# THE RELATIONSHIP BETWEEN SOCIOECONOMIC STATUS PARAMETERS AND INFLAMMATION IN PREGNANT WOMEN IN TURKEY

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# DECLARATION OF ORIGINALITY

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ABSTRACT

The Relationship Between Socioeconomic Status Parameters

and Inflammation in Pregnant Women in Turkey

Socioeconomic status (SES) is associated with prenatal physiology including inflammation. However, the contribution of different SES parameters to inflammation during pregnancy, such as timing (early life vs. current) and measurement (objective vs. subjective), has not yet clearly identified. In consideration of timing or sensitive period and pathway models, the present study examines how timing of SES affect inflammation (C-reactive Protein; CRP) during the second trimester of pregnancy. With regard to timing or sensitive period model, early and current SES parameters are expected to be negatively linked to CRP. Early subjective SES (E-SSES) and current subjective SES (C-SSES) are hypothesized to have a negative impact on CRP controlling for average number of bedrooms (E-OSES: BN) and current objective SES (C-OSES), respectively. In consideration of pathway model, effect of E-OSES: BN on CRP is expected to be through C-OSES. Participants were 76 women ($M$ = 31.71, $SD$ = 3.78) in their second trimester of pregnancy from BABIP birth cohort in Istanbul, Turkey. Parental education (E-OSES: PE) and E-OSES:BN were used as early objective SES (E-OSES) parameters. C-OSES included participant's education and home income. E-SSES and C-SSES were determined by scores of MacArthur Scales. CRP was measured from blood plasma. The results showed that higher C-OSES predicted elevated CRP levels. Future studies are needed to elucidate how the effect of C-OSES on CRP may pose a risk factor for offspring's health.

# ÖZET

## Türkiye’deki Hamile Kadınlarda Sosyoekonomik Durum Parametreleri ve İnflamasyon Arasındaki İlişki

Sosyoekonomik durum (SES), inflamasyon dahil olmak üzere, doğum öncesi fizyoloji ile ilişkilidir. Bununla birlikte, zamanlama (erken ve mevcut) ve ölçüm (objektif ve öznel) gibi farklı SES parametrelerinin inflamasyona katkısı tanımlanmamıştır. Zamanlama veya hassas dönem ve yol modelleri göz önüne alındığında, bu çalışma, hamileliğin ikinci trimesterinde, SES’in zamanlamasının inflamasyonu (C-reaktif Protein; CRP) nasıl etkilediğini incelemektedir. Zamanlama veya hassas dönem modeli ile ilgili olarak, erken ve mevcut SES parametreleri CRP ile negatif bağlantılı olması beklenmektedir. Erken öznel SES (E-SSES) ve mevcut öznel SES’in (C-SSES), sırasıyla ortalama yatak odası sayısı (E-OSES: BN) ve mevcut objektif SES (C-OSES) kontrol edildiğinde, CRP üzerinde olumsuz etkisi olduğu varsayılmaktadır. Yol modeli dikkate alındığında, E-OSES: BN'nin CRP üzerindeki etkisinin C-OSES aracılığıyla olması beklenmektedir. Katılımcılar, İstanbul, Türkiye'deki BABIP doğum kohortundan hamileliğin ikinci trimesterinde 76 kadındı ($M$ = 31.71, $SD$ = 3.78). Ebeveyn eğitimi (E-OSES: PE) ve E-OSES: BN, erken objektif SES (E-OSES) parametreleri olarak kullanılmıştır. C-OSES, katılımcının eğitimini ve ev gelirini içeriyordu. E-SSES ve C-SSES, MacArthur ölçeklerinden alınan puanlarla belirlendi. CRP kan plazmasından ölçüldü. Sonuçlar, yüksek C-OSES'in, yüksek CRP seviyelerini öngördüğünü gösterdi. C-OSES'in CRP üzerindeki etkisinin, bebeklerin sağlığı için nasıl bir risk faktörü oluşturabileceğini açıklamak için yeni çalışmalara ihtiyaç vardır.

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*To my little sister, Zehra…*

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# ABBREVIATIONS

| | |
|---|---|
| BMI | Body Mass Index |
| CES-D | Centre for epidemiologic studies depression scale |
| C-OSES | Current Objective SES |
| CRP | C-Reactive Protein |
| C-SSES | Current Subjective SES |
| CTQ | Childhood Trauma Questionnaire |
| E-OSES | Early Objective SES |
| E-OSES: BN | Early Objective SES: Bedroom Number |
| E-OSES: PE | Early Objective SES: Parental Education |
| E-SSES | Early Subjective SES |
| HPA | Hypothalamic–Pituitary–Adrenal |
| IL-6 | Interleukin-6 |
| LES | Life Experiences Survey |
| MPF | Maternal-Placental-Fetal |
| MSPSS | Multidimensional Perceived Social Support Scale |
| OSES | Objective SES |
| PSQI | Pittsburgh Sleep Quality Index |
| PSS | Perceived Stress Scale |
| SES | Socioeconomic Status |
| SPSS | Statistical Package for the Social Sciences |
| SSES | Subjective SES |
| STAI-X S | State-Trait Anxiety Inventory X State |

# CHAPTER 1

# INTRODUCTION

Socioeconomic status (SES), an overall measure of one's economic and social position in the society, has long been associated with health and well-being outcomes, such as mortality, psychosocial development and vulnerability to various disorders from prenatal period to adulthood (Adler et al., 1994; Adler & Ostrove, 1999; Braveman, Cubbin, Egerter, Williams, & Pamuk, 2010; Cutler, Lleras-Muney, & Vogl, 2012; Fryers, Melzer, & Jenkins, 2003; Muntaner, Eaton, Miech, & O'Campo, 2004; Smith, 2004). SES is suggested to exert these effects through altering various endophenotypes, such as those of the neuroendocrine, immune and metabolic systems (Kim, Evans, Chen, Miller, & Seeman, 2018; McEwen & Gianaros, 2010; Sawyer, Zunszain, Dazzan, & Pariante, 2019). Furthermore, these changes due to adverse experiences are not only affecting individuals going through these changes, yet also can be transmitted across generations through multiple pathways. In this regard, the prenatal period is especially a sensitive time-frame for the transmission of SES disadvantage from mother to the fetus, such as triggering changes in the Maternal-Placental-Fetal (MPF) stress biology (Entringer, Buss, & Wadhwa, 2010; Kuzawa, 2012; Thayer & Kuzawa, 2014; Sawyer et al., 2019; Wadhwa, 2005). Consequently, through fetal programming, such exposures may make the fetus more vulnerable to various diseases across the lifespan (Wadhwa, Buss, Entringer, & Swanson, 2009).

Despite the extensive investigation of SES and its association with health and well-being, the findings are often mixed and difficult to interpret. In general, one major reason of this complexity is the variety of SES parameters used in research (Lynch & Kaplan, 2000). Studies differ highly in terms of the type (e.g. income,

education, occupation), timing (early life vs. current) and measurement (objective vs. subjective) of SES. Hence, depending on the SES parameters used, the findings may change. Importantly, various studies emphasized the role of subjective SES (SSES; i.e. the way one perceives his or her standing in the community) beyond the objective SES measures (OSES; e.g. income, education, occupation; Goodman et al., 2003; Ostrove, Adler, Kuppermann, & Washington, 2000; Sapolsky, 2004). However, SSES measures have started to receive research attention only in the last decade. Furthermore, compared to general population, there is a paucity of research on prenatal period that examines modulation of MPF stress biology by SES, which makes it even harder to understand the underlying mechanism of SES in relation to health during pregnancy. These findings and the gap in the literature altogether suggest the importance of measuring different characteristics of SES in order to identify its impact on health and well-being, especially during prenatal period.

A major biological mechanism underlying the relationship between SES and health is thought to be the alterations in the immune system (McEwen & Gianaros, 2010; Miller et al., 2009; Steptoe, 2012). Given the multifaceted nature of SES and its adverse intergenerational effects, it is of the utmost importance to understand how unique SES parameters may affect inflammatory status during prenatal period. However, there are only a few studies examining unique contributions of SES parameters to inflammation during prenatal period. Here, the current study adopted a life-course approach in the investigation of SES and uniquely tested timing or sensitive period model and pathway model. Secondly, the present study aims to examine whether SSES is a stronger predictor CRP during the prenatal period, controlling for OSES.

