

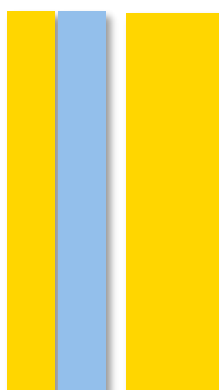
2º CICLO DE ESTUDOS
MESTRADO EM SAÚDE PÚBLICA

The association between prenatal exposure to adversity and internalizing and externalizing problems in adolescence

Nydia Yasmin Salimo

M

2025



The association between prenatal exposure to adversity and internalizing and externalizing problems in adolescence

Nydia Yasmin Salimo

Supervisor:

Mariana Amorim

Instituto de Saúde Pública da Universidade do Porto

Dissertation submitted to the Faculty of Medicine of the University of Porto, for the degree of Master's in Public Health.

Porto, 2025

This thesis was developed within the scope of the project “In the shadow of violence: a life-course approach to unfold the scars on the body and mind over childhood and adolescence”, financed by national funds through the FCT - Foundation for Science and Technology, I.P. (Ref. 2022.06837.PTDC; DOI 10.54499/2022.06837.PTDC).

Acknowledgements

I wish to express my sincere gratitude to my supervisor, Professor Mariana Amorim, for her kind and rigorous guidance, constant support and availability throughout this work. I also extend my acknowledgement to the participants, the research teams, both initial and current, and the hospital staff. Finally, I am grateful to Allah and to my family for their support during this academic journey.

Table of contents

1. Introduction	1
1.1 The Prenatal period.....	2
1.2. Prenatal exposure to adversity.....	3
1.3. Prenatal exposure to adversity and the link to later internalizing and externalizing problems.....	5
1.4. Internalizing and externalizing problems in adolescence	6
2. Objectives	9
3. Methodology	10
3.1. Study design and participants.....	10
3.2. Data collection and variables.....	10
3.3. Statistical analysis	12
3.4. Ethical considerations	12
4. Results	13
5. Discussion	15
References.....	18

List of tables

Table 1. Characteristics of participants at baseline and 13 years follow-up (n=4,640).

Table 2. Stressful life events and physical violence during pregnancy according to maternal sociodemographic characteristics at baseline (n=4,640).

Table 3. Internalizing and externalizing problems and depressive symptoms of participants at age 13 according to maternal sociodemographic characteristics at baseline and adversity during pregnancy (n=4,640).

Table 4. Associations (Odds Ratio and 95% Confidence Interval, OR (95%CI)) of stressful life events and physical violence during pregnancy and internalizing and externalizing problems in adolescence.

Table 5. Sociodemographic characteristics and adverse experiences of participants and non-participants at 13 years follow-up.

List of abbreviations

ANC - Antenatal Care

CBCL - Child Behaviour Checklist

CI - Confidence Interval

DMs - Developmental Milestones

DOHaD - Development Origins of Health and Disease

DOT - Development Origin Theory

EB - Externalizing Behaviour

GP - Gestational Period

HPA - Hypothalamic-Pituitary-Adrenal

IB - Internalizing Behaviour

IEPs - Internalizing and Externalizing Problems

IUE - Intrauterine environment

IPV - Intimate Partner Violence

LBW - Low Birth Rate

MD - Mental Disorder

MHDs - Mental Health Disorders

OR - Odds Ratio

PEA - Prenatal Exposure to Adversity

PMADs - Prenatal Mood and Anxiety Disorders

PNP - Prenatal Period

PSFs - Psychosocial Factors

SEFs - Socioeconomic factors

SES - Socioeconomic Status

SLEs - Stressful Life Events

tRFs - Transfer RNA Fragments

WHO - World Health Organization YLDs - Years Lived with Disability

Abstract

Background

The prenatal period (PNP) represents a sensitive window in human development during which maternal biological, psychosocial, and socioeconomic factors exert significant influence on the intrauterine environment, thereby shaping fetal growth and neurodevelopment. Prenatal exposure to adversity, including maternal mental health disorders (MHDs) and stressful life events (SLEs), has been consistently associated with negative developmental outcomes. Evidence suggests that such exposures may predispose offspring to internalizing and externalizing problems in adolescence, a developmental stage characterized by rapid physical, cognitive, emotional, and social transitions.

Objectives

The aim of this study is to examine the association between exposure to SLEs and violence during pregnancy and the development of internalizing and externalizing problems as well as depressive symptoms during adolescence.

Methods

This study utilized a longitudinal design using data from Generation XXI, a Portuguese population-based birth cohort comprising 8,647 infants, with analyses restricted to 4,640 participants with data available at baseline and 13 years follow up. Maternal stressful life events (SLEs) and physical violence during pregnancy were assessed via structured self-report questionnaires at baseline, while adolescent depressive symptoms, internalizing and externalizing problems were evaluated at age 13 using validated instruments (BDI-II and SDQ). Sociodemographic covariates, including maternal age, education, income, employment and marital status, were also collected. Logistic regression analyses were conducted to estimate associations between prenatal exposure to adversity and adolescent outcomes, adjusting for relevant confounders, with statistical significance set at $p < 0.05$.

Results

A total of 30.4% of mothers reported one stressful life event (SLE) during pregnancy and 17.7% reported experiencing two or more while physical violence was experienced by 0.7%. SLE exposure was more frequent among younger, less educated, unemployed, single or divorced mothers, and lower household income. At 13 years of age, 11.7% of adolescents presented high internalizing problems, 11.2% high externalizing problems and 12.4% depressive symptoms, with boys exhibiting more externalizing problems and girls reporting

more depressive symptoms. After adjustment for maternal sociodemographic characteristics, exposure to ≥ 2 SLEs during pregnancy was significantly associated with internalizing problems (OR=1.40, 95% CI: 1.08-1.80) and externalizing problems (OR=1.34, 95% CI: 1.03-1.74) and depressive symptoms (OR=1.39, 95% CI: 1.10-1.76). No significant associations observed for physical violence during pregnancy.

Conclusions

The study shows that exposure to multiple SLEs during pregnancy is significantly associated with internalizing and externalizing during adolescence, independent of maternal sociodemographic factors. Physical violence during pregnancy, although more frequent among socioeconomically disadvantaged mothers, was not significantly related to adolescent outcomes. These findings highlight the enduring impact of cumulative prenatal stress on offspring mental health and underscore the importance of addressing maternal stress prior and during pregnancy.

Keywords: Prenatal adversity, adolescence, internalizing problems, externalizing problems, psychosocial factors.

Resumo

Introdução

O período pré-natal representa um período sensível no desenvolvimento humano, durante o qual os fatores biológicos, psicossociais e socioeconômicos maternos exercem uma influência significativa no ambiente intrauterino, moldando, assim, o crescimento e o neuro desenvolvimento fetal. A exposição pré-natal a adversidades, incluindo perturbações de saúde maternas e eventos de vida stressantes, tem sido consistentemente associada a resultados adversos no desenvolvimento. A literatura sugere que tais exposições podem predispor os filhos para problemas de internalização e externalização na adolescência, fase do desenvolvimento caracterizada por rápidas transições físicas, cognitivas, emocionais e sociais.

Objetivos

O objetivo deste estudo é examinar a associação entre a exposição a eventos de vida stressantes e a violência física durante a gravidez e o desenvolvimento de problemas de internalização e externalização, bem como de sintomas depressivos, durante a adolescência.

