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When more is not better: cumulative stress impact on maternal mental health and children's temperament.

Quando il troppo stroppia: l'impatto dello stress cumulativo sulla salute mentale materna e sul temperamento infantile

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INTRODUCTION

Pregnancy is an extremely challenging period in a woman's life, a time marked by significant transformations and reactivations of previous relationships and traumas. Pregnancy can mean both hope and crisis. If the second option is verified, mothers-to-be may experience high levels of prenatal maternal stress and low levels of maternal mental health which in turn have detrimental consequences on the offspring, programming the child's development.

Previous stressors and traumas are relieved during pregnancy, and, together with an environment of fear and uncertainty, such as the one created by the Covid-19 Pandemic may influence negatively the overall maternal well-being.

The current study investigates how cumulative life-time maternal stressors and traumas influence the mother-to-be maternal mental health and stress levels, and how in turn, this may affect the offspring negative affect, a construct which origins are highly epigenetic.

The first chapter will explore the theoretical frame of this study, beginning with the Developmental Origins of Health and Disease Hypothesis (DOHaD), which hypothesizes the programming effect of prenatal maternal well-being on the offspring. The construct of PNMS or Prenatal Maternal Stress is then presented; following the programming effect on the child's developmental outcomes are explained. Finally, we review the detrimental consequences of experiencing pregnancy in adverse environments, such as Natural Disasters and the Covid-19 Pandemic.

The second chapter will delve into the main construct of this work: Cumulative Stress. The detrimental consequences of cumulative exposure to stressors during the life course

far exceeds the ones from a single stressor exposure. We here considered five different stressors, which alone have strong warning effect on someone's mental health: low socio-economic status, abuse during childhood and/or adulthood, being diagnosed with a prenatal condition and experiencing the objective hardship of the Pandemic.

Finally, in the Third chapter the current research is presented, which is part of a longitudinal study implemented by the Department of Developmental Psychology and Socialization of the University of Padova. We here describe the aims and the hypothesis of our study, the procedure, the methods, and the materials employed. Results, strength, and limits are then discussed.

CHAPTER 1

PRENATAL MATERNAL STRESS

1.1 FETAL PROGRAMMING

It is now well established how exposure to an adverse in utero environment may interfere with the fetus's and the offspring's wellbeing. Factors acting early in life "program" the set point of physiological systems, perhaps to prepare the individual for life under suboptimal conditions (Welberg et al., 2001).

1.1.1 Prenatal Brain Plasticity

Brain plasticity, the neurons and neural circuits' capacity to change, structurally and functionally, in response to external and internal stimuli, is an experience-dependent mechanism. This property is fundamental for the adaptability of our behavior, for learning and memory processes, brain development, and brain repair (Sale et al., 2014). As a result, experience can shape neural circuit development particularly during "sensitive" or critical periods of early development since neural networks are highly sensitive to experience. During embryonic and fetal development, despite the overwhelming impact of genetic control, the external stimuli have a strong influence on the developing structures. One source of alteration is the maternal intake of food and pharmacologically active substances, or the development of illnesses and the exposure to environmental toxins and pollutants (Thompson et al., 2009). In addition, prenatal stress, that may derive from more subtle variations in the quality of environmental stimulation has a deleterious impact on fetal development (Sale et al., 2014). In humans, potential factors leading to prenatal

stress may include exposure to major natural disasters, loss of the partner, divorce, serious illness, or death of a relative or friend, or internal sources, such as maternal disorders during pregnancy, anxiety, and depression.

1.1.2 Barker Fetal Programming Hypothesis

The fetal programming hypothesis (D. J. Barker, 1990), often referred to as the Developmental Origins of Health and Disease (DOHaD) theory (P. D. Gluckman, Hanson, & Buklijas, 2010), has been applied to both animals (Kapoor et al., 2009; McArdle et al., 2006) and human research (Barker, 1995; Egliston et al., 2007). What Barker and Gluckman claimed is that environmental factors acting early in life (usually in fetal life) have profound effects on vulnerability to diseases later in life, often in adulthood. First studies validating this hypothesis were conducted by Barker himself 1986, when he found how Chronic Heart Diseases (CHD) were most common in the poorest parts of the UK. Areas of the country with high rates of infant mortality in the past, correlated with high rates of heart disease in the present. High infant mortality appears to be more common in those areas where it is registered high rates of Low Birth Weight (LBW), reduced infant growth, and poor nutrition and health of pregnant women (Delisle, 2002.). Barker developed his "early origins" hypothesis based on retrospective studies showing an inverse association of birth weights and CHD mortality and morbidity rates.

The *"Barker hypothesis"* postulates that many organs and their respective functions undergo programming during embryonic and fetal life, which determines the set point of physiological and metabolic responses that carry into adulthood. It derives that any stimulus or insult at a critical period of embryonic and fetal development can result in

developmental adaptations that produce permanent structural, physiological, and metabolic changes, thereby predisposing an individual to cardiovascular, metabolic, and endocrine disease in adult life (Kwon & Kim, 2017).

Over the years, many studies have been conducted trying to validate Barker's Hypothesis and trying to understand the underlying mechanisms. Some of the most relevant finding that may explain the association between fetal programming and chronic diseases are here cited. Overexposure of the fetus to glucocorticoid because of the activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis in stressful intrauterine conditions has been found to link with chronic diseases. HPA axis gets activated in both animals and humans as a consequence of stress exposure, resulting in glucocorticoid release, which regulate the physiological responses to a stressor. Short-term exposure to high fetal glucocorticoid levels may increase glucose production, allowing an adaptive response to an imminent risk. Chronic exposure to high levels of fetal glucocorticoids may have various permanent effect on the cardiovascular system and may alter renal morphogenesis and renin angiotensin system. It may also influence insulin-like growth factors and operate a permanent up-regulation of gluconeogenesis. Maternal malnutrition, which influences the insulin-like growth factor system (glucose-insuline-IGF-1), the primary axis regulating fetal growth, is related to the "thrifty phenotype" theory proposed by Hales and Barker in the early '90s. This theory implies that metabolism would respond adaptively, becoming "thrifty" when the fetal nutrient supply is limited, in order to salvage vital organs, particularly the brain, at the expense of growth (Delisle, 2002.)

These kind of adaptive responses to a threatening environment may affect the subsequent phenotype of the individual organism, making it “fit” to the environmental conditions of later life. This mechanism is named phenotypic plasticity.

1.1.3 The Predictive Adaptive Response (PAR) hypothesis

Mammals have developed the capacity to respond in an appropriate way in utero, presumably to improve fitness, and be better prepared for the environment in which they would find themselves after birth (Gluckman et al., 2005). The fetus obtains its information about the environment from its mother, by variation in the nutrients, hormones or other chemicals which cross the placenta from the mother.

PARs or *Predictive Adaptive Responses* can be described as a form of developmental plasticity that evolved as adaptive responses to environmental cues acting early in the life cycle, but where the advantage of the induced phenotype is primarily manifest in a later phase of the life cycle (P. D. Gluckman, Hanson, et al., 2005)

The PAR mechanism was first recognized by Hales and Barker with the name of *Thrifty Phenotype Hypothesis* proposing how early life events (i.e., maternal malnutrition) are associated with an increased disease risk in adult populations (i.e., Type 2 diabetes) and with fetal nutrition becoming “thrifty” having differential impact on the growth of different organs, with selective protection of brain growth. Consequently, altered brain growth permanently changes the structure and function of the body. This kind of response has the adaptive goal to salvage vital organs at the expanse of growth (Hales & Barker, 2001).

PARs, therefore, are a form of phenotypic plasticity. The resulting phenotype may not be advantageous in the environment immediately following the inducing cue (i.e., malnutrition) but is likely to be beneficial in an anticipated future environment, acting as a predictor of the nature of the environment (P. D. Gluckman, Hanson, et al., 2005). This delay between the inducing cue and phenotypic response implies that environmental cues during early stages of life provide a prognosis about the future conditions of the world that the individual will live in (Bateson, 2001; P. D. Gluckman, Dphil, et al., 2005).

Many examples are reported in animal and human studies; for instance, in humans, the thermal environment during a crucial period soon after birth determines the number of sweat glands activated by cholinergic innervation, even though the ability to sweat is less important in infants because they have a higher surface area to volume ratio than adults and thus lose heat more readily. The individual is then committed to that pattern of thermoregulation for life which is adaptive for the environment in which he was born (Kawahata & Sakamoto, 1951).

These kinds of adaptations, inherited by our ancestors, are the products of biological and psychological mechanisms evolved to solve recurrent survival and reproduction challenges (Buss, 1995). Humans, however, now live in environments which are far from the ones our ancestors used to live in and those adaptive mechanisms may no longer be linked to the environment in the same way. This phenomenon is known as *evolutionary mismatch* and has profound implications for not only the functioning of mechanisms, but also human psychology ("Corrigendum: The Evolutionary Mismatch Hypothesis: Implications for Psychological Science, 2018). Similarly, early life challenges may induce changes that prepare an individual for life in a more hostile environment and are

therefore predominantly beneficial; *but what if a gap is registered between the programmed and the later actual environment?* The mismatch hypothesis states that a mismatch between fetal expectation of its postnatal environment and actual postnatal environment contribute to later adult disease risk (P. D. Gluckman, Dphil, et al., 2005). For example, we are not usually exposed to the type of danger for which extra vigilance (anxiety), or readily distracted attention (ADHD) would be helpful, and these symptoms can both be distressing and impede formal learning.

Many studies have found links between maternal stress during pregnancy and subsequent developmental patterns in offspring. Maternal stress appears associated with a range of psychological outcomes in offspring, including hyperactivity, anxiety and vigilance, aggression and externalizing behavior, and readily distracted attention (Glover, 2011). These outcomes may reflect programming in utero mechanisms and predictive responses to an adverse environment, preparing the fetus for a dangerous or unpredictable postnatal setting. The Fetal Programming Hypothesis or DOHaD (Developmental Origins of Health and Diseases) and the PAR hypothesis (Predictive Adaptive Response) are here fundamental to explain this link between prenatal maternal stress due to an adverse environment and children's adverse outcomes. These effects may reflect predictive adaptive responses, with the fetus preparing for a dangerous or unpredictable postnatal environment (Frankenhuis & del Giudice, 2012).

1.2 PRENATAL MATERNAL STRESS (PNMS)

1.2.1 Is it stressful to become a mother?

Pregnancy is far from an ordinary time in a woman's life, so much about her changes in such a brief period and she find herself adapting to those changes for her own and her

child's physical and psychological health (Slade, 2009). Pregnancy is a stressful period for some women because it entails numerous demands and changes in physical conditions, roles, and interpersonal relationships. This is a time of transformation and transition, which could mean both hope and crisis. Why would pregnancy be such a disruptive time of life has been thoroughly studied; first of, the mother-to-be finds herself going through enormous physical, hormonal, neurochemical, and neurobiological shifts. Hormones secreted during pregnancy are responsible for all those changes that allow the pregnancy to proceed and the fetus to develop, but they are also accountable for the mood fluctuations and upheaval that are intrinsic to pregnancy (Slade, 2019). Particularly crucial in the so called "parental brain" is the activation of menta lizing, empathy, and mirroring networks in the mother-to-be that promote the development of socioemotional networks in the baby (Feldman, 2015). The activation of these networks depends on a delicate balance between neuroendocrine systems. These include the oxytocin [OT] system, which ensures attachment and bonding (Feldman, 2015; Levine et al., 2007); the hypothalamic-pituitary-adrenal [HPA] axis, which regulates stress and ensures response to danger (Toepfer et al., 2017); and, finally, dopaminergic reward centers, which activate pleasure centers in the brain, involved in the mother's feeling of wholeness in spending time with her baby (Strathearn et al., 2009). Also, cortisol and other stress hormones interact with oxytocin to reduce anxiety, increase calmness, and intensify the incentive value of the attachment target (Feldman et al., 2007).

It is very significant how hormones fluctuations are further implicated in the development of psychiatric disturbances during the antenatal and post-natal periods. For instance, women who are vulnerable to postpartum psychiatric episodes might have an abnormal response to the hormonal fluctuations of pregnancy and childbirth (Meltzer-Brody et al.,

2018). These changes happening within the body and the brain meet with and even bigger transformation; within the mother-to-be, internal representations of self and other, of attachment and caregiving are reactivated. Becoming a mother activates her internalized representation of the relationship with her own mother. Complex relationships with the caregiver call for a harder experience (Pines, 1972). The future mom finds herself being many things: a woman, a daughter, a wife/partner, a working person and now, also a mother (Slade, 2019; Slade, 2009). Adapting to a new self, can be challenging. Most, if not all, of a woman's relationships will be changed by her becoming a mother. Her relationship with the partner must expand to include a third person with competing needs and desires. The couple will be shifting to a relationship of co-parenthood (Minuchin, 1974) which should entail bidirectional support and agreement in the new role of parents (Mchale, 2007). Her relationship with her own mother and her family, colleagues and friends will change as well. These transformations may conduct to a sense of loss and loneliness, therefore external support, in terms of emotional, instrumental, and informative support especially from friends and family appears to be a fundamental protective factor (Parolin & Sudati, 2014). Furthermore, in a cultural environment in which the care of children remains largely women's responsibility, unpaid and unsupported by the state, women are expected to compromise their education, their careers and their free time in order to care of the family (C. Lee, 1997). The degree to which the mother-to-be is able to manage and integrate these developmental shifts is related to several internal and external factors (Slade, 2009). Factors such as coping, traits, social support, and health behaviors influence women's psychosocial experience of pregnancy directly and moderate the effects of psychosocial variables such as maternal stress (Lobel et al., 2008). This period is characterized by high vulnerability; being

psychologically vulnerable may set in motion patterns that have long-term consequences for not only the mother, but for the baby as well (Slade 2009). Among the most at risk during pregnancy are women with prior psychiatric difficulties, as well as those with histories of trauma, abuse, and loss, teenage mothers, who are usually coping not only with the stress of becoming a parent during adolescence, but with additional stressors deriving from poverty, inadequate social support, and histories of disrupted attachment and trauma or mothers who are living an unintended pregnancy (Slade, 2019; Slade, 2009).

