

# **under the skin**

**Early-life stress exposure and the co-occurrence of mental and physical health problems**

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# PREFACE

## Note

This is a work in progress. Stay tuned :)

Dear reader,

Let me begin this book the only way that feels right: with a little note of honesty. Writing this was hard, much harder than I anticipated. Perhaps out of pride, or because of this irresistible greed I feel to dissect and point out limitations - that, I am told, makes for a good scientist as much as a horrible friend - I kept wondering whether any of this would be worth your time.

I guess 5-years-ago me hoped, at this point, they could promise you sensational scientific breakthroughs and game-changing statistical tricks ahead. Well, it looks like we may both have to settle for a somewhat less glamourous, but perhaps more truthful, process of scientific discovery.

So here is a collection of small steps toward understanding, many little increments of knowledge, a couple of false starts, a few frustratingly inconclusive results, and a handful of insights (some grim, some hopeful).

Still here? Didn't think so... let's talk about early-life stress, shall we?

*“In the depth of winter, I found there was, within me, an invincible summer.”*  
Albert Camus – Summer (1954)

# 1 General Introduction

## 1.1 Early-life stress (ELS)

When my mother was pregnant with me, my older brother died of a congenital condition. I never met the little guy, never experienced any grief myself. Yet, for the longest time I thought that, somehow, his death had cast a sort of shadow over the rest of my life. And I was not the only one. The idea that exposure to stressful experiences during “*critical*” periods of early development wields profound, long-term impact on emotional and physiological regulation, is nothing new. Sigmund Freud, among others, made quite a sensational career out of it, and - perhaps partly because of the success of psychoanalytic theories - the scientific literature on the topic today is almost intimidatingly vast.

So vast in fact, that it requires a pinch of terminology clarification, before we can dive into it. For the remainder of this book, I will use the term “Early-Life Stress” (ELS) to refer to a host of adverse life events or conditions, that are experienced during the first years of life, e.g., in childhood, and, even earlier, during gestation. These experiences (sometimes also referred to as “childhood trauma”, “maltreatment”, “early adversity”, or “adverse childhood experiences”) encompass a wide range of stressors, including neglect and abuse, bereavement, bullying but also poverty, material deprivation and/or parental psychopathology (Heim, 2020).

ELS is a widely studied concept, partly because it is surprisingly common: more than half the population experiences at least one form of ELS before the age of 18 years (Madigan et al., 2024). But more importantly, ELS is one of strongest, most consistent predictors of mental health problems later in life, particularly depression (LeMoult et al., 2020; Li et al., 2016; Li et al., 2023).

Systematic scientific investigations into ELS and its consequences, really gained momentum in the late 90s, when large-scale epidemiological studies, began to also highlight a relationship between ELS and an increased risk of chronic diseases and premature mortality (e.g. (Felitti et al., 1998)). This line of evidence also proved very robust over time, so ELS is now a well-recognised risk factor for cardio-metabolic health problems, including obesity (Danese & Tan, 2014; Wiss & Brewerton, 2020), type 2 diabetes (Zhu et al., 2022), hypertension and cardio-vascular disease (Jacquet-Smailovic et al., 2022; Jakubowski et al., 2018).

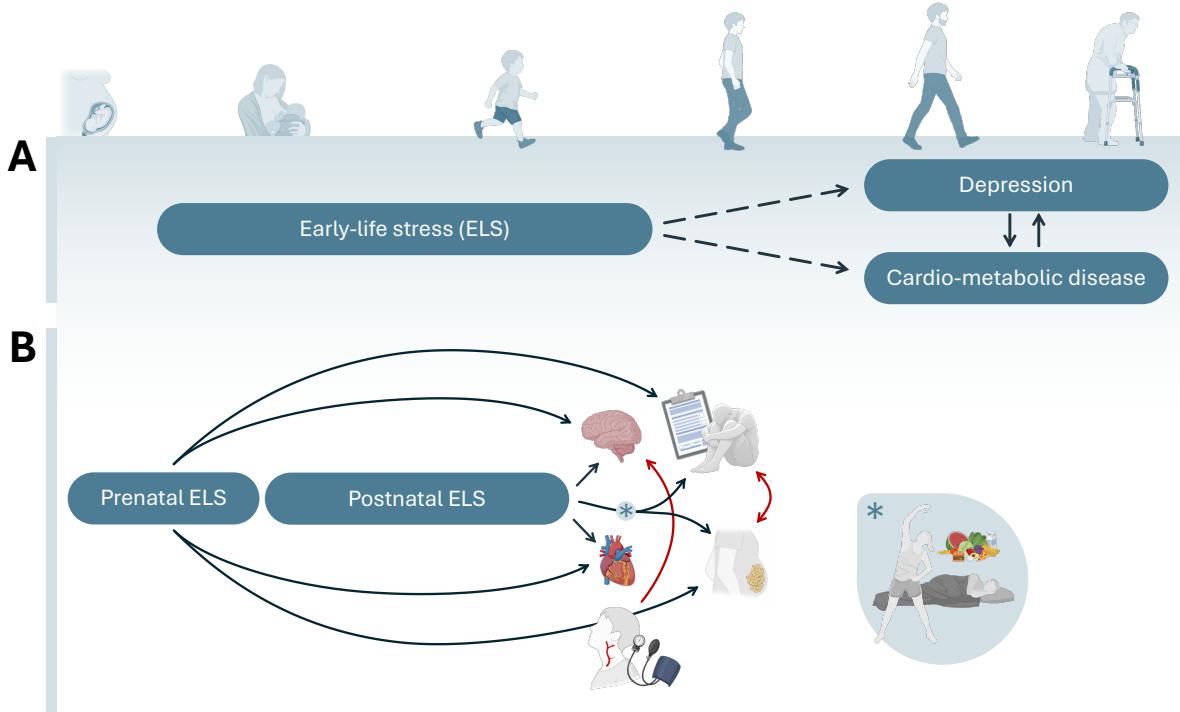
## **1.2 Mental & physical health: a comorbidity paradigm**

Interestingly, parallel to this growing interest in the effects of stress and psychosocial factors on physical health, the early 2000s also witnessed a surge of epidemiological studies uncovering the relationship between depression and cardio-metabolic health problems(Luppino et al., 2010; Penninx et al., 2001; Van der Kooy et al., 2007). Historically, these two conditions had been largely investigated as separate entities, each with distinct risk factors and treatment approaches. Their connection was not entirely overlooked (see for example early theoretical work by Engel (1977)), but it remained peripheral to mainstream medical research until relatively recently.

As more evidence accumulated that depression and cardio-metabolic conditions tend to co-occur (Anwar et al., 2018; Blasco et al., 2020; Gutiérrez-Rojas et al., 2020), several potential mechanisms have been proposed to explain this observed comorbidity (Milaneschi et al., 2019). One possibility is that these conditions share common risk factors, such as genetic liability for instance, but also ELS exposure, as discussed above and supported by a recent large scale meta-analysis (Souama et al., 2023). It is also possible that experiencing depression may directly increase the risk of developing cardio-metabolic health problems later in life. For example, in two meta-analyses based on longitudinal data, depression was found to be risk factor for obesity and diabetes (Ditmars et al., 2022; Mannan et al., 2016). Other longitudinal meta-analyses however, have also shown, in turn, that poor cardio-metabolic health was a robust predictor of later depression (Zhou et al., 2024), supporting the hypothesis of a bi-directional relationship.

## **1.3 ELS and psycho-physical health: towards an integrated approach**

So far, we have described a triangle of relationships - i.e., between *a*) ELS and mental health, *b*) ELS and cardio-metabolic health, and *c*) mental and cardio-metabolic health (Figure 1.1 A), which received considerable attention in the medical literature. This isn't surprising. Depression and cardio-metabolic conditions are among the leading causes of death and disability worldwide, shaping an enormous public health burden which is largely preventable (Anwar et al., 2018). ELS is a promising shared risk factor, which can be measured years - and even decades - before clinical symptoms emerge, making it an ideal candidate for informing early detection and improving the integrated prevention of psycho-physical health problems.



**Figure 1.1: Schematic representation of this thesis, in the context of previous literature**

(A) A schematic summary of the existing evidence, on the relationships under study. This is largely based on adult outcomes and retrospectively measured ELS exposure (indicated by the dashed line).

(B) A Schematic summary of the relationships examined in this thesis.

However, there are three key challenges that need to be addressed, before these findings could be effectively translated into clinical practice.

Firstly, as briefly noted above, the literature is very heterogeneous in its definition of ELS, with many studies focusing on specific types of adversity (e.g., childhood neglect and abuse). However, there is convincing evidence that exposure to multiple stressors - i.e., different sources of stress, as well as repeated or continued exposure over time - has much worse consequences for psycho-physical health, compared to individual stressors (Evans et al., 2013; Hughes et al., 2017). This underscores the importance of identifying children who face multiple forms of ELS, as they may represent a particularly vulnerable population, who should be prioritized in intervention programs.

Secondly, existing studies typically only address one “side” of this triad of relationships. For instance, while ELS has been linked to both depression and obesity independently, its role in determining their co-occurrence remains heavily understudied. Consequently, it is hard to establish the relative importance of ELS as a risk factor for each disorder in isolation

vs. their comorbidity, which poses an obstacle to the development of integrated prevention and intervention (Anwar et al., 2018).

Lastly, the overwhelming majority of studies investigating either the role of ELS, or the(bidirectional) relationships between mental and physical health, has been conducted in adult or aging populations.

On one hand, this brings about important measurement issues. Namely, the proposed relationship between ELS and adult psycho-physical health relies heavily on retrospective reports of ELS exposure, which may have introduced recall bias, unrealistically inflating the association estimates reported by the literature (Reuben et al., 2016).

On the other hand, both depression and cardio-metabolic health problems very often find their onset well before adulthood. A growing number of adolescents, for instance, experience depressive symptoms before the age of 20 years (Keeley, 2021; Patalay & Gage, 2019). Concurrently, while cardio-metabolic endpoints such as myocardial infarction and diabetes are traditionally associated with later life stages, their prodromal forms, including hypertension, dyslipidemia, and obesity, manifest more and more frequently between childhood and adolescence (NCD-RisC, 2017; WHO, 2022). Intervening during this early developmental window could be crucial to mitigate the progression of such prodromal psycho-physical symptoms into chronic mental and physical health conditions later in life.

In this context, prospective cohort studies that begin at conception and capture a broader spectrum of ELS exposures and psycho-physical symptoms, are essential to map causal pathways and inform on optimal intervention windows.