Métodos

Este estudo adotou um desenho longitudinal, utilizando dados da Geração XXI, uma coorte de nascimentos de base populacional portuguesa que incluiu 8.647 bebés, com análises restritas a 4.640 participantes com dados disponíveis no início do estudo e 13 anos de idade. Os eventos de vida stressantes maternos e a violência física durante a gravidez foram avaliados através de questionários estruturados de autorrelato no início do estudo, enquanto que os sintomas depressivos, bem como os problemas de internalização e externalização nos adolescentes foram avaliados aos 13 anos de idade, utilizando instrumentos validados (BDI-II e SDQ). Foram também recolhidas covariáveis sociodemográficas, incluindo idade materna, escolaridade, rendimento, situação profissional e estado civil. Foram conduzidas análises de regressão logística para estimar as associações entre a exposição pré-natal à adversidade e os resultados de saúde na adolescência, ajustando para variáveis relevantes, com significância estatística definida em $p < 0,05$.

Resultados

Um total de 30,4% das mães referiu um evento de vida estressante durante a gravidez e 17,7% referiu ter experienciado dois ou mais, enquanto 0,7% referiu violência física. A exposição a evento de vida estressante foi mais frequente entre as mães mais jovens, com menor escolaridade, desempregadas, solteiras ou divorciadas e com menores rendimentos familiares. Aos 13 anos de idade, 11,7% dos adolescentes apresentaram problemas de internalização elevados, 11,2% problemas de externalização elevados e 12,4% sintomas depressivos, sendo que os rapazes apresentavam mais frequentemente problemas de externalização e as raparigas referiam mais frequentemente sintomas depressivos. Após ajuste para as características sociodemográficas maternas, a exposição a ≥ 2 SLEs durante a gravidez mostrou-se significativamente associada a problemas de internalização (OR = 1,40, IC 95%: 1,08-1,80), e problemas de externalização (OR = 1,34, IC 95%: 1,03-1,74). Não foram observadas associações significativas para a violência física durante a gravidez.

Conclusões

O estudo demonstra que a exposição a múltiplos eventos estressantes durante a gravidez está significativamente associada a sintomas de internalização e externalização durante a adolescência, independentemente dos fatores sociodemográficos maternos. A violência física durante a gravidez, embora mais frequente entre as mães em situação socioeconómica desfavorecida, não se associou significativamente com os resultados na adolescência. Estes resultados destacam o impacto a longo prazo do stress pré-natal cumulativo na saúde mental dos filhos e realçam a importância de abordar o stress materno antes e durante a gravidez.

Palavras-chave: Adversidade pré-natal, adolescência, problemas de internalização, problemas de externalização, fatores psicossociais.

1. Introduction

To understand internalizing and externalizing problems (IEPs) that may arise during adolescence, it is essential to first consider the formative years of a child's life, particularly the gestational period (GP). Pregnancy represents a highly sensitive window in which biological and environmental factors interact to shape both immediate and long-term health outcomes in the offspring. In this context, maternal mental health has been recognized by previous literature as a key determinant. For example, the study of (Glover, 2014) highlighted the importance of improving the detection of maternal depression and anxiety during pregnancy, as these conditions are often overlooked despite their significant influence on maternal well-being and child development. Indeed, maternal emotional states contribute significantly to adverse child outcomes, including behavioural and cognitive difficulties (Lautarescu et al., 2020).

The Development Origins of health and disease (DOHaD) framework, rooted in the Developmental Origins Theory (DOT), provides a conceptual basis for understanding how early life exposures influence health trajectories across the life course later health. Originally applied to cardiac and metabolic outcomes (Barker, 2007), this model has since been extended to neurodevelopmental and psychiatric phenotypes, with fetal programming considered as a key mechanism (Glover et al., 2023).

One biological pathway of particular relevance is the hypothalamic-Pituitary-Adrenal (HPA) axis, a neuroendocrine system that plays a central role in stress regulation. It functions primarily as a stress response mechanism, serving as a neuroendocrine link between perceived stressors and physiological reactions. The principal function of the HPA-axis is the release of glucocorticoids, particularly cortisol in humans, which subsequently trigger a short term physiological response to stress. This pathway is essential for maintaining homeostasis and allostasis under stress conditions, thereby contributing to survival, longevity, development and the overall regulation of physiological balance (Fulford & Harbuz, 2005). Cortisol plays a critical role in regulating the stress response, metabolism, inflammation, and immune function. As cortisol is continuously monitored to maintain homeostasis, dysregulated or persistently elevated levels can be detrimental to both maternal and fetal health (Thau et al., 2023). Within the context of pregnancy, elevated maternal cortisol represents a potential mechanism linking prenatal adversity to offspring outcomes. Fetal development is a highly complex process, beginning at conception and

culminating in birth, and exposure to maternal stressors during this period can disrupt optimal growth and neurodevelopment. Evidence indicates that cortisol levels measured in late gestation may be particularly influential compared to early or mid-pregnancy, suggesting a possible critical window of vulnerability (Zijlmans et al., 2015). Supporting studies by (Buss et al., 2012) demonstrated that high maternal cortisol levels during early gestation were linked to children's later emotional and behavioural problems, suggesting that prenatal stress may contribute to both internalizing and externalizing difficulties. Importantly, sex-specific effects were reported, with girls appearing more vulnerable to emotional problems than boys (Buss et al., 2012).

Beyond biological stress markers, genetic predispositions further modulate these associations. A study by Silveira et al. (2017), found that cumulative prenatal adversities, when interacting with genetic factors, predicted behavioural and developmental alterations observable as early as two years of age.

All together, these findings underscore that prenatal exposure to adversity can have enduring effects on child development. This enhances the need to investigate the long-term associations between prenatal adversity and adolescent outcomes, particularly regarding the emergence of internalizing and externalizing behavioural problems.

1.1 The Prenatal period

The Prenatal period (PNP) encompasses the entirety of a woman's gestational phase, spanning from conception to the birth of the neonate. This stage represents a critical window in fetal development, during which maternal factors exert direct influence on the intra-uterine environment and, consequently, on fetal growth and maturation (Federenko & Wadhwa, 2004; Muglia et al., 2022; Van den Bergh et al., 2020). Pregnancy itself constitutes a profound and sensitive life event for women, characterized by rapid and complex physiological, hormonal, and psychological transformations (Federenko & Wadhwa, 2004). These changes heighten maternal vulnerability to stress and mental health disorders (MHDs), further emphasizing the need for comprehensive prenatal care that addresses both physical and mental health dimensions.

The health and well-being of the child cannot be assessed solely at birth. Maternal exposure to psychosocial, environmental, or biological adversity, occurring either before conception or throughout gestation plays a decisive role in shaping intrauterine conditions

(Lewis et al., 2016; Van den Bergh et al., 2020). Such exposures may have enduring consequences for the offspring's developmental trajectory. Women experiencing mental health disorders (MHDs), whether pre-existing or emerging during pregnancy, face an elevated risk of delivering infants with low birth weight (LBW), neurological impairments, and disruptions in emotional and behavioural regulation (Federenko & Wadhwa, 2004; Lewis et al., 2016; Mandl et al., 2024). These outcomes constitute the immediate manifestations of prenatal adversity, which may be resolved within a short timeframe or persist, re-emerging later in life.

Notably, during adolescence, the impact of early exposures may manifest as internalizing behaviours (IB), such as anxiety and depression, as well as externalizing behaviours (EB), such as aggression, and conduct problems (Glynn et al., 2018; Madigan et al., 2018). The psychological state and overall well-being of the mother during gestation hold substantial significance for optimal fetal development. Prenatal mood and anxiety disorders (PMADs) affect an estimated 15–21% of mothers (Byrnes, 2018), with disproportionately higher prevalence rates in low- and middle-income countries compared to high-income countries, reflecting disparities in healthcare access, socioeconomic stability, and psychosocial support systems (Woody et al., 2017)

1.2. Prenatal exposure to adversity

Prenatal exposure to adversity (PEA) refers to the experience of stressful and potentially harmful conditions during the gestational period that may influence both maternal health and fetal development. During this period, adversity often takes the form of stressful life events (SLEs), which may arise from psychosocial and socioeconomic circumstances.