Literature agrees on the significant effect of depressive and anxious disorders on the perinatal period. Prenatal Depression presents itself with a symptomatology which could be somehow similar to a Depressive Disorder that may arise in other time periods during life. Symptoms include depressed mood, markedly diminished interest, or pleasure in many, if not all activities, significant weight loss or weight gain or decrease or increase in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt nearly every day, recurrent thought of death and recurrent suicidal ideation or attempt (American Psychiatric Association, 2013). During pregnancy, pregnant women experience fantasies and feeling of failure and inadequacy related to the role they are about to cover, anxiety regarding the fetus's health, sadness, irrit ability, perception of a low social and partner support (Monti et al., 2014). Mothers appear to be more vulnerable to depression during the prenatal period rather than the post-natal, this may have something to do with the role of an unresolved loss of her own identity before pregnancy (Monti et al., 2014). Evans and colleagues document how depressive disorder has, in fact, a prevalence of 13,5 % during pregnancy and of 9,1 % post-partum (Evans et al., 2001). Risk factors for

depression during pregnancy are having a history of depression, a family history of depression or bipolar disorder, childhood maltreatment, cigarette smoking, low income, age younger than 20 years, insufficient social support, and domestic violence (Stewart, 2011).

Similarly, prevalence of anxiety symptoms may be higher during pregnancy than in the postpartum period. Lee and colleagues, also propose how anxiety disorders may even be more common during pregnancy than depression (A. M. Lee et al., 2007). High prevalence of anxiety disorders during pregnancy may have to do with re-transcription processes of the mother-to-be personal and social identity which may trigger high and pathological levels of anxiety (Monti et al., 2014). Anxiety during pregnancy, especially the last months of gestation, might have an adaptive meaning, allowing the mother-to-be to prepare herself for childbirth, entering in what Winnicott called "primary maternal preoccupation". However, anxiety levels may reach clinical significance. Brockington and colleagues (Brockington et al., 2006) report some of the most cited and significant fears by mothers-to-be such as pathological fear of fetal abnormality or death, excessive worry of inadequacy as mother and fear of childbirth (tokophobia). Other recurring themes may be financial worries, housing problems, postpartum depression, obstetric concerns, family dynamics, loss of freedom, the sex of the child, problems with other children, the mother's general health, and telling the family about the pregnancy. In addition, chronically or severely anxious mothers may feel overwhelmed and fatigued which might impact their diet and sleep habits and consistency of prenatal care. Through this and many other biological mechanisms, maternal anxiety affects the fetus's and newborn's health in various ways (Shahhosseini et al., 2015). Mothers-to-be are more at risk for developing an anxious symptomatology when: of a younger age, have a history

of alcoholism, smoking and mental health problems, have a low self-esteem, have low social support, experience high conflict with the partner or their own family, have chosen medically assisted procreation (A. M. Lee et al., 2007). Depression and anxiety are highly comorbid during the antenatal period. High anxiety and anxiety sensitivity during pregnancy is one of the strongest risk factors for depression (Verreault et al., 2014). In the same way, women with feelings of anxiety are at increased risk of suffering from depression during pregnancy (Edwards et al., 2008).

Lastly, traumatic birth experiences, such as preterm birth, obstetric complications, child's deficits, history of mental health disorders and low social support may lead to the onset of a Post-Traumatic Stress Disorder. Pregnancy PTSD is often explained by a birth complication which was not well managed. Common PTSD symptoms are flashbacks, depersonalization, hypervigilance, nightmares, emotional flattening, intrusive thoughts and memories, depression and anxiety, difficulties in the attachment relationship, fear of sexual intimacy, avoidance of childbirth or vaginal birth (Monti et al., 2014). Morland and colleagues, report how as many as 3-7 % of pregnant women meet diagnostic criteria for PTSD, and many of these women are likely to have comorbid mood and other anxiety disorders (Morland et al., 2007). When diagnosed during pregnancy, PTSD has been associated with suicidality, panic disorders, and preterm delivery (Slade, 2009).

Maternal psychopathology and stress during pregnancy are among the most common intrauterine exposures associated with a negative impact on the offspring's health. Inter-generational transfer of psychopathology and stress is believed to be caused by a combination of intrauterine environment, genetics, and postnatal environmental factors (Molenaar et al., 2019). Previous research has shown associations between intrauterine

maternal psychopathology and stress and child outcomes to be independent of genetics and postnatal factors (Molenaar et al., 2019). How would intrauterine stress affect the fetal and infant well-being has been systematically studied; the most widely investigated candidate system that could be altered by an adverse intrauterine environment, is the hypothalamic-pituitary-adrenal (HPA) axis (Braithwaite et al., 2014; Talge et al., 2007), which plays a key role in many homeostatic systems in the body and in the body's response to stress. It is proposed that dysregulation of the maternal hypothalamic-pituitary-adrenal (HPA) axis determines fetal exposure to stress hormones (i.e., glucocorticoids) influencing development and birth outcomes and programming the fetal HPA axis, linking early life development with later life disease (Duthie & Reynolds, 2013). During pregnancy, the regulation of the maternal HPA axis undergoes dramatic changes. The fetus is protected from high levels of maternal glucocorticoids by the action of the placental enzyme HSD11B2. Although a significant proportion of cortisol (80 – 90%) is metabolized by the placenta during gestation, excess levels of cortisol may reach the fetus. As maternal cortisol levels are so much higher than fetal levels, even modest variations in placental HSD11B2 can significantly alter fetal glucocorticoid exposure (Duthie & Reynolds, 2013). It has been suggested that maternal exposition to a variety of different stressors ranging from anxiety/depressive symptoms to acute stressors such as loss or exposure to natural disasters may lead to interindividual variation in HPA axis activity in pregnancy.

Further, maternal environmental exposures, including stress during pregnancy, can affect maternal and offspring epigenetic patterns (i.e., DNAm). Therefore, maternal and offspring genetic variants (i.e., heritable, stable variations in the genetic code) and epigenetic patterns (i.e., chemical marks to the genetic code that can affect which genes

are turned on or off) are likely to both contribute to the health of the mother and offspring. Nowak and colleagues found that associations among stress during pregnancy and DNA methylation were most commonly noted when perceived stress, anxiety, or depression served as a predictor. Epigenetic modification of DNA within HPA axis-related genes, responsible for stress response, seem to involve the glucocorticoid receptor, which is encoded by the NR3C1 gene, affecting which genes are turned on and off as well as a many physiological processes in nearly all cell types (Nowak et al., 2020). Immunological mechanisms offer another alternative mechanism. In this case, prenatal maternal distress may be associated with elevated inflammation. Increased inflammation, which is reliably linked with increased risk of miscarriage and other obstetric complications, may alter fetal development (O'Connor et al., 2014). Finally, several studies have considered uterine blood flow; adrenaline hormones which accompany distress may cause blood vessel constriction that may impair oxygen flow to the fetus and may account for neurodevelopmental outcomes (O'Connor et al., 2014).

1.2.2 Prenatal Maternal Stress and its effects on the offspring's outcomes

It is now well established in animal models, and increasingly in humans, that stress experienced by the mother during pregnancy has many short and long-term effects on the child (Bergh et al., 2005; Swanson et al., 2009; Talge et al., 2007; van den Bergh & Marcoen, 2004). A wide range of prenatal exposures which cause distress to the mother have been studied, including acute and chronic stressors, anxiety and depression which have all been found to be associated with effects on the fetus and the child (O'Connor et al., 2002). Studies have established how fetal exposure to high levels of maternal stress correlates with not only an increased risk for spontaneous abortion and preterm labor and

for having a malformed or growth-retarded baby (reduced head circumference in particular) (Mulder et al., 2002), but also with a higher risk of anxiety (O’Connor et al., 2002), attention deficit/hyperactivity disorder (ADHD) (Huizink e t al., 2007; O’Connor et al., 2003) and conduct disorder (Barker & Maughan, 2009; O’Connor et al., 2003) as well as altered function of the HPA axis (O'Connor; O'Donnell et al., 2009) and cognitive deficits in the offspring. How developmental psychopathology may be a consequence of prenatal maternal stress exposure has been thoroughly explained by Barker which suggests that the intrauterine signals that compromise fetal growth also act to “program” tissue differentiation in a manner that predisposes to later illness (O’Donnell & Meaney, 2017).

How do we explain the rise of emotional, behavioral, and cognitive problems?

Our emotions and behaviors, just like our internal mechanisms, have been shaped by natural selection (Nesse & Ellsworth, 2009). Attacks by predators, exclusion from the group, and opportunities for mating were sufficiently important and frequent to have shaped special patterns of behavior. For example, sadness and emotional withdrawal, which are typically involved in depression, may lead to avoidance of potentially harmful actions. Crying may elicit support by others. Fatigue, especially in winter, as in seasonal affective disorder, may help save energy (Gluckman et al., 2009). Maternal prenatal stress and anxiety may, in contrast, program the offspring to deal with a future dangerous or stressful environment, in order to survive. The programming effects may not be specifically associated with a particular clinical diagnosis or depression in the mother, but the original range of conditions or life events which made her feel generally stressed (Glover, 2011).

Here are reported some of the most associated psychopathologies with prenatal stress.

Anxiety: Several studies have found that prenatal stress or anxiety is associated with increased levels of anxiety (Bergh et al., 2005; O'Connor et al., 2002) , or internalizing problems (de Bruijn et al., 2009 (Kingsbury et al., 2016)) in the child.

Cognitive function: Numerous studies have found an association between prenatal stress and children performing less well in cognitive tests. The prenatal stresses studied include life events (Bergman et al., 2007), exposure to a Canadian ice storm (Laplante et al., 2008), increased state anxiety (Mennes et al., 2006) and exposure to pregnancy-specific anxiety and increased daily hassles (Huizink et al., 2003).

Attentional Deficit and Hyperactivity Disorder: An increase in symptoms of ADHD is one of the outcomes most commonly found to be associated with prenatal stress (O'Connor et al., 2002; Rodriguez & Bohlin, 2005; van den Bergh & Marcoen, 2004). From an evolutionary point of view, distracted attention may be adaptive in a dangerous environment, which the pregnant mother has experienced as stressful. Sensitivity to small signals, such as a new sound, may alert one to the approaching presence of a predator or a hostile human (Glover, 2011).

Conduct disorder: Externalizing problems (Van den Bergh & Marcoen, 2009) and conduct disorder have been shown to be associated with prenatal stress or anxiety. Barker and Maughan (E. D. Barker & Maughan, 2009) found that prenatal anxiety was especially associated with conduct disorder that persists into adolescence. Evolutionary speaking, more aggressive behavior, breaking the rules, or behaving in a way different

from the group may be adaptive in a stressful environment in which there is a shortage of resources, or more danger from outsiders (Archer, 2009; Glover, 2011).

1.3 PREGNANCY IN ADVERSE CONTEXTS

1.3.1 Prenatal Maternal Stress (PNMS) in the context of a Natural Disasters

As seen before, retrospective studies on humans, and experimental research with animals, suggest that prenatal maternal stress can influence the physical, behavioral, and cognitive outcomes of the offspring. However, there are important gaps and methodological constraints in the existing literature. Research on prenatal maternal stress deriving from exposure to a natural disaster while in pregnancy, tries to disentangle these limits.

Natural disasters can be defined as potentially traumatic events collectively experienced, with an acute onset and a time-limited nature, that might be attributed to a natural cause ("Methods for Disaster Mental Health Research.," 2006). The nature of a calamity allows to study multiple facets of pregnant women's stress response (i.e., objective hardship, subjective emotional reactions, and/or cognitive evaluation of the event), which would not be allowed in most human studies where randomly assign pregnant women to different stressful events would be unethical. This ensures high levels of internal validity. In this research field, mothers are exposed to stressful events with stable characteristics (degree of uncertainty, urgency…), to degrees that varied from very little to extreme, independent of mother–child genetic inheritance and other co-occurring risk factors, such as socioeconomic status, parental personality traits, race, and age. The sudden onset of the calamity allows to study the impact of a natural disaster on infant development in various pregnancy trimesters, which would be nearly impossible to do

with other prenatal life events that have gradual onsets (i.e., the breakdown of a relationship, or the death of a relative). Three well studied natural experiments that have been fundamental to unravel some methodological weakness on prenatal maternal stress are the Project Ice Storm, the Iowa Flood Study, and the Queensland Flood Study. Throughout these projects, objective exposure to the calamity, in terms of threat, loss, change and scope and subjective maternal distress resulted directly associated with birthweight, offspring stress and emotion regulation difficulties, risk for developmental psychopathology, neurodevelopment and physical growth. Objective hardships deriving from a calamity might reflect specific characteristics of the event, that may act on the mother and the fetus's health. For instance, during a natural disaster, pregnant women may be exposed to malnutrition, hypothermia, dehydration, inability to access medical care, physical strain, exposure to carbon monoxide which might undermine her own nutrition, dysregulate her physiological stress reactivity and increase the risk for a variety of pregnancy complications(S. King et al., 2015).