## 1.4 This thesis: one step back in time

This thesis (Figure 1.1 B) aims to address some of these limitations and open questions.

**Part 1** will focus on characterizing the prospective relationship between ELS and adolescent psycho-physical health. First, in Chapter 2, I quantify the relationship between ELS exposure during two key developmental periods (i.e. pregnancy and childhood) and adolescent *a)* internalizing symptoms, *b)* adiposity, and *c)* their comorbidity. Chapter 3 further explores whether three common lifestyle factors (i.e., physical activity, sleep duration, and diet quality) may moderate the associations identified in Chapter 2. I will then take a closer look at the potential “biological scars” that pre- and postnatal ELS exposure may leave behind on children’s brains (Chapter 4) and on their hearts (Chapter 5).

In **Part 2** I will then characterize the reciprocal relationship between mental and cardio-metabolic health across childhood and adolescence. Chapter 6 examines the longitudinal co-development of depressive symptoms and several markers of cardio-metabolic health from childhood to early adulthood. In Chapter 7, I assess the relationship between early cardiovascular health markers (i.e., arterial health and blood pressure) and the developing brain.

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# **PART 1: The role of ELS in the development of mental and physical health**

## 2 ELS and adolescent psycho-physical health

Adapted from:

**Differential effects of pre- and postnatal early-life stress on internalizing, adiposity and their comorbidity**

**Defina, S.**, Woofenden, T., Baltramaityte, V., Pariante, C. M., Lekadir, K., Jaddoe, V. W., Serdarevic, F., Tiemeier, H., Walton, E., Felix, J. F., & Cecil, C. A. M., \*on behalf of the EarlyCause Consortium. (2023). *JAACAP*. DOI [DOI](#)

### Abstract

Objective: Depression and obesity are two highly prevalent and often comorbid conditions. Exposure to early-life stress (ELS) has been associated with both depression and obesity in adulthood, as well as their preclinical manifestations during development. However, it remains unclear whether: *(i)* associations differ depending on the timing of stress exposure (prenatal vs postnatal) and *(ii)* ELS is a shared risk factor underlying the comorbidity between the two conditions.

Methods: Leveraging data from two large population-based birth cohorts (ALSPAC: n=8428 (52% male participants); Generation R: n=4268 (48% male participants)), we constructed comprehensive cumulative measures of prenatal (in utero) and postnatal (from birth to 10 years) ELS. At age 13.5 years we assessed: a) internalizing symptoms (using maternal reports); b) fat mass percentage (using dual-energy X-ray absorptiometry); c) their comorbidity, defined as the co-occurrence of high internalizing and high adiposity.

Results: Both prenatal (*total effect* [95%CI] = 0.20 [0.16; 0.22]) and postnatal stress ( $\beta$  [95%CI] = 0.22 [0.17; 0.25]) were associated with higher internalizing symptoms, with evidence of a more prominent role of postnatal stress. A weaker association (primarily driven by prenatal stress) was observed between stress and adiposity (prenatal: 0.07 [0.05; 0.09]; postnatal: 0.04 [0.01; 0.07]). Both pre- (OR [95%CI] = 1.70 [1.47; 1.97]) and postnatal stress (1.87 [1.61; 2.17]) were associated with an increased risk of developing comorbidity.

Conclusions: We found evidence of *(i)* timing and *(ii)* shared causal effects of ELS on psychocardiometabolic health in adolescence, but future research is warranted to clarify how these associations may unfold over time.

## **Links**

**Supplementary materials:** <https://osf.io/s7f9h/files/osfstorage>



**Project's code:** <https://github.com/SereDef/association-ELS-PCM-project>



**ELS score:** <https://github.com/SereDef/cumulative-ELS-score>



## **Keywords**

Early-life stress; Internalizing symptoms; Adiposity; Comorbidity; Generation R; ALSPAC.

## **Abbreviations**

Avon Longitudinal Study of Parents and Children (ALSPAC), Body Mass Index (BMI), Child Behavior Checklist (CBCL), Confidence Interval (CI), Dual-Energy X-ray Absorptiometry (DXA), Early-Life Stress (ELS), False Discovery Rate (FDR), Generation R Study (GenR), Natural Direct Effect (NDE), Natural Indirect Effect (NIE), Odds Ratio (OR), Strengths and Difficulties Questionnaire (SDQ), Total Effect (TE).

## 2.1 Introduction

The co-occurrence of depression and obesity is a rising public health concern, affecting increasingly younger populations (Sutaria et al., 2019). Individuals with obesity are ~30-40% more likely to develop depression compared to the general population (Pereira-Miranda et al., 2017). In turn, depression also increases the risk of developing obesity (Pratt & Brody, 2014) and related cardiometabolic disease (Hare et al., 2014). While the relationship between depression and adiposity is likely multifactorial and complex, the observed comorbidity between the two may be partially explained by shared environmental risk factors, such as exposure to stressful experiences early in life (Shonkoff et al., 2012).

Indeed, early-life stress (ELS) is a well-established risk factor for both adult depression (Li et al., 2016) and obesity (Danese & Tan, 2014). In children and adolescents, ELS exposure in utero and postnatally (e.g., adverse childhood experiences) have been separately linked to preclinical manifestations of depression, such as internalizing problems (Cecil et al., 2017; Van den Bergh et al., 2020), and several adiposity measures (Burgueño et al., 2020; Elsenburg et al., 2017).

Identifying critical exposure windows (i.e., prenatal vs postnatal) can provide important insights into the best timing for prevention and intervention programs, and shed light on the mechanisms through which stress may lead to disease (Hartman & Belsky, 2018). However, very few studies prospectively investigated the influence of both pre- and postnatal stress on these outcomes, and, because stress shows continuity over time, it is unclear whether *(a)* previously reported postnatal associations may partly reflect preceding prenatal exposures (i.e., prenatal ELS as confounder), and *(b)* observed prenatal associations may be partly mediated by postnatal ELS (i.e., postnatal ELS as mediator).

Further, existing studies have examined ELS associations with internalizing and adiposity either separately (Slopen et al., 2014) or as part of a broader “multisystemic” disease constructs (Juster et al., 2016). It remains unknown whether ELS represents a shared risk factor for comorbid emotional problems and adiposity. Establishing such association is important, since protocols for the integrated detection and management of these health conditions are lacking (Anwar et al., 2018), and differential patterns of ELS exposure may help identify subgroups of adolescents at higher risk for comorbidity.

To address these gaps, we leveraged longitudinal data from two population-based prospective birth cohorts to examine *(i)* how pre- and postnatal ELS (up to age 10 years) associate to internalizing symptoms and adiposity in early adolescence (i.e., at age 13 years), taking into account potential confounding and mediation effects; and *(ii)* whether ELS accounts for comorbidity between internalizing problems and excess adiposity, above its contribution to each health outcome individually. Based on previous findings, we expect that both pre- and postnatal ELS prospectively associate with internalizing symptoms and adiposity, as well as their comorbidity. No a priori hypotheses were specified regarding the relative importance of pre- vs postnatal ELS.

## 2.2 Methods

This manuscript follows STROBE guidelines (Elm et al., 2008).

### 2.2.1 Participants

Our sample was drawn from two population-based cohorts: the Generation R Study (GenR), including 9,778 pregnant women in Rotterdam (the Netherlands), who delivered their babies between April 2002 and January 2006 (Kooijman et al., 2016); and the Avon Longitudinal Study of Parents and Children (ALSPAC) involving 14,541 pregnant women in Avon (UK), with delivery dates between April 1991 and December 1992 (Boyd et al., 2013; Fraser et al., 2013). The [ALSPAC website](#) contains details of all the data that is available through a fully searchable data dictionary and variable search tool.

Response rates at the 13 years follow-up were 64% in GenR and 61% in ALSPAC. Participants with > 50% missing ELS variables in the pre- or postnatal period were excluded, as were all twins. In the case of non-twin siblings, only one was selected (see Figure S1, available online). The final sample included 4268 (GenR) and 8428 (ALSPAC) children.

### Ethical standards

Ethical approval was obtained from the medical ethical committee of Erasmus MC, University Medical Center Rotterdam and from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Written informed consent was obtained for all participants and both studies conform with the World Medical Association Declaration of Helsinki (2013).

### 2.2.2 Measures

#### Prenatal and postnatal ELS

The prenatal (i.e., maternal exposure during pregnancy) and postnatal (i.e. from birth to 10 years) cumulative ELS scores comprise information about five stress domains in line with previous literature (Cecil et al., 2014; Rijlaarsdam et al., 2016): life events (e.g., death of a parent), contextual risk (e.g., financial difficulties), parental risk (e.g., parental psychopathology), interpersonal risk (e.g., family conflicts) and direct victimization (only postnatally, e.g. maltreatment or bullying). Note that, consistent with other work using this measure (Schuurmans et al., 2022), we use the term “postnatal” (in contrast to “prenatal”) to encompass stressors experienced across childhood (i.e., until the age of 10 years), rather than immediately following birth. A detailed description of the ELS scores is provided in online [Supplement 1](#) (see also the score’s [GitHub repository](#) for further details and scripts). Briefly, ~100 stress items were selected from each cohort, dichotomized into no risk (=0) or risk (=1), and assigned to a

domain based on expert knowledge (see Figure 2.1 for an overview of included items). Within each domain, dichotomized risks were summed and divided by the number of items in the domain. Finally, domain scores were summed within periods to obtain prenatal and postnatal stress scores.

### **Internalizing symptoms**

Internalizing symptoms were measured at an average age of 13.5 years (range: 12.5-16.8 years) using the Child behavior checklist (CBCL 6-18) (Achenbach, 1999) in GenR and the Strengths and difficulties questionnaire (SDQ) (Goodman et al., 2000) in ALSPAC. Both instruments are well-validated parental reports of emotional and behavioral functioning referring to the past 6 months, and have been shown to be comparable (Goodman & Scott, 1999). The CBCL internalizing subscale consists of 32 items rated on a 3-point scale, e.g., “*my child feels worthless or inferior*”. The SDQ emotional problems subscale contains 5 items rated on a 3-point scale, e.g., “*often unhappy, down-hearted or tearful*”.

### **Adiposity (fat mass)**

Body composition was measured using a dual-energy X-ray absorptiometry (DXA) scanner at an average age of 13.5 years (range: 12.5-16.6 years). Technical details of these measurements are provided elsewhere (Boyd et al., 2013; Voortman et al., 2016). Fat mass percentage was calculated by dividing the total body fat mass (kg) by the weight (kg) and multiplying by 100. To explore the importance of body fat distribution, measurements of android fat mass were also extracted from DXA scans.