Evidence shows that exposure to these stressors during gestation is associated with alterations in maternal physiology, particularly dysregulation of the HPA axis (Howland et al., 2017). This dysregulation may, in turn, affect offspring neurodevelopment and elevate the risk of behavioural problems particularly IEPs during adolescence (Tien et al., 2020). Maternal prenatal stress thus reflects the physiological and behavioural responses elicited when acute or chronic psychosocial demands exceed a woman's coping resources, thereby disrupting psychological homeostasis. These processes can initiate biological and

developmental pathways that contribute to long-term emotional and behavioural vulnerabilities in the offspring (Lipschutz et al., 2024)

Psychosocial factors

Psychosocial factors (PSFs) refer to influences on an individual's health, behaviour, and overall well-being that arises from the interplay between psychological (e.g., thoughts, emotions, attitudes) and social dimensions (e.g., relationships, culture, environmental conditions) (Upton, 2013). These factors are particularly relevant during pregnancy, a period marked by heightened vulnerability to stress and mental health challenges.

Mental health issues during pregnancy, most notably anxiety and depression, are recognized risk factors for childhood behavioural problems. Findings from Kingston et al. (2018), highlight a significant association between maternal depression and both IEPs in children, particularly when maternal depressive symptoms are prolonged. These results underscore the importance of early screening and the provision of adequate care to reduce the risk of adverse developmental outcomes in offspring.

The public health significance of these findings is reinforced by data from the World Health Organization (WHO). Globally, approximately 10% of pregnant women and 13% of women in the postpartum period experience a mental disorder (MD), primarily depression (World Health Organization, 2025). These rates are considerably higher in low and middle-income countries estimated at 15.6% during pregnancy and 19.8% postpartum.

Multiple factors can exacerbate a woman's mental state during pregnancy. While partner support can serve as a protective factor during this sensitive period, intimate partner violence (IPV) has profoundly negative effects on both maternal mental health and offspring outcomes. In a systematic worldwide review, (Román-Gálvez et al. (2021) reported that at least one in four pregnant women were exposed to some form of (IPV), with the highest prevalence observed in East Africa and Southeast Asia. Given the well-documented consequences of IPV on offspring neurodevelopment and emotional regulation, these statistics are alarming from both clinical and public health perspectives.

Socioeconomic factors

Socioeconomic factors (SEFs) encompass multiple dimensions of an individual's social and economic position, including income, educational attainment, occupational status,

and overall social standing (*Socioeconomic Status*, n.d.). These factors not only have a direct influence on health but also interact with psychosocial factors (PSFs) to shape maternal well-being during pregnancy, thereby affecting offspring health and development across the life course.

Higher socioeconomic status (SES) is generally associated with increased access to health information, improved decision-making capacity, and the adoption of healthier lifestyle behaviours during pregnancy. Conversely, low (SES) is often linked to limited healthcare access, nutritional deficiencies, heightened exposure to stress, and reduced psychosocial support conditions that can negatively affect fetal growth and neurodevelopment (Verbeek et al., 2019).

Evidence from systematic review and meta-analyses examining the influence of SES on pregnancy outcomes, underscored its critical role in shaping maternal and child health. Findings consistently demonstrated that lower SES is associated with adverse outcomes, including preterm birth, low birth weight (LBW), and increased risk of perinatal complications (Thomson et al., 2021). These findings highlight socioeconomic disadvantage as a key determinant of inequalities in early developmental trajectories.

1.3. Prenatal exposure to adversity and the link to later internalizing and externalizing problems

For decades, research has recognized that prenatal adversity, particularly prolonged exposure to SLEs, is associated with an increased risk of emotional and behavioural difficulties in later stages of development, including both IPs and EPs. These associations have traditionally been understood through psychosocial and neurodevelopmental frameworks, yet recent advances in epigenetics have provided novel insights into the biological mechanisms underlying these links.

Epigenetic studies have begun to reveal how maternal stress during the gestational period (GP) can induce molecular changes that influence offspring development from early childhood into adolescence and beyond. A recent investigation by (Vaknine Treidel et al., 2025) offers compelling evidence in this domain. The study examined blood-derived transfer RNA fragments (tRFs) small non-coding RNA molecules involved in gene regulation in pregnant women who reported varying levels of stress during the first trimester. Participants were categorized into low-, medium-, and high-stress groups, and maternal blood

samples were compared with umbilical cord blood at birth. The results demonstrated distinct sex-specific patterns in tRFs alterations. Female neonates exhibited more pronounced changes in tRFs profiles compared to males. Notably, some of these altered tRFs target molecules are involved in cholinergic signalling, particularly acetylcholine, a neurotransmitter crucial for the parasympathetic regulation of physiological arousal and stress recovery. Disruption of this pathway could plausibly influence stress reactivity across the lifespan, thereby increasing vulnerability to both Ips such as anxiety and depression and EPs such as aggression and conduct problems during adolescence (Vaknine Treidel et al., 2025).

These findings contribute to a growing body of literature suggesting that prenatal stress may exert long-lasting effects via biological embedding, where early environmental conditions become physiologically incorporated into the developing organism's regulatory systems. This perspective aligns with the broader developmental origins of health and disease (DOHaD) theory (Barker, 1990; Glover et al., 2010), which posits that prenatal and early-life experiences can shape health trajectories into adulthood. Thus, it is essential to examine how these early vulnerabilities manifest during adolescence, a sensitive developmental stage marked by profound psychological, biological, and social transitions. Indeed, IEPs often emerge or intensify during this period, reflecting both the enduring impact of prenatal exposures and the new challenges inherent to adolescent development.

1.4. Internalizing and externalizing problems in adolescence

Adolescence represents a critical developmental stage characterized by the transition from childhood to adulthood, encompassing profound physical, cognitive, social, and emotional changes. This period is generally defined as spanning ages 11 to 19 and is further subdivided into three stages: early adolescence (11–13 years), middle adolescence (14–17 years), and late adolescence (18–19 years) (Salmela-Aro, 2011).

While adolescence is often viewed as a time of self-discovery, autonomy building, and rapid personal growth, it is also accompanied by unique vulnerabilities and psychosocial challenges. The mental health of adolescents has become a prominent focus of global public health, given the sensitivity of this life stage and the potential long-term consequences of psychiatric morbidity.

Internalizing symptoms refer to inwardly directed emotional and behavioural difficulties, such as withdrawal, somatic complaints, and anxiety or depression. In contrast, externalizing symptoms are outwardly directed behaviours, including aggression, rule-breaking, and delinquency. This classification, first proposed by Achenbach (1966), continues to provide valuable conceptual and clinical utility in guiding research, assessment, intervention, and policy.

IEPs in adolescence are often the continuation or amplification of behavioural difficulties originating in childhood. According to the WHO (World Health Organization, 2024), Depression is estimated to affect 1.4% of adolescents aged 10–14 years, while anxiety disorders affect approximately 4.4% in the same age group (IHME, 2019). These conditions not only compromise immediate well-being but also increase the risk of substance use, academic underachievement, social exclusion, and suicidal behaviours later in life.

Understanding adolescent mental health requires not only a focus on symptomatology but also on the developmental context in which these difficulties arise. Developmental milestones (DMs) provide a valuable framework for interpreting the biological, cognitive, and psychosocial changes that characterize adolescence, and for identifying why this stage represents both an opportunity for growth and a period of heightened risk for IEPs.

Developmental milestones

DMs are markers that describe expected stages in a child's cognitive, emotional, social, and physical growth, spanning from infancy through childhood and into adolescence. Their primary purpose is to guide the identification of typical developmental trajectories and to assist in assessing whether a child's progress aligns with established patterns (Misirliyan et al., 2023).