1.3.2 COVID- 19

In December 2019, an outbreak of pneumonia of unknown origin was reported in Wuhan, Hubei Province, China. The global spread of SARS-CoV-2 and the thousands of deaths caused by coronavirus disease (COVID-19) led the World Health Organization to declare a pandemic on 12 March 2020 (Ciotti et al., 2020). To date, the world has registered 6,23 million deaths due to Covid-19 and a total of 512 million cases, making it one of the biggest pandemics ever registered in human history. Patients with SARS-CoV-2 infection may present symptoms ranging from mild to severe with a large portion of the population being asymptomatic carriers. The most common reported symptoms include fever (83%),

cough (82%) and shortness of breath (31%). As with other respiratory viruses, SARS-CoV-2 transmission occurs with high efficacy and infectivity mainly through the respiratory route. Droplet transmission is the main recognized route, although aerosols may represent another important route (Ciotti et al., 2020).

The rapidly evolving situation has drastically altered people's lives, as well as multiple aspects of the global, public, and private economy. Socio-economic implications of the coronavirus pandemic are alarming; social distancing, self-isolation and travel restrictions have led to a reduced workforce across all economic sectors and caused many jobs to be lost. Schools have closed down, the need for commodities and manufactured products has decreased, while both medical and food request has significantly increased (Nicola et al., 2020). The nature of uncertainty and fear which characterizes a natural disaster as much as a pandemic is leading to an increase in mental health problems. Many studies have found a growth in suicide as well as mental disorders associated with suicide (Mamun & Ullah, 2020; McIntyre & Lee, 2020; Thakur & Jain, 2020). Again, separate lines of research have also reported an increase in psychological distress in the general population, persons with pre-existing mental disorders, as well as in healthcare workers (Wang et al., 2020).

During the first months of 2020, Italy was dramatically affected by the outburst of the coronavirus disease of 2019. The lockdown and containment strategies together with the rapid spread of the virus contributed to an emerging scenario of global stress and a threat to public health (Barello et al., 2020; Xiong et al., 2020). Exposure to stress may be especially harmful during pregnancy, which is, as seen above, an early sensitive period

characterized by high plasticity and heightened susceptibility to adverse environmental conditions (Provenzi et al., 2021).

1.3.3 Pregnancy during COVID-19

Women living their pregnancy during the Covid-19 Pandemic appear to be one of the most at risk categories for mental health problems. Recent studies have, in fact reported high levels of stress and reduced psycho-social well-being among pregnant women during the pandemic (López-Morales et al., 2021). Depression and anxiety are the most common mental health problems experienced by pregnant women during the pre and postnatal periods (Howard et al., 2014). As seen above, these kinds of difficulties may interfere with the fetus and offspring well-being. Berthelot and colleagues found that pregnant women assessed during the COVID-19 pandemic reported more distress and psychiatric symptoms than pregnant women assessed before the pandemic, mainly in the form of depression and anxiety symptoms (Berthelot et al., 2020).

Why would pregnancy during the pandemic be an even more stressful period for a mother-to-be has been studied in the past years. First, the pandemic context has introduced changes in medical routines during pregnancy, making the women feeling unprepared to deliver (Preis et al., 2020). Moreover, mothers may have experienced or perceived reduced social support during pregnancy, which is one of the significant risk factors for depression among pregnant women (Negron et al., 2013), may have had worries regarding threat to her own life or harm to the baby. The stigma associated with hospitals due to COVID-19 has led to underutilization of healthcare services, the fear of acquiring infection in the hospital setting or on the way to the hospital may have led the mothers to reach for medical care only later during the pregnancy (Fakari & Simbar,

2020). Mothers-to-be may have worried about not getting needed care and may have been exposed to stressors such as loss of employment, changes to relationship with their own partner and feelings of isolation. This may have in turn contributed to further elevate their levels of distress and anxiety (Lebel et al., 2020). The relative absence of fathers during and after delivery may have further contributed to the maternal stress, not letting the father-to-be provide that kind of support during the pregnancy experience that has been promoted in the last decades (Lista & Bresesti, 2020).

1.3.4 Objective exposure to Covid-19 during pregnancy

Exposure to objective hardship caused by pandemic countermeasures constitute a major prenatal stressor, affecting prenatal maternal health and consequently the offspring's outcomes. King and Laplante (S. King & Laplante, 2015) identified four major components of objective disaster exposures, which have been adapted by Giesbrecht and colleagues (Giesbrecht et al., 2021)to the COVID-19 context: scope, loss, threat, and change. Scope, in Giesbrecht perspective, refers to the duration (amount of time for which major aspects of someone 's lives were disrupted) and intensity of the hardship (number of individuals within a certain community or geographic are who were similarly affected). Loss refers to financial, social, and physical losses experienced as a result of the pandemic. For example, the loss of employment, savings, closures of schools, and daycares. Threat refers to physical and health-related consequences of exposure to the stressor (being infected with SARS-CoV-2 or hospitalization of a close friend with COVID-19). Finally, change refers to all the adjustments required by the pandemic daily, regarding prenatal care, work, and social interaction caused by the COVID-19 pandemic (working from home, altering a birth plan, and reductions in physical activity or diet

quality). Objective changes to the environment, due to COVID-19 and the real threats that this virus poses to maternal/child health, create the conditions for susceptible individuals to experience subjective stress (L. S. King et al., 2021). Considering how important maternal mental health during pregnancy is for the mother-to-be and for her future child, Covid-19 offers a fundamental opportunity to study the longitudinal effects that PNMS deriving from a pandemic may have on the mothers-to-be and on the offspring.

CHAPTER 2: CUMULATIVE STRESS

2.1 CUMULATIVE STRESS

2.1.1 What is Cumulative Stress?

The "cumulative stress" hypothesis states that aversive experiences early in life predispose individuals to be more vulnerable to aversive challenges later in life. The cumulative effects of stress exposure from birth to adulthood, lead to the build-up of allostatic load which refers to the cumulative burden of chronic stress and life events, and thus would increase the likelihood of developing a disease (Nederhof & Schmidt, 2012).

Exposure to multiple stressors, or repeated exposure to the same stressors over time, far exceeds the detrimental health consequences of single exposures (Evans et al., 2013; Turner & Lloyd, 1995). The idea that cumulative exposure to adversities would increase mental health risk was first suggested by Rutter who observed that most children experiencing a single physical or psychosocial risk factor suffered little if any permanent harm. However, the sample of children experiencing multiple risk factors were much more likely to experience psychological disorders (Rutter, 1981). Tuner and Lyod observed a relationship between number of traumas experienced prior to age 18 and lifetime risk for Major Depressive Disorder, and Substance Abuse or Dependence, as well as for potentially problematic levels of depressive symptomatology (Turner & Lloyd; A. Donald, 1995; Hammen, 2015; Bowen et al., 2018)

The cumulative physiological "cost", in terms of heightened neural and neuroendocrine responses, of prolonged stress in known as allostatic load. This concept was introduced by McEwen and Stellar in 1993 (McEwen, 1993), who built their theory starting from the

definition of allostasis, the ability of the organism to achieve stability through change (Sterling & Ever, 1988). When environmental challenges exceed the individual ability to cope, then allostatic overload follows (McEwen & Wingfield, 2003). It derives that the cumulative effect of experiences in daily life that involve ordinary events (subtle and long-standing life situations) as well as major challenges (life events), and the physiological consequences of the resulting health-damaging behaviors will cause the individual to experience an allostatic load (Guidi et al., 2021). Literature reports that subjects with allostatic overload have significantly higher levels of self-rated stress, psychological distress and abnormal illness behavior than those without (Tomba & Offidani, 2012). Studies found links between allostatic load and depressive and anxious symptoms (Juster et al., 2011, 2018), Post Traumatic Stress Disorder (Glover, 2006), Psychotic Disorders (Chiappelli et al., 2017) and Alcohol Dependence (Adinoff et al., 2017). Particularly during pregnancy, literature reports higher vulnerability to multiple stressors exposure (Braveman et al., 2010). Specifically, lower income ethnic minority women are more likely to experience financial hardships (Braveman et al., 2010), racism or discrimination (Nuru-Jeter et al., 2009), and interpersonal violence (Hien & Bukszpan, 1999).

2.1.2 Cumulative Risk (CR) index

Cumulative risk (CR) model, first designed by Rutter (Rutter & Quinton, 1984), have the objective to identify a set of proven risk factors (e.g., low maternal education, maternal depression, father absent), dichotomizing them (as extant or not), and adding them to derive a risk score of 0 (no risk factors) to an upper limit (representing all risk factors considered) for each individual in a given sample. Multiple risks are then combined into

a single index to predict an outcome of interest (Atkinson et al., 2015). Viewed within this framework, the effect of any one risk factor, if it occurs in isolation from other risk factors, is quite small, whereas a cumulative combination of multiple risk factors, regardless of the type of the stressor, increases the likelihood of maladaptive outcomes (Corapci, 2008). In general, a CRI summarizes background variables from multiple settings, allowing for a satisfactory predictive power, especially when sample sizes are relatively small (Corapci, 2008).

Cumulative risk indices offer many scientific advantages including the fact that they assimilate related phenomena and integrate diverse bodies of scholarship, they are also simple and parsimonious (Evans et al., 2013), therefore their application and effects tend to be more replicable and less sample dependent than more complex risk models (Mersky et al., 2018b). Compared to single-factor models, multifactorial risk models show a greater explanatory power and often explain significant variance in health and well-being (G. W. Evans et al., 2013). Cumulative risk models come with their limitations, for instance, each adversity is weighted equally, disregarding interactions among risks and risk exposure (Evans et al., 2013).

2.2 LOW SES EXPOSURE

There is a broad consent that social and economic conditions have an impact on health, particularly in maternal and child health (Larrañaga et al., 2013). Socioeconomic disadvantage can be harmful for the mother's health and can influence the offspring's well-being. The World Health Organization (WHO) describes how structural inequalities in power, income, and other resources lead to "the unequal distribution of health-damaging experiences" that may affect mental health (World Health Organization, 2014).

Consistently, individuals who have lower incomes also have higher incidences of depressive, anxiety, and substance use disorders (Kessler, 1994; Muntaner, 2004). Similarly, among pregnant women, those with lower incomes also report greater symptoms of depression (Fellenzer & Cibula, 2014; Koleva et al., 2011), anxiety (Bödecs et al., 2013; Faisal-Cury & Rossi Menezes, 2007), and poorer birth outcomes (Blumenshine et al., 2010). Pregnancy may represent a particularly sensitive window for mother-to-child transmission of socioeconomic disparities in health. These kinds of disadvantages may expose the fetus to psychological stressors and environmental toxins, tobacco and drugs, obesity, and inadequate nutrition, lower levels of education, and engage in higher risk and health-demoting practices (G. W. Evans et al., 2004.; Kramer et al.). Poverty has been associated to unintended or teenage pregnancy and being a single mother (Hobcraft & Kiernan, n.d.). These exposures, together with the lack of practical or emotional social support and the inability to access medical care can affect characteristics of the gestational milieu (Hanson & Gluckman, 2014; Wadhwa et al., 2011). Exposure to a low Socio-Economic Status during pregnancy has, in fact, been associated with a higher risk for gestational diabetes (Bo et al., 2002), stillbirth (Stephansson et al., 2001), preterm birth (Peacock et al., 1995), abortion, preeclampsia (Silva et al., 2008) and eclampsia. Not only the transmission of these inequalities happens from the mother to the fetus, but research highlight how children and young people from disadvantaged families are two-to-three times more likely to develop mental health problems compared to economically advantaged children (Reiss, 2013). Maternal mental health is a well-known risk factor for child psychopathology and has been identified as a potential mediator in the association between socio-economic conditions and children's mental health outcomes (Carneiro et al., 2016).

The programming mechanisms underlying intergenerational transmission of socio-economic insult is not known and is likely to be multifactorial and operate through exposures including stress, poverty, housing, poor diet, and lower education levels.

Räikköne and colleagues, found how low SES, particularly lower maternal level of education, is associated with upregulation of placental growth restriction (GR) and HSD11B1 gene expression. This combination may regenerate active glucocorticoids in placenta and increase placental sensitivity to glucocorticoids, potentially leading to greater placental and fetal glucocorticoid exposure. This may have immediate offspring effects on risk of diverse physical and mental disorders that become manifest decades later (Räikkönen et al., 2014). Low socio-economic support is particularly relevant in the pandemic context. Women who were already experiencing challenges due to socioeconomic inequality, in fact, appear to be the most vulnerable to experiencing pandemic-related stress and adversity (King et al., 2021).