### **Comorbidity**

To compute psycho-cardiometabolic comorbidity, internalizing symptoms and fat mass percentage were first dichotomized into high versus low-moderate, based on a cohort-specific 80th percentile cut-off value. The dichotomized values were then used to assign children to four groups: “healthy” (both outcomes <80th percentile); “high internalizing” (internalizing >80th & fat mass percentage 80th); “high adiposity” (internalizing 80th & fat mass percentage >80th); and “comorbid” (both outcomes >80th percentile). For additional information see Table 2.1 and online [Supplement 2](#).

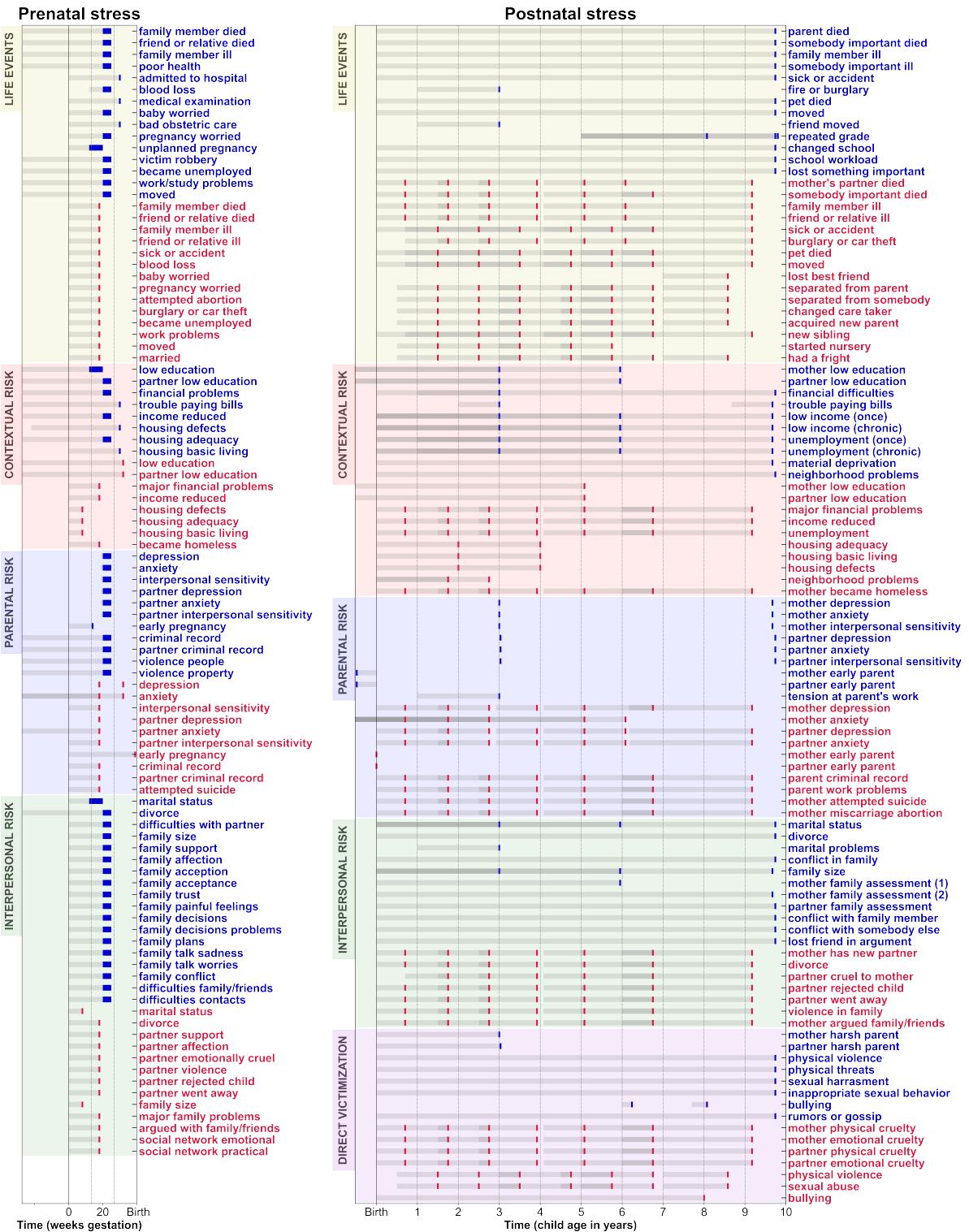


Figure 2.1: Temporal structure of the prenatal and postnatal early-life stress (ELS) score

The two graphs summarize the complex temporal structure of the prenatal (on the left) and postnatal (on the right) ELS scores. Time is depicted on the x-axis on the scale of weeks (gestation) for prenatal and years for postnatal items. For each question/item on the y-axis, a coloured dot represents the timepoint(s) at which the item was measured, and a grey shadow indicates the time period the question refers to (e.g., "since pregnancy" or "in the last year"). Red dots and labels refer to ALSPAC items and blue dots/labels refer to Generation R items. Items are grouped by domain, as indicated by the background color (yellow for life events, red for contextual risk, blue for parental risk, green for interpersonal risk and purple for direct victimization). The solid black vertical line indicates the beginning of the exposure period of interest, i.e., conception (or start of pregnancy) for prenatal items and birth for postnatal items. The dashed grey lines additionally provide temporal markers, i.e., trimesters in the prenatal period and a span of 1 year in the postnatal period.

## Covariates

During pregnancy, mothers reported on their smoking status, alcohol consumption, and pre-pregnancy body mass index (BMI). Information about child sex and date of birth was extracted from registries. Ethnic background (only available for GenR children) was determined by questionnaire-based assessment of the country of origin of participants' parents. Following Statistics Netherlands' guidelines (Alders, 2001), if one of the parents was born abroad, the child's ethnicity was determined according to that parent. If both parents were born abroad, the child was classified according to the mother's birthplace. Six large national groups were identified (i.e., Cape Verdean, Dutch, Dutch Antillean, Moroccan, Surinamese, and Turkish). Smaller national groups were aggregated into five additional categories: "Africa and Middle East", "Asia and Oceania", "Europe", "Latin America", and "North America" ([Figure S5](#)). See Table 2.1 and online [Supplement 3](#) for additional information on covariates measurement and distribution.

### 2.2.3 Statistical analysis

Analyses were run separately in the two cohorts, using R version 4.0.3 (R Core Team, 2021) All scripts are available on the project [GitHub repository](#). Missing values in the exposure, covariate and outcome variables were imputed by conditional multiple imputation (Van Buuren, 2018) using 60 iterations and 30 imputed datasets (for a complete assessment of missing values and detailed imputation strategy see [Supplement 4](#) and [Table S1](#), available online). Model parameters were fit in each imputed dataset and then pooled according to Rubin's rules. Pre- and postnatal stress, internalizing and adiposity were standardized using a z transformation. All statistical tests were two-sided and interpreted at a p-value significance threshold of 0.05. To account for multiple comparisons, false discovery rate (FDR) correction was applied.

### **Association of prenatal ELS with internalizing symptoms and adiposity**

For each continuous outcome (i.e., internalizing and adiposity), we performed a causal mediation analysis featuring prenatal stress as the exposure and postnatal stress as mediator (Wang & Arah, 2015). The method is described in detail in online *Supplement 5*. In summary, the “total” effect of prenatal ELS on each outcome was decomposed into a direct (i.e., not due to postnatal ELS) and indirect pathway (i.e., acting through postnatal ELS), allowing us to quantify the direct and mediated contribution of prenatal stress.

### **Association of postnatal ELS with internalizing symptoms and adiposity**

For each continuous outcome, four multiple linear regression models were run: 1) baseline (covariate only) model; 2) prenatal stress + covariates model; 3) postnatal stress + covariates model; and 4) prenatal + postnatal stress + covariates model. The baseline model served as reference for the computation of  $R_{inc}^2$ ; the prenatal model was used to ensure comparability of estimates between approaches.

### **Association of prenatal and postnatal ELS with comorbidity**

For the combined comorbidity outcome, two multinomial logistic regression models were performed, using the “healthy” group as reference, and pre-/postnatal stress as independent predictors. The odds ratios (OR) and 95% confidence intervals (CI) of developing comorbidity were visually compared to those of developing high internalizing and high adiposity only, to determine whether pre-/postnatal stress influence comorbidity beyond either health problem alone.

### **Follow-up and sensitivity analyses**

We examined effect modification by sex and by ethnic background - in GenR only, given its multi-ethnical composition (Kooijman et al., 2016). Additionally, to explore the relative contribution of different types of stress, three regression models (for internalizing, adiposity and comorbidity) were run including all 9 domain scores (4 prenatal and 5 postnatal) as independent predictors.

To assess the impact of the imputation procedure on our results, we ran the analyses in the subsample with complete outcome data (i.e., both internalizing and adiposity). Finally, we tested the stability of our results using android fat mass as an alternative measure of adiposity.

## 2.3 Results

### 2.3.1 Sample descriptives

Sample characteristics were pooled across imputed datasets and summarized in Table 2.1. Briefly, the ALSPAC sample included 8428 (48% male) children, whose mothers were 30% highly educated (i.e., held a college or university degree). The GenR sample included 4268 (52% male) participants, 62% of which were “Dutch” and 14% had highly educated (i.e., “higher, phase 2”) mothers. Pre- and postnatal ELS were moderately correlated ( $r = \text{GenR}: 0.56$ ; ALSPAC: 0.48; see online Supplement 1), whereas the correlation between internalizing symptoms and adiposity was weak ( $r = \text{GenR}: 0.15$ ; ALSPAC: 0.11).