## 1.1 SES: A life-course approach

Disadvantageous SES may exert its adverse effects throughout the lifetime. In the context of early life exposure, low E-OSES may increase one's exposure to poor physical environment conditions, such as overcrowding, poor house conditions as well as low neighborhood and school quality that might be toxic to one's health (e.g., exposure to mold and polluted air in addition to poor water and food quality). It might be also associated with increased conflict in the family and exposure to harsh family environment. These might, in turn, deteriorate individuals' psychosocial development (e.g., increased negative affect, poor emotion regulation, language or reading impairment, high aggression, social withdrawal, hyperactivity, high hostility and pessimism), increase engagement in poor health behavior (e.g., less physical activity, unhealthy diet and higher substance use) and restrict their access to preventive care (Chen & Miller, 2013; Cohen, Janicki-Deverts, Chen, & Matthews, 2010; Conroy, Sandel, & Zuckerman, 2010). These adverse experiences are thought to be biologically embedded through dysregulation of physiological pathways which is increasingly investigated in the last decade (Chen & Miller, 2013; Cohen et al., 2010).

Given adverse effects of disadvantageous SES together with other stressors associated with it, as illustrated above, researchers have long sought to understand consequences of timing or duration of exposure to low SES in relation to physiological pathways. In this regard, several models are suggested (Cohen et al., 2010; Yang, Gerken, Schorpp, Boen, & Harris, 2017). A dominant paradigm is the timing or sensitive period model which highlights the importance of sensitive or critical periods (Cohen et al., 2010; Yang et al., 2017). It states that potentially life-long biological changes may develop as a result of exposure to disadvantageous SES

during sensitive periods, such as the prenatal period and early childhood. This, in turn, may influence predisposition to numerous diseases and psychological disorders (Yang et al., 2017). In addition to timing or sensitive period model, there are several other conceptual models that are believed to account for how disadvantageous SES pose a risk factor for psychological problems. Firstly, accumulation of risk model suggests that it is the accumulation of exposures to disadvantageous SES (i.e. either early or later in life) altogether forms additive effects of these experiences (Cohen et al., 2010; Yang et al., 2017). Second, the pathway model claims that low early SES exerts its adverse effects later in life through the pathway it establishes to current SES. Hence, in this model, the association between low early SES and health in adulthood is mediated by current SES levels (Yang et al., 2017). Thirdly, the social mobility or change model argues that current SES may modulate effects of early SES on health. That is, upward or downward mobility in SES levels can alleviate or intensify adverse effects of low early SES, respectively (Cohen et al., 2010; Yang et al., 2017). Findings to date have shown that these models might be complementing each other (Yang et al., 2017). In the current study, timing or sensitive period model was evaluated in consideration of early SES parameters to investigate the importance of early environment on adulthood physiology. The model was also evaluated with regard to current SES parameters to examine prenatal period as a critical time frame for physiology of pregnant women. The present study also tests pathway model to assess whether the association between E-OSES: BN and CRP might be through C-OSES. Accumulation of risk model and ~~s~~social mobility or change model are not investigated in the current study because of SES characteristics of the participants and small number of participants with low C-OSES.

### 1.1.1 Objective SES and its association with physical and mental health

Association between disadvantageous OSES and poor physical and mental well-being has been highlighted by many studies to date (for a review: Reiss, 2013). For instance, a recent multi-cohort study revealed that low OSES was related to eighteen health conditions including physical diseases and psychological disorders (Kivimäki et al., 2020). Researchers further attempted to investigate unique associations between timing of the exposure to lower OSES (i.e. early vs recent) and poor health conditions. In this regard, low E-OSES in the first 18 years of life was found to predict increased vulnerability to various disorders regardless of C-OSES (Cohen et al., 2013; Cohen, Doyle, Turner, Alper, & Skoner, 2004; Miller & Chen, 2013). For instance, Cohen et al. (2013) revealed that fewer years of parental home ownership as a proxy for E-OSES from age 0 to 18 was linked to vulnerability to upper respiratory disease independent of C-OSES. In addition, other studies revealed that it is not E-OSES or C-OSES *per se* contributing to health later in life. Rather, each parameter has unique contributions and it is the changes in OSES over the lifetime that cumulatively influences well-being (Luo & Waite, 2005; Turrell et al., 2002). However, it should be noted that in contrast to above mentioned studies that considered E-OSES including home ownership during the first 18 years of life, the letter studies only measured parental education and occupation. For example, Turrell et al. (2002) conducted a cross-sectional study and assessed parental education and occupation at age 10.

SES is also among the widely studied constructs in relation to life-long approaches to mental health (Lemstra et al., (2008). Research have revealed an association between low C-OSES and major mental disorders, such as anxiety disorders, schizophrenia and depression (Fryers, Melzer, & Jenkins, 2003; Muntaner,

Eaton, Miech, & O'Campo, 2004). For instance, a reduction in household income was found to pose a risk for development of anxiety and mood disorders (De Graaf, Ten Have, Tuithof, & Van Dorsselaer, 2013; Sareen, Afifi, McMillan, & Asmundson, 2011). On the other hand, when area-based SES was taken into account (i.e. rather than individual-level SES parameters), likelihood of having a mood disorder was higher for both women with high and those with low C-OSES (Williams et al., 2011), suggesting a U-shaped relationship between C-OSES and mood disorder. In another study, low C-OSES and reduction in income was linked to anxiety disorders in women only compared to men (Mwinyi et al., 2017), pointing out susceptibility of especially women to adverse effects of disadvantageous SES. Hence, there are equivocal findings in the literature due to differential use of SES parameters, which might be also modulated by sex differences.

As in the case of physical health problems, not only C-OSES but also E-OSES has been shown to affect health and risk for developing psychological disorders, including depression and anxiety disorders in adulthood (Cohen, Janicki-Deverts, Chen, & Matthews, 2010; Gilman, Kawachi, Fitzmaurice, & Buka, 2002). However, research yielded mixed findings in terms of the importance of timing. Whereas some researchers revealed importance of E-OSES over C-OSES (Gilman et al., 2002; Angelini, Howdon, & Mierau, 2019), others yielded opposite findings (Lähdepuro et al., 2019). For instance, in a birth cohort study, Lähdepuro et al., (2019) showed a significant association between low E-OSES measured as parental occupation and higher anxiety in adulthood, yet this association was fully mediated by C-OSES. In a birth cohort study again, Luo and Waite (2005) showed that although both E-OSES (i.e. parental occupation) and C-OSES influenced health in adulthood, C-OSES was shown to be the pathway through which E-OSES affected

adult health. Furthermore, an upward mobility in later life was found to diminish adverse effects of low E-OSES. In support of sensitive period model, in a multi-site cohort study, Gilman et al. (2002) found that people with low E-OSES were more likely to be diagnosed with major depression controlling for C-OSES. E-OSES in this study was based on parental occupation again; however, in contrast to above mentioned studies, E-OSES was examined at two time points (i.e. during prenatal period and at the age of seven). Similarly, Angelini et al. (2019) showed low E-OSES to be related to higher incidence of depressive symptoms in adulthood regardless of C-OSES. However, E-OSES in this study was based on several E-OSES parameters at age 10, such as, number of rooms and facilities in the house, number of books and occupation of the breadwinner in the house. As opposed to studies conducted with Western and European population, a contrasting finding was put forward by Ochi, Fujiwara, Mizuki, and Kawakami (2014). In a sample of Japanese individuals, they found that high E-OSES as measured by number of years of parental education predicted high prevalence of major depression controlling for C-OSES. Moreover, this relationship was present for women but not men. Rather, generalized anxiety disorder was positively linked to E-OSES in men but not in women controlling for C-OSES. These equivocal findings altogether suggest the necessity of investigating timing of the exposure to disadvantageous SES along with importance of demographic factors when identifying its impact on health and well-being.