2.3 PSYCHOLOGICAL, PHYSICAL, SEXUAL ABUSE DURING CHILDHOOD AND ADULTHOOD

2.3.1 Fetal abuse

During pregnancy, the fetus may be exposed to various forms of violence that can have dramatic effects on the offspring's well-being. For instance, a mother-to-be may abuse of illegal and legal substances that are then absorbed by the placenta having various effect on the fetus. Direct effects include abnormal growth and/or maturation, alterations in neurotransmitters and their receptors, and brain organization (Behnke et al., 2013), while indirectly drugs can exert a pharmacologic effect on the mother-to-be which then acts on the fetus, including altered biological mechanisms and maternal health behaviors. These

altered behaviors, which include poor nutrition, decreased access/compliance with health care, increased exposure to violence, and increased risk of mental illness and infection, may place the fetus at risk (Bauer et al., 2002). Fetal tobacco exposure as well as alcohol exposure have been linked with low birth weight and intrauterine growth restriction. Fetal growth effects are also reported in studies of prenatal opiate exposure. Direct and indirect effect of prenatal substance abuse have not only short but also long-term effects on the fetus and on the offspring. For instance, neurobehavioral consequences, such as abnormalities of muscle tone, impaired orientation, increased startles, and tremors have been studies in association to maternal abuse of tobacco, alcohol, and marijuana (Bauer et al., 2002). Long-term effects to prenatal tobacco exposure include behavioral outcomes such as impulsivity, attention problems, hyperactivity, negative and externalizing behaviors (Brook et al., 2000; Fried et al., 1992; Kotimaa et al., 2003; Kristjansson et al., 1989; Thapar et al., 2003; Wakschlah & Hans, 2002). Similarly, prenatal alcohol exposure is linked with significant attention problems in offspring, as well as adaptive behavior problems spanning early childhood to adulthood (Coles et al., 1997; Nanson & Hiscock, 1990; Streissguth et al., 2004). Finally, inattention and impulsivity at 10 years of age have been associated with prenatal marijuana exposure (Goldschmidt et al., 2000). Hyperactivity and short attention span have been noted in toddlers prenatally exposed to opiates (Rosen & Johnson, 1985) and older exposed children have demonstrated memory and perceptual problems (Lifschltz & Wilson, 1991). One last form of prenatal fetal abuse is domestic violence. Prenatal domestic violence exposure not only acts on the mother's mental health, but as a consequence, it may also influence a variety of children's outcomes, such as a difficult temperament (Quinlivan & Evans, 2005), more externalizing behaviors (physical aggression, disobeying rules, cheating, stealing, or destruction of

property) and internalizing symptoms (anxiety or depression) (Martinez-Torteya et al., 2016) and increased levels of trauma symptoms (being easily startled, repeating the same action without enjoyment) (Lannert et al., 2014).

Identifying these kinds of exposures appears to be of extreme importance since it has been found that maternal abuse of alcohol (Flannigan et al., 2021), tobacco (Soares et al., 2016) and drugs (Currie & Tough, 2021) and maternal experience of domestic violence (Lamers-Winkelman et al., 2012) during pregnancy are strongly correlated with an adverse environment and a higher risk of suffering of adverse childhood experiences (ACEs).

2.3.2 ACEs

Adverse childhood experiences (ACEs) have been described as potentially traumatic events that occur in childhood (0-17 years) and can have negative lasting effects on health and well-being. ACEs were first described in relation to health outcomes by a large study by CDC-Kaiser in 1998. Kaiser identified three categories of ACEs, each divided into subcategories: Household Challenges, Neglect and Abuse (Boullier & Blair, 2018). Abuse can be divided into three categories: physical, psychological, or emotional and sexual abuse. Physical abuse is defined as an act of physical violence enacted voluntarily by a parent or a family member. It is the act of inflicting harm to the child in order to punish him/her, whenever he/she acts in a way that is not approved by the parent or to inhibit future similar behaviors. The will to harm the minor may be satisfied causing contusions, burns, wounds, fractures, and poisoning all of which will need medical intervention. Physical abuse is the easiest form of abuse to identify, and for this reason, the most talked about. Physical violence is most common in young children (0-3 years),

since birth and the first years of life are thought to be one of the most intense and disorganizing times in a human being's life; also, children this age have few if no ability to react and report the violence.

Psychological or emotional abuse is the most hidden and destabilizing form of abuse. It includes all those actions that, acting at the level of interpersonal relationship, have a negative effect on the psychological development of the minor. It is a much more serious form of violence than physical or sexual because it is subtle and not easy to recognize. Unfortunately, because of this, it is often given little importance, underestimating its damaging psychopathological consequences. The minor is constantly terrified, yelled at, rejected, devalued, isolated, used by an adult that sends ambiguous and paradoxical messages, subjecting the child to high levels of psychological stress.

Lastly, with sexual abuse we mean the set of practices with a sexual or erotic background to which children are subjected who, because of their immaturity and dependence on adults, are not aware of what they suffer and therefore are not even able to choose. This type of abuse includes incest, harassment, rape, pornography, pedophilia, and exhibitionism.

Not only adverse childhood experiences have tremendous consequences on the child's psychological health, but they can also affect the developing brain, immune and endocrine systems. Due to the adversity in their environment, children who experience more hostile events are more likely to develop behaviors that are harmful to health, such as smoking, drinking alcohol or antisocial behavior. This is a risk factor for a poorer adult health with higher risk of many diseases including cancer, cardiovascular, liver and lung diseases (Boullier & Blair, 2018). As seen before, the experience of multiple, chronic traumatic

events such as abuse or neglet during childhood affect brain development by overstimulating the autonomic nervous system (Pervanidou & Chrousos, 2007) and dysregulating the hypothalamic—pituitary–adrenal axis (Trickett et al., 2010). Long-term dysregulation of these systems leads to an allostatic load, which is believed to be responsible for physical and psychiatric diseases as the individual ages (Trickett et al., 2010). ACEs have been linked to several physical health consequences, including cardiovascular disease (Felitti et al., 1998), chronic lung disease (Anda et al., 2008), headaches (Anda et al., 2010), autoimmune disease (Dube et al., 2009) and sleep disturbances (Chapman et al., 2013). ACEs were also associated with early death (Brown et al., 2009) and obesity, smoking, sleep disturbances and general poor health (Dube et al., 2010). Of importance, ACE was significantly correlated with negative mental health consequences such as depression (Chung et al., 2008), anxiety (Green et al., 2010), PTSD (Green et al., 2010), as well as substance dependence partially mediated by mood and anxiety disorders(Douglas et al., 2010) and suicidal ideation/attempts (Afifi et al., 2008). Childhood abuse is also linked with a damaged evolution of fundamental cognitive and emotional functions such as, intelligence, attention, perception, memory with negative consequences on school performance, difficulties in problem solving and a reduced Intelligence Quotient (IQ) and Development Quotient (Egeland et al., 1983; Egeland & Sroufe, 1981; M. F. Erickson & Egeland, 2002; Koenen et al., 2003; Trickett et al., 2010). Findings also show that people exposed to family aggression and violence have a substantially higher risk of becoming a victim (women) or perpetrator (men) of IPV as adults (Whitfield et al., 2003a). This result is of main importance, an early intervention on abused children may stop this intergenerational transmission of violence.

2.3.3 Violence Against Women (VAW)

The Declaration on the Elimination of Violence Against Women (1993) defines violence against women as *"any act of gender-based violence that results in, or is likely to result in, physical, sexual, or psychological harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or private life"*. Violence against women is present in most societies but it often goes unrecognized. Between 16% and 52% of women suffer physical violence from their male partners, and at least one in five women suffer rape or attempted rape in their lifetimes. Literature shows that women's experience of violence has direct consequences not only for their own well-being, but also for that of their families and communities (Crowell & Burgess, 1996). Furthermore, abuse can have long-term mental health consequences, including depression, suicide attempts and post-traumatic stress disorder. Unwanted pregnancies, sexually transmitted diseases and other sexual and reproductive health issues may also be involved in sexual assault. As seen before, violence against women can also have inter-generational repercussions (World Health Organization, 1997).

The most common form of violence against women is domestic violence. Research consistently demonstrates that a woman is more likely to be injured, raped, or killed by a current or former partner than by any other person. Domestic violence (also known as intimate partner violence, or IPV) is a serious public health issue worldwide and involves physical violence, sexual violence, stalking, and/or psychological aggression committed by a current or former intimate partner and has significant adverse impact on health and well-being. Between 3% and 6% of pregnant women in the United States experience a physical form of domestic violence, according to the U.S. Centers for Disease Control

and Prevention's (CDC) (Holmes, 2019). Women who experience domestic violence during pregnancy are twice as likely to miss prenatal care appointments or initiate prenatal care later than recommended (Chambliss, 2008). Experiencing domestic violence has also been associated with poor nutrition, inadequate gestational weight gain, and higher rates of smoking, alcohol use, and substance use (Holmes, 2019). Domestic violence implicates lower maternal mental health, with higher rates of depression (Chambliss, 2008) and post-traumatic stress disorder (Hellmuth et al., 2014). Women who experience domestic violence during pregnancy have a higher risk of preterm birth and delivering low birth weight neonates (Shah & Shah, 2010). IPV is often associated with other household risks that may undermine psychological functioning such as partner alcohol use and mental health problems, poverty, household crime, and housing insecurity (Capaldi et al., 2012; Crane et al., 2016).

Research indicates that all forms of sexual violence increase the likelihood of other forms of violence victimization, and that both partner and non-partner sexual violence increase the risk of mental health problems, including trauma and stressor-related disorders as well as mood and anxiety disorders (Abrahams et al., 2014; Campbell et al., 2009).

2.4 PREGNANCY EXPERIENCE

Mothers during pregnancy build expectations on how their child is going to be. Every mother wishes for her child to be healthy, when given an adverse prenatal diagnosis, parents are deeply shocked and experience acute grief. Women who are exposed to such complications are known to be at increased risk of developing similar complications in future pregnancies (Forray et al., 2009). Mother and child wellbeing are intimately connected during pregnancy and the first 1000 days of the infant's life. A mother's well-

being, in terms of environmental experiences, physical health, and psychological distress affect her interactions with her infant, which in turn have physiological, neurological, and psychological long-term consequences (O'sullivan & Monk, 2020). Pregnancy related complications are an example of this bidirectional relationship. Mothers' psychological distress is both a risk factor for and a consequence of chronic maternal diseases which can affect infants' neurodevelopment.

Preeclampsia or PE is a multiorgan disorder of pregnancy associated with significant maternal and neonatal morbidity and mortality. Preeclampsia (PE) is a serious life event that can change women's psychological profile. Stern and colleagues highlighted how women who had suffered from PE reported significantly worse quality of mental life compared to controls (Stern et al., 2014).

Intrauterine Growth Restriction (IUGR) is an impoverished fetal growth pattern associated with neonatal morbidity and mortality (Lees et al., 2013). Mothers are confronted with distressing informations about their offspring's abnormal size and growth rate; as a consequence, their parental representations of themselves and their child are affected by the diagnosis, making it a plausible traumatic event.

Gestational diabetes mellitus (GDM) is glucose intolerance diagnosed during the current pregnancy associated with an increased risk of perinatal mortality and morbidity (Beischer' et al., 1996), an increased risk of obesity or impaired glucose tolerance (IGT) in the offspring (Silverman et al., 1995), and a very high risk of the mother converting to type 2 diabetes in later life.

Prenatal Maternal stress and mental health, in fact, acts on fetus's abnormalities in a programming way, as hypothesized by the Developmental Origins of Health and Disease (DOHaD); the fetus adapts to the in-utero environment, foreshadowing the postnatal environment in which he will live in, based on signals from the mother, thereby promoting survival in the postnatal world. Recent human studies, moreover, suggest a direct relationship between prenatal maternal stress and several pregnancy complications. Mulder and colleagues reviewed how prenatal maternal distress, in terms of loss, stress in the workplace, increased psychological problems and maternal depression and anxiety, are associated with fetal complications, such as spontaneous abortion, structural malformations, preeclampsia, preterm delivery and low birth weight (Mulder et al., 2002). This may be explained by a dysregulation of the HPA axis, which in abnormal circumstances (preeclampsia, preterm delivery), may produce a rapid increase in blood concentrations of CRH, ACTH, and cortisol increase prematurely.

Pregnant women who have been diagnosed with a high risk-pregnancy complication are, understandably, often anxious or suffer from depression related to the uncertainty that surrounds their pregnancy and the associated risks to their child's future health (O'sullivan & Monk, 2020). For instance, Daniells and colleagues found high levels of state anxiety right after the diagnosis of GDM (Daniells et al., 2003); similarly, M. Engelhard reports an increase of PTSD symptoms after receiving a preeclampsia diagnosis (Engelhard et al., 2002).

2.5 CUMULATIVE STRESS AND MATERNAL MENTAL HEALTH

It is suggested that cumulative trauma exposure may increase psychopathology in general and damage personality structures and basic capacities to feel, trust, and relate to others (Neria et al., 1998).