Table 2.1

<b>Sample descriptives</b>	<b>GenR</b> <i>(n = 4268)</i>	<b>ALSPAC</b> <i>(n = 8428)</i>
<b>Prenatal stress</b> , median (range)		
Total score	0.42 (0–2.60)	0.48 (0–2.34)
Life events	0.13 (0–0.67)	0.07 (0–0.57)
Contextual risk	0.25 (0–1.00)	0.25 (0–0.88)
Parental risk	0.00 (0–0.71)	0.10 (0–0.83)
Interpersonal risk	0.06 (0–0.95)	0.00 (0–0.84)
<b>Postnatal stress</b> , median (range)		
Total score	0.64 (0–3.59)	2.69 (0.17–16.43)
Life events	0.23 (0–0.82)	1.07 (0–3.50)
Contextual risk	0.20 (0–1.00)	0.50 (0–2.90)
Parental risk	0.00 (0–0.79)	0.57 (0–3.62)
Interpersonal risk	0.00 (0–0.79)	0.29 (0–5.49)
Direct victimization	0.13 (0–0.86)	0.00 (0–3.10)
<b>Internalizing score</b> , median (range)	4.00 (0–41)	1.00 (0–10)
<b>Fat mass percentage</b> , median (range)	24.7 (8.5–54.6)	23.9 (4.9–56.3)
<b>Outcome groups</b> , n (%)		
Healthy	2791 (65)	5916 (70)
High internalizing	623 (15)	795 (9)
High adiposity	631 (15)	1476 (18)
Comorbid	223 (5)	241 (3)
<b>Sex</b> , n (%)		
Male participants	2087 (48)	4370 (52)
Female participants	2181 (52)	4058 (48)
<b>Ethnic background</b> , n (%)		

Table 2.1

**Sample descriptives**

Generation R (GenR) and ALSPAC cohorts

Africa and Middle East <sup>a</sup>	115 (2.7)	
Asia and Oceania <sup>a</sup>	100 (2.3)	
Cape Verdean	100 (2.3)	
Dutch	2673 (62.6)	
Dutch Antillean	118 (2.8)	
Europe <sup>a</sup>	334 (7.8)	
Latin America <sup>a</sup>	72 (1.7)	
Moroccan	176 (4.1)	
North America <sup>a</sup>	25 (0.6)	
Surinamese	296 (6.9)	
Turkish	247 (5.8)	
<b>Age of the child</b> , median (range), years	13.5 (12.6–16.6)	13.5 (12.8–15.0)
<b>Pre-pregnancy BMI</b> , median (range), kg/m <sup>2</sup>	22.6 (14.4–50.2)	22.1 (12.5–48.6)
<b>Maternal smoking</b> , n (%)		
Never	3228 (76)	4412 (52)
Until (early) pregnancy	390 (9)	2524 (30)
During pregnancy	650 (15)	1492 (18)
<b>Maternal alcohol consumption</b> , GenR: n (%); ALSPAC: median (range)		
Never	1694 (40)	
Until early pregnancy	596 (14)	
Continued occasionally	1570 (37)	0.50 (0 – 3.5)
Continued frequently	407 (10)	
<b>Maternal education</b> , n (%) <sup>b</sup>		
Low	1716 (40.2)	4216 (50.0)
Medium	1278 (29.9)	3001 (35.6)
High	1274 (29.9)	1212 (14.4)
<b>Household income</b> , n (%) <sup>c</sup>		
Low	702 (16.4)	1318 (15.6)
Medium	2070 (48.5)	4324 (51.3)
High	1497 (35.1)	2786 (33.1)

Table 2.1

---

**Sample descriptives**

Generation R (GenR) and ALSPAC cohorts

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Note: Sample descriptives pooled across 30 imputed datasets. BMI = Body-mass index.

**a Ethnic background grouping:**

Africa and Middle East = Iran (n=11); Iraq (10); South Africa (8); Angola (7); Eritrea (7); Israel (6); Cameroon (5); Egypt (5); Nigeria (5); Ethiopia (4); Algeria (3); Ghana (3); Lebanon (3); Liberia (3); Syria (3); Tanzania (3); Côte d'Ivoire (2); Guinea (2); Mozambique (2); Saudi Arabia (2); Senegal (2); Zimbabwe (2); Africa (1); Armenia (1); Burundi (1); Congo (1); French Congo (1); Gambia (1); Kenya (1); Mali (1); Mauritania (1); Palestine (1); Sierra Leone (1); Somalia (1); Sudan (1); Togo (1); Tunisia (1); Uganda (1); Yemen (1).

Asia and Oceania = Indonesia (n=23); Pakistan (9); Australia (6); China (6); Japan (6); Philippines (6); Thailand (6); India (5); Afghanistan (4); Hongkong (4); South Korea (4); Vietnam (4); Bangladesh (3); Korea (3); Taiwan (3); Kazakhstan (2); New Zealand (2); Dutch New Guinea (1); East Timor (1); Singapore (1); Sri Lanka (1).

Europe = Germany (n=55); Belgium (35); United Kingdom (30); France (29); Portugal (22); Spain (18); Yugoslavia (18); Poland (16); Italy (12); Bosnia-Herzegovina (11); Russia (10); Croatia (7); Czech Republic (7); Switzerland (7); Hungary (6); North Macedonia (6); Serbia-Montenegro (5); Denmark (4); Ireland (4); Norway (4); Sweden (4); Greece (3); Lithuania (3); Romania (3); Austria (2); Kosovo (2); Ukraine (2); Canary Islands (1); Estonia (1); Finland (1); Luxembourg (1); Madeira Islands (1); Moldova (1); Monaco (1); Slovakia (1); Slovenia (1).

Latin America = Colombia (n=18); Brazil (11); Dominican Republic (8); Chile (6); Venezuela (6); Cuba (4); Mexico (4); Argentina (3); Peru (3); Ecuador (2); Guyana (2); Belize (1); Bolivia (1); Haiti (1); Paraguay (1); Trinidad and Tobago (1).

North America = United States of America (n=16); Canada (9).

**b Maternal education:** low = “secondary, phase 2” or lower in GenR, “None”, “CSE”, “Vocational” or “O level” in ALSPAC; medium = “higher, phase 1” in GenR, “A level” in ALSPAC; high = “higher, phase 2” in GenR, “(College or university) degree” in ALSPAC. Categorization based on ISCED 2011.

**c Household income:** low = < €1600 /month in GenR, < £200 /week in ALSPAC; medium = between €1600 and € 4000 /month in GenR, between £200 and £400 /week in ALSPAC; high = > € 4000 /month in GenR, > £400 /week in ALSPAC.

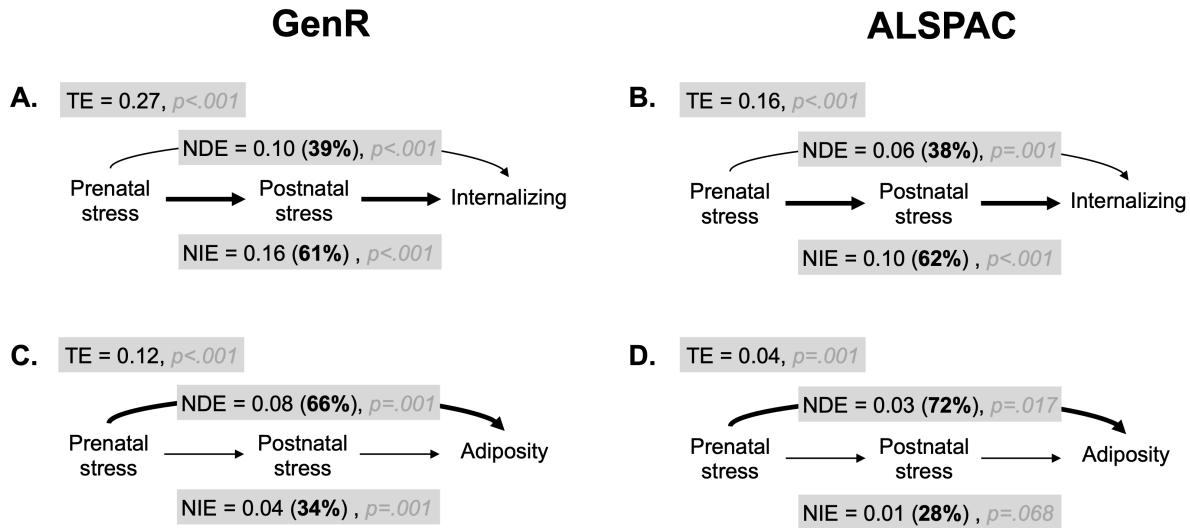
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### 2.3.2 Associations of prenatal ELS with internalizing symptoms and adiposity

Results of the mediation analysis linking prenatal stress to internalizing and adiposity were highly consistent across cohorts (see Figure 2.2 and online [Table S2](#)).

About ~60% of the total effect (TE) of prenatal stress on internalizing symptoms (TE [95%CI]

= GenR: 0.27 [0.23;0.30]; ALSPAC: 0.16 [0.13;0.18]) was mediated through postnatal stress (GenR: 0.16 [0.14;0.19]; ALSPAC: 0.10 [0.08;0.11]). The TE of prenatal stress on adiposity (GenR: 0.12 [0.09;0.15]; ALSPAC: 0.04 [0.03;0.06]) was smaller compared to internalizing and largely (~70%) operating via the direct pathway (GenR: 0.08 [0.04;0.12]; ALSPAC: 0.03 [0.01;0.05]).



*Figure 2.2: Prenatal early-life stress (ELS) contribution (causal mediation analysis results)*

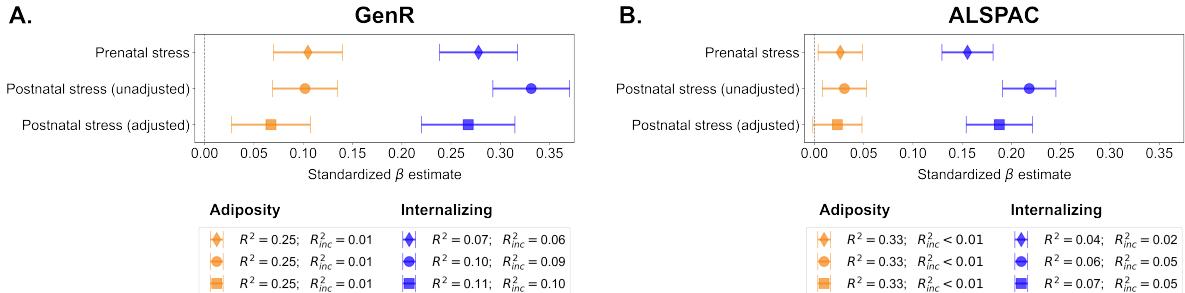
(A-D) The causal estimates for the total effect (TE), natural direct (NDE) and natural indirect effect (NIE) of prenatal stress on internalizing symptoms (A. Generation R and B. ALSPAC) and adiposity (C. Generation R and D. ALSPAC) are displayed in the grey boxes. The percentage of the total effect due to direct and indirect pathway is reported between brackets and the respective p-values are marked in grey. The predominant path is highlighted with a thicker arrow. NDE = natural direct effect; NIE = natural indirect effect; TE = total effect.

### **2.3.3 Association of postnatal ELS with internalizing symptoms and adiposity**

Results of the hierarchical regressions examining the association of postnatal stress with internalizing and adiposity were also largely similar across cohorts (see Figure 2.3; online *Tables S3 and S4*).