During the early years of adolescence rapid changes occur in both mind and body. One of the most significant developmental milestones in this stage is identity formation, a critical process of self-exploration in which individuals examine their values, beliefs, social roles, and sense of belonging. Importantly, identity formation does not begin at the onset of adolescence but is instead the culmination of experiences from earlier life stages. According to Branje (2022), the development of personal identity in adolescence is characterized by systematic maturation and increasing stability, shaped by life events, developmental transitions, and the cumulative impact of everyday experiences. A confident

sense of identity is linked to better functioning across multiple domains of life, and supportive family relationships and friendships have a strong positive association with healthy identity development.

Psychosocial development is also an essential DM during adolescence, including the interplay between emotional well-being, social functioning, and the contextual environment. A comprehensive understanding of the global prevalence of years lived with disability (YLDs) associated with mental disorders requires consideration of age specific patterns. According to Kieling et al. (2024), the prevalence of mental disorders rises substantially during early adolescence 10 to 14 years when compared to younger children aged 5 to 9 years. Overall, more than one in ten youths live with at least one diagnosable mental disorder, making mental disorders the leading cause of non-fatal disability in children and adolescents. The age group of 5 to 24 accounts for a substantial proportion of the 31.14 million YLDs representing over 20% of all YLDs in that age span. Notably, the concentration of disability burden is particularly high among 10 to 14-year range, highlighting the potential for long term consequences if mental health needs are not addressed. A broader perspective on adolescent mental health is offered by the conceptual framework proposed by (Wellbeing, 2022), which emphasizes the interconnections between mental health and psychosocial well-being across the life course. This framework highlights that the influence of environmental factors evolves over time, expanding from the immediate family to include peers, community, society, and the broader national and political context. It also shows how intersections such as race, ethnicity, sexual orientation, gender, and socioeconomic status can generate inequalities in knowledge, diagnosis, help-seeking behaviours, and access to care. While individual and interpersonal factors tend to exert a direct influence, policy, community, and structural determinants often shape adolescent mental health trajectories in more indirect yet highly significant ways.

2. Objectives

The aim of this study is to examine the association between exposure to SLE and violence during pregnancy and the development of internalizing and externalizing problems during adolescence.

Specifically, we aim to:

1. Assess the prevalence of maternal exposure to SLE and violence during the first, second, and third trimesters of pregnancy, as well as its associated factors.
2. Examine the association between in utero exposure to SLE and violence and the development of internalizing and externalizing problems at 13 years of age.

3. Methodology

3.1. Study design and participants

This is a longitudinal study using data from the Generation XXI, a population-based birth cohort which comprised of 8,495 mothers giving birth to 8,647 live infants. Participants of this study were recruited at birth (2005-2006) across five public maternity units in the metropolitan area of Porto, Portugal (Alves et al., 2012, Larson et al. 2013). Baseline evaluation was conducted shortly after birth, and the participants were subsequently evaluated at the ages 4, 7, 10 and 13 years (86%, 80%, 74% and 54% participation rate, respectively). Evaluation at 18 years is still ongoing. In all study waves, information on socioeconomic and demographic characteristics, obstetric history, history of disease, and health-related behaviours was collected by trained interviewers using structured questionnaires. This study analyses data from baseline and 13 years follow up (n= 4,640).

3.2. Data collection and variables

Exposures

Maternal SLEs during pregnancy were assessed at baseline, using a self-reported questionnaire. This instrument captured a wide range of stressors experienced by mothers across each trimester of pregnancy, including moving house, worsening financial situation, theft or assault, own unemployment, unemployment of the partner, serious illness of a child, serious illness of the partner or another family member, death of a child, death of the partner, death of another close person, divorce or separation, car accident, or other distressing event. To account for the cumulative effects of multiple SLEs, a variable was created by summing the number of reported experiences and categorizing them into three groups: 0, 1, and ≥ 2 SLEs.

Physical violence during pregnancy was assessed at baseline by asking mothers: "Since you became pregnant, has anyone hit, slapped, kicked, or otherwise physically assaulted you?". A dichotomous variable was then created (Yes/No).

Outcomes

At 13 years of age, depressive symptoms were self-reported by the adolescents, and internalizing, and externalizing problems were reported by the caregivers.

Depressive symptoms were assessed using the Portuguese version of the Beck Depression Inventory-II (BDI-II) (Campos & Gonçalves, 2011), a widely used 21-item self-report questionnaire designed to measure the presence and severity of depressive symptoms. A cut-off score of 13 was applied (Coelho et al., 2002) and participants with a total score of 13 or higher were considered to have depressive symptoms.

Internalizing and externalizing behaviours were assessed using the Portuguese version of the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997; Fleitlich et al., 2005). This validated instrument allows caregivers to report adolescents emotional and behavioural difficulties by responding to 25 items using a 3-point scale (0-not true, 1-somewhat true, 2-very true), divided into five subscales: emotional symptoms, conduct problems, hyperactivity, peer relationship problems, and prosocial behaviours. For each subscale, scores can range from 0 to 10 if all items are completed. The internalizing score ranges from 0 to 20 and is calculated as the sum of the emotional symptoms and peer relationship problems subscales. The externalizing score also ranges from 0 to 20 and is calculated as the sum of the conduct problems and hyperactivity subscales. Participants were classified as having "close to average/slightly raised" internalizing problems if they scored 0–8 points, and "high/very high" if they scored 9–20 points. Similarly, participants were classified as having "close to average/slightly raised" externalizing problems if they scored 0–10 points, and "high/very high" if they scored 11–20 points.

Other covariates

Mothers reported age, educational level, household income, employment status and marital status at baseline. Mothers' age at baseline was categorized in three groups: 25 years or less, between 26 and 35 years, and more than 35 years old. Maternal education was measured as the number of years of formal schooling and categorized as 9 years or less, 10–12 years, and >12 years. The household monthly income included salaries and other sources of income. Categories were defined as having $\leq 1000\text{€}$ disposable per month; between 1001€ and 2000€; and $> 2000\text{€}$ per month. Unemployment status was used to assess whether participants were unemployed. Data on the maternal marital status was assessed by asking participants if they were married/living with a partner or single/divorced.

3.3. Statistical analysis

All statistical analysis was performed using Statistical Package for the Social Science (SPSS), version 29.0. The chi-square test was used to compare proportions. To identify the associations between SLEs and physical violence during pregnancy and internalizing and externalizing problems and depressive symptoms at 13 years of age, logistic regression analyses were performed. We calculated odds ratios with 95% confidence intervals (OR, 95% CI) and adjusted for child's sex, maternal education, maternal marital status and household income. Associations were statistically significant when the p-value was less than 0.05 ($p < 0.05$).

3.4. Ethical considerations

The Generation XXI complies with the current national legislation. Participants, their parents or legal tutors received detailed information about the research purposes and objectives, voluntary nature of participation, clearly stating that no penalty will be applied to those that refuse participation, expected duration of the evaluation, confidentiality and anonymity of all the information provided. All phases of the study complied with the Ethical Principles for Medical Research Involving Human Subjects expressed in the Declaration of Helsinki.

All follow-up evaluations have been approved by the Ethics Committee of S. João Hospital Center/University of Porto Medical School and by the Portuguese Data Protection Authority, except the 13-year follow-up which was approved by the ISPUP Ethics Committee. Procedures follow the National Committee of Data Protection requirements. The ISPUP Data Protection Officer advises researchers in matters of data protection and supervises data protection impact assessments when necessary. Oral and written informed consent was obtained from participants/legal representatives after explaining the study's purpose, voluntary participation, lack of penalties for non-participation and confidentiality.

4. Results

Characteristics of mother's children are presented in Table 1. At baseline, 68.8% of mothers were between 26 and 35 years old, 47% had 9 or less years of formal education, 84.9% were employed and 95.5% were married or lived with a partner. Regarding household income, 48.2% reported having 1,001€-2,000€ per month. Moreover, 30.4% of mothers reported experiencing 1 stressful life event and 17.7% reported experiencing 2 or more stressful events during pregnancy. More specifically, 39.6% reported 1 stressful experience during the first trimester, 39.4% during the second trimester and 41.8% during the third trimester, while 17.7% experienced ≥ 2 stressful experiences during the first trimester, 10.9% during the second and 12.9% during the third one. With regard to physical violence, 0.7% of mothers reported having been victims during pregnancy (Table 1).