As we previously described, literature has confirmed how adverse childhood experiences (ACEs) tend to co-occur (Green et al., 2010), and that exposure to a greater number of ACEs increases the risk of later physical and mental health problems (Hughes et al., 2017). Less is known about the role of cumulative risk of life events in adulthood, however, it has been shown that suffering from any kind of intimate partner violence (IPV) is common and may have dramatic consequences on the woman's mental health (Lagdon et al., 2014). Research validates a lifelong approach on cumulative risk exposure, in fact, enduring one or more adverse experiences during childhood is linked with an increased risk of adverse adult experiences such as IPV, homelessness, and poverty (Roos et al., 2013; Whitfield et al., 2003b; Zielinski, 2009). Each of these adult adversities has been linked to poor mental health as well (Dillon et al., 2013; Lippert & Lee, 2015; Walker & Druss, 2017). The accumulation of different stressors and life events may have a deleterious effect on the adult's mental health, even though, few research have studied this hypothesis. For instance, LaNoue et al. found that, in a sample of adults recruited from clinics, depression levels in adults increased in relation to higher adversity scores in childhood and adulthood (Lanoue et al., 2012). Again, Stumbo et al. (2015) reports how, in a sample of adults recovering from a serious mental illness, cumulative lifetime exposure to both childhood and adult adverse experiences was not only high (up to 94%), but also correlated with poorer psychological functioning and recovery scores. However,

in linear regression analyses, adverse adult experiences were more important predictors of outcomes than adverse childhood experiences (Stumbo et al., 2015). This is consistent with life course theory, which assumes that outcomes tend to be more strongly associated with proximal risks than distal risks (Björkenstam et al., 2017; Mersky et al., 2012). Mersky and colleagues, report how adult adverse experiences, in a sample of women of low-income families receiving home visits, were frequent. IPV in the form of emotional and physical abuse was particularly prevalent. Many participants also reported homelessness and discrimination, outside of domestic interactions. Each adversity appeared interrelated with one another and was independently associated with depression, anxiety, and Post-Traumatic Stress Disorder. Each psychological impairment increased in relation to the number of adult adversities reported. When having suffered from an adverse childhood experience was taken into account, the effects of cumulative adult adversity were even larger in magnitude(Mersky et al., 2018b). Finally, results reported by Neria and collaborators showed that, in a sample of adults hospitalized for psychosis, the majority of the patients experienced one or more traumatic event in their lifetime. Trauma exposure occurred more frequently in women than in men. Among those exposed to trauma, over one quarter had PTSD, which was more frequent in women, patients who endured adverse childhood experiences and in patients with multiple, life-threatening, and ongoing exposures (Neria et al., 2002).

Pregnancy, which is itself a fragiletime in a woman's life, acts as a setpoint for the child's health. Studies examining the relationship between chronic psychosocial stress and pregnancy outcomes suggest that adverse pregnancy may originate long before conception. High allostatic load deriving from chronic exposure to life events such as poverty, exposure to violence both during childhood and adulthood, exposure to adverse

pregnancy experiences, exposure to the hardship deriving from a global pandemic, may contribute to increased allostatic load and by extension, increased risk of negative child's outcomes. Allostatic load may impact somatic function over the life course, affecting reproductive functions. This perspective is particularly interesting given that the risk of adverse child outcomes is exceptionally high among certain subpopulations marked by high allostatic load.

As seen above and as explained by the Developmental Origins of Health and Disease Hypothesis, prenatal exposure to an adverse environment and to high levels of prenatal maternal stress may "program" the fetus to a plausible adverse postnatal environment. Prenatal maternal stress has been linked with infant's anxiety (Bergh et al., 2005; O'Connor et al., 2002), lower cognitive functioning (Bergman et al., 2007), ADHD (O'Connor et al., 2002; Rodriguez & Bohlin, 2005; van den Bergh & Marcoen, 2004) and conduct disorder (Van den Bergh & Marcoen, 2009). Research has also suggested how prenatal maternal mental health, in terms of anxiety, depression or PTSD diagnosis, may influence the offspring's outcomes in various ways. Poor mental health has been seen to be associated with different risk factors, such as past personal or family history of psychiatric illness or substance abuse, past personal history of sexual, physical, or emotional abuse, current exposure to intimate partner violence, current social adversity, and coincidental adverse life events (Satyanarayana et al., 2011). Additionally, women who have endured two or more stressful life events were 3.7-times more likely to report depressive symptoms during pregnancy (Rubertsson et al., 2005).

It has been shown that the mother's mental health problems in pregnancy predict various negative outcomes in the offspring.

For instance, many studies have found a link between maternal prenatal anxiety and ADHD symptoms, internalizing and externalizing behaviors, cognitive and motor functioning, and difficult temperament. Van den Bergh has found that high levels of maternal anxiety during pregnancy enhances the offspring's susceptibility for developing a childhood disorder. In fact, even after controlling for numerous confounding variables, maternal state anxiety during pregnancy explained between 9% and 22% of the variance in the risk for developing ADHD symptoms, externalizing problems, and anxiety in 8- and 9-years-old (van den Bergh et al., 2006). Similarly, O' Connor and colleagues found how high levels of maternal anxiety doubled the risk for hyperactivity and inattention problems, conduct disorder, and emotional problems at 4 and 6 years (O'Connor et al., 2002, 2003). Again, Van den Bergh and collaborators found that antenatal anxiety explained 10% to 25% of the variance in neonatal movements and behavioral states in hyperactivity, frequent crying, sleeping, and feeding difficulties, and difficult temperament during the first 7 months of life (van den Bergh et al., 1989). In Huizink et al., perceived stress and pregnancy-related anxieties linked with difficult temperament at 3 months and attention regulation and mental and motor development at 3 and 8 months (Huizink et al., 2003) . Finally, in Brouwers et al., 2001, maternal prenatal anxiety was significantly related to observer report measures of attention at 3 weeks and 12 months of age, as well as to mental development at 24 months of age (Brouwers et al., 2001).

Maternal antenatal depression has been found related with offspring's antisocial outcomes and violent behaviors at 16 years of age. Furthermore, mothers with a history of conduct problems were at elevated risk to become depressed in pregnancy (Hay et al., 2010). Again, in Maki, 2003, mothers' reports of depression during pregnancy predicted antisocial behavior in their adult offspring 30 years later (Mäki et al., 2003). Pawbly and

colleagues found antenatal maternal depression to predict a depression diagnosis in their offspring at 16 years (Pawlby et al., 2009). Barker reported how prenatal depression was prospectively associated with both a small increase in child externalizing difficulties and a small decrease in verbal IQ, with depression having a more significant effect on the child's maladjustment than depression (Barker et al., 2011). Further, one study has found that mothers who developed PTSD in response to 9/11 had lower morning and evening salivary cortisol levels, compared to mothers who did not develop PTSD. Maternal morning cortisol levels were inversely related to their rating of infant distress and response to novelty (i.e., loud noises, new foods, unfamiliar people). Also, mothers who had PTSD rated their infants as having greater distress to novelty than did mothers without PTSD (Brand, 2006). Again, results from a systematic review, suggest that PTE's (potentially traumatic experiences) during pregnancy were associated most strongly with indicators of increased negative affectivity and decreased effortful control/regulation (N. L. Erickson et al., 2017; Korja et al., 2017). Furthermore, maternal mental health in terms of anxiety, depression and PTSD symptoms has been recently linked with infants' negative temperament (Blair et al., 2011; DAVIS et al., 2007). One review, in particular, has found a link between maternal exposure to life events (in terms of natural disasters and intimate partner violence) and an impairment in the offspring's temperament, especially negative affect (N. L. Erickson et al., 2017a).

Moreover, there might be psychological as well as biological sequelae to the mother's mental health in pregnancy. The vast majority of children exposed to maternal mental health impairment during pregnancy, may suffer from an adverse postpartum environment, in which basic needs are not fulfilled, further influencing the infant's mental health and developmental outcomes.

Seeing how maternal exposure to different stressors during the life course has an impact not only on the woman's mental health, but on the offspring as well, it appears of main importance to identify those who are more at risk for psychological consequences during pregnancy due to chronic stress exposure, in order to protect the children and the mothers-to-be also.

CHAPTER 3

"WHEN MORE IS NOT BETTER: CUMULATIVE STRESS IMPACT ON MATERNAL MENTAL HEALTH AND CHILDREN'S TEMPERAMENT"

3.1 INTRODUCTION

Cumulative exposure to traumatic events during the life course leads to the buildup of an allostatic load. Pregnancy, which is a fragile time in a woman's life, represents a period of added vulnerability to lifetime exposure to cumulative stressors. The detrimental consequences of cumulative stressors far exceed the ones from a single stressor, leading to lower levels of maternal mental health during pregnancy and higher levels of prenatal maternal stress (PNMS). The intrauterine environment acts as a setpoint for the fetus's and the offspring 's growth. High levels of maternal stress and low levels of maternal mental health act in a way that this environment becomes adverse, programming how the child is going to develop after birth.

Pregnancy is far from an ordinary time in a woman's life, mothers find themselves adapting to many changes for their own and their child's physical and psychological health (Slade, 2009), making this a potentially stressful period. During pregnancy, changes happening within the body and the brain meet with the changes happening from within. Mothers-to-be experience the reactivation of internal representations of self and other, of attachment and caregiving, having to face potentially traumatic experiences. Being psychologically vulnerable may set in motion patterns that have long-term

consequences for not only the mother, but for the baby as well (Slade 2009). Among the most at risk during pregnancy are women with prior psychiatric difficulties, as well as those with histories of poverty, trauma, abuse, and loss, inadequate social support, and histories of disrupted attachment and trauma (Slade, 2019; Slade, 2009). For instance, living in a violent domestic environment may set the child up for traumatic experiences that make her more vulnerable during future pregnancies. Having victimized adverse childhood experiences (ACEs), potentially traumatic events that occur in childhood (0-17 years), can also have negative lasting implications not only for health across the lifespan, but also for the next generation. ACEs are in fact correlate with negative mental health consequences such as depression (Chung et al., 2008), anxiety (Green et al., 2010), PTSD (Green et al., 2010) and suicidal ideation/attempts (Afifi et al., 2008) in the mother and with lower dyadic functioning and biobehavioral health outcomes in the offspring (Roubinov et al., 2021). Another potential long-term outcome of exposure to ACEs is an increased risk of being a victim of violence in adulthood (Taillieu et al., 2020). Victimizing physical, sexual, psychological abuse, both in a domestic and a non-domestic environment, can have long-term mental health consequences, including depression, suicide attempts, alcohol, and drug abuse, eating disorders, anxiety, sexual dysfunctions, obsessive compulsive disorder, multiple personality disorder and post-traumatic stress disorder (Kumar et al., 2013). During pregnancy, a woman's history of past abuse increases her risk of depression and posttraumatic stress disorder. And these, in turn, increase the risk of pregnancy and neonatal complications (Kendall-Tackett, 2007).

In a broader view, the environment in which we live in may suffer from sudden and adverse events that change dramatically our everyday life. This is the case of natural disasters, wars, and Pandemics. The Covid-19 pandemic, that we are experiencing

nowadays, have challenged our perception of how the world functions and thus increasing uncertainty and unpredictability. The Covid-19 Pandemic has been widely studied as a strong stressor, leading to high levels of distress (Wang et al., 2020), heightening the risk of suicide as well as mental disorders associated with suicide (Mamun & Ullah, 2020; McIntyre & Lee, 2020; Thakur & Jain, 2020). Women living their pregnancy during the Covid-19 Pandemic appear to be one of the most at risk categories for mental health problems. Recent studies have, in fact reported high levels of stress and reduced psycho-social well-being among pregnant women during the pandemic (López-Morales et al., 2021).

An adverse and unequal environment can also be experienced in the context of family poverty. Socio-Economic Status is a powerful factor that can alter lifetime developmental trajectories (Evans & Kim, 2013), making individuals more vulnerable to mental health disorders (Kessler, 1994; Muntaner, 2004). This is particularly relevant during pregnancy which may represent an exceptionally sensitive window for mother-to-child transmission of socioeconomic disparities in health (G. W. Evans et al., 2004.; Kramer et al.) where the fetus may be exposed to psychological stressors and teratogenous agents (G. W. Evans et al., 2004.; Kramer et al).

Finally, the conditions of the current pregnancy may weight on the maternal mental health and, if traumatic, may constitute of a life event. While pregnant, mothers' psychological distress is both a risk factor for and a consequence of chronic maternal diseases, such as gestational diabetes, preeclampsia, Intrauterine Growth Restriction, and others. When given an adverse prenatal diagnosis, parents are deeply shocked and may experience acute grief. Pregnant women who have been diagnosed with a high risk-pregnancy

complication are, understandably, often anxious or suffer from depression related to the uncertainty that surrounds their pregnancy and the associated risks to their child's future health (O'sullivan & Monk, 2020).

In light of what has been so far observed, a theoretical question may come to mind: What does it happen if not once, but two or more of these risk factors for maternal vulnerability are experienced during the life course?