Higher postnatal stress associated with increased internalizing symptoms both before ( $\beta$  [95%CI] = GenR: 0.33 [0.29;0.37]; ALSPAC: 0.22 [0.19;0.25]) and after adjustment for prenatal stress (GenR: 0.27 [0.22;0.31]; ALSPAC: 0.19 [0.15;0.22]).

Higher postnatal stress also associated with increased adiposity (GenR: 0.10 [0.07;0.13]; ALSPAC: 0.03 [0.01;0.05]). The association remained after prenatal stress adjustment in GenR (0.07 [0.03;0.11]), but not in ALSPAC (0.02 [0.00;0.05]).



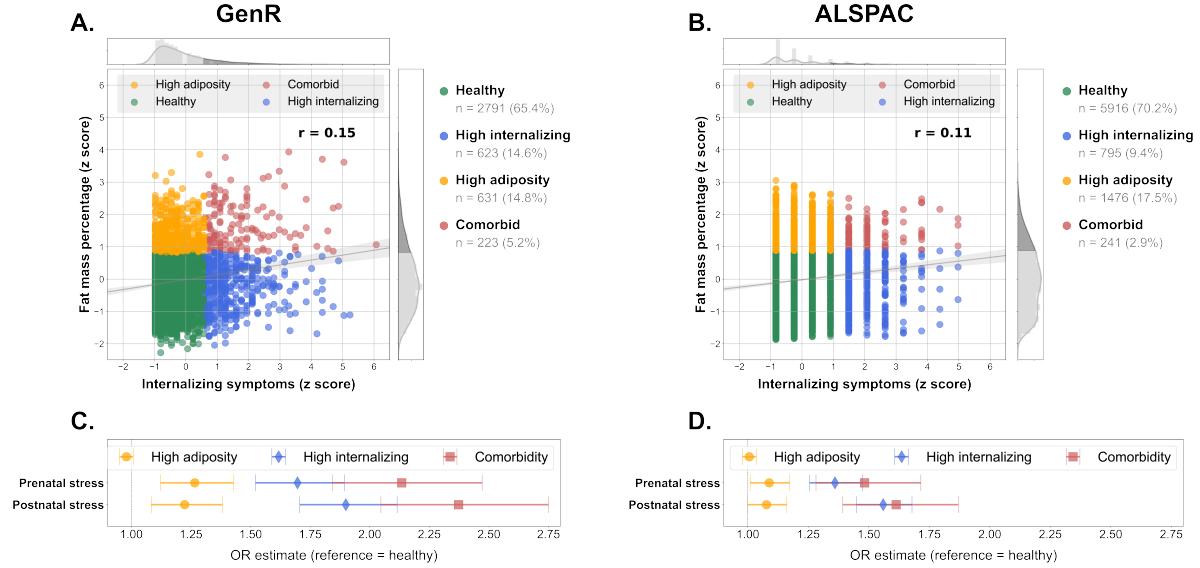
**Figure 2.3: Postnatal early-life stress (ELS) contribution (hierarchical regression results)**

(A, B) In each cohort (A. Generation R and B. ALSPAC), the standardized beta estimates of pre- and postnatal ELS (and their 95% confidence intervals) are represented along the x-axis, using different color sets for internalizing symptoms (light and dark blue) and adiposity (yellow and orange). Estimates generated by the prenatal only model are presented on the first row and marked in lighter colours (i.e., light blue and yellow); these correspond to the TE displayed in Figure 2. Postnatal ELS beta estimates, before (round marker) and after (square marker) prenatal adjustment, are displayed in darker colors (blue and orange). For each model, the total and incremental  $R^2$  is reported in the legend below the graphs. The first number provides an indication of total model fit; the latter quantifies the increase in variance explained due to the introduction of the predictor (compared to the covariate only model).

### 2.3.4 Association of prenatal and postnatal ELS with comorbidity

Higher stress in the prenatal (OR [95%CI] = GenR: 2.13 [1.84;2.47]; ALSPAC: 1.48 [1.28;1.71]) and postnatal periods (GenR: 2.37 [2.05;2.75]; ALSPAC: 1.61 [1.39;1.87]) was associated with higher odds of belonging to the comorbidity group compared to the healthy group (see Figure 2.4 and online *Table S5*). This association was the strongest compared to all other (single-

outcome) groups. However, the CIs of the comorbidity estimates did overlap with those of high internalizing only (Figure 2.4 C and D).



**Figure 2.4: Pre- and postnatal early-life stress (ELS) and psycho-cardiometabolic comorbidity**

(A, B) Scatterplots of internalizing symptoms (on the x axis) and fat mass percentage (on the y axis), for the Generation R (A) and ALSPAC (B) cohorts. The univariate distributions of both primary outcomes are shown on the respective axes, with darker shadow indicating the 80th percentile cut-off used in construction of the comorbidity variable. Colour indicates the assigned group (green = healthy; blue = high internalizing; yellow = high adiposity; red = comorbid). Group sizes (i.e., n and percent of the total cohort sample) were pooled across imputed datasets and reported on the right of each scatterplot. (C, D) Effect estimates for pre- and postnatal stress (and their 95% CIs) on the odds ratio (OR) scale are represented along the x-axis, with different colours depending on the comparison they refer to (yellow = healthy vs. high adiposity; blue = healthy vs. high internalizing; red = healthy vs. comorbid), in Generation R (C) and ALSPAC (D) children.

### **2.3.5 Follow-up analyses**

#### **Interaction with sex and ethnic background**

After stratifying by sex, in GenR, the association between prenatal ELS and adiposity was larger in girls than in boys ( $Z=1.89$ ,  $p=.029$ ), whereas that of postnatal ELS was slightly larger in boys ( $Z=-1.38$ ,  $p=.083$ ). A similar pattern of associations was found in ALSPAC but with smaller magnitudes (see *Figures S2-S4* and *Tables S6-S9*, available online).

In GenR, Cape Verdian and Dutch Antillean children experienced the highest cumulative prenatal and postnatal stress followed by Turkish, Surinamese and Moroccan children (*Figure S5-B*). We did not find evidence for a significant interaction between pre- or postnatal ELS and the examined ethnic background groups on any outcome of interest (i.e., internalizing symptoms, adiposity or comorbidity; see *Table S10* and *Figure S5-C*, available online). Note however that the association between pre-/postnatal ELS and comorbidity in the “North American” group could not be estimated due to insufficient number of observations (i.e., comorbidity group size = 5).

#### **Contribution of specific stress domains**

Across cohorts, internalizing symptoms were consistently associated with higher prenatal and postnatal parental risk (e.g., parental psychopathology), postnatal life events and direct victimization (see *Figure S6* and *Table S11*, available online). We found no consistent associations for adiposity. Only postnatal parental risk was consistently associated comorbidity status (vs. healthy) across cohorts (see *Figure S7* and *Table S12*, available online).

#### **Sensitivity analyses**

Restricting the analyses to participants with complete outcome data ( $n =$  GenR: 2749; ALSPAC: 4096) did not substantively change the reported findings (see *Figure S8* and *Tables S13-S15*, available online), nor did the use of android fat mass rather than fat mass percentage as a proxy of adiposity (see *Figure S9* and *Table S16*, available online). None of the main conclusions was impacted by FDR correction.

## **2.4 Discussion**

Our aim was to elucidate the role of ELS on adolescent internalizing problems and adiposity, as well as their comorbidity, based on prospective data from two population birth cohorts. We highlight two key findings. Firstly, exposure to cumulative stress is strongly associated with internalizing symptoms (especially postnatal ELS) and, to a lesser extent, with adiposity

(especially prenatal ELS). Secondly, both pre- and postnatal stress associate with psycho-cardiometabolic comorbidity more strongly than to individual health outcomes.

Our first objective was to disentangle the relative contribution of prenatal and postnatal stress exposure to adolescent internalizing symptoms and adiposity.

We found that, although both pre- and postnatal ELS contribute to internalizing symptoms, the impact of postnatal stress is larger and it is not explained by prenatal confounding, while ~60% of the prenatal effect was mediated through postnatal stress. This finding aligns with previous studies investigating the contribution of prenatal and postnatal exposure to specific stressors (Clayborne et al., 2021; Plant et al., 2015), and holds promising clinical implications given that several aspects of the postnatal environment may be modifiable (Yap et al., 2016). In particular, parental risk factors (such as psychopathology), direct victimization (e.g., maltreatment) and life events emerged as independent predictors of internalizing symptoms in our exploratory analyses, indicating that these may represent important targets for intervention.

To our knowledge, no study to date has explored such timing effects on adiposity or related outcomes. Here, we found that ~70% of the effect of prenatal stress on adiposity was “direct” (i.e., not mediated by postnatal stress); the effect of postnatal stress, both as mediator and as predictor in the adjusted models, was smaller and resulted statistically significant only in GenR. While it is important to note that the effect sizes observed in the adiposity models were markedly smaller than for internalizing symptoms, these findings provide some indication that fat accumulation processes could be particularly vulnerable to (stress-induced) alterations of the prenatal environment. This is in line with previous theoretical (Barker, 1998; Gluckman et al., 2008) and empirical (Entringer et al., 2012; Entringer, 2013) accounts showcasing the impact of stress and stress hormones during prenatal life on the programming of metabolic function and obesity risk. In our exploratory follow-up analyses, we additionally found some evidence that adiposity may be more strongly associated with prenatal stress in girls, versus postnatal stress in boys. However previous accounts of these sex differences are mixed (Murphy & Loria, 2017; Paternain et al., 2013), and differences in pubertal development may be an important confounding factor that was not accounted for in our analysis.

It is also possible that stronger associations between postnatal ELS and adiposity will emerge later in development. Indeed, accumulating postnatal risks may influence biological (e.g., inflammatory and neuro-endocrine) and behavioral factors (e.g., diet and exercise) that in turn increase physical health burden, but this might become evident only later in life (Danese & Tan, 2014; Elsenburg et al., 2017).

Our second aim was to examine whether ELS relates to psycho-cardiometabolic comorbidity, as suggested by some theoretical accounts (Juster et al., 2016), but never explicitly investigated before. If comorbidity was a discrete stress-related pathophysiological process, then the effect of ELS on comorbidity would differ from the effect of ELS on mental and physical health separately. This expectation was partially confirmed by our data: ELS increased the risk of developing comorbidity compared to being healthy and this estimate was highest relative to

all other groups. However, the overlap between CIs of the comorbidity and the internalizing-only estimate indicates that neither pre- nor postnatal stress levels were sufficient to predict whether a child will develop comorbidity vs. internalizing problems alone. Notably, cross-sectional correlations between internalizing and adiposity at age 13 were small (and so were the comorbidity group sizes), which may partly explain these findings. However, comorbidity is known to increase with age (Barnett et al., 2012) and it is possible that pre- / postnatal stress may serve as better discriminators between comorbidity and internalizing problems in older samples, with higher comorbidity rates.