At 13 years of age, 51.6% of participants were boys, 11.7% of them presented high/very high levels of internalizing problems, 11.2% presented high/very high externalizing problems and 12.4% presented depressive symptoms (Table 1).

In comparison with participants who reported no stressful events during pregnancy, those who experienced one or ≥ 2 were significantly younger, more frequently unemployed, single, and from households with lower income ($p < 0.05$). Regarding physical violence during pregnancy, participants with lower education, who were unemployed, single or divorced, and with lower household income reported experiencing it more frequently than their counterparts (Table 2).

Table 3 shows the internalizing and externalizing problems and depressive symptoms of participants at age 13, according to maternal sociodemographic characteristics at baseline and adverse experiences during pregnancy. High or very high levels of internalizing problems were more frequently present in participants whose mothers had ≤ 9 years of education, were unemployed, single or divorced, living in households with ≤ 1000 € of income at baseline, and experienced ≥ 2 stressful life events during, compared to their counterparts. High or very high levels of externalizing problems at age 13 were more frequently observed in boys, participants whose mothers had ≤ 9 or 10-12 years of education, were single or divorced, lived in households with ≤ 1000 € per month, and experienced ≥ 2 stressful life events during pregnancy, compared with their counterparts. Regarding depressive symptoms, these were more frequently reported by girls, by participants

whose mothers had lower education, were single or divorced, lived in households with a monthly income of $\leq 1000\text{€}$, and experienced ≥ 2 stressful events during pregnancy, compared with their counterparts (Table 3).

Table 4 shows the crude and adjusted associations of stressful life events and physical violence during pregnancy and internalizing and externalizing problems. Participants who experienced ≥ 2 SLEs during pregnancy showed higher odds of presenting high or very high levels of internalizing problems at age 13 (OR= 1.52 , 95%CI: 1.20-1.91), high or very high levels of externalizing problems (OR= 1.42, 95% CI: 1.12-1.80) as well as reporting depressive symptoms (OR= 1.39, 95% CI: 1.10-1.76). When adjusted for child's sex, maternal education, maternal marital status and household income, experiencing 2 or more stressful events during pregnancy is significantly associated with high or very high levels of internalizing problems (OR= 1.40, 95% CI: 1.08-1.80) and externalizing problems (OR= 1.34, 95% CI: 1.03-1.74). Physical violence during pregnancy did not show a statistically significant association with any of the outcomes.

5. Discussion

The findings of this study highlight a significant association between prenatal exposure to SLEs and the development of IEPs in adolescence. While 30.4% of mothers experienced at least one SLE during pregnancy and 17.7% reported two or more, the exposure was more prevalent among women with lower income, education, unemployment, single or divorced status. At age 13, 11.7% of adolescents presented high internalizing problems, 11.2% high externalizing problems, and 12.4% depressive symptoms. Gender-specific differences were observed, with girls reporting depressive symptoms more frequently, whereas boys were more likely to exhibit externalizing problems. Further analyses demonstrated that exposure to two or more prenatal SLEs was associated with increased odds of both internalizing problems and externalizing problems in adolescents, even after adjusting for key sociodemographic factors. Conversely, physical violence during pregnancy was not significantly associated with adolescents' outcomes.

These findings are consistent with a growing body of research demonstrating that maternal stress during pregnancy may act as a predictor of long term effects on offspring's mental health (Clayborne et al., 2023). They further support the concept that such association represents a developmental phenomenon, illustrating how early adversity can have enduring consequences across the lifespan of the offspring (Kingsbury et al., 2016).

The observed gender-specific differences corroborate with previous literature indicating that girls are more susceptible to depression and internalizing problems, whereas boys are more prone to aggression and other externalizing behaviours (Sutherland & Brunwasser, 2018; Vaknine Treidel et al., 2025). Such patterns may be driven by a combination of biological susceptibilities, socialization processes, and contextual environments, highlighting the importance of considering gender when interpreting these findings and developing interventions.

Sociodemographic vulnerabilities are also an important find to consider. Women from disadvantaged backgrounds were more likely to encounter adverse exposure, with related negative health consequences for their offspring (Thomson et al., 2021). These observations can be interpreted in light of the family stress model, which posits that economic adversity increases parental stress and

diminishes parenting capacity, thereby fostering an environment conducive to internalizing and externalizing problems in children (Conger et al., 2010). Structured support for mothers during pregnancy and the early postpartum period has been shown to significantly improve maternal and child health outcomes, particularly in interventions targeting lower-income mothers (Olds et al., 2019).

Promoting maternal health during pregnancy is not only beneficial for children but also for society at large. Strengthening social protection policies and mental health support in this critical period may help reduce the intergenerational transmission of psychological problems. Furthermore, the evidence supports the need for gender-sensitive approaches to intervention, given the differential manifestation of maternal stress exposure in boys and girls. Addressing gender-specific patterns may improve the precision of intervention strategies and enhance outcomes across populations.

Strength and Limitations

The study has strengths and limitations that need to be acknowledged. This study leverages data from the Generation 21, a large population-based birth cohort from the Porto metropolitan area in Portugal. This cohort provides a substantial and representative sample studied during 13 years, enhancing the statistical power and generalizability of our findings within the study population. The inclusion of multiple covariates strengthens the internal validity of the findings by accounting for potential confounders that may influence the association between prenatal exposure to adversity and the development of internalizing and externalizing problems in adolescence.

One limitation of the study includes the reliance on self-reported data that may introduce bias, as participants might underreport or overreport their experiences due to social desirability or recall bias. Additionally, the 13-year follow-up was interrupted due to the COVID-19 pandemic, resulting in a lower-than-expected number of participants ($n=4,640$, 54.0%) and a more socioeconomically advantaged sample and with less stressful experiences during pregnancy (Table 5), as reported in other studies (Howe et al., 2013). This underestimated the prevalence and impact of stressful and violent experiences during pregnancy on adolescents' emotional and behavioral problems.

Conclusion

This study shows that exposure to multiple stressful life events during pregnancy is significantly associated with internalizing and externalizing problems in adolescence, independent of maternal sociodemographic factors. Although physical violence during pregnancy was more prevalent among socioeconomically disadvantaged mothers, it was not significantly related to adolescent outcomes. Overall, these findings highlight the enduring impact of cumulative prenatal stress on offspring's mental health and underscore the importance of addressing maternal stress both prior to and during pregnancy.