The "cumulative stress" hypothesis states that greater exposure to stress and traumatic life events increases disease risk and neurobiological abnormalities in a dose dependent manner (Paquola et al., 2017). The cumulative stress exposure from birth to adulthood leads to the build-up of an allostatic load which refers to the cumulative burden of chronic stress and life events (Nederhof & Schmidt, 2012). Not only the allostatic load weakens the organism, making it more vulnerable to physical consequences, but it also acts on someone's psychological resilience. It is, in fact, been observed a relationship between number of traumas experienced and lifetime risk for Major Depressive Disorder, Substance Abuse or Dependence, higher levels of self-rated stress, psychological distress, depressive and anxious symptoms, Post Traumatic Stress Disorder and Psychotic Disorders (Turner & Lloyd; A. Donald, 1995; Hammen, 2015; Bowen et al., 2018; Tomba & Offidani, 2012; Juster et al., 2011, 2018; Glover, 2006; Chiappelli et al., 2017; Adinoff et al., 2017). Research validates a lifelong approach on cumulative risk exposure, therefore life events happening during both adulthood and childhood increase the risk for higher stress levels and lower mental health. Particularly during pregnancy, a period of increased physical and psychological demands, literature reports higher vulnerability to multiple stressors exposure (Braveman et al., 2010; Rubertsson et al., 2005).

The fetus and child directly experience the mother's life and are shaped by it. A mother's environmental experiences, physical health, and psychological distress affect her interactions with her infant, which in turn have long-term consequences on the offspring. Prenatal maternal stress has been linked with infant’s anxiety (Bergh et al., 2005; O’Connor et al., 2002), lower cognitive functioning (Bergman et al., 2007), ADHD (O’Connor et al., 2002; Rodriguez & Bohlin, 2005; van den Bergh & Marcoen, 2004) and conduct disorder (Van den Bergh & Marcoen, 2009). Research has also suggested how prenatal maternal mental health may influence the offspring’s outcomes in various ways; for instance, it has been found a programming effect of prenatal maternal mental health in terms of depression, anxiety and PTSD symptoms on children’s temperament, which is a strong predictor for many adolescents and adult outcome.

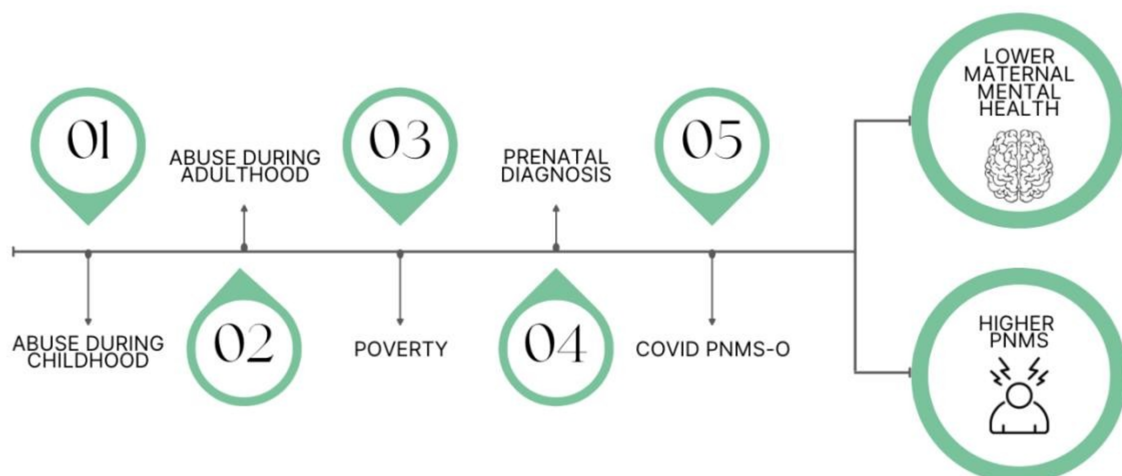
In the current study, we examine maternal exposure to stressful experiences and life events during the life course to investigate the effects on maternal mental health during pregnancy and prenatal maternal stress and to further explore the outcomes on the child’s temperament in a population of women who experienced pregnancy during the Italian Covid-19 lockdown (April 2020).

3.2 AIMS AND HYPOTHESIS

First Hypothesis: The *primary aim* of this research is to explore how maternal cumulative exposure to life events, such as infant and adult psychological, physical, sexual abuse, low Socio-Economic Status, Objective Exposure to the Pandemic (i.e., contracting Covid-19 during pregnancy, experiencing loss due to the pandemic, having relatives or cohabitant contracting the virus) and pregnancy related complications (i.e., diagnosis of preeclampsia, gestational diabetes, Intrauterine Growth Restriction, or other

pathologies) may influence the overall maternal mental health levels and the prenatal maternal stress (PNMS). Chronic exposure to the stress deriving from experiencing life events from birth to adulthood, lead to the build-up of an allostatic load (Nederhof & Schmidt, 2012), and exposure to multiple stressors, or repeated exposure to the same stressors over time, has worst detrimental health consequences of single exposures (G. W. Evans et al., 2013; Turner & Lloyd, 1995). Given how subjects with allostatic overload have significantly higher levels of self-rated stress and psychological distress (Tomba & Offidani, 2012) and given how links have been found between allostatic load and depressive and anxious symptoms (Juster et al., 2011, 2018), Post Traumatic Stress Disorder (Glover, 2006), Psychotic Disorders (Chiappelli et al., 2017) and Alcohol Dependence (Adinoff et al., 2017) we expect lower levels of maternal mental health (in terms of Post-Traumatic Stress Disorder, Anxiety and Depression) and higher levels of prenatal maternal stress (PNMS) during pregnancy at the growth of life events experienced.

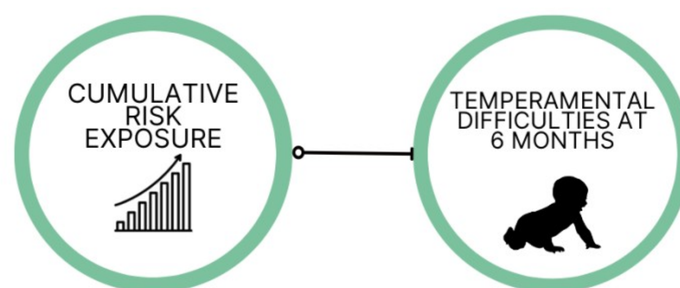
Figure 1. *Hypothesis 1*



The higher the number of life events experienced, the lower the levels of maternal mental health and the higher the levels of prenatal maternal stress during pregnancy.

Second Hypothesis: Further, the secondary aim of our research was to explore the relationship between maternal exposure to different cumulative stressors during the life course and the infant's temperament at 6 months. Maternal psychological stress occurring preconceptionally and during gestation has been seen to be strongly related to a range of maladaptive outcomes in offspring (Mulder et al., 2002; Huizink et al., 2007; O'Connor et al., 2003; Barker & Maughan, 2009; O'Connor et al., 2003;O'Connor; O'Donnell et al., 2009), these links are likely mediated by stress-induced physiological changes that affect the in utero environment; again cumulative lifetime stress, particularly exposure to traumatic events during the lifetime, is especially likely to lead to persistent psychophysiological alterations in the mother (Christopher, 2004; Tiedje, 2003) that, in turn, influence perinatal outcomes, offspring neurobehavioral development, and other complex disorders. With this being considered, we hypothesized that fetal exposure to lifetime maternal cumulative stress, may influence the child's temperament, measured with the IBQ (Infant Behavior Questionnaire), at 6 months.

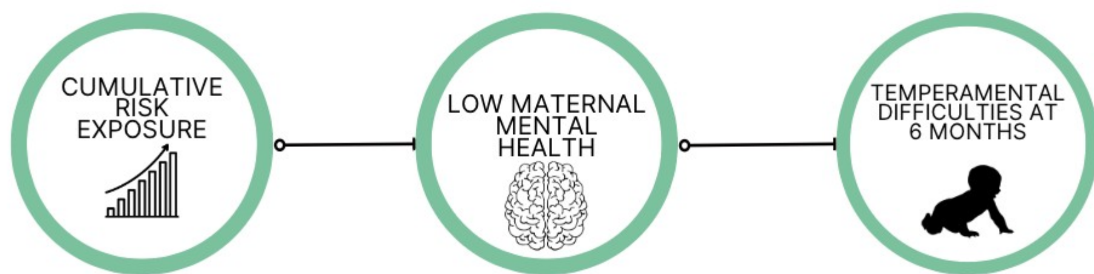
Figure 2. *Hypothesis 2*



The higher the number of life events experienced by the mother, the higher the levels of temperamental difficulties in the infant at 6 months

Third Hypothesis: Lastly, we investigated whether low levels of maternal mental health during pregnancy caused by cumulative exposure to life events, may influence the child's temperament at 6 months. Maternal mental health has a strong programming effect on the fetus and on the offspring, studies have found numerous links between maternal mental well-being during pregnancy and infant's temperament (Glynn et al., 2018; Howland et al., 2020; Erickson et al., 2017). Keeping in mind how cumulative exposure to life events influences the individual's mental health, we hypothesized the existence of a link between maternal mental health during pregnancy and child temperamental characteristics at 6 months.

Figure 3. *Hypothesis 3*



The higher the number of life events experienced by the mother, the lower the levels of maternal mental health and the higher the levels of temperamental difficulties in the infant at 6 months.

2.3 METHOD

2.3.1. Participants and procedures

This study takes part in a longitudinal project of the Department of Developmental and Socialization Psychology (DPSS) of the University of Padova. In the theoretical frame of Prenatal Maternal Stress, this project's objective is to investigate the materna l mental health and the infant's well -being in a sample of mothers who experienced pregnancy

during the Italian Covid-19 Lockdown. Mothers-to-be were first recruited through social media posting during a specific window of Italian national lockdown (April 8th to May 4th 2020). Participants were eligible for the research if: *i)* pregnant at the time of assessment, *ii)* Italian residents, *iii)* older than 18 years, *iv)* fluent in Italian. The original sample included 2502 responders (*t0*), of which 1618 agreed to be contacted again for future phases of the study and only 830 actually participated in the survey when contacted approximately 6 months after their expected due date (*t1*). Participants were excluded in case of miscarriage or voluntary abortion, twin birth or if they had already given birth from at least two weeks at the time of the first assessment. In each survey, participants completed the questionnaires upon reading the written consent form and explicitly agreeing to participate. The Institutional Review Board of the University of Padova approved the first phase of the study on April 6th, 2020, and the second phase of the study on October 10th, 2020.

The first time point of the study (*t0*), occurred between April 8th 2020 and May 4th 2020 during the Italian lockdown. The first online survey assessed the mothers' mental health and the perceived stress due to the pandemic. They were also asked if they agreed to be contacted again in the future. If the answer was positive, mothers were contacted for *t1*, or the second phase of the project, six months after childbirth, between December 12th 2020 and May 8th 2021 to complete an online survey about their mental well-being and perceived stress and social support, direct exposure to the virus and its effects (prenatally and post-partum), birth outcomes (i.e., child's sex, birth weight, age at delivery) and maternal impressions of infant temperament.

Further, mothers were contacted for the third time-point (*t2*) twelve months after delivery. Questionnaires, received by email, assessed the infant motor, socio-emotional, cognitive, communicative, and behavioral development, maternal mental health, and parenting outcomes.

2.3.2 Methods and materials

Cumulative risk index. At the first *(t0*) and second *(t1*) assessment, mothers were asked to answer a string of question regarding Socio-Economic Status, Gestational Complications, Psychological, physical, sexual abuse during childhood and/or adulthood, COVID-19 Objective hardship. Answers to each of these questions were then dichotomized and computed into a single index (CR index) and mothers were categorized as having experiences 1, 2, 3, 4, or 5 of the said stressors during the life course.

Socio-Economic Status (SES): During pregnancy (*t0*), women were asked what they thought the economic status of their family was. Options were: *i)* low (income lower than 12.000 euros); ii*)* medium-low (income between 12.000 and 25.000 euros); *iii)* medium (income between 25.000 and 50.000 euros); *iv)* medium-high (income between 50.000 and 75.000 euros); *v)* high (income higher than 75.000 euros). The index was then computed, and participants were scored as "1" if they perceived their economic status as either low or medium-low, and were scored as "0" for the remaining categories.

Prenatal diagnosis: at 6 months after delivery *(t1)* mothers were asked if they had experiences one or more of the following gestational conditions: gestational diabetes, IUGR (intrauterine growth restriction), preeclampsia or other pathologies. The index was

then computed, and participants were scored as "1" if they experienced at least one of the said conditions, and were scored as "0" if they did not.

Psychological, physical, sexual abuse during childhood and/or adulthood: again, at *t1,* participants were asked if they had suffered abuse or maltreatment during childhood and/or adulthood. They were then asked if they considered what they had victimized, as physical, sexual, or psychological abuse. Participants were scored as "1" if they had victimized at least one of the said conditions, and were scored as "0" if they did not for both, abuse during childhood and adulthood.

COVID-19 Objective hardship: The survey at *t1* included a set of questions investigating the direct exposure to COVID-19 objective effects, during pregnancy. Women were asked: *"Did you contract SARS-CoV-2?"; "Did any of the people who lives with you contract the SARS-CoV- 2?"; "Did any of your relative contract SARS-CoV-2?"; "Did you experience the loss of a loved one due to SARS-CoV-2?"*. The items were then computed into a single index and the variables were dichotomized between participants who scored 0 and participants who scored higher than 0.

