., Jones, P.B., 2014. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. JAMA Psychiatry 71 (10), 1121–1128. https://doi.org/10.1001/jamapsychiatry.2014.1332.

Kinnunen, M.-L., Kaprio, J., Pulkkinen, L., 2005. Allostatic load of men and women in early middle age. J. Individ. Differ. 26 (1), 20–28.

Lamers, F., Milaneschi, Y., Smit, J.H., Schoevers, R.A., Wittenberg, G., Penninx, B.W.J.H., 2019. Longitudinal association between depression and inflammatory markers: results from the netherlands study of depression and anxiety. Biol. Psychiatry 85 (10), 829–837. https://doi.org/10.1016/j.biopsych.2018.12.020.

Lewis, G., Pelosi, A.J., Araya, R., Dunn, G., 1992. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. Psychol. Med. 22 (2), 465–486.

Martín-Higarza, Y., Fontanil, Y., Méndez, M.D., Ezama, E., 2020. The direct and indirect influences of adverse childhood experiences on physical health: a cross-sectional study. Int. J. Environ. Res. Public Health [Electron. Resour. ] 17 (22). https://doi.org/10.3390/ijerph17228507.

McEwen, B.S., 1998. Protective and damaging effects of stress mediators. N. Engl. J. Med. 338 (3), 171–179.

McEwen, B.S., 2003. Mood disorders and allostatic load. Biol. Psychiatry 54 (3), 200–207.

McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol. Rev. 87 (3), 873–904.

McEwen, B.S., 2017. Allostasis and the epigenetics of brain and body health over the life course: the brain on stress [Review]. JAMA Psychiatry 74 (6), 551–552. https://doi.org/10.1001/jamapsychiatry.2017.0270.

McEwen, B.S., Nasca, C., Gray, J.D., 2016. Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. Neuropsychopharmacology 41 (1), 3–23.
McGorry, P.D., Mei, C., Dalal, N., Alvarez-Jimenez, M., Blakemore, S.-J., Browne, V., Dooley, B., Hickie, I.B., Jones, P.B., McDaid, D., 2024. The lancet psychiatry commission on youth mental health. Lancet Psychiatry 11 (9), 731–774.
Merikangas, K.R., He, J.-p, Burstein, M., Swanson, S.A., Avenevoli, S., Cui, L., Benjet, C., Georgiades, K., Swendsen, J., 2010. Lifetime prevalence of mental disorders in US adolescents: results from the National comorbidity survey replication–adolescent supplement (NCS-A). J. Am. Acad. Child Adolesc. Psychiatry 49 (10), 980–989.
Merrick, M.T., Ports, K.A., Ford, D.C., Afifi, T.O., Gershoff, E.T., Grogan-Kaylor, A., 2017. Unpacking the impact of adverse childhood experiences on adult mental health. Child Abus. Negl. 69, 10–19.
Miller, B.J., Gassama, B., Sebastian, D., Buckley, P., Mellor, A., 2013. Meta-analysis of lymphocytes in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 73 (10), 993–999.
Northstone, K., Lewcock, M., Groom, A., Boyd, A., Macleod, J., Timpson, N., Wells, N., 2019. The Avon Longitudinal Study of Parents and Children (ALSPAC): an update on the enrolled sample of index children in 2019. Wellcome Open Res. 4.
Nugent, K.L., Chiappelli, J., Rowland, L.M., Hong, L.E., 2015. Cumulative stress pathophysiology in schizophrenia as indexed by allostatic load. Psychoneuroendocrinology 60, 120–129. https://doi.org/10.1016/j.psyneuen.2015.06.009.
Parker, G., Brotchie, H., 2010. Gender differences in depression. Int. Rev. Psychiatry 22 (5), 429–436.
Perry, B.I., Zammit, S., Jones, P.B., Khandaker, G.M., 2021. Childhood inflammatory markers and risks for psychosis and depression at age 24: examination of temporality and specificity of association in a population-based prospective birth cohort. Schizophr. Res. 230, 69–76.
Pillinger, T., Beck, K., Gobjila, C., Donocik, J.G., Jauhar, S., Howes, O.D., 2017. Impaired glucose homeostasis in first-episode schizophrenia: a systematic review and meta-analysis. JAMA Psychiatry 74 (3), 261–269. https://doi.org/10.1001/jamapsychiatry.2016.3803.
Shortreed, S.M., Forbes, A.B., 2010. Missing data in the exposure of interest and marginal structural models: a simulation study based on the framingham heart study. Stat. Med. 29 (4), 431–443.
Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J.B., Jones, P., Kim, J.H., 2022. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol. Psychiatry 27 (1), 281–295.
Sterling, P. (1988). Allostasis: A New Paradigm to Explain Arousal Pathology. *Handbook of Life Stress, Cognition and Health.* ⟨https://ci.nii.ac.jp/naid/10019518960/en/⟩.
Sullivan, S.A., Kounali, D., Cannon, M., David, A.S., Fletcher, P.C., Holmans, P., Jones, H., Jones, P.B., Linden, D.E.J., Lewis, G., Owen, M.J., O'Donovan, M., Rammos, A., Thompson, A., Wolke, D., Heron, J., Zammit, S., 2020. A population-based cohort study examining the incidence and impact of psychotic experiences from childhood to adulthood, and prediction of psychotic disorder. Am. J. Psychiatry 177 (4), 308–317. https://doi.org/10.1176/appi.ajp.2019.19060654.
Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., van Os, J., Bentall, R.P., 2012. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr. Bull. 38 (4), 661–671. https://doi.org/10.1093/schbul/sbs050.
Westerlund, H., Gustafsson, P.E., Theorell, T., Janlert, U., Hammarstrom, A., 2012. Social adversity in adolescence increases the physiological vulnerability to job strain in adulthood: a prospective population-based study [Research Support, Non-U.S. Gov't]. PLoS ONE [Electron. Resour. ] 7 (4), e35967. https://doi.org/10.1371/journal.pone.0035967.
Widom, C.S., DuMont, K., Czaja, S.J., 2007. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Arch. Gen. Psychiatry 64 (1), 49–56.