References

- Achenbach, T. M. (1966). The classification of children's psychiatric symptoms: a factor-analytic study. *Psychological Monographs*, 80(7), 1–37. <https://doi.org/10.1037/H0093906>
- Barker, D. J. P. (1990). The fetal and infant origins of adult disease. *British Medical Journal*, 301(6761), 1111–1111. <https://doi.org/10.1136/BMJ.301.6761.1111>
- Barker, D. J. P. (2007). The origins of the developmental origins theory. *Journal of Internal Medicine*, 261(5), 412–417. <https://doi.org/10.1111/J.1365-2796.2007.01809.X>
- Branje, S. (2022). Adolescent identity development in context. *Current Opinion in Psychology*, 45, 101286. <https://doi.org/10.1016/J.COPSYC.2021.11.006>
- Buss, C., Davis, E. P., Shahbaba, B., Pruessner, J. C., Head, K., & Sandman, C. A. (2012). Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. *Proceedings of the National Academy of Sciences of the United States of America*, 109(20). <https://doi.org/10.1073/PNAS.1201295109>,
- Byrnes, L. (2018). Perinatal Mood and Anxiety Disorders. *Journal for Nurse Practitioners*, 14(7), 507–513. <https://doi.org/10.1016/j.nurpra.2018.03.010>
- Campos, R. C., & Gonçalves, B. (2011). The portuguese version of the beck depression inventory-II (BDI-II) preliminary psychometric data with two nonclinical samples. *European Journal of Psychological Assessment*, 27(4), 258–264. <https://doi.org/10.1027/1015-5759/A000072>
- Clayborne, Z. M., Nilsen, W., Torvik, F. A., Gustavson, K., Bekkhus, M., Gilman, S. E., Khandaker, G. M., Fell, D. B., & Colman, I. (2023). Prenatal maternal stress, child internalizing and externalizing symptoms, and the moderating role of parenting: Findings from the Norwegian mother, father, and child cohort study. *Psychological Medicine*, 53(6), 2437–2447. <https://doi.org/10.1017/S0033291721004311>,
- Coelho, R., Martins, A., & Barros, H. (2002). Clinical profiles relating gender and depressive symptoms among adolescents ascertained by the Beck Depression Inventory II. *European Psychiatry*, 17(4), 222–226. [https://doi.org/10.1016/S0924-9338\(02\)00663-6](https://doi.org/10.1016/S0924-9338(02)00663-6)

- Conger, R. D., Conger, K. J., & Martin, M. J. (2010). Socioeconomic status, family processes, and individual development. *Journal of Marriage and Family*, 72(3), 685–704. <https://doi.org/10.1111/J.1741-3737.2010.00725.X>,
- Federenko, I. S., & Wadhwa, P. D. (2004). Women's Mental Health During Pregnancy Influences Fetal and Infant Developmental and Health Outcomes. *CNS Spectrums*, 9(3), 198–206. <https://doi.org/10.1017/S1092852900008993>
- Fulford, A. J., & Harbuz, M. S. (2005). An introduction to the HPA axis. *Techniques in the Behavioral and Neural Sciences*, 15(PART 1), 43–65. [https://doi.org/10.1016/S0921-0709\(05\)80006-9](https://doi.org/10.1016/S0921-0709(05)80006-9)
- Glover, V. (2014). Maternal depression, anxiety and stress during pregnancy and child outcome; What needs to be done. *Best Practice and Research: Clinical Obstetrics and Gynaecology*, 28(1), 25–35. <https://doi.org/10.1016/j.bpobgyn.2013.08.017>
- Glover, V., O'Connor, T. G., & O'Donnell, K. (2010). Prenatal stress and the programming of the HPA axis. *Neuroscience and Biobehavioral Reviews*, 35(1), 17–22. <https://doi.org/10.1016/j.neubiorev.2009.11.008>
- Glover, V., O'Connor, T. G., & O'Donnell, K. J. (2023). Fetal Programming and Public Policy. *Journal of the American Academy of Child & Adolescent Psychiatry*, 62(6), 618–620. <https://doi.org/10.1016/J.JAAC.2022.11.010>
- Glynn, L. M., Howland, M. A., Sandman, C. A., Davis, E. P., Phelan, M., Baram, T. Z., & Stern, H. S. (2018). Prenatal maternal mood patterns predict child temperament and adolescent mental health. *Journal of Affective Disorders*, 228, 83–90. <https://doi.org/10.1016/j.jad.2017.11.065>
- Howe, L. D., Tilling, K., Galobardes, B., & Lawlor, D. A. (2013). Loss to follow-up in cohort studies: Bias in estimates of socioeconomic inequalities. *Epidemiology*, 24(1), 1–9. <https://doi.org/10.1097/EDE.0B013E31827623B1>,
- Howland, M. A., Sandman, C. A., & Glynn, L. M. (2017). Developmental origins of the human hypothalamic-pituitary-adrenal axis. *Expert Review of Endocrinology & Metabolism*, 12(5), 321. <https://doi.org/10.1080/17446651.2017.1356222>
- IHME. (2019). *Global Burden of Disease Collaborative Network and Institute for Health Metrics and Evaluation*. <https://vizhub.healthdata.org/gbd-results/?params=gbd-api-2019-permalink/380dfa3f26639cb711d908d9a119ded2>

- Kieling, C., Buchweitz, C., Caye, A., Silvani, J., Ameis, S. H., Brunoni, A. R., Cost, K. T., Courtney, D. B., Georgiades, K., Merikangas, K. R., Henderson, J. L., Polanczyk, G. V., Rohde, L. A., Salum, G. A., & Szatmari, P. (2024). Worldwide Prevalence and Disability From Mental Disorders Across Childhood and Adolescence: Evidence From the Global Burden of Disease Study. *JAMA Psychiatry*, 81(4), 347–356. <https://doi.org/10.1001/JAMAPSYCHIATRY.2023.5051>
- Kingsbury, M., Weeks, M., MacKinnon, N., Evans, J., Mahedy, L., Dykxhoorn, J., & Colman, I. (2016). Stressful Life Events During Pregnancy and Offspring Depression: Evidence From a Prospective Cohort Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 55(8), 709–716.e2. <https://doi.org/10.1016/j.jaac.2016.05.014>
- Kingston, D., Kehler, H., Austin, M. P., Mughal, M. K., Wajid, A., Vermeyden, L., Benzies, K., Brown, S., Stuart, S., & Giallo, R. (2018). Trajectories of maternal depressive symptoms during pregnancy and the first 12 months postpartum and child externalizing and internalizing behavior at three years. *PLOS ONE*, 13(4), e0195365. <https://doi.org/10.1371/JOURNAL.PONE.0195365>
- Lautarescu, A., Craig, M. C., & Glover, V. (2020). Prenatal stress: Effects on fetal and child brain development. *International Review of Neurobiology*, 150, 17–40. <https://doi.org/10.1016/BS.IRN.2019.11.002>
- Lewis, A. J., Austin, E., & Galbally, M. (2016). Prenatal maternal mental health and fetal growth restriction: A systematic review. *Journal of Developmental Origins of Health and Disease*, 7(4), 416–428. <https://doi.org/10.1017/S2040174416000076>,
- Lipschutz, R., Kulesz, P. A., Elgbeili, G., Biekman, B., Laplante, D. P., Olson, D. M., King, S., & Bick, J. (2024). Maternal mental health mediates the effect of prenatal stress on infant temperament: The Harvey Mom Study. *Development and Psychopathology*, 36(2), 893–907. <https://doi.org/10.1017/S0954579423000160>,
- Madigan, S., Oatley, H., Racine, N., Fearon, R. M. P., Schumacher, L., Akbari, E., Cooke, J. E., & Tarabulsky, G. M. (2018). A Meta-Analysis of Maternal Prenatal Depression and Anxiety on Child Socioemotional Development. *Journal of the American Academy of Child & Adolescent Psychiatry*, 57(9), 645–657.e8. <https://doi.org/10.1016/J.JAAC.2018.06.012>

