



Prenatal and early postnatal stress and later life inflammation

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ABSTRACT

Background: Evidence suggests that maternal psychological and social stress during the prenatal period and in childhood represent an important condition that may adversely impact the anatomy and physiology of the developing child with implications for a number of health-related conditions and disorders. In a large prospective study, we aim to address if social stressors in the prenatal and early postnatal periods, as individual exposures as well as their accumulation, are associated with a range of inflammatory markers in late middle-aged offspring.

Methods: The study sample includes Danish men and women born between 1959 and 1961 ($n = 1206$) who were members of the Copenhagen Perinatal Cohort and participated in the Copenhagen Aging and Midlife Biobank in 2009–2011 (age 49–52). Information on social stressors was collected through an interview with the mothers at the first antenatal visit and postnatal stressor data was collected at year one follow-up. A series of ordinary least square regression models were performed with the stress measures as the exposures and C-reactive protein (CRP), Interleukin-6 (IL-6), Interleukin-10 (IL-10), and Tumor necrosis factor α (TNF- α) separately as the outcomes.

Results: The individual prenatal maternal stressors (being unmarried and having an unwanted pregnancy) and the prenatal index were associated with higher levels of CRP and IL-6 among offspring but not with IL-10 or TNF- α . Low social status, but not living away from parents or having an unmarried mother in the first year of life, was associated with higher levels of CRP and IL-6. The accumulation of social stressors in the early postnatal period was associated with higher levels of CRP and IL-6 but not IL-10 and TNF- α . The accumulation of stressors in the prenatal and postnatal periods combined was associated with higher levels of CRP and IL-6, but not with IL-10 or TNF- α .

Conclusions: The findings suggest that exposure to the accumulation of prenatal and early life stressors, is associated with higher levels of CRP and IL-6 in later life. This may indicate that the effects of early stressors on later inflammation operate through pathways with clear links to cardiovascular disease.

1. Introduction

The *developmental programming of health and disease hypothesis* suggests that health and disease susceptibility is determined by a dynamic interplay between genetics and the environment, in particular during intrauterine and early postnatal life (Entringer et al., 2015). Accumulating evidence suggests that maternal psychological and social stress during the prenatal period represent an important condition that may adversely impact the anatomy and physiology of the developing fetus with implications for a number of health-related conditions and

disorders (Entringer et al., 2010; Wadhwa, 2005). In a comprehensive review of prenatal stress and developmental programming of human health and disease risk, Entringer et al. suggest that the effects of maternal stress on health are mediated by stress related alterations in maternal-placental-fetal endocrine and immune/inflammatory processes (Entringer et al., 2010). Animal studies demonstrate that stress exposure *in utero* has lasting effects on immune system function, with studies of non-human primates showing that maternal stress impairs the ability of offspring immune systems to respond adequately to immune challenges (Coe et al., 1999; Coussons-Read, 2012). This may be due to

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stress hormones, such as glucocorticoids, passing over from mother to infant through fetal circulation, thereby accessing the developing nervous system (Coussons-Read, 2012).

There are few observational studies in humans on the association between prenatal stress and inflammation. However, the studies identified support these findings, suggesting that maternal stress exerts lasting effects on immune function in humans. O'Connor et al. have shown that maternal prenatal stress and anxiety influences offspring immune system development and may lead to reduced adaptive immunity in infants. (Marques et al., 2013; O'Connor et al., 2013) A Case Control study found that young adults exposed to maternal stress *in utero* exhibited dysregulation of key physiological parameters, including insulin resistance, metabolic syndrome, and altered immune function (Entringer et al., 2015; Entringer et al., 2008b). The same study demonstrated that experiencing a stressful major life event during pregnancy was associated with increased production of cytokines, including Interleukin-6 (IL-6) and Interleukin-10 (IL-10) *in vitro* among adult female offspring (Entringer et al., 2008a). Increased levels of inflammation in turn are associated with a number of age related diseases, such as cardiovascular diseases and type II diabetes (Alexandraki et al., 2006; Danesh et al., 2008).

Exposure to social stressors in the first year of life may also exert negative influences on immune function and inflammatory profiles in later life. Stress early in life has been shown to be associated with a number of related disorders occurring in later life, such as metabolic syndrome (Pedersen et al., 2016), type 2 diabetes (Masters et al., 2015), and cardiovascular disease. All of these disorders are strongly associated with inflammation (Cevenini et al., 2013). Perceiving a situation as stressful activates the physiological stress response. If the stress becomes chronic, prolonged activation of these systems can result in detrimental effects on immunity and other bodily systems (Rabin, 1999). Previous studies lend support to this hypothesis. Slopen et al. found that the accumulation of childhood social adversity was associated with higher levels of C-reactive protein (CRP) among 355 adults (Slopen et al., 2015). Danese et al. found that children who were exposed to adverse psychosocial experiences were at elevated risk of higher CRP levels at age 32 (Danese et al., 2009).