### 1.1.2 Subjective SES and its association with physical and mental health

Researchers have argued that not only SES as measured by objective means (e.g. education, income) but people's evaluation of their socioeconomic standing in their

community or country might play a role in its association with vulnerability to health and disease (Adler, Epel, Castellazzo, & Ickovics, 2000; Demakakos, Nazroo, Breeze, & Marmot, 2008; Euteneuer, 2014; Sapolsky, 2004; Singh-Manoux, Adler, & Marmot, 2003; Singh-Manoux, Marmot, & Adler, 2005). According to "averaging hypothesis", SSES accounts for a "cognitive average" of one's socioeconomic position that includes both social and economic aspects. They claimed that SSES contains a cognitive calculation of recent and future prospects with regard to socioeconomic position. Therefore, SSES is thought to account for effects of SES on health and well-being better than OSES parameters (Singh-Manoux et al., 2005).

Attempts to investigate its relationship to health and well-being, indeed, yielded robust effects of SSES. Various studies emphasized the role of SSES beyond the OSES measures (e.g. income, education, occupation; Goodman et al., 2003; for reviews in relation to cardiovascular disorders and physical health: Cundiff & Matthews, 2017; Tang, Rashid, Godley, & Ghali, 2016; for a meta-analysis in relation to adolescent health: Quon & McGrath, 2014). A recent meta-analysis found C-SSES being positively linked to physical health and psychological well-being controlling for C-OSES (Zell, Strickhouser, & Krizan, 2018). In a preliminary study, Adler et al. (2000) showed that high C-SSES predicted improved physiological and psychological well-being regardless of C-OSES. Another study revealed that during adolescence both C-OSES and C-SSES were linked to obesity during adolescence. However, when effects of these parameters were simultaneously assessed in logistic models, the relationship of C-OSES to obesity during adolescence was reduced to a non-significant value, suggesting a more robust effect of SSES over OSES (Goodman et al., 2003). Similarly, in a sample of adolescents, McLaughlin, Costello, Leblanc, Sampson, and Kessler, (2012) revealed that among various C-OSES

parameters, C-SSES was the most robust predictor of psychological disorders. With regard to physical illnesses, low C-SSES found to be closely linked to increased vulnerability to developing common cold independent of C-OSES (Cohen et al., 2008). In another study, C-SSES, but not C-OSES, was found to moderate the association between shorter sleep duration and increased vulnerability to upper respiratory illness. Results yielded that among people with shorter sleep duration, those with lower C-SSES showed susceptibility to common cold, yet this association was non-significant for those with lower sleep duration and high C-SSES (Prather, Janicki-Deverts, Adler, Hall, & Cohen, 2017). In addition, a study conducted with Asian immigrants in the US revealed that C-SSES measures predicted self-rated physical and mental health, psychological distress and physical discomfort controlling for C-OSES (Gong, Xu, & Takeuchi, 2012). Finally, Bradshaw, Kent, Henderson, and Setar (2017) found C-SSES to be negatively linked to body mass index (BMI) in a longitudinal study with adolescences. However, their results suggested E-OSES and C-OSES as contributors to this association. It should be noted that E-OSES in this study was measured by means of parental education, income and neighbor quality. Parental education and income questions were answered by parents. Therefore, it should be carefully compared with studies utilizing retrospective measures. Altogether, these studies suggest that it is of the utmost importance to include SSES measures when examining adverse effects of disadvantageous SES on health and well-being while controlling for OSES measures.

## 1.2 Lifelong health: Biological mechanisms

Prolonged exposure to stress has long-lasting effects on neurobiological, neuroendocrine, inflammatory and metabolic systems throughout lifetime (Kim, Evans, Chen, Miller, & Seeman, 2018; McEwen & Gianaros, 2010; Sawyer, Zunszain, Dazzan, & Pariante, 2019; Steptoe, 2012). In this regard, disadvantageous SES is an example of chronic stress and further increases exposure to other stressors; therefore, the biological mechanism through which SES exerts its effects needs to be thoroughly investigated. In terms of neurobiological mechanisms of stress, research focus is mostly on the brain regions that involve in stress perception, appraisal and regulation, such as, hippocampus, amygdala and medial prefrontal cortex. These brain regions also interact with primary physiological stress systems in the body, which are Hypothalamic–Pituitary–Adrenal (HPA) axis and Sympathetic-Nervous-System (SNS) reactivity. Chronic exposure to stress, for instance, induces continuous activation of the HPA-axis, which may lead to "glucocorticoid resistance" in immune cells, preventing the downregulation of inflammatory response. Consequent elevation of inflammation levels is thought to have a key role in biological embedding of vulnerability to psychological disorders (Cohen et al., 2012; Pariante, 2017; Perrin, Horowitz, Roelofs, Zunszain, & Pariante, 2019). Furthermore, elevation of inflammation levels not only pose a risk factor for individuals who are experiencing it; yet, for instance, increased maternal inflammation may also affect offspring's health when exposed during prenatal period. Indeed, during prenatal period, maternal inflammation was linked to preterm birth (Wadhwa, Culhane, Rauh, & Barve, 2001), alterations in newborn brain connectivity as well as working memory performance at the age of 2 (Rudolph et al., 2018), body composition (Entringer et al., 2012), vulnerability to attention deficit and hyperactivity disorder at

4 to 6 years of age (Gustafsson et al., 2020) and child neurodevelopmental delay (Girchenko et al., 2020). On the other hand, there is no study that measured disadvantageous SES with regard to its timing (early life vs. current) and measurement (objective vs. subjective) during prenatal period and investigated its effects on inflammatory status.

### 1.2.1 Early vs current OSES and inflammation

Given the multifaceted nature of SES and its adverse effects across generations, the potential mechanisms underlying the association between SES parameters and health remains to be elucidated further. Researchers posit that disadvantageous SES and consequently chronic stress due to adverse life experience can affect vulnerability to psychological disorders through biological pathways (Hackman, Farah, & Meaney, 2010; Kim et al., 2018; McEwen & Gianaros, 2010; Miller et al., 2009; Sawyer et al., 2019; Steptoe, 2012). The focus of the current study is inflammation which is known to be the process of immune system's response to pathogens, infections or physical injury to protect the body. However, as it is stated previously, a dysfunction in this system or its chronic stimulation may cause low-grade or chronic inflammation (for a review: Hänsel, Hong, Cámara, and von Känel, 2010). Indeed, the research to date revealed the association between disadvantageous SES a proxy for chronic psychosocial stress and biomarkers of the immune system, such as CRP, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) (for a recent review: Muscatell, Brosso, and Humphreys, 2020). For example, low E-OSES as measured by home ownership between age 0 and 12 was found to predict expression of proinflammatory phenotypes during adolescence regardless of C-OSES in a sample of females (Miller & Chen, 2007). Conducting a genome-wide transcriptional profiling, Miller et al.

(2009) further revealed that low E-OSES characterized by low parental occupation (i.e. during the first 5 years of age) predicted resistance to glucocorticoid signaling and increased inflammatory and adrenocortical activity controlling for C-OSES, perceived stress and habits.

Apart from gene expression patterns, individual inflammation markers of the immune system have also been associated with SES. Findings are mixed due to differential use of SES parameters. Some studies revealed importance of E-OSES over/controlling for C-OSES (Lockwood, John-Henderson, & Marsland, 2018; Packard et al., 2011), whereas some others showed indirect path from E-OSES to inflammation via C-OSES (Matthews et al., 2016). Furthermore, the relationship between SES and inflammatory markers is suggested to be more consistent for the acute phase protein of inflammatory system, CRP and less for the proinflammatory marker, IL-6 (Petersen et al., 2008). In an early study, the, CRP levels were found to be elevated in participants with low C-OSES controlling for age, sex, BMI and health factors (e.g, smoking and alcohol) (Owen, Poulton, Hay, Mohamed-Ali, & Steptoe, 2003). In a biethnic group consisting of Black and White individuals, Gruenewald, Cohen, Matthews, Tracy, and Seeman, (2009) showed that both CRP and IL-6 were negatively correlated with C-OSES as measured by education controlling for age but this association was insignificant for Black males.