This study has several important strengths. We analysed data from two large population-based cohorts with remarkably consistent results, which adds confidence to the robustness and generalizability of our findings. We used a longitudinal and comprehensive assessment of ELS, enabling us to quantify the relative contribution of pre- and postnatal exposure to a broad spectrum of stressors. We focused on two pre-clinical health markers which manifest in adolescence and may be important targets for early prevention. Also, the challenge of incomplete data and possible selection bias was thoroughly addressed by multiple imputation and sensitivity analyses. However, it is important to note that our measures of ELS and internalizing symptoms rely primarily on parent reports, which might have introduced information bias. Further, although several important confounders were taken into account, it will be important in the future to examine the role of other potential contributors, including (epi-)genetic influences (Inoue et al., 2022), pubertal status, disability/functional impairment and other behavioral factors (e.g., sleep, exercise, diet).

In conclusion, current approaches to the prevention and management of depression and obesity have yielded limited success. We believe the adoption of an integrated, developmental framework is necessary to improve our understanding and set the stage for better detection and prevention of these disorders, both in isolation and in their comorbid form. We provide evidence that both pre- and postnatal ELS associate with adolescent internalizing symptoms (with prenatal < postnatal stress), adiposity (with prenatal > postnatal stress), and their comorbidity at age 13. While recommendations for how to best intervene when a higher psychosocial stress burden is identified are still at embryonic stage, one novel suggestion emerging from our findings is that prenatal stress may be an underrecognized factor for identifying children at higher risk of overweight. We would therefore advise clinicians to enquire about prenatal stress exposure as part of routine pediatric assessments, so that adequate monitoring and lifestyle preventative measures can be introduced as early as infancy.

Finally, as we follow these children, it will be informative to see how these associations evolve over time. For instance, the association between ELS exposure and adiposity-related outcomes may not emerge fully until adulthood and it is possible that the nature of the relation between ELS and comorbidity also differs as a function of developmental stage.

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### 3 Lifestyle factors, ELS and adolescent psycho-physical health

Adapted from:

**The role of lifestyle factors in the association between early-life stress and adolescent psycho-physical health: Moderation analysis in two European birth cohorts**

**Defina, S., Woofenden, T., Baltramonaityte, V., Tiemeier, H., Fairchild, G., Felix, J. F., Cecil, C.A.M., & Walton, E.** (2024). *Preventive Medicine*. [DOI](#)

#### Abstract

**Objective:** Early-life stress (ELS) is an established risk factor for a host of adult mental and physical health problems, including both depression and obesity. Recent studies additionally showed that ELS was associated with an increased risk of comorbidity between mental and physical health problems, already in adolescence. Healthy lifestyle factors, including physical activity, sleep and diet have also been robustly linked to both emotional and physical wellbeing. However, it is yet unclear whether these lifestyle factors may moderate the association between ELS and psycho-physical comorbidity.

**Methods:** We investigated whether (a) participation in physical activity, (b) sleep duration, and (c) adherence to a Mediterranean diet, moderated the relationship between cumulative ELS exposure over the first 10 years of life and psycho-physical comorbidity at the age of 13.5 years. Analyses were conducted in 2022-2023, using data from two large adolescent samples based in the UK (ALSPAC; n=8428) and The Netherlands (Generation R; n=4268).

**Results:** Exposure to ELS was significantly associated with a higher risk of developing comorbidity, however this association was not modified by any of the three lifestyle factors investigated. Only physical activity was significantly associated with a reduced risk of comorbidity in one cohort ( $OR_{ALSPAC}$  [95%CI] = 0.73 [0.59; 0.89]).

**Conclusions:** In conclusion, while we found some evidence that more frequent physical activity may be associated with a reduction in psycho-physical comorbidity, we did not find evidence in support of the hypothesised moderation effects. However, more research is warranted to examine how these associations may evolve over time.

## Links

**Supplementary materials:** <https://osf.io/2wz4u/files/osfstorage>



**Project's code:** <https://github.com/SereDef/lifestyle-moderators-project>



**ELS score:** <https://github.com/SereDef/cumulative-ELS-score>



## Keywords

Adverse Childhood Experiences; Comorbidity; Physical Activity; Sleep; Diet, Mediterranean; Depression; Adiposity; moderation analysis.

## Abbreviations

Avon Longitudinal Study of Parents and Children (ALSPAC), Body Mass Index (BMI), Confidence Interval (CI), Child Behavior Checklist (CBCL), Dual-energy X-ray absorptiometry (DXA), Early Life Stress (ELS), Food Frequency Questionnaire (FFQ), Generation R (GenR), Odds Ratio (OR), Strengths and Difficulties Questionnaire (SDQ), Variance Inflation Factor (VIF), United Kingdom (UK).

### **3.1 Introduction**

Over the past few decades, the prevalence of comorbid mental and physical diseases has risen dramatically, posing a major challenge for health services across the world (Launders et al., 2022; Ronaldson et al., 2021). In particular, multiple large studies have shown a substantial degree of comorbidity between common mood disorders, such as depression and anxiety, and cardio-metabolic conditions, including diabetes, obesity and cardiovascular disease (Fisher et al., 2014; Gold et al., 2020; Souama et al., 2023). Mounting evidence is further suggesting an early origin of these psycho-physical comorbidity patterns, involving shared risk factors and pathophysiological pathways that begin already in utero (Milaneschi et al., 2019). One of such risk factors is psychosocial stress – including for instance family conflict, financial difficulties or victimization, experienced in the first years of life – here collectively defined as early-life stress (ELS). For example, a recent study conducted in two independent population-based samples reported that exposure to ELS during gestation and throughout the first 10 years of life prospectively associated with increased internalizing symptoms<sup>1</sup>, adiposity, as well as their co-occurrence in adolescence (Defina et al., 2023). The study focused on broad, pre-clinical measures of depression/anxiety (i.e. internalizing symptoms) and cardio-metabolic risk (i.e. adiposity) respectively. However, these associations were also shown to persist into mid- and late adulthood and manifest into clinical diagnoses (Bright et al., 2016; Milaneschi et al., 2019; Souama et al., 2023), highlighting the early developmental origins of these risk pathways.

While these findings certainly support the importance of primary prevention programmes aimed at reducing the incidence of ELS, preventing ELS may not always be possible. As such, there is a need to identify alternative modifiable factors that could mitigate the negative impact of ELS on later health, and inform the development of complementary intervention strategies.

Healthy lifestyle factors, including physical activity, sleep and diet have been robustly linked to both emotional and physical wellbeing (Briguglio et al., 2020; Firth et al., 2020). For example, regular physical activity was associated with reduced internalizing (Wheatley et al., 2020) and depressive symptoms (Oberste et al., 2020), as well as with lower body mass index (BMI) (Schwarzfischer et al., 2017) in children and adolescents. Adolescents reporting longer sleep durations have also been shown to be at lower odds of developing depression and obesity (Owens et al., 2014). Moreover, diet quality, particularly adherence to a Mediterranean diet, was associated with reduced internalizing symptoms (Orlando et al., 2022) and risk of depression (Shafiei et al., 2023), as well as with lower adiposity (Tognon et al., 2014) in childhood.

However, it remains unclear whether any of these lifestyle factors could effectively attenuate the association between ELS exposure and the risk of comorbidity between mental and physical

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<sup>1</sup>Internalizing symptoms (Achenbach, 1966) refer to a host of problems, including feelings of sadness, withdrawal, anxiety, loneliness or somatic complaints that are typical of early manifestations of depression and anxiety during childhood and adolescence.

health problems, in early adolescence.

To address this gap, we replicated and extended Defina et al.'s (2023) approach, by investigating the interaction between cumulative ELS exposure and (a) participation in physical activity, (b) sleep duration, and (c) adherence to a Mediterranean diet, on adolescent psycho-physical comorbidity, defined as the co-occurrence of high internalizing symptoms and high adiposity.

## 3.2 Methods

This study follows STROBE guidelines (Elm et al., 2008).

### 3.2.1 Participants

Our sample was drawn from two ongoing population-based longitudinal birth cohorts: the Avon Longitudinal Study of Parents and Children (ALSPAC) involving a total of 14,833 pregnant women whose children were born in Avon (UK) between 1991 and 1992 (Boyd et al., 2012; Fraser et al., 2013); and the Generation R (GenR) Study, involving 9,778 pregnant women, with children born in Rotterdam (the Netherlands) between 2002 and 2006 (Kooijman et al., 2016). Please note that the [ALSPAC website](#) contains details of all the data that is available through a fully searchable data dictionary and variable search tool. More detailed information about ALSPAC study numbers can be found in [Supplementary Text S1](#), available online.

Response rates at the 13 years follow-up were 61% in ALSPAC and 64% in GenR. Participant selection criteria have been previously described (Defina et al., 2023). In summary, children with more than 50% missing ELS items in either the pre- or postnatal period were excluded. All twins were further excluded and, in the case of non-twin siblings, only one was retained in the sample. The final sample included 8,428 and 4,268 children in ALSPAC and GenR respectively.

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee, the University of Bath Psychology Research Ethics Committee (reference number: 20-195), and from the Medical Ethical Committee of Erasmus MC, University Medical Center Rotterdam (MEC-198.782.2001.31).

### 3.2.2 Measures

#### Early Life Stress (ELS) exposure

A detailed description of the ELS exposure score can be found elsewhere [Defina et al. (2023); [ELS score repository](#)]. Briefly, a prenatal (i.e., maternal exposure during pregnancy) and

postnatal (i.e. from birth to 10 years) cumulative ELS score was constructed in each cohort by combining ~100 stress-related items (e.g., death of a relative; financial difficulties; parental psychopathology; maltreatment or bullying). Prenatal and postnatal stress scores were then summed to obtain a total ELS exposure score, spanning from pregnancy to age 10 years.

### **Physical and mental health outcomes**

Following the same approach as Defina et al. (2023), we defined psycho-physical comorbidity as the co-occurrence of high internalizing symptoms and high adiposity.

Internalizing symptoms were assessed by parental reports when children were on average 13.5 years old (range: 12.5-16.8 years) using the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997) in ALSPAC and the Child Behavior Checklist (CBCL 6-18) (Achenbach, 1999) in GenR. Both instruments are well-validated reports of emotional and behavioural functioning referring to the past 6 months, and have been shown to be comparable ( $r=0.74$ ) (Goodman & Scott, 1999).