Maternal Mental Health: peri-natal maternal mental health has been assessed in terms of symptoms of Depression, Anxiety and Post-Traumatic Stress Disorder (PTSD) symptoms. An index was then computed dichotomizing the variables between participants who scored positively in at least one of the four questionnaires used for assessment (BDI, EPDS, STAI-S, PCL-50) and participants who didn't.

Depression was investigated through the *Edinburgh postnatal depression scale (EPDS)* and the *Beck Depression Inventory (BDI)*; The EPDS is a ten items self-report

questionnaire based on a 1-week recall, developed by Cox and colleagues in 1996(J. Cox, 1996). This instrument is widely validated for the assessment of post-natal depression and anxiety (J. L. Cox et al., 1987). The EPDS has been found to be a reliable instrument in screening for prenatal depression. The BDI is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression. Individuals are asked to answer considering the way they have felt for the past two weeks (Beck et al., 1987).

Anxiety was measured using the *State Trait Anxiety Inventory- State version* (Spielberger, 1985), a 10-item scale assessing anxiety-related symptoms or emotions using a 4-point Likert scale ranging from 1 (not at all) to 4 (very much). State anxiety scores can range from a minimum of 10 to a maximum of 40. State anxiety refers to how the subject is feeling at the time of the assessment *(i.e., how the subject feels `now*'). The STAI has been used for research purposes with pregnant and nonpregnant samples and has good internal consistency.

Post-Traumatic Stress Disorder was assessed through the *PTSD checklist for DSM-5* (Weathers et al., 2013). The PCL-5 is a 20-item self-report measure that assesses symptoms over the last week in accordance with the DSM-5 symptom criteria for PTSD. Items are rated on a 5-point Likert-type scale (0 = not at all to 4 = extremely). PCL-5 has been used to assess PTSD symptomatology during pregnancy in numerous studies.

Prenatal Maternal Stress due to the Pandemic: Maternal stress during pregnancy due to the Pandemic was assessed with a tailored made questionnaire, asking the mother-to-be to express her perception of safety, from 0 (I did not feel safe) to 7 (I felt totally safe) to the following questions: "*Did you feel safe going to the planned medical exams?", "Did you feel safe in receiving adequate and prompt care?", "Did you feel safe in giving*

birth in the Hospital of your choosing?", "Did you feel safe in having the possibility of your partner assisting you during birth?", "Did you feel safe in being protected from possible Covid-19 infection in the Hospital?", "Did you feel safe in having easy access to commodities for your child and yourself?", "Did you feel safe in receiving support by relatives during the days before birth?", "Did you feel safe in receiving your friends support during the days before birth?'. Answers where then computed into a single index expressing the level of PNMS.

Infant Behavior Questionnaire (IBS): The Infant Behavior Questionnaire is a parent-report instrument to evaluate the child's temperament, whose original version is presented with 94 items and containing six scales (Rothbart, 1981). The IBQ was here administered at 6 months postpartum (t1) in its Very Short Form (IBQ-R VSF) composed of 37 items (Putnam et al., 2014). In the VSF, items selected measure three broad temperament dimensions as opposed to the 14 in the longer IBQ–R scale. The three broad components are negative emotionality (NEG), positive affectivity/surgency (PAS), and orienting/regulatory capacity (ORC). Mothers are asked to report the frequency of a certain behaviour of the child, referring to the past seven days. The answers are on a 7-point scale, where the score 1 corresponds to "Never" and the score 7 to "Always". In addition, the answer option "not applicable" is also provided to be used in the case where, during the last week, the mother has not observed the child in the situation described.

3.3.3 Statistical analyses

Statistical analyses were conducted using the software R (R Core Team, 2013) and RStudio (R Core Team, 2019). We first conducted descriptive analysis of the main sample, describing mean, standard deviation, frequency and percentage of maternal

variables, perinatal characteristics of the newborns, and clinical-obstetric variables. Similarly, we described variables of interest, and, in order to create the cumulative risk index (CR) we dichotomized the variables of interest and we added them into a single score.

To test our hypothesis, we selected a list of confounding factors to control for; the chosen one were number of children, maternal age, maternal title of study, history of maternal depression before pregnancy, marital status. We then proceeded testing our first hypothesis. To do so, we conducted four linear regression models investigating the relationship between cumulative risk and: *Model 1)* maternal mental health; *Model 2)* Anxiety; *Model 3)* Depression; *Model 4)* PTSD.

For the second hypothesis, we further conducted a linear regression model investigating the relationship between maternal cumulative risk and infant's negative affect (using the IBQ questionnaire).

Lastly, we conducted one final linear regression model to study if an effect could be found between the infant's temperament and maternal cumulative risk, if weighted for maternal mental health during pregnancy.

3.4 RESULTS

3.4.1 Sample characteristics

Our final sample consisted in 2299 mothers selected within the original sample of 2502 women. Mothers were selected, considering the ones that had completed each questionnaire used for the evaluation of maternal health during pregnancy. Participants'

characteristics in terms of socio-demographic informations, clinicial-obstretic characteristics, and perinatal feature are reported in ***Table 1***.

Table 1. *Study participants' socio-demographic, clinical-obstetric and perinatal features (n=2299)*

VARIABLES		VALUES
Maternal Variables		
Age, mean (range)		32,37 (18-51)
Nationalty, N (%)	Italian	2217 (96,9%)
	Other	70 (3,1%)
Region, N (%)	North	1536 (67,5%)
	Center	364 (15,9%)
	South and Islands	377 (16,6%)
Qualification	Doctorate or Specialisation	118 (5,1%)
	Masters' degree	647 (28,2%)
	Bachelor's degree	504 (22%)
	High School Diploma	920 (40,1%)
	Middle High School Diploma	105 (4,6%)
	Primary School Diploma	1 (0,4%)
Marital status, N (%)	Maiden	149 (6,6%)
	Cohabitant	823 (36,5%)
	Married	1248 (55,4%)
	Divorced	17 (0,76%)
Previous pregnancies, N (%)	No	1435 (62,5%)
	Yes	861 (37,5%)
Children, N (%)	No	1622 (71,1%)
	Yes	658 (29,7%)
Depression before pregnancy	No	632 (77%)
	Yes	189 (23%)
Previous Abortions	No	1768 (78.37%)
	Yes	488 (21.63%)
Characteristics of current pregnancy		
Planned pregnancy N (%)	No	539 (23,5%)
	Yes	1757 (76,5%)
Difficulty conceiving N (%)	No	1838 (80,4%)
	Yes	449 (19,6%)
Assisted conception N (%)	No	2143 (93,7%)
	Yes	144 (6,3%)

Gestational period, mean, sd (range)		25,66 (3-41)
Trimester of pregnancy N (%)	First trimester	273 (11,9%)
	Second trimester	762 (33,3%)
	Third trimester	1156 (50,5%)
	Given birth less than 2 weeks	98 (4,3%)
	Infants' variables	
Infants' gender N (%)	Female	423 (50%)
	Male	423 (50%)
Birth weight (in gr), mean (range)		3297,1 (1250-4980)
Birth length (in cm), mean (range)		50,3 (34,6-68)
Gestational Age at birth, mean (range)		39,3 (25-45)
Neonatal Intensive Therapy N (%)	No	779 (92,3%)
	Yes	65 (7,7%)

3.4.2 Variables of interest distribution

In the final sample, 73 mothers answered that they have experienced, either **psychological, sexual and/or physical abuse during adulthood** (10,6% of the sample). Again, 55 participants, equal to the 9,9% of the sample, reported having experienced an abuse (sexual, physical and/or psychological) **during childhood**.

Considering **socio-economic Status (SES** , when asked "how would you consider your family's economic situation?", 650 participants (28,7% of the final sample) perceived their economic status as low and 187 participants as medium low (8,2% of the sample).

In terms of Prenatal Diagnosis, 163 mothers, 7,1% of the final sample, reported to have experienced one of the said conditions. These diagnoses were distributed as following:

29 mothers reported a IUGR diagnosis (3,6%), 84 mothers reported a gestational diabetes diagnosis (10,4%), 29 mothers reported a preeclampsia diagnosis (4%) and finally 91 mothers reported other prenatal conditions (12,6%).

Last, 98 mothers answered that they have experienced at least one of the said **negative experiences related to the pandemic**, 12,79% of the final sample.

The dichotomized answers were then added to derive a Cumulative risk score from 0 (no risk factor experienced) to 5 (having experienced all the risk factors). No woman had experienced each one of the selected stressors, and only 93 women had experienced two or more stressors. Distribution of maternal cumulative exposure to life events is presented in ***Figure 3*** and ***Table 2***.

Figure 3: *Distribution of maternal cumulative exposure to life events.*

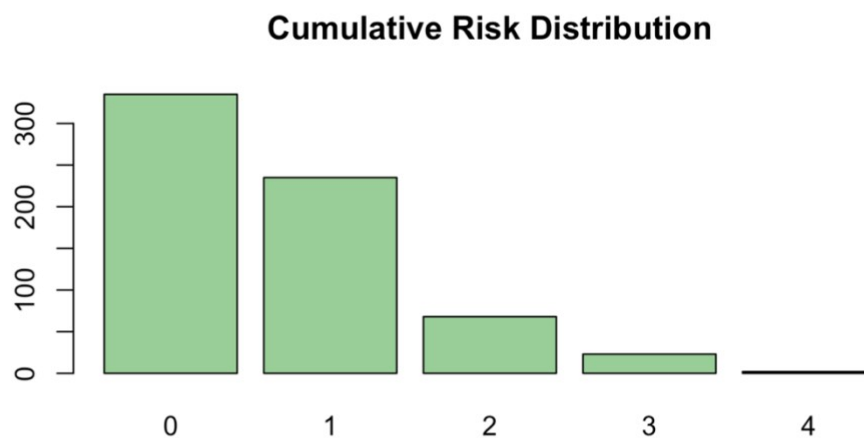


Table 2: *Frequency of maternal cumulative exposure to life events.*

	Number of stressors experienced					
	0	**1**	**2**	**3**	**4**	**5**
N	335	235	68	23	2	0
%	50.53	35.44	10.26	3.47	0.30	0

3.4.3 Data analysis Aim 1

The first linear regression model wanted to investigate the relationship between maternal Subjective Prenatal Maternal Stress due to Covid-19 and the cumulative stress index. No significant effect was found within out sample. Results are presented in ***table 3***.

Table 3: *Multivariate Linear Regression Model between Subjective PNMS due to the Pandemic and Maternal Cumulative Risk Index.*

	Covid_PNMS ~ Cumulative index			
	b	***SE***	***t***	***Pr***
Intercept	32.59	3.70	8.82	<.001
Cumulative Index	.76	.53	1.44	.149
Depression before pregnancy	.01	1.01	.01	.99
Age	.08	.10	.75	.45
Title of study	.13	.24	.54	.59
Marital status	.01	.22	.07	.94
Children	-1.21	.75	-1.62	.10
R-adjusted			*-.002*	
F-statistic			*0.79 on 6 and 628 DF*	
p-value			*0.57*	

3.4.4 Data analysis Aim 2

Secondarily, a linear regression was conducted using as variables the cumulative index and the maternal mental health; a strong significant effect was found between the two variables; the effect does not change when the covariates are taken into account. We then proceeded exploring the relationship between cumulative index and maternal depression, anxiety, and PTSD symptoms during pregnancy. From each of the three models, what can be observed is that at the growth of life events experienced, the levels of prenatal maternal anxiety, depression, and PTSD are heightened. Interesting, we also found a strong effect on maternal mental health explained by the number of children: maternal mental health

lowered, and anxiety, depression and PTSD levels heightened at the growth of the number of children had before the current pregnancy. Results are presented in ***Table 4*.**

Table 4: *Multivariate Linear Regression Models between: Maternal Cumulative Risk Index and Prenatal Maternal Mental Health (**Model 1**); Maternal Cumulative Risk Index and Prenatal Maternal Anxiety, as measured with the STAI-S Questionnaire (**Model 2**); Maternal Cumulative Risk Index and Prenatal Maternal Depression, as measured with the EPDS and BDI Questionnaires (Model 3); Maternal Cumulative Risk Index and Prenatal Maternal Post Traumatic Stress Disorder, as measured with the PCL-5 Questionnaire (**Model 3**).*

	Model 1: maternal mental health ~ cumulative index				**Model 2: STAI_t0 ~ cumulative index**				**Model 3: EPDS_t0 ~ cumulative index**				**Model 4: PTSD_t0 ~ cumulative index**			
	b	*SE*	*t*	*Pr*	*b*	*SE*	*t*	*Pr*	*b*	*SE*	*t*	*Pr*	*b*	*SE*	*t*	*Pr*
Intercept	.43	.17	2.50	.01	37.9	3.84	9.86	.01	8.24	1.76	4.67	<.001	<.001	<.001	3.07	<0.01
Cumulative Index	.11	.02	4.31	<.001	1.78	.56	3.25	<.001	1.16	.25	4.62	<.001	<.001	<.001	4.99	<.001
Depression before pregnancy	.01	.05	.15	.88	-.03	1.05	-.03	.97	-.35	.48	-.73	.46	<.01	<.01	-.96	.34
Age	-.001	.005	-.28	.78	-.02	.1	-.24	.81	-.07	.05	1.44	.15	<.01	<.01	.00	.99
Title of study	.001	.01	.30	.76	.35	.25	1.39	.16	.14	.11	1.25	.21	<.01	<.01	1.08	.26
Marital status	.001	.01	.18	.85	.1	.23	.44	.67	.02	.1	.15	.88	<.01	<.01	-.09	.92
Children	.08	.03	2.25	.02	2.18	.78	2.82	<.001	.73	.35	2.08	.004	<.01	<.01	2.02	.04
R-adjusted	.035				.032				.04784				.048			
F-statistic	4.83 on 6 and 635 DF				4.52 on 6 and 634 DF				6.367 on 6 and 635 DF				6.43 on 6 and 635 DF			
P-value	<0.01				<0.01				<0.01				<0.01			

3.4.5 Data analysis Aim 3

From the findings displayed in ***Table 5*** a statistically significant effect can be found explaining the relationship between maternal exposure to cumulative life events and child temperamental difficulties at six months. Further a significant effect on children's temperament at 6 months can be explained by the number of children had before the current pregnancy.