In addition to these studies with a focus on C-OSES, numerous studies investigated effect of E-OSES in relation to C-OSES in predicting inflammatory status. For instance, Taylor, Lehman, Kiefe, and Seeman, (2006) revealed that low E-OSES by means of parental education measured prospectively and harsh family environment were linked to higher CRP levels. Furthermore, this relationship was found to be via psychological functioning (i.e. including mastery, social support and

depressive symptoms) in adulthood and current BMI. Similarly, Packard et al., (2011) found that paternal occupation as E-OSES parameter at the age of 11 predicted adult CRP levels controlling for C-OSES. In addition to studies using parental education as a measure of E-OSES, Carroll, Cohen, and Marsland (2011) showed that lower E-OSES as measured by average number of parental vehicle and house ownership as well as bedroom number in the first 18 years of life predicted increased IL-6 levels regardless of C-OSES, age, gender, BMI and physical activity. On the other hand, the reverse association between E-OSES and CRP levels was found to be mediated by BMI and C-OSES in a sample of women (Matthews et al., 2016).

The adverse effects of low E-OSES on inflammation was highlighted in recent systematic reviews and meta-analyses (Milaniak & Jaffee, 2019; Liu et al., 2017). The meta-analysis by Milaniak and Jaffee (2019) showed that low E-OSES predicts increased inflammation independent of C-OSES, current BMI, demographics, physical activity and smoking. Interestingly, however, this association was absent in studies with longitudinal designs. A recent longitudinal study by Kokosi, Flouri, and Midouhas (2020) published after this review used an average score of maternal education, paternal social class based on occupation, overcrowding, house ownership and financial difficulties for E-OSES measure at first 3 years of age. They further assessed negative life events from 3 to 9 years of age and measured CRP and IL-6 levels at age 9. Results revealed an association between low E-OSES and high IL-6 but not CRP levels controlling for negative life events experienced at 0-3 years of age, gender, BMI and financial difficulties. Furthermore, negative life events experienced over 3 to 9 years of age partially mediated this relationship. Another meta-analysis and review by Liu et al. (2017)

specifically revealed the relationship between low E-OSES and CRP levels in adulthood. They further examined the effect of C-OSES in a subgroup of studies; however, inclusion of C-OSES as a covariate did not decrease the association between E-OSES and CRP. In summary, these equivocal findings again show difficulty of interpreting and comparing the studies in the literature. Moreover, findings clearly indicate a discrepancy between prospective and retrospective measuring of SES parameters in relation to inflammatory status. Lastly, findings point out the importance of including covariates, such as recent negative life events, when exploring the effects of early SES.

### 1.2.2 Early vs current SSES and inflammation

In addition to OSES parameters, researchers have sought to reveal the potential role of early or current SSES in predicting inflammation levels in adulthood (Euteneuer, 2014). In a preliminary study, Derry et al. (2013) found people with low C-SSES had higher IL-6 reactivity following Trier Social Stress Test (TSST, a well-known laboratory paradigm for acute stress induction) in comparison to individuals with high C-SSES. Regarding E-SSES, research to date on the association between E-SSES and biological measures mostly utilized ladders (i.e. MacArthur Scale of Subjective Social Status) where participants retrospectively rank their mother's and father's social standing during their childhood and adolescence (Gianaros et al., 2008; John-Henderson, Marsland, Kamarck, Muldoon, and Manuck (2016); Murdock et al., 2018). John-Henderson, Stellar, Mendoza-Denton, and Francis (2015) revealed an interaction between E-SSES and social support by means of presence of a supportive figure in predicting IL-6 reactivity when exposed to a stressful task. Furthermore, this effect was regardless of C-SSES. Particularly, they

found that poor E-SSES accounted for lower IL-6 levels following the stressful task only when the supportive figure was present. However, presence or absence of the supportive figure did not alter IL-6 reactivity of individuals with high E-SSES. In addition, neither E-OSES nor C-OSES interacted with social support in explaining IL-6 reactivity. In their second study, they adopted TSST. Results suggested individual interaction effects of both E-SSES and C-SSES with social support in predicting IL-6 reactivity. However, their final analysis revealed E-SSES as a more robust predictor of IL-6 reactivity compared to C-SSES. Overall, this study highlighted the central role of E-SSES in explaining IL-6 reactivity. It should be noted that E-SSES in this study was measured by rating of parental social class on a scale from 1 to 5. In their more recent paper, John-Henderson et al. (2016) further investigated negative life events in relation to C-OSES, E-OSES, C-SSES and E-SSES in predicting IL-6 levels. They revealed individuals with low E-SSES (i.e. measured by nation version of MacArthur Ladder) and high reports of negative life events had elevated IL-6 levels as opposed to people with high reports of negative life events but high E-SSES. In summary, these studies support the robustness of SSES parameters, particularly E-SSES, over OSES and their inverse association with inflammatory status. Furthermore, negative life events and social support were revealed as important contributors, thus future studies should also adopt these measures while investigating the association between SES parameters and CRP.

### 1.3 The importance of prenatal period on SES and inflammation association

Having introduced the adverse effects of disadvantageous SES on well-being over the life-course and the evidence for the importance of critical periods, it is of the utmost importance to examine how SES might exert its effects during prenatal

period. Pregnancy, as one of the most sensitive time-frame throughout the life-course, allows transmission of these adverse effects across generations (Aizer & Currie, 2014). Research with pregnant women showed education together with occupation and family income as C-OSES parameters (Parker, Schoendorf, & Kiely, 1994), maternal early social environment (Morton, De Stavola, & Leon, 2014), maternal childhood hardships including low E-OSES assessed at several time point during childhood (Harville, Boynton-Jarrett, Power, & Hyppönen, 2010) to be associated with low birth weight, preterm birth, newborn's size at birth. However, a critical question has been how these adverse effects "get under the skin" and become "biologically embedded" (Hertzman, 1999; Kim et al., 2018)?

Starting with "Barker's hypothesis" (or the fetal origins hypothesis), the attempts to reveal "Developmental Origins of Health and Disease (DOHaD)" have been flourishing (O'Donnell & Meaney, 2017; Wadhwa et al., 2009). To date, researchers have provided support for the developmental origins of poor psychosocial development of offspring, underlining the importance of prenatal period and suggesting susceptibility of intrauterine environment to perturbations (Buss, Entringer, & Wadhwa, 2012; Entringer, Buss, & Wadhwa, 2015; Entringer et al., 2012; Wadhwa et al., 2009). In this regard, researchers posit that adverse effects of low SES may alter physiological and biological development of the fetus by fetal programming, which may in turn lead to phenotypic changes posing a risk factor for poor health and psychological dysfunction. Specifically, it is suggested that stress exposure stemming from disadvantageous SES may induce changes in MPF stress biology (e.g., immune, endocrine and metabolic systems), which might be detrimental to offspring's well-being.

Given the importance of prenatal period in terms of intergenerational transmission of mothers' experiences and its effects on fetus, researchers have attempted to understand the association between maternal OSES and MPF biology as well as infant birth and developmental outcomes. For instance, low C-OSES was linked to placenta transcriptional profile suggesting an increased immune activation and dampened fetal maturation (Miller et al., 2017a). Likewise, a recent study with pregnant women revealed that both childhood abuse and lower C-OSES predicts higher levels of CRP through BMI during pregnancy (Finy & Christian, 2018). In addition, another study associated low E-OSES with birth outcomes, such as shorter gestation length and preterm birth rates. Furthermore, these associations were partially explained by IL-6 levels (Miller et al., 2017b). A recent study examined how E-OSES as measured by parental home ownership (i.e. during the first eighteen years of life) and C-OSES might influence stress reactivity during pregnancy, which was measured by the activation of HPA-axis activity (i.e. cortisol hormone levels). Disadvantageous SES was found to be associated with elevated prenatal hair cortisol, a biomarker of chronic stress. However, the effect of E-OSES on hair cortisol was explained by C-OSES (Bosquet Enlow et al., 2019), underlining the necessity of adopting a life-course approach when examining these adverse effects of SES (Yang et al., 2017).

Attempts to delineate effect of SSES on maternal well-being during pregnancy as well as on birth outcomes have showed robustness of SSES again beyond OSES. In a pioneering study, Ostrove, Adler, Kuppermann, & Washington (2000) found that C-SSES predicted self-rated health irrespective of C-OSES among White and Chinese American pregnant women in their first trimester. Similarly, Stewart, Dean, Gregorich, Brawarsky, & Haas (2007) found that White pregnant

women in their first trimester with higher C-SSES reported better physical health. In terms of mental health, one study with a sample of pregnant Mexican American and Mexican immigrant women showed a reverse association between C-SSES and depression as well as perceived social stress among Mexican Americans (Fleuriet & Sunil, 2014). In consideration of E-SSES, Kingston, Sword, Krueger, Hanna, and Markle-Reid (2012) found a positive relationship between E-SSES and prenatal stress yet this association was through C-SSES.