- Mandl, S., Alexopoulos, J., Doering, S., Wildner, B., Seidl, R., & Bartha-Doering, L. (2024). The effect of prenatal maternal distress on offspring brain development: A systematic review. *Early Human Development*, 192, 106009. <https://doi.org/10.1016/J.EARLHUMDEV.2024.106009>
- Misirliyan, S. S., Boehning, A. P., & Shah, M. (2023). Development Milestones. *StatPearls*. <https://www.ncbi.nlm.nih.gov/books/NBK557518/>
- Muglia, L. J., Benhalima, K., Tong, S., & Ozanne, S. (2022). Maternal factors during pregnancy influencing maternal, fetal, and childhood outcomes. *BMC Medicine*, 20(1). <https://doi.org/10.1186/S12916-022-02632-6>
- Olds, D. L., Kitzman, H., Anson, E., Smith, J. A., Knudtson, M. D., Miller, T., Cole, R., Hopfer, C., & Conti, G. (2019). Prenatal and infancy nurse home visiting effects on mothers: 18-year follow-up of a randomized trial. *Pediatrics*, 144(6). <https://doi.org/10.1542/PEDS.2018-3889>,
- Román-Gálvez, R. M., Martín-Peláez, S., Fernández-Félix, B. M., Zamora, J., Khan, K. S., & Bueno-Cavanillas, A. (2021). Worldwide Prevalence of Intimate Partner Violence in Pregnancy. A Systematic Review and Meta-Analysis. *Frontiers in Public Health*, 9, 738459. <https://doi.org/10.3389/FPUBH.2021.738459/BIBTEX>
- Salmela-Aro, K. (2011). Stages of Adolescence. *Encyclopedia of Adolescence*, 1, 360–368. <https://doi.org/10.1016/B978-0-12-373951-3.00043-0>
- Silveira, P. P., Pokhvisneva, I., Parent, C., Cai, S., Rema, A. S. S., Broekman, B. F. P., Rifkin-Graboi, A., Pluess, M., O'Donnell, K. J., & Meaney, M. J. (2017). Cumulative prenatal exposure to adversity reveals associations with a broad range of neurodevelopmental outcomes that are moderated by a novel, biologically informed polygenetic score based on the serotonin transporter solute carrier family C6, member 4 (SLC6A4) gene expression. *Development and Psychopathology*, 29(5), 1601–1617. <https://doi.org/10.1017/S0954579417001262>,
- Socioeconomic status*. (n.d.). APA Dictionary of Psychology (by American Psychological Association). Retrieved August 13, 2025, from <https://dictionary.apa.org/socioeconomic-status>
- Sutherland, S., & Brunwasser, S. M. (2018). Sex Differences in Vulnerability to Prenatal Stress: a Review of the Recent Literature. *Current Psychiatry Reports*, 20(11). <https://doi.org/10.1007/S11920-018-0961-4>,

- Thau, L., Gandhi, J., & Sharma, S. (2023). Physiology, Cortisol. *StatPearls*.
<https://www.ncbi.nlm.nih.gov/books/NBK538239/>
- Thomson, K., Moffat, M., Arisa, O., Jesurasa, A., Richmond, C., Odeniyi, A., Bambra, C., Rankin, J., Brown, H., Bishop, J., Wing, S., McNaughton, A., & Heslehurst, N. (2021). Socioeconomic inequalities and adverse pregnancy outcomes in the UK and Republic of Ireland: A systematic review and meta-analysis. *BMJ Open*, 11(3). <https://doi.org/10.1136/BMJOPEN-2020-042753>,
- Tien, J., Lewis, G. D., & Liu, J. (2020). Prenatal risk factors for internalizing and externalizing problems in childhood. *World Journal of Pediatrics*, 16(4), 341–355. <https://doi.org/10.1007/S12519-019-00319-2>,
- Upton, J. (2013). Psychosocial Factors. *Encyclopedia of Behavioral Medicine*, 1580–1581. https://doi.org/10.1007/978-1-4419-1005-9_422
- Vaknine Treidel, S., Lobmaier, S. M., Sharma, R., Madrer, N., Dubnov, S., Shulman, D., Greenberg, P., Bennett, E. R., Greenberg, D. S., Turjeman, A., Zelgert, C., Zimmermann, P., Frasc, M. G., Carmel, L., Antonelli, M. C., & Soreq, H. (2025). Maternal prenatal stress induces sex-dependent changes in tRNA fragment families and cholinergic pathways in newborns. *Molecular Psychiatry*, 30(9). <https://doi.org/10.1038/S41380-025-03011-2>,
- Van den Bergh, B. R. H., van den Heuvel, M. I., Lahti, M., Braeken, M., de Rooij, S. R., Entringer, S., Hoyer, D., Roseboom, T., Räikkönen, K., King, S., & Schwab, M. (2020). Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. *Neuroscience & Biobehavioral Reviews*, 117, 26–64. <https://doi.org/10.1016/J.NEUBIOREV.2017.07.003>
- Verbeek, T., Bockting, C. L. H., Beijers, C., Meijer, J. L., van Pampus, M. G., & Burger, H. (2019). Low socioeconomic status increases effects of negative life events on antenatal anxiety and depression. *Women and Birth*, 32(1), e138–e143. <https://doi.org/10.1016/j.wombi.2018.05.005>
- Wellbeing, P. (2022). *Child and Adolescent Mental Across the Life Course Towards an Integrated Conceptual Framework for Research and Evidence Generation*. www.unicef-irc.org
- Woody, C. A., Ferrari, A. J., Siskind, D. J., Whiteford, H. A., & Harris, M. G. (2017). A systematic review and meta-regression of the prevalence and incidence of perinatal depression. *Journal of Affective Disorders*, 219, 86–92. <https://doi.org/10.1016/J.JAD.2017.05.003>

- World Health Organization. (2024, October). *Mental health of adolescents*.
<https://www.who.int/news-room/fact-sheets/detail/adolescent-mental-health>
- World Health Organization. (2025). *Perinatal mental health*.
<https://www.who.int/teams/mental-health-and-substance-use/promotion-prevention/maternal-mental-health>
- Zijlmans, M. A. C., Riksen-Walraven, J. M., & de Weerth, C. (2015). Associations between maternal prenatal cortisol concentrations and child outcomes: A systematic review. *Neuroscience & Biobehavioral Reviews*, 53, 1–24.
<https://doi.org/10.1016/J.NEUBIOREV.2015.02.015>

Table 1. Characteristics of participants at baseline and 13 years follow-up (n= 4,640).

Mothers' characteristics at baseline		n (%)
Age (years)	≤ 25	815 (17.6)
	26-35	3192 (68.8)
	>35	633 (13.6)
Education (years)	≤9	2140 (47.0)
	10-12	1064 (23.4)
	>12	1346 (29.6)
Unemployment	No	3887 (84.9)
	Yes	690 (15.1)
Marital status	Married/living with partner	4423 (95.5)
	Single/divorced	206 (4.5)
Household monthly income (€)	≤ 1000	1350 (33.1)
	1001-2000	1963 (48.2)
	>2000	760 (18.7)
Stressful life events during pregnancy, n	0	2317 (51.9)
	1	1358 (30.4)
	≥2	791 (17.7)
Stressful life events during 1T of pregnancy, n	0	1002 (49.7)
	1	798 (39.6)
	≥2	217 (10.8)
Stressful life events during 2T of pregnancy, n	0	998 (49.7)
	1	790 (39.4)
	≥2	219 (10.9)
Stressful life events during 3T of pregnancy, n	0	916 (45.3)
	1	844 (41.8)
	≥2	261 (12.9)
Physical violence during pregnancy	No	3706 (99.3)
	Yes	27 (0.7)
Children's characteristics at 13 years		
Child's sex	Girl	2246 (48.4)
	Boy	2394 (51.6)
Internalizing problems	Close to average/slightly raised	3973 (88.3)
	High/very high	527 (11.7)
Externalizing problems	Close to average/slightly raised	3997 (88.8)
	High/very high	505 (11.2)
Depressive symptoms	No	3979 (87.6)
	Yes	564 (12.4)

Note: The total may not add 4,640 due to missing values.

Table 2. Stressful life events and physical violence during pregnancy according to maternal sociodemographic characteristics at baseline (n=4,640).