Table 5: *Multivariate Linear Regression Model between Maternal Cumulative Risk Index and the infant's temperament at six months ((Negative Affect from IBQ).*

	Negative affect ~ Cumulative index			
	b	***SE***	***t***	***Pr***
Intercept	40.58	4.26	9.53	<.001
Cumulative Index	1.31	.61	2.17	.03
Depression before pregnancy	-1.07	1.16	.92	.36
Age	.01	.12	.07	.94
Title of study	-.48	.28	1.72	.08
Marital status	.12	.26	.42	.67
Children	1.66	.85	1.95	.01
R-adjusted		.01		
F-statistic		2.141 on 6 and 621 DF		
p-value		.047		

3.4.6 Data analysis Aim 4

When maternal mental health was taken into account, cumulative risk was not found to have an effect on the children's temperament. Although, what was found to be significant was the relationship between maternal mental health and the children's outcome.

Table 6: *Multivariate Linear Regression Model between Maternal Mental Health (STAI-S, BDI, EPDS, PCL-5), as explained by the Cumulative Risk Index and the infant's temperament at six months ((Negative Affect from IBQ).*

	Negative affect ~ Cumulative index + Maternal Mental Health			
	b	*SE*	*t*	*Pr*
Intercept	39.40	4.25	9.27	<.001
Cumulative Index	.99	.61	1.62	.19
Maternal Mental Health	2.94	.97	3.03	<.001
Depression before pregnancy	-1.11	1.15	-.96	.34
Age	.01	.11	.09	.93
Title of study	-.49	.28	-1.78	.08
Marital status	.09	.26	.39	.69
Children	1.44	.85	1.69	.09
R-adjusted		.02		
F-statistic		3.17 on 7 and 620 DF		
P-value		.03		

3.5 DISCUSSION

With the present study we aimed at investigating how lifetime exposure to stressful events potentially weakens the organism, making it more vulnerable to psychological consequences that in turn have a programming effect on the next generation. Within the theoretical frame of cumulative stress, we hypothesized that at the growth of the number of life events experienced by the mother, higher levels of prenatal maternal stress and lower levels of prenatal maternal mental health would have been reported.

Our first hypothesis was not found to be significant: maternal levels of prenatal distress due to the Covid-19 Pandemic, did not heighten at the increase of life events experienced. To our knowledge, no study has so far investigated this specific link. Previous research has nonetheless found a relationship between number of live events experienced and levels of psychological distress, especially if life events have been experienced ever since childhood (i.e., ACEs) (Williams et al., 2007). The absence of a direct association between cumulative lifetime exposure to life events and PNMS does not necessarily implicate no effect of stress exposure but rather it might hide a floor effect of such

exposure which may change the dose-response. It has in fact been seen how when exposure is high, chronic, and severe it may no longer correlate with symptoms of distress since each individual has potentially reached a limit that overwhelms coping abilities (Masten & Osofsky, 2010). On the contrary, cumulative exposure to life events was found to be highly correlated with maternal mental health during pregnancy. At the increase of life events experienced, lower levels of maternal mental health and higher levels of anxiety, depression and PTSD symptoms were reported. Accordingly, in a non-pregnant sample, Mersky and colleagues, found how being exposed to both adult and childhood adverse experiences, in a sample of woman of low-income families linked with higher levels of anxiety, depression and PTSD (Mersky et al., 2018). Again, Evans and colleagues found that childhood and adulthood stressors were significantly associated with increased risk of prenatal depression. Most notable was the increased risk of prenatal depression from cumulative stress during childhood and adulthood (Evans et al., 2022). Pregnancy represents itself as a period of heightened vulnerability; reactivation of previous representations and traumatic events, together with an increased stress dictated by the pandemic and/or the economic status of the family may leave these women feeling overwhelmed, weighting on coping abilities and thus explaining lower levels of mental health. In fact, the childbearing year has many triggers or reminders of past trauma that may make a person feel like the trauma is happening again or may make a mother-to-be stress about how to keep her child safer from traumatic experiences as the ones she has victimized during life. Interestingly, we also found a strong effect on maternal mental health explained by the number of children. Having a child involves, not only physical and biological changes, but also emotional, psychosocial, and interpersonal processes such as conflicts of dependency/independency, being cared for and taking care of, and

the family expanding from a dyad to a triad (Bitzer & Alder, 2000), all potentially stressful. Previous pregnancies may have set in motion representations and past stressful experiences related to childbirth and/or motherhood. To not consider the economic weight of a second, third or fourth child on the economic status of the family, already weakened by the pandemic, which could further generate distress in the mother. Again, in a society such as ours, where women are expected to both take care of the offspring and of the house while having a job, additional distress may derive from the thought of the future organization of such tasks. These variables, which were not here taken into account, may have influenced the maternal mental health status, bringing additional worries to an already vulnerable time such as pregnancy.

Keeping in mind the Developmental Origins of Health and Diseases Hypothesis, or the Barker Hypothesis, we then hypothesized that maternal cumulative exposure to life events would influence the children's temperament. Linear regre ssion models found this to be true; at the growth of stressful events experienced by the mother, children were reported by the caregivers as having a more negative affect. To our knowledge, no study has so far investigated the effect of maternal exposure to cumulative trauma on the offspring development. Nonetheless, it is well known how maternal mental health and prenatal maternal stress have a strong influence on various children's outcomes. Although, when maternal mental health was considered, maternal cumulative exposure to life events did not have any significant effect on the offspring's temperament, while maternal mental health did have an influence on the children's negative affect, the lower the maternal mental health during pregnancy, the higher the reports of negative affect in the offspring. It is well established how cumulative exposure to life events is strongly linked with higher levels of psychological distress and lower levels of mental health. Cumulative lifetime

stress, particularly exposure to traumatic events, is especially likely to lead to persistent psychophysiological alterations in the mother that, in turn, influence perinatal outcomes, offspring neurobehavioral development, and other complex disorders. Temperament, and in particular temperamental reactivity (arousability of affect, motor activity, and attention), seem to be influenced by epigenetic mechanisms linked with fetal programming effects (Monk et al., 2012). For instance, Glynn et al., found that mood entropy during pregnancy predicts maternal reports of negative affectivity in infancy (Glynn et al., 2018), again Howland and colleagues found that higher maternal distress during pregnancy in terms of depression, anxiety and perceived stress, predicted higher fetal heart rate, which in turn was associated with lower orienting/regulation and with higher negative affectivity (Howland et al., 2020). A review from Erickson and colleagues (Erickson et al., 2017) validates only partially these results, finding how mothers who suffered from depression, anxiety and comorbid depression and anxiety during pregnancy reported their children as having a difficult temperament in a little more than half of the studies, suggesting that other factors may predict the epigenetic outcome of temperament. Overall, maternal mental health during pregnancy acts to increase the risk of having an infant who is less likely to express joy (e.g., smiling and positive affect); is experienced as "difficult" (e.g., crying/fussing excessively); and is more dysregulated or fearful highlighting the role of fetal programming on child and adult development (Erickson et al., 2017). In an evolutionary point of view, having a difficult temperament has been suggested to improve survival of infants during drought among the Masai in East Africa (deVries & Sameroff, 1984). Being "difficult" may be an adaptive response programmed during pregnancy to guarantee a better survival after birth.

3.6 STRENGHTS AND LIMITS

For the purposes of this study a cumulative risk index was used which offers many scientific advantages, assimilating and integrating diverse constructs and risk factors. Cumulative risk measures are simple and parsimonious (G. W. Evans & Kim, 2013) so that their application and estimated effects tend to be more replicable and less sample dependent than more complex risk models. Cumulative risk models also appear as robust predictors of a wide array of health outcomes. Furthermore, measuring cumulative adversity in both childhood and adulthood has the potential to unveil continuities and discontinuities in risk over time and helps to have a better understanding of the social distribution of risk. Our index also considers the timing of stress exposure across the life course. We here examined three life period: childhood, adulthood, and pregnancy, with the first and the last being particularly sensitive periods in an individual's life, setting long term consequences for self and others. Victimizing adverse childhood experiences can cause permanent damage to the developing brain and alter the functioning of the immune, neurological, and endocrine systems in an individual, predisposing them to high risk of chronic diseases and early death (Nelson et al., 2020). Children are also more prone to develop harmful behaviors and to experiencing lower levels of mental health. Further, pregnancy is itself a vulnerable life period in which prenatal maternal stress consequences not only weigh on the mother to be, but also on the child programming how he/she is going to develop.

Cumulative risk indexes come with their limitations. Primarily composite scores weigh all risk factors the same and therefore avoid assumptions about the relative strength of different risk factors. Further, the cumulative stress hypothesis is based on a deterministic

(psycho)pathological model, for which the more stress exposure, the worse the outcome. As argumented by Nederhof, a more integrated model, which considers individual differences may be better fit to understand the programming effect of stressors accumulation (Nederhof & Schmidt, 2012).

Finally, the cumulative composite score index is widely used in clinical samples, where lifetime exposure to life events is more likely. We here decided to use this index in a normative sample in order to investigate how traumatic events exposure is distributed in a non-clinical population. Beginning with a wide sample of 2199 women, only 235 reported to have experienced two or more of the risk factors selected. A limit of this research in indubitably the small sample which limits the generalizability of the results.

Another limitation of this research is the use of maternal-report questionnaire to investigate the children's temperament. Such reports may be biased since it is known that maternal characteristics such as personality and mood can influence maternal ratings of child behavior.

3.7 FUTURE RESEARCH AND CONCLUSIONS

Coronavirus Pandemic has affected everyone around the world. Pregnant women, in particular, appear to be exceptionally vulnerable to the psychological consequences of such an extraordinary event. The COVID-19 pandemic has caused financial stress and disrupted daily life, leaving many families without a regular salary. Further, with the Sars-Covid-19 Pandemic more and more episodes of interpersonal domestic violence and child domestic abuse have been reported (Bryant et al., 2020).

Similar events with the same character of uncertainty, urgency, and uncontrollability such as Covid-19 are happening. For instance, the Russian and Ukrainian War represents one of the most unexpected events in our modern history, which psychological consequences are deserving of attention. Pregnant refugees and their unborn children are uniquely vulnerable to higher rates of death, disease and mental health challenges that can persist after birth (Sophia Gauthier, 2022). The risk of physical harm, malnutrition, higher rates of depression, anxiety and PTSD which are common between war-trauma victims can have long-lasting repercussions for both the mother and her fetus (Sacchi, 2022). Again, as the climate changes, human population grows, asset wealth accumulates, and societies become more urbanized and interconnected, the risk for natural disasters and their consequences heightened. Natural disasters have warning consequences on both pregnant women and their offspring.

Future research will have to investigate how to take better emotional care of pregnant women in general and of at-risk categories such as the one here investigated. As results of this study seem to show, being exposed to cumulative life events can have long lasting consequences not only on the mother, but also on the child. A tempestive and precautionary intervention for women who are more fragile and vulnerable appears to be of main importance. Further, considering how the number of adverse childhood experiences has heightened due to the pandemic and economic consequences of the war and the lockdown appear tragic, it will be more and more common for mothers-to-be to live in such conditions as the one experienced by the women in our sample.

It is also of note how Pandemic children have grown in a context of post-natal deprivation. Lock-down, the mandatory use of a mask, the fear of social contact have led to a socially

poor environment which can be deleterious for the cognitive and social growth of children. Future research will have to explore how this deprivation has affected the children development and offer new programs to repair possible damages.

In conclusion, cumulative life-time exposure to Traumas and minor stressors has an impact on a woman's mental health and stress levels. Pregnancy, which is itself a fragile time in a woman's life, appear tobe a period of heightened vulnerability to chronic stress. Particularly, being pregnant during a World-wide Pandemic generates further concerns in the mother-to-be, for her own and her child's health. Low maternal mental health during pregnancy is highlycorrelated with numerous negative children's outcomes. For instance, a more negative affect is often observed in children whose mothers experienced Depression, Anxiety or PTSD during pregnancy. A better and more thorough care of at-risk mothers may guarantee for a better maternal mental health, which in turn affects the offspring development.

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