Adiposity was measured using total body fat mass percentage estimated via dual-energy X-ray absorptiometry (DXA) scanner (ALSPAC: Lunar Prodigy DXA scanner, GE Healthcare; GenR: iDXA scanner, GE Healthcare, Madison, WI) at the average age of 13.5 years (range: 12.5-16.6 years).

Finally, to obtain psycho-physical comorbidity, internalizing symptoms and fat mass percentage were first dichotomized into high versus low-moderate, based on a cohort-specific 80th percentile cut-off value. The dichotomized values were then used to assign children to 4 groups: “Healthy” (both outcomes <80th percentile); “High internalizing” (internalizing >80th & fat mass percentage 80th); “High adiposity” (internalizing 80th & fat mass percentage >80th); and “Comorbid” (both outcomes >80th percentile). Note that the 80th percentile cut-off was based on previous validation studies (Achenbach & Rescorla, 2001; Bourdon et al., 2005; Flegal et al., 2010; Weber et al., 2014) and the resulting size of the comorbidity group was larger than expected by chance (permutation test  $p < 0.01$ ; see *Supplement 2* in Defina et al. (2023)).

### **Lifestyle factors**

**Physical activity.** Frequency of physical activity was measured via questionnaires when children were on average 10.7 years old (range: 10.6-14.7) in ALSPAC and 9.7 years (range: 8.9-12.4) in GenR. ALSPAC mothers were asked about the “*Average number of times their child participated in vigorous physical activity in past month*” (“none”, “less than once a week”, “1-3 times a week”, “4-6 times a week” and “daily”), while GenR children reported “*How often did they play sports at a sports club or team?*” (“once a week”, “2 times a week”, “3 times a week”, “4 times a week”, or “5 or more times a week”).

**Sleep.** In the ALSPAC sample, sleep duration (hours) was calculated using maternal reports of the “*Time their child usually goes to sleep and wakes up on normal school days*”, collected at the mean age of 11.7 years (range: 11.4-13.8).

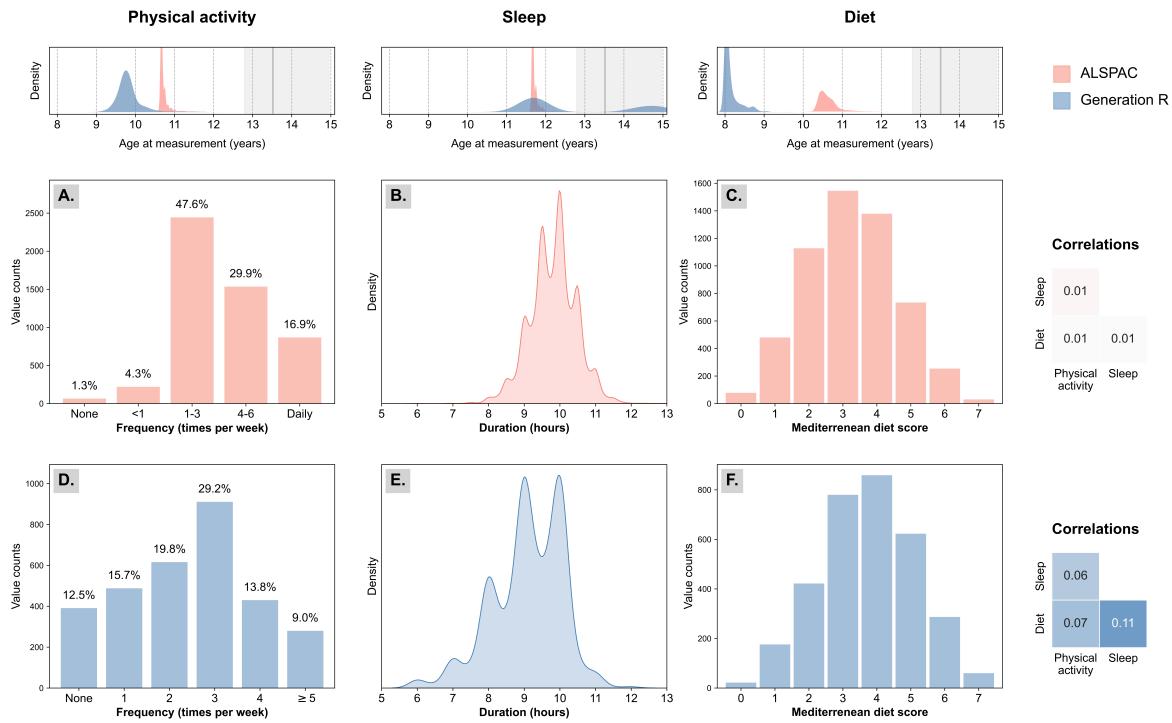
In GenR, a selected subsample of children [N=1,483; Koopman-Verhoeff et al. (2019)] completed a sleep diary including questions about the time they went to bed and woke up, on nine consecutive days (i.e., 5 weekdays and 4 weekend days). These self-reports were used to calculate average sleep duration across the nine days. Mean age of measurement was 12.7 years (range: 10.4-15.6), however, due to logistical reasons, data collection was split into two waves, resulting in a 3-years age difference between the first and second group (i.e., 11 and 14 years; see Figure 3.1 B). Sleep duration values measured after either outcome of interest were set to missing (N=519).

**Diet.** Nutritional intake was assessed at 10.6 years (range: 9.8-12.2) in ALSPAC and at 8.2 years (range: 7.5-10.8) in GenR, using a 3-day child-reported food diary (Cribb et al., 2011), and the 4-week parent-reported food frequency questionnaire [FFQ; Dutman et al. (2011)], respectively.

ALSPAC participants were asked to record all foods and drinks consumed over three individual days (preferably one weekend and two weekdays, not necessarily consecutive), using household measures. The structured diary was designed for the child to complete with the help of their parents. They would then bring the diary to the clinic visit where, if possible, any uncertainties were clarified by a member of the nutrition team. Food records were transformed into food codes and associated weights using the DIDO software (Price et al., 1995).

The FFQ consists of 71 food items relevant for the energy intake of Dutch children (Netherlands Nutrition Centre, 1998). Information on frequencies, types, and portion sizes was converted into grams of individual food items per day based on standard Dutch portion sizes (Velde et al., 2019).

A Mediterranean diet adherence score (ranging from 0 to 7) (Trichopoulou et al., 2003) was constructed by assigning 1 point for the elevated (i.e., median) consumption of five beneficial food groups (i.e., vegetables, legumes, fruits and nuts, cereal, and fish), and 1 point for the restricted (i.e., < median) consumption of two detrimental food groups (i.e., meat and dairy products). Details of specific items included in the food groups in each cohort can be found in *Supplementary Text S2*.



**Figure 3.1: Lifestyle factors characteristics in ALSPAC and Generation R children (UK, 2002-2005; The Netherlands, 2010-2016)**

(A-F) Characteristics of physical activity, sleep and diet measurements in the ALSPAC (A-C; in pink) and GenR cohorts (D-F; in blue). In the top panel, the distributions of child age at moderator measurement are depicted for both cohorts. A grey line and shadow also indicate the average and range of child age at outcome measurement. The central and bottom panel depict the distribution and correlation between the three lifestyle factors in ALSPAC and GenR respectively.

### 3.2.3 Statistical analysis

Analyses were run separately in the two cohorts, using R version 4.1.0 (R Core Team, 2021) (scripts publicly available [here](#)).

Missing values in all variables of interest (i.e., exposures, outcomes, moderators and covariates) were imputed by conditional multiple imputation (Buuren & Groothuis-Oudshoorn, 2011) using 60 iterations and 30 imputed datasets (for a complete assessment of missing values and detailed imputation strategy see *Supplementary Text S3* and *Supplementary Table S1*, available online). Model parameters were fit in each imputed dataset and then pooled according to Rubin's Rules. To account for multiple comparisons, false discovery rate correction was applied.

## Main analyses

To address our primary hypotheses, three multinomial logistic regressions (i.e., one for each lifestyle factor) were performed, with psycho-physical risk group as a dependent variable. The reference level was set to “healthy”. These models included: *a*) the main effect of total ELS, *b*) that of each lifestyle factor (separately; i.e., physical activity, sleep and diet) and *c*) their interaction, as well as the full set of covariates. In order to generate meaningful and comparable estimates for the main effects of interest, both ELS scores and lifestyle factor variables were standardized using a z transformation before entering the models. The covariate set included child sex, age at outcome measure, ethnicity (dichotomized into “White” and “non-White”), maternal smoking and alcohol consumption during pregnancy and maternal pre-pregnancy BMI. To diagnose multicollinearity between independent variables we computed generalized variance inflation factors (VIF) for each predictor (James et al., 2013).

## Follow-up analyses

Several follow-up analyses were conducted, whereby the three main models (i.e., for physical activity, sleep and diet) were modified to:

- a) Feature \*(i)\* internalizing symptoms and \*(ii)\* adiposity (rather than their comorbidity)
  - b) Examine pre-/postnatal ELS (rather than the total ELS score) as main stress exposure;
  - c) Assess the effect of adhering to international guidelines regarding weekly physical activity
- We dichotomised the physical activity variable according to the WHO recommended guideline for...

We additionally explored potential non-linear associations between each lifestyle factor and the main outcomes of interest by including second- and third-degree polynomial terms in the models. To assess the extent to which maternal health and lifestyle behaviour may have moderated the relationships of interest (Epstein et al., 2023; Heslehurst et al., 2019), we further investigated the interaction between ELS and maternal BMI on child comorbidity. Finally, to assess the impact of the imputation procedure on our results, we ran the analyses in the subsample with complete moderator and outcome data.

## 3.3 Results

### 3.3.1 Sample characteristics

Sample characteristics were pooled across imputed datasets and summarized in Table 1. Briefly, the ALSPAC sample included 8,428 (48% male) children, whose mothers were 96% White and 30% highly educated (i.e., held a college or university degree). The GenR sample included 4,268 (52% male) participants, 71% of which were encoded as “White” (i.e., European, North

American, Japanese or Indonesian) and 14% had highly educated (i.e., “higher, phase 2”) mothers. The distribution of each lifestyle factor and their correlations are displayed in Figure 1. The proportion of children categorized as comorbid was small (2.9% in ALSPAC and 5.1% in GenR), as also reflected by the weak correlations between internalizing scores and adiposity ( $r = \text{ALSPAC: } 0.10; \text{ GenR: } 0.12$ ; see Supplementary Table S2).