SSES during pregnancy was also found to have effects on habits during postpartum period and birth outcomes. For instance, Reitzel et al. (2007) showed that pregnant women who quit smoking were more likely to start smoking during postnatal period if they have low C-SSES. Moreover, this association was regardless of demographic factors including race/ethnicity and C-OSES. A recent study further revealed that low C-SSES during prenatal period pose a risk factor for high birth weight controlling for C-OSES (Goplerud, Hernandez, & Johnson, 2021). Altogether these studies provided a support for SSES as a stronger indicator of well-being during perinatal period.

In consideration of the potential role of SSES on MPF biology, there is only one recent study which established the inverse association between C-SSES and inflammatory state taken as a composite score of IL-6, CRP and TNF-α levels (Scholaske, Buss, Wadhwa, & Entringer, 2020). Furthermore, this association was not significant for C-OSES measure. Hence, here again, SSES was found as a more robust predictor of maternal health during pregnancy. However, no study to date has investigated E-SSES in the context of inflammatory status during prenatal period.

## 1.4 Present study

Research has established the significance of both timing and type of the exposure to disadvantageous SES and their effects on well-being. On the top of this, having introduced its intergenerational effects and susceptibility of fetus to intrauterine perturbations during prenatal period, the current study seeks to reveal the potential associations between different SES parameters and CRP levels during prenatal period in pregnant women from ongoing Bogazici Mother-Baby Relationship Project (BABIP) prospective birth cohort (Duman, Atesyakar, & Ecevitoglu, 2020). In an attempt to test timing or sensitive period model, SES in both early life and prenatal period are evaluated. In this regard, E-OSES: BN, E-OSES: PE, E-SSES, C-OSES and C-SSES might be inversely associated with CRP. In addition, I expect to find a robust negative effect of E-SSES and C-SSES on CRP levels controlling for E-OSES: BN and C-OSES, respectively. Finally, in consideration of pathway model, I hypothesize that the effect of E-OSES: BN on CRP might be indirect through C-OSES.

# CHAPTER 2

# METHODS

## 2.1 Participants

Participants were pregnant women aged from 23 to 40 ($N$ = 76; $M$ = 31.71, $SD$ = 3.78) recruited from BABIP prospective birth cohort (Duman et al., 2020) At the first time point, they were within their second trimester (20-26 weeks of gestation; $M$ = 23.04 weeks, $SD$ = 1.64 weeks). Inclusion criteria was being older than 18 years of age, being from Turkey, speaking Turkish, living in Istanbul, having a singleton intrauterine pregnancy and exhibit no severe pregnancy complications. Exclusion criteria included developing severe pregnancy complications, being diagnosed with a disorder or using medication that influences stress response and immune systems. Recruitment process included flyers, online advertisements and communications through doctor's offices. As a compensation for their contribution to the project, participants were provided with informative booklets and online seminars about pregnancy, gifts and developmental reports for their infants at 4-months postpartum.

For the purpose of the current study, blood samples, questionnaires and interviews collected at their first visit, which took two hours, were used. Please see Figure 1 for the flow diagram. Out of the 83 participants, 3 withdrew from the study, 2 failed to complete the self-report questionnaires and 2 failed to give blood samples, leading to a final number of 76 participants. Descriptive characteristics of these participants are provided in Table 1. All participants were married. The majority of pregnancies were reported to be wanted pregnancies (89%). Five participants reported in vitro fertilization treatment for conception. Participants were on overage from middle class ($M$ = 13300.74 TL, $SD$ = 10557.50 TL) and their education levels

were as the following: 43% graduate degree, 49% undergraduate degree, 5% vocational degree and 3% high school degree.

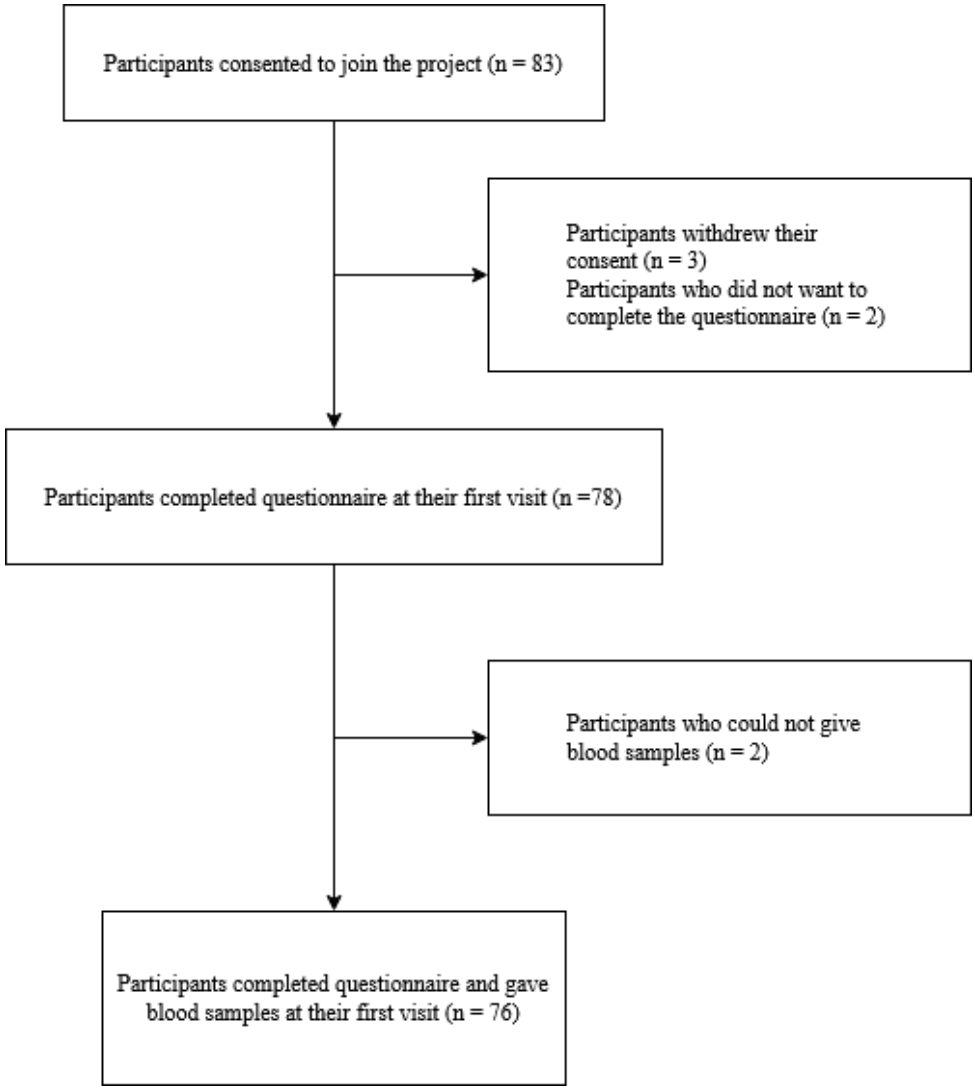


Fig 1. Participant flow diagram for psychosocial and biological measures

Table 1. Descriptive Characteristics of the Participants

| | *M* | *SD* | Range |
|---|---|---|---|
| Age | 31.71 | 3.78 | 23-40 |
| Gestation week | 23.04 | 1.64 | 20-26 |
| Pre-pregnancy BMI | 25.15 | 3.26 | 19-32 |
| Monthly income (TL) | 13.300 | 10.557 | 3000-75000 |
| | *%* | | |
| In vitro fertilization | 6.6 | | |
| Nulliparous | 67.1 | | |
| Wanted pregnancy | 89.5 | | |

In terms of health for the past year, 90% of the participants experienced pregnancy-related sicknesses. Forty women reported feeling nauseous with 27 experiencing vomiting, 18 had diarrhea, 17 had vaginal bleeding, 22 experienced anemia and 15 had cystitis. No women reported experiencing rubella, mumps, measles, varicella, zona, toxoplasmosis or HIV/AIDS. In terms of chronic diseases, 3 women were diagnosed with gestational diabetes and used insulin shots, 1 women was diagnosed with hypertension and 1 with hypotension. Nine women reported having a thyroid disease, 1 women had insulin resistance, 1 had epilepsy, 1 reported thalassemia, 7 had migraine, 11 had eczema, 1 had asthma and 1 had kidney disorder. One women had polycystic ovary syndrome, 2 experienced a sexually transmitted disease and 1 women had drug addiction. Twenty eight women experienced allergies and 11 women reported food intolerance. With regard to psychological disorders, 1 women reported having diagnosed with major depression and 5 reported being diagnosed with anxiety where 1 women used SSRI antidepressant. Thirteen women reported feeling like having a psychological problem, one of which reported using antidepressant.