Sociodemographic characteristics	Stressful life events during pregnancy			Physical violence	
	0	1	≥2	No n (%)	Yes n (%)
Total	2317 (51.9)	1358 (30.4)	791 (17.7)	3706 (99.3)	27 (0.7)
Maternal age at baseline (years)					
≤ 25	365 (15.8)	254 (18.7)	175 (22.1)	656 (17.7)	8 (29.6)
26-35	1610 (69.5)	941 (69.3)	505 (63.8)	2584 (69.7)	16 (59.3)
>35	342 (14.8)	163 (12.0)	111 (14.0)	466 (12.6)	3 (11.1)
Maternal education at baseline (years)					
≤9	1081 (47.4)	608 (45.7)	378 (48.8)	1685 (46.3)	19 (73.1)
10-12	534 (23.4)	311 (23.4)	185 (23.9)	854 (23.5)	3 (11.5)
>12	665 (29.2)	411 (30.9)	211 (27.3)	1102 (30.3)	4 (15.4)
Maternal unemployment at baseline					
No	2056 (89.8)	1138 (84.9)	542 (69.2)	3148 (85.3)	18 (66.7)
Yes	234 (10.2)	203 (15.1)	241 (30.8)	542 (14.7)	9 (33.3)
Maternal marital status at baseline					
Married/living with partner	2238 (96.8)	1287 (95.0)	732 (92.7)	3537 (95.6)	20 (74.1)
Single/divorced	75 (3.2)	68 (5.0)	58 (7.3)	162 (4.4)	7 (25.9)
Household monthly income at baseline (€)					
≤ 1000	619 (30.5)	370 (30.7)	320 (46.1)	1051 (32.0)	14 (58.3)
1001-2000	1033 (50.9)	585 (48.5)	271 (39.0)	1600 (48.7)	9 (37.5)
>2000	379 (18.7)	250 (20.7)	103 (14.8)	637 (19.4)	1 (4.2)

Notes: The total may not add 4,640 due to missing values; bold indicates statistical significant differences (p<0.05).

Table 3. Internalizing and externalizing problems and depressive symptoms of participants at age 13 according to maternal sociodemographic characteristics at baseline and adversity during pregnancy (n=4,640).

Sociodemographic characteristics and adverse experiences		Internalizing problems		Externalizing problems		Depressive symptoms	
		Close to average/slightly raised n (%)	High/very high n (%)	Close to average/slightly raised n (%)	High/very high n (%)	No n (%)	Yes n (%)
Total		3973 (88.3)	527 (11.7)	3997 (88.8)	505 (11.2)	3979 (87.6)	564 (12.4)
Child's sex							
	Girl	1929 (88.1)	260 (11.9)	2010 (91.7)	181 (8.3)	1794 (81.5)	408 (18.5)
	Boy	2044 (88.4)	267 (11.6)	1987 (86.0)	324 (14.0)	2185 (93.3)	156 (6.7)
Maternal education at baseline (years)							
	≤9	1763 (85.3)	304 (14.7)	1813 (87.6)	256 (12.4)	1794 (85.8)	296 (14.2)
	10-12	927 (89.6)	108 (10.4)	906 (87.5)	129 (12.5)	923 (88.2)	124 (11.8)
	>12	1218 (92.1)	104 (7.9)	1218 (92.1)	104 (7.9)	1187 (90.1)	131 (9.9)
Maternal unemployment at baseline							
	No	3357 (89.0)	416 (11.0)	3366 (89.2)	408 (10.8)	3356 (87.9)	460 (12.1)
	Yes	562 (84.5)	103 (15.5)	577 (86.6)	89 (13.4)	572 (85.8)	95 (14.2)
Maternal marital status at baseline							
	Married/living with partner	3806 (88.6)	488 (11.4)	3828 (89.1)	468 (10.9)	3808 (87.9)	524 (12.1)
	Single/divorced	162 (83.1)	33 (16.9)	160 (82.1)	35 (17.9)	160 (80.0)	40 (20.0)
Household monthly income at baseline (€)							
	≤ 1000	1100 (84.3)	205 (15.7)	1114 (85.3)	192 (14.7)	1112 (84.5)	204 (15.5)
	1001-2000	1702 (89.2)	207 (10.8)	1723 (90.3)	186 (9.7)	1712 (88.8)	217 (11.2)
	>2000	692 (93.4)	49 (6.6)	680 (91.6)	62 (8.4)	669 (89.6)	78 (10.4)
Stressful life events during pregnancy (n)							
	0	1992 (88.9)	248 (11.1)	1993 (88.9)	250 (11.1)	2007 (88.4)	264 (11.6)
	1	1180 (89.3)	141 (10.7)	1198 (90.8)	122 (9.2)	1163 (87.7)	163 (12.3)
	≥2	647 (84.1)	122 (15.9)	653 (84.9)	116 (15.1)	655 (84.5)	120 (15.5)
Physical violence during pregnancy							
	No	3172 (88.1)	429 (11.9)	3203 (88.9)	400 (11.1)	3188 (87.8)	443 (12.2)
	Yes	23 (92.0)	2 (8.0)	20 (80.0)	5 (20.0)	22 (81.5)	5 (18.5)

Notes: The total may not add 4,640 due to missing values; Bolds represent statistically significant differences.

Table 4. Associations (Odds Ratio and 95% Confidence Interval, OR (95%CI)) of stressful life events and physical violence during pregnancy and internalizing and externalizing problems in adolescence.

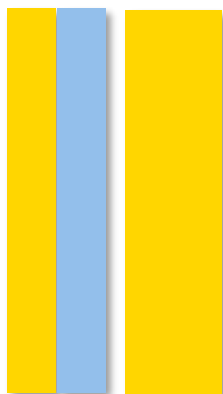
	Internalizing problems (High/very high)		Externalizing problems (High/very high)		Depressive symptoms (Yes)	
	Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Stressful life events during pregnancy, n						
0	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
1	0.96 (0.77; 1.20)	0.94 (0.74; 1.19)	0.81 (0.65; 1.02)	0.78 (0.61; 1.01)	1.07 (0.87; 1.31)	1.06 (0.84; 1.33)
≥2	1.52 (1.20-1.91)	1.40 (1.08; 1.80)	1.42 (1.12; 1.80)	1.34 (1.03; 1.74)	1.39 (1.10; 1.76)	1.28 (0.99; 1.66)
Physical violence during pregnancy						
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	0.64 (0.15; 2.74)	0.61 (0.14; 2.66)	2.00 (0.75; 5.36)	1.59 (0.52; 4.87)	1.64 (0.62; 4.34)	1.29 (0.45; 3.68)

* Adjusted for child's sex, maternal education, maternal marital status, household income; bold indicates statistical significant differences (p<0.05).

Table 5. Sociodemographic characteristics and adverse experiences of participants and non-participants at 13 years follow-up.

		Participants	Non- participants	p-value
Mothers' characteristics at baseline		n (%)	n (%)	
Total		4640 (53.7)	4007 (46.7)	
Age (years)				
	≤ 25	815 (17.6)	1445 (36.1)	
	26-35	3192 (68.8)	2159 (53.9)	
	>35	633 (13.6)	403 (10.1)	<.001
Education (years)				
	≤9	2140 (47.0)	2594 (67.0)	
	10-12	1064 (23.4)	715 (18.5)	
	>12	1346 (29.6)	563 (14.5)	<.001
Unemployment				
	No	3887 (84.9)	2995 (75.5)	
	Yes	690 (15.1)	972 (24.5)	<.001
Marital status				
	Married/living with partner	4423 (95.5)	3655 (91.6)	
	Single/divorced	206 (4.5)	336 (8.4)	<.001
Household monthly income (€)				
	≤ 1000	1350 (33.1)	1674 (49.8)	
	1001-2000	1963 (48.2)	1292 (38.4)	
	>2000	760 (18.7)	398 (11.8)	<.001
Stressful life events during pregnancy, n				
	0	2317 (51.9)	1900 (49.4)	
	1	1358 (30.4)	1120 (29.1)	
	≥2	791 (17.7)	827 (21.5)	<.001
Physical violence during pregnancy				
	No	3706 (99.3)	3199 (98.6)	
	Yes	27 (0.7)	47 (1.4)	.003

Note: The total may not add 8647 due to missing values; bold indicates statistical significant differences (p<0.05).



SEDE ADMINISTRATIVA

FACULDADE DE MEDICINA

INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