### 3.3.2 Main analyses

We did not find evidence in support of any of the hypothesised moderation effects (Supplementary Table S3). Increased ELS was significantly associated with higher risk of developing comorbidity (vs. being healthy; Figure 2A; ORs: 1.65-1.67 in ALSPAC and 2.70-2.75 in GenR), but this association was not modified by any of the three lifestyle factors we investigated (Figure 2B-D). Conversely, while comorbidity risk was generally lower in children who engaged in favourable lifestyle behaviours (Figure 2A), this effect was only significant for physical activity and only in one of the two cohorts (ORALSPAC [95%CI] = 0.73 [0.59;0.89]). The magnitude of multicollinearity was low in all the models (VIF = 1.17; see Supplementary Table S3).

### 3.3.3 Follow-up analyses

When internalizing symptoms and adiposity were examined as two separate outcomes, a similar pattern of results emerged (Supplementary Tables S4; Figure 3). ELS was significantly associated with increased internalizing symptoms and adiposity, but neither association was modified by physical activity, sleep or diet. Only the main effect of physical activity on internalizing symptoms was statistically significant in both cohorts ( ALSPAC [95%CI] = -0.05 [-0.08;-0.03]; GenR [95%CI] = -0.05 [-0.09;-0.02]). Engagement in two of the three favourable lifestyle behaviours was linked to lower adiposity levels, but only in one of the two cohorts ( ALSPAC [95%CI]: physical activity = -0.08 [-0.10;-0.06]; sleep = -0.02 [-0.05;0.01]). Findings did not change substantially when ELS exposure was restricted to the prenatal or postnatal periods only (Supplementary Table S5), nor when lifestyle factors were dichotomized into adherence and non-adherence to international guidelines (Supplementary Table S6). The non-linear relationships between each lifestyle factor and the main outcomes of interest are represented in Supplementary Figure S1. Only for the relationship between sleep and internalizing symptoms did we find any evidence for a non-linear (inverse logarithmic) trend. We did not find a statistically significant interaction between ELS exposure and maternal BMI on child comorbidity (Supplementary Table S7). The sensitivity analysis conducted in the subsample with complete outcome and moderator data (sample size = ALSPAC: 3680-4237; GenR: 961-2369) also did not impact our main conclusions (Supplementary Table S8).

### 3.4 Discussion

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## 4 ELS and intracortical myelination

Adapted from:

**Early-life stress exposure and intracortical myelination in childhood: a population-based neuroimaging study**

**Defina, S., Manzoni, D., Tiemeier, H., Brouwer, R.M., Cecil, C.A.M., & Muetzel R.L.** (*in preparation*)

### **Abstract**

Objective:

Method:

Results:

Conclusion:

**4.1 Introduction**

**4.2 Methods**

**4.3 Discussion**

**References**

## 5 ELS and cardiac morphology

Adapted from:

Early-life stress exposure and heart morphology in childhood: a prospective population-based study

Defina, S., Kamphuis, A., Gaillard, R., & Felix, J. F. (*in preparation*)

### Abstract

Objective:

Method:

Results:

Conclusion:

## **5.1 Introduction**

In summary, this book has no content whatsoever (Boyd et al., 2012; Fraser et al., 2013). But I shall write it anyway cause. Cause I kind of do have no choice so, checking justification works

## **5.2 Methods**

## **5.3 Discussion**

## **References**

# PART 2: Reciprocal relationships between mental and physical health problems

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## **6 Longitudinal psycho-physical co-development**

Adapted from:

**Longitudinal co-development of depressive symptoms and cardio-metabolic risk factors from childhood to young adulthood**

Defina, S., Cecil, C.A.M., Felix, J.F., Walton, E., & Tiemeier, H. (*under revision*)

### **Abstract**

Objective:

Method:

Results:

Conclusion:

## **6.1 Introduction**

In summary, this book has no content whatsoever (Boyd et al., 2012; Fraser et al., 2013). But I shall write it anyway cause. Cause I kind of do have no choice so, checking justification works

## **6.2 Methods**

## **6.3 Discussion**

## **References**

## **References**

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# **7 Arterial health and brain development**

Adapted from:

**Lkjbdsgcdajkh**

Defina, S., Cecil, C.A.M., Felix, J.F., Walton, E., & Tiemeier, H. (*under revision*)

## **Abstract**

Objective:

Method:

Results:

Conclusion:

**7.1 Introduction**

**7.2 Methods**

**7.3 Discussion**

**References**

# **8 General discussion**

In this dissertation ... We focus on adolescence, a critical developmental period, when many mental health problems first emerge, and early signs of cardio-metabolic dysregulation begin to manifest. By examining these relationships prospectively, this thesis seeks to provide a clearer understanding of how ELS impacts psycho-physical health during this formative stage of life.

I started this book with a confession: I hated writing this. Since you made it this far (or anyway happened to open this doomed chapter), you won the dubious reward of knowing why. Here is a collection of things I would have done differently, followed by a few things I wish we all did differently.

## **8.1 Modelling ELS**

### **8.1.1 Parental reports**

Like most previous literatures, children's stress exposure information was obtained via parental report and thus likely reflect a combination of parents' own stress experiences, psychological state, and personality.

### **8.1.2 Missing piece: resilience**

## **8.2 Alternative modelling methods**

A cumulative risk approach examines the number of stressors experienced rather than the intensity or the pattern of stress exposure. We define stressors dichotomously and then sum across multiple dichotomous exposures. As an additive model, this technique is a straightforward, way of identifying children at increased odds for developing a range of maladaptive outcomes, including cognitive deficits, behavioral adjustment problems, and poor physical health.

Multiple stressors exposures can sometimes overlap (e.g., harsh and unresponsive parenting) or be independent (e.g., life events), but in each case prediction is enhanced by combining multiple risks in the model. Multiple stressors exposures can sometimes overlap (e.g., material deprivation and overcrowding) or be independent (e.g., death of a parent and overcrowding),

but in each case prediction is enhanced by combining multiple risks in the model. There are several advantages of formulating indices of multiple stress exposures into a composite score. Measurement error is reduced, validity is enhanced because no one singular measure adequately captures the full meaning of the construct of interest, avoids the issue of collinear predictors in the same general linear model, which may lead to unstable estimates and diminish statistical power. For example, many low-income families live in substandard housing, located in high crime neighborhoods; their children may attend schools with inadequate facilities, staffed by less experienced teachers; and many live in single parent households.

it does not take into account interaction between the individual stressors Singling out the effects of school noise exposure on reading quality without taking into account these overlapping risk factors for reading deficits could overestimate the harmful impacts of noise on reading deficits. On the other hand, noise by itself may have negligible impact on reading deficits except when accompanied by household disadvantage or only if the exposure happens within the context of a school with inadequate facilities and staff. In the latter case, by isolating the singular impact of noise exposure as a risk factor for reading deficits, we might erroneously conclude that noise does not matter. It may in fact be a contributing risk factor for reading deficits but only when considered within the natural ecological context wherein high noise schools typically operate. Another way to think about this is that perhaps there is no main effect of noise on reading deficits but an interaction or moderator effect. Noise matters but only in the presence of certain other variables. As we explain below however, the use of an interactive, nonadditive model of multiple risk exposure is often not possible when a large number of risk factors are under consideration. Use of additive models of multiple risk factors is a common approach for dealing with this dilemma.

## 8.3 Modelling comorbidity

### 8.3.1 old data, old insights: mental health

How do we measure mental health? Badly In this thesis, we relied on standardized questionnaires, such as the Strengths and Difficulties Questionnaire (SDQ), which provide a composite score of emotional and behavioral difficulties. While these tools are widely used and validated, they are not without limitations. Self-reports and parent-reports are subject to biases, including social desirability and recall bias. Furthermore, these measures often fail to capture the dynamic and context-dependent nature of mental health, which can fluctuate over time and across environments.

Future research should aim to integrate multi-method approaches, combining self-reports, observational data, and physiological markers, to provide a more comprehensive assessment of mental health.

### **8.3.2 old data, old insights: BMI**

Measuring mental health is an inherently hard task: it requires coming up with a tangible (or better, measurable) quantity to stand in for an abstract, multifaceted and frustratingly complex construct. You would think the job is considerably easier when the object of study is something like adiposity, which enjoys a much longer, solid tradition of objective measurement and clinical usefulness. Well, let's talk about BMI.

In this thesis, we made our best effort to stir away from BMI when we measured adiposity and here are a few thoughts on why I'd defend this choice.

The concept of BMI was introduced in 1835 by Adolphe Quetelet, a Belgian astronomer. Quetelet became increasingly interested in defining the characteristics of the "average man" (*l'homme moyen*, to use his words)... among French and Scottish conscripts. (a concept that was about to become very popular among Eugenics enthusiasts)

BMI has since become a widely used tool in public health and clinical settings, although it was never intended to be a diagnostic measure of individual health or adiposity. Its simplicity and ease of use have contributed to its popularity, so much so that, today, virtually everyone has heard of BMI.

but it has significant limitations, particularly in distinguishing between muscle and fat mass, and in accounting for variations in body composition across different populations.

### **8.3.3 Alternative modelling methods**

network

## **8.4 So what was this all for?**

So what was this all for? Excellent question. Kept me up a few nights I argued prevention of comorbidity was key, but am I actually any closer, even purely theoretically to a useful insight?

### **8.4.1 Preventing ELS**

In Chapter 3 you can find me saying: "*While these findings certainly support the importance of primary prevention programmes aimed at reducing the incidence of ELS, preventing ELS may not always be possible. As such, there is a need to identify alternative modifiable factors that could mitigate the negative impact of ELS on later health, and inform the development of complementary intervention strategies.*"

## **Lifestyle**

In the same chapter I did not find evidence of such promising “modifiable factors”. That was surprising to me, but also, as I later came to find out not so rare in the research on lifestyle factors.

## **SES**

What seems to emerge from the studies is that the key factor across physical and mental health was the contextual risk component of the ELS score. Let's unpack that. The key stress indicators within contextual risk are low parental education, financial and neighborhood problems. These are constructs commonly referred to as low socio-economic status (SES).

## **8.5 Ethnicity**

In some chapters, ethnicity was reduced to “White” vs. “non-White” (most often because of limitation of the data), however this is a major limitation.

## **8.6 Science is dead, and we killed it**

Before I let you go, dear reader, there is one more thing I need to get off my chest, if you'll let me. I began this book with a confession: writing this was so much harder than I expected, and in all honesty this is a big part of why. Potential publication bias may limit the generalizability of our conclusions. Studies with null findings are less likely to be published than those with statistically significant results.

journals should not gatekeep knowledge

code is the scientific product

## **References**