## 2.2 Measures

### 2.2.1 Questionnaire measures

Participants' demographic and psychosocial information were collected by self-report questionnaires and interviews conducted during their first visit at their second trimester. The participants were asked to provide demographic information such as marital status, age, gestational week, education and household income. They were also given questionnaires regarding their health and routines, such as pregnancy complications, BMI, use of alcohol, smoking, current or past diagnosis of diseases and use of medications. As detailed below, standardized questionnaires were used to measure psychosocial factors (e.g. general state anxiety, depressive symptoms, perceived stress, childhood trauma, perceived social support and negative life events) at the first time point (i.e. 20-26 weeks of pregnancy).

#### 2.2.1.1 Objective SES

In order to measure E-OSES, participants were asked to assess multiple items related to their family and childhood environment. First, they reported on parental education by rating their mothers' and fathers' education levels (i.e. 0 = illiterate … 7 = doctoral degree). Maternal and paternal education levels were standardized and averaged to obtain E-OSES: PE. In addition, we asked participants to report the number of bedrooms in their family home from birth to 18 years of age. E-OSES: BN is suggested to be a more robust measure of SES than income and more dynamic than parental education (Azad et al., 2012; Marin, Chen, & Miller, 2008). We calculated the average number of bedrooms by dividing the total number of bedrooms by total number of houses for each participant. Then, we divided this score by number of people (i.e. parents, siblings and others) living in the house other than

the participant in order to have E-OSES: BN score. Some of the participants failed to remember number of bedrooms, particularly when they lived at that home for a short period of time at a young age. For those participants, we only included the homes they were able to recall in the analyses. C-OSES was assessed by participants' current education level and monthly household income. Education level was defined as the highest completed education (i.e. 0 = illiterate … 7 = doctoral degree). Education level and household income scores were standardized and averaged to have C-OSES score.

#### 2.2.1.2 Subjective SES

Participants' perception of their mothers' and fathers' social standing relative to other people in Turkey during their childhood (i.e., before the age of 18) was asked via use of translated and adapted version of MacArthur Scale of Subjective Social Status (Adler et al., 2000) to assess E-SSES. We used the nation version of the scale. Participants were presented with two ladders to separately rate their mothers' and fathers' social standing during their childhood, with higher scores indicating higher E-SSES. Two scores were averaged to have a parental score corresponding to E-SSES. Similarly, participants' perception of their social standing was asked via use of nation version of MacArthur Scale of Subjective Social Status (Adler et al., 2000) to measure C-SSES. It required participants to place an "X" on the rung on which they feel they stand in comparison to people in Turkey with higher rungs on the ladder indicating higher C-SSES (Please see Appendices A and B).

#### 2.2.1.3 State anxiety inventory X (STAI-X State)

As a measure of general state anxiety participants had experienced at the time of their first visit (i.e. 20-24 weeks of gestation), we utilized the Turkish version of State Anxiety Inventory X **(**STAI-X State Questionnaire; Spielberger, Sydeman, Owen, & Marsh, 1999; Turkish: Öner & Le Compte, 1985). STAI-X State is 20-item ($\alpha = .93$) self-report questionnaire on a 4-point Likert scale (1: Not at all, 4: Very much so). The items aim to capture the current anxiety (e.g. I am presently worrying over possible misfortunes). STAI-X State total scores range from 20 to 80 with higher scores indicating higher state anxiety. A cut point of 39-40 is suggested to reveal clinically significant state anxiety symptoms (Knight, Waal-Manning, & Spears, 1983). STAI-X State was shown to be a reliable and valid in the Turkish version as well (Öner & Le Compte, 1985). In the analyses, STAI-X State scores were used as a continuous variable.

#### 2.2.1.4 Childhood trauma questionnaire (CTQ)

Turkish version of the Childhood Trauma Questionnaire (CTQ) was adopted to assess childhood maltreatment. It is a 28-item ($\alpha = .81$) questionnaire with five subscales – that is, physical, emotional and sexual abuse as well as physical and emotional neglect (Bernstein et al., 1994; Turkish: Şar, Öztürk, and Ikikardeş, 2012). CTQ is represented on a 5-point Likert scale (1: Never True, 5: Very Often True). In addition to five subscales with each having 5 items, there are 3 items used to measure any potential denial of maltreatment. Total scores range from 25 to 125 and higher scores indicate higher maltreatment. Reliability and validity of the Turkish version was tested and revealed by Şar et al. (2012). CTQ total scores were used as a continuous variable and held as a covariate in the statistical analyses.

#### 2.2.1.5 Multidimensional scale of perceived social support (MSPSS)

Multidimensional Scale of Perceived Social Support (MSPSS) was utilized to examine perceived social support. It consists of 12-items (α = .81) with unique subscales for family, friends and significant other (Zimet, Powell, Farley, Werkman, & Berkoff, 1990; Turkish: Eker, Arkar, & Yaldız, 2001). Example items for each subscale are as follows: "I can talk about my problems with my family", "I can count on my friends when things go wrong" and "There is a special person with whom I can share my joys and sorrows". Total scores range from 7 to 84 and it is represented on a 7-point Likert scale (1: Very strongly disagree, 7: Very strongly agree). Higher scores shows high levels of social support. Furthermore, its total score was used as a covariate in this study.

#### 2.2.1.6 Perceived stress scale (PSS)

Participants' perception of the stress they had experienced in the last one month prior to the assessment date was measured by Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983; Turkish version: Erci, 2006). For instance, the participants were asked to report "In the last month, how often have you been upset because of something that happened unexpectedly?" and "In the last month, how often have you found that you could not cope with all the things that you had to do?". It is a 14-item self-report on a 5-point Likert scale (1: Never, 5: Very often). The scores are ranging from 10 to 50 with high scores showing elevated levels of perceived stress. Cronbach's α in this study for perceived stress scale was .84.

#### 2.2.1.7 Centre for epidemiologic studies depression scale (CES-D)

Centre for Epidemiologic Studies Depression Scale was utilized to assess recent depressive symptoms over the week prior to the time of assessment (Radloff, 1977; Turkish version: Tatar & Saltukoglu, 2010). CES-D is a 20-item (α = .62) self-report questionnaire on 4-point Likert scale (1: "Rarely or none of the time", 4: "Most or all the time"). Higher scores indicate higher depressive symptoms. Example items from the questionnaire are "I did not feel like eating; my appetite was poor", "I felt fearful" and "I had crying spells".

#### 2.2.1.8 Pittsburgh sleep quality index (PSQI)

Pittsburgh Sleep Quality Index was used as a self-report measure to examine sleep quality and disturbances over the last one month at the time of the assessment (Buysse, 1989; Turkish version: Ağargün, Kara, & Anlar, 1996). It has 24 items (α = .73) in total, some of them are represented on a Likert-type scale (e.g., "During the past month, how would you rate your sleep quality overall?" and some of the questions are open-ended (e.g., "During the past month, when have you usually gotten up in the morning?"). Total score ranges from 0 to 21 and high scores indicate less sleep quality in general.

#### 2.2.1.9 Life experiences survey (LES)

Life Experiences Survey (Sarason, Johnson, & Siegel, 1978; Turkish version: Yarış, 2010) is used to measure positive and negative life experiences in a year prior to pregnancy and the impact ratings of these experiences. It contains 57 items, the first 44 items referring to specific events are used (α = .63). The participants were asked whether they experienced those events, and if yes, whether they perceived it as

positive, negative or neutral event. The ratings range from extremely positive (3) to no impact (0) to extremely negative (-3). Intensity scores of positive and negative experiences were calculated via dividing total of the rating scores by number of events experienced. For the current study, only total intensity score of the negative events was utilized.