In addition to the direct physiological effects of early stress on inflammation, stress may indirectly influence levels of inflammatory markers through behavioral pathways (for example through smoking, physical activity or alcohol consumption) (McDade et al., 2006), through body composition (Pedersen et al., 2015), or through conditions such as depression, which has been shown to be associated with higher levels of pro-inflammatory cytokines (Dentino et al., 1999; Lutgendorf et al., 1999).

While previous studies have focused on the effects of social and psychosocial stress in the prenatal period and later in childhood, the first year of life is a sensitive period that has not been the focus of studies of early stress exposure and inflammatory profiles in adulthood. Further, a majority of previous prospective studies have exclusively used CRP as a marker of inflammation (Slopen et al., 2015) and there is little data about anti-inflammatory mediators such as IL-10 in this area. Therefore, in a large prospective study we aim to address if social stressors in the prenatal period and the first year of life are associated with a range of inflammatory markers in late middle-aged offspring. To elucidate the aspects of social stressors that are particularly salient with regard to inflammation, we will study the association between individual stressors and circulating inflammatory markers. We will test the hypothesis that the accumulation of social stressors in the prenatal period and during the first year of life is associated with a higher risk of pro-inflammatory profiles.

2. Materials and methods

The study sample comprised Danish men and women who were members of the Copenhagen Perinatal Cohort (CPC) (Zachau-

Christensen and Ross, 1975) and participated in the Copenhagen Aging and Midlife Biobank (CAMB) (Lund et al., 2015). The CPC is made up of 9125 consecutive deliveries by 8949 pregnant women born at the Copenhagen University Hospital (Rigshospitalet) from October 1959 to December 1961, with 8400 infants surviving the first month (Zachau-Christensen and Ross, 1975). The CPC was followed up several times in childhood and adulthood and in 2009–2011 all CPC participants who were alive and living in eligible geographical areas ($n = 5196$) were invited to participate in CAMB. A total of 1719 participants aged 49–52 years old participated in the CAMB clinical examination constituting a 33% participation rate. Participants with missing data on prenatal exposures ($n = 58$), year one exposures ($n = 303$) and covariates ($n = 152$) were excluded, leaving 1206 men and women for the analyses.

2.1. Social stress

This study focuses on different types of social stressors that are encompassed by the *stimulus oriented theory of stress* with a focus on external events or conditions that typically lead to psychological distress, behavioral disruption or deterioration in performance (Derogatis, 1993).

2.1.1. Unwanted pregnancy

In this study we include reporting an unwanted pregnancy as a stressor, as unintended pregnancy has been shown to be associated with the risk of maternal depression and parenting stress (Bahk et al., 2015).

2.1.2. Single during pregnancy and early motherhood

We operationalize single motherhood in the prenatal and postnatal periods as social stressors in this study. Single mothers tend to be more socially and economically deprived than households with both parents (Weston and Smyth, 2000). Furthermore, in this historical period, single motherhood was stigmatized in Danish society.

2.1.3. Low socioeconomic status

Low socioeconomic status is reliably associated with a number of important social and environmental conditions that contribute to chronic stress burden (Baum et al., 1999). For example, socioeconomic status contributes to levels of chronic and acute stressors through factors such as exposure to adverse social environments, discrimination, structural disadvantage and exposure to crime (Aiello and Kaplan, 2009). Information about socioeconomic status was recorded at a one-year follow-up.

2.1.4. Living away from parents

Living away from parents in the first year of life was also considered a stressor in the early postnatal period. Research indicates that early separation from caregivers has adverse effects on children's well-being (Bowlby, 1982), including socio-emotional development problems (Howard et al., 2011; Zeanah et al., 2005). Further, the early caregiving environment has been shown to markedly alter stress response development in children and parental separation may have a negative impact on this environment (McLaughlin et al., 2015).

Information on **prenatal stressors** and covariates was collected through an interview with the mothers at the first antenatal visit and included: 1. Maternal civil status at conception: a) married: mother married/mother married during pregnancy, b) unmarried: mother single/divorced/widowed/separated; 2. Attitude towards pregnancy: a) wanted, b) unwanted, with the term unwanted indicating that the pregnancy was not desired at the time of conception.

Information on **early postnatal stressors** was collected at year one follow-up with a physician-conducted interview and included: 1. Maternal civil status at year one: a) married: mother married/mother married to child's father or other after birth, b) unmarried: single/divorced/widowed/separated; 2. Living away from parents defined by

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