### 2.2.2 Inflammation measures

In order to measure CRP, participants provided their blood samples collected by a nurse after at least 30 minutes following the participants' arrival. EDTA tubes were inverted 8 times after collection and put on ice immediately. Afterwards, the blood tubes were transferred to our laboratory. EDTA tubes were centrifuged at 1500g at 4°C for 10 minutes, and plasma was aliquoted and stored at -80 °C. High sensitivity CRP levels were determined from these samples via use of Roche Cobas Cardiac C-Reactive Protein (Latex) High Sensitive at Centro Laboratories, Istanbul. Reference interval was 0.1 - 2.8 mg/L. Moreover, the inter-assay coefficient of variation (CV) and the intra-assay CV were below 1%.

## 2.3 Procedure

All procedures in this study were approved by Bogazici University Human Research Ethics Committee (Please see Appendix C). As mentioned earlier, the current study is part of the larger ongoing BABIP cohort and followed its procedures for each participant (Duman et al., 2020). However, the scope of the current study is restricted to the first time point of this cohort (i.e. 20-26 weeks of gestation). Participants were first contacted over the phone, and eligible participants were invited to Biruni Laboratories. Following their arrival to the laboratory, their

informed consents were taken and they were provided with instructions on sampling procedures. This was followed by an interview session in which participants were mainly asked about their health history. Afterwards, participants' blood samples were collected by registered nurses into EDTA tubes. Participants were then instructed to complete self-report questionnaires. At the same time, the blood samples were immediately transferred to our laboratory in an icebox, centrifuged at 4° C, 1500g for 10 minutes, aliquoted and kept at -80° C to be later sent to Centro Laboratories for analyses. Two research assistants were responsible for entry of all data and it was controlled by the third research assistant.

### 2.4 Statistical analyses

All variables were assessed for outliers by detecting values higher than 3.29 standard deviation (SD) above the mean; they were winsorized to $5^{th}$ and $95^{th}$ percentile. For each variable again, normality check was done by assessing z-score of skewness and kurtosis. Variables with z-scores of skewness and kurtosis higher than 3.29 were considered to have non-normal distribution and transformed accordingly (Kim, 2013). IBM SPSS v23 was used to conduct all analyses.

#### 2.4.1 SES parameters

Bivariate associations between all SES parameters and their potential relationship with covariates were examined. Pearson's correlation coefficients and partial correlations were used when two variables were normally distributed and continuous. Demographic information (i.e. age, gestation week, pre-pregnancy and current BMI) and psychosocial variables (i.e. recent depressive symptoms, perceived stress, perceived social support, sleep quality, childhood trauma, negative life events,

general state anxiety) were considered as covariates. Their associations with each SES parameter were analyzed by Pearson's correlations. The covariates that were found to be significantly associated with each SES parameter were taken as covariates in partial correlation analyses investigating the association between different SES parameters. It should be noted that significantly correlated psychosocial variables were standardized and averaged to have composite covariate scores for these analyses.

### 2.4.2 CRP

CRP values were checked for presence for non-normal distribution and log transformation was applied accordingly. Numerous covariates were taken into account in relation to CRP: demographic information (i.e. age, gestation week, pre-pregnancy and current BMI) and psychosocial variables (i.e. recent depressive symptoms, perceived stress, perceived social support, sleep quality, childhood trauma, negative life events, general state anxiety), habits (i.e. smoking, drinking and physical exercise). Furthermore, the potential influence of health variables (e.g. reported disorders, sicknesses and use of medicines) were assessed. Possible associations between CRP levels and covariates were analyzed by bivariate correlations and t-tests. Among all covariates, the ones that were significantly linked to CRP levels were included in the subsequent analyses. However, here again, significantly correlated covariates were standardized and averaged to have a composite covariate score. Also, significant health variables were grouped together to have one covariate score for health.

### 2.4.3 Analyses of sensitive period model

Timing or sensitive period model was assessed in consideration of both early environment and prenatal period to examine their effect on CRP during pregnancy. Partial correlations were run to investigate the association of CRP with E-OSES: BN, E-OSES: PE, E-SSES, C-OSES and C-SSES controlling for covariates of CRP.

### 2.4.4 Effects of subjective SES parameters

In the light of studies suggesting a more robust effect of SSES, I used multiple regression analyses to investigate whether E-SSES and C-SSES are predicting CRP levels controlling for E-OSES: BN and C-OSES, respectively, together with covariates of CRP. All covariates including E-OSES: BN and C-OSES in the corresponding analyses were entered in the first stage of the regression models. The second stage only included E-SSES and C-SSES. Later, each analysis was run again with only significant covariates of CRP found in the first analysis.

### 2.4.5 Analyses of pathway model

In the light of pathway model, Hayes' PROCESS analyses for mediation (Model 4) in SPSS were used to assess potential mediating role of C-OSES on the association between E-OSES: BN and CRP (Figure 2). This analysis was controlled for all significant covariates of CRP. However, here again, if a covariate turned out to be non-significant, I conducted the same analyses with only significant covariates.

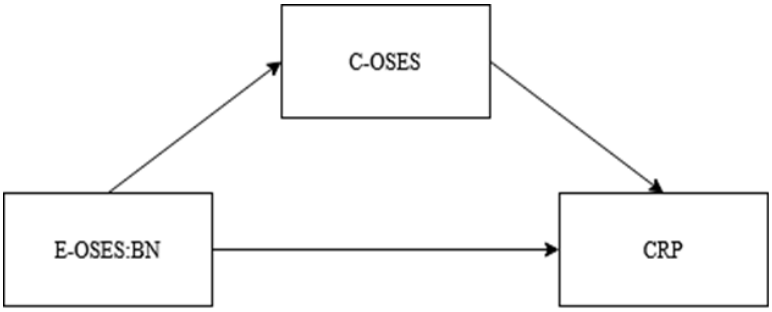


Fig 2. Proposed mediation model for the relationship between E-OSES: BN and CRP partially mediated by C-OSES

# CHAPTER 3

# RESULTS

## 3.1 Descriptive statistics and correlation analyses of SES parameters

As an E-OSES parameter, standardized scores of maternal education was positively correlated with paternal education, $r$ (74) = .61, $p$ < .001, and thus were averaged to calculate E-OSES: PE score for each participant (Table 2). For C-OSES, participants' education level and monthly household income scores were standardized by converting them into z-scores after monthly income scores were log transformed. Standardized scores of educational level scores were positively correlated with log transformed and standardized scores of monthly income, $r$ (72) = .36, $p$ = .002. Therefore, education level and monthly income were averaged to calculate C-OSES. Regarding E-SSES, participants' rankings of MacArthur ladders for their mothers and fathers were averaged after a significant positive correlation was observed, $r$ (73) = .67, $p$ < .001. MacArthur ladder was further used for self-rating of C-SSES. Please see Table 3 for SSES scores.

Table 2. Parental Education

| Education % | Mothers | Fathers |
|---|---|---|
| Less than high school | 51.4 | 33.8 |
| High school | 18.9 | 25.7 |
| Higher education | 29.8 | 40.6 |

Table 3. SSES Scores

| | *M* | *SD* | Range |
|---|---|---|---|
| C-SSES | 6.87 | 1.07 | 4-9 |
| E-SSES: Mother | 5.59 | 2.11 | 1-10 |
| E-SSES: Father | 5.8 | 2.12 | 0-10 |

3.1.1 Covariates for SES parameters: Descriptive statistics and association with SES parameters

Among hypothesized covariates, only age was positively correlated with C-OSES ($r$ (73) = .34, $p$ = .003) and also marginally positively associated with C-SSES ($r$ (68) = .23, $p$ = .062). Hence, age was considered to be a covariate in further analyses of C-OSES and C-SSES. Please see Table 4 for correlations.

In addition to demographic variables, numerous psychosocial measures and health variables were hypothesized as covariates. Please see Table 5 for their descriptive details.

Table 4. Bivariate Correlations Between Demographics and SES variables

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1. C-OSES | - | | | | | | | | |
| 2. C-SSES | .39** | - | | | | | | | |
| 3. E-OSES: PE | .38** | .18 | - | | | | | | |
| 4. E-OSES: BN | .31** | .22 | .49** | - | | | | | |
| 5. E-SSES | .26* | .24 | .50** | .52** | - | | | | |
| 6. Age | .34** | .23 | -.14 | .01 | -.01 | - | | | |
| 7. Gestation week | .07 | .05 | .07 | .06 | .03 | .1 | - | | |
| 8. Current BMI | .01 | .09 | .11 | -.18 | .11 | .1 | .12 | - | |
| 9. Pre-preg BMI | .03 | .11 | .06 | .14 | .11 | -.17 | .05 | .95** | - |

Note: * $p < .05$ and ** $p < .01$.

Table 5. Psychosocial Characteristics of Participants

| | *M* | *SD* | Range |
|---|---|---|---|
| STAI-X State | 31.97 | 8.55 | 20-58 |
| CES-D | 10.96 | 8.21 | 0-33 |
| PSS | 14.42 | 5.92 | 0-30 |
| CTQ | 33.17 | 7.93 | 25-58 |
| PSQI | 4.41 | 2.26 | 1-11 |
| MSPSS | 65.26 | 11.06 | 43-84 |
| LES | 1.34 | 0.89 | 0-3 |
| Current BMI | 24.85 | 3.22 | 19-32 |
| Pre-pregnancy BMI | 22.79 | 3.96 | 17-37 |

Bivariate associations between SES and psychosocial variables were examined. Results revealed a negative association between C-OSES and general state anxiety ($r$ (76) = -.25, $p$ = .03). C-OSES was negatively correlated with scores of childhood trauma ($r$ (75) = -.33, $p$ = .004), suggesting the link between higher childhood trauma and lower C-OSES. Furthermore, C-OSES was marginally negatively associated with depressive symptoms ($r$ (76) = -.19, $p$ = .09) and positively associated with perceived social support ($r$ (75) = .20, $p$ = .08). C-SSES was negatively correlated with general state anxiety ($r$ (71) = -.41, $p$ < .001), depressive symptoms ($r$ (71) = -.33, $p$ = .005) and perceived stress ($r$ (71) = -.32, $p$ = .006). Regarding E-OSES parameters, both E-OSES: PE ($r$ (74) = -.24, $p$ = .03) and E-OSES: BN ($r$ (69) = -.33, $p$ = .005) were negatively linked to childhood trauma scores. Finally, E-SSES scores were negatively associated with general state anxiety during the second trimester (r (73) = -.28, p = .01) and childhood trauma (r (72) = -.54, p < .001). There was also a positive correlation between E-SSES and perceived social support scores (r (72) = .24, p = .03). Lastly, E-SSES scores were negatively associated with recent depressive symptoms at a marginal level (r (73) = -.23, p = .05). Sleep quality as examined by PSQI and intensity of negative life events

experienced during a year prior to pregnancy were not related to SES parameters. Therefore, STAI-X State, CES-D, PSS, CTQ and MSPSS were included as covariates in the future models according to the SES parameter they are associated with. For instance, among these variables, only CTQ was taken as a covariate in E-OSES models. Please see Table 6 for all associations between SES parameters and hypothesized psychosocial covariates.

Table 6. Bivariate Correlations Between Psychosocial Measures and SES Variables

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. C-OSES | - | | | | | | | | | | | |
| 2. C-SSES | .39** | - | | | | | | | | | | |
| 3. E-OSES: PE | .38** | .18 | - | | | | | | | | | |
| 4. E-OSES: BN | .31** | .22 | .50** | - | | | | | | | | |
| 5. E-SSES | .26* | .24 | .50** | .52** | - | | | | | | | |
| 6. STAI-X S | -.25* | -.41** | -.06 | -.005 | -.28* | - | | | | | | |
| 7. CES-D | -.2 | -.33** | -.07 | -.1 | -.23 | .55** | - | | | | | |
| 8. PSS | -.17 | -.32** | .1 | .04 | -.15 | .58** | .68** | - | | | | |
| 9. CTQ | -.33** | -.19 | -.24* | -.33* | -.54** | .43** | .41** | .40** | - | | | |
| 10. PSQI | -.13 | -.12 | -.08 | -.07 | -.06 | .12 | .27* | .26* | -.17 | - | | |
| 11. MSPSS | .2 | .17 | .04 | .06 | .24* | -.24* | -.15 | -.29** | .22 | .18 | - | |
| 12. LES | -.09 | .11 | -.13 | -.01 | -.17 | .04 | .05 | .09 | -.12 | .08 | -.14 | - |

Note: * $p < .05$ and ** $p < .01$.

### 3.1.2 Bivariate associations between SES parameters

In order to assess potential bivariate associations between SES parameters, correlation analyses were run. For each analysis, covariates that were found to be significantly associated with each SES parameter in the analysis were controlled for. The findings are summarized in Table 7 below.

Table 7. Bivariate Correlations Between SES Parameters

| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 1. E-OSES: BN | - | | | | |
| 2. E-OSES: PE | .45** | - | | | |
| 3. C-OSES | .34** | .45** | - | | |
| 4. E-SSES | .50** | .50** | .15 | - | |
| 5. C-SSES | .18 | .20 | .31* | .08 | - |

Note: * $p < .05$ and ** $p < .01$.

## 3.2 Descriptive statistics and correlation analyses of CRP

In consideration of demographics, results revealed that only current ($r\,(73) = .485$, $p < .001$) and pre-pregnancy BMI ($r\,(72) = -.487$, $p < .001$) were associated with CRP (Table 8). However, to avoid multicollinearity, only pre-pregnancy BMI scores were considered to be a covariate in the further analyses.

Table 8. Bivariate Correlations Between Demographics and CRP

| | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 1. CRP | - | | | | |
| 2. Age | -.05 | - | | | |
| 3. Gestation Week | -.05 | .1 | - | | |
| 4. Current BMI | .48** | .1 | .12 | - | |
| 5. Pre-preg BMI | -.48** | -.18 | -.05 | -.95** | - |

Note: * $p < .05$ and ** $p < .01$.

With regard to smoking variables, t-test analyses only differentiate between ever-smokers ($M$ = .63, $SD$ =.34) and non-smokers ($M$ = .46, $SD$ =.29) in terms of CRP levels at a marginal level, ($t$ (43) = -1.74, $p$ = .08). Next, for the alcohol consumption habits, results suggested a marginally significant difference between groups who reported alcohol consumption three months prior to pregnancy ($M$ = .46, $SD$ =.34) and who reported no alcohol consumption ($M$ = .64, $SD$ =.30), ($t$ (43) = 1.89, $p$ = .06). Lastly, with regard to physical exercise, there was a marginally significant negative correlation between exercise frequency three months prior to pregnancy and CRP levels at second trimester ($r$ (45) = -.287, $p$ = .05). Hence, ever-smoking as well as alcohol consumption and exercising habits three months prior to the beginning of pregnancy were taken as a covariate in the future analyses with CRP.

Potential bivariate association between psychosocial measures and CRP were also tested. Results revealed only a marginally significant association between CRP and childhood trauma ($r$ (73) = .20 $p$ = .08). There was no other significant correlation between CRP and other psychosocial measures including general state anxiety, depressive symptoms, perceived stress, sleep quality, perceived social support and intensity of negative life events ($p$s > .1). Please see Table 9 for the summary of correlation analyses.

Table 9. Bivariate Correlations Between Psychosocial Measures and CRP

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| 1. CRP | - | | | | | | | |
| 2. STAI-X S | .05 | - | | | | | | |
| 3. CES-D | .04 | .55** | - | | | | | |
| 4. PSS | .08 | .58** | .68** | - | | | | |
| 5. CTQ | .2 | .43** | .41** | .40** | - | | | |
| 6. PSQI | .19 | .12 | .27* | .26* | -.17 | - | | |
| 7. MSPSS | .03 | -.24* | -.15 | -.29** | .22 | .18 | - | |
| 8. LES | .8 | .04 | .05 | .09 | -.12 | .08 | -.14 | - |

Note: * $p < .05$ and ** $p < .01$.

Regarding chronic disorders and illnesses experienced during the course of pregnancy as well as over a year, a series of t-tests were run to check potential differences between exposed group and non-exposed groups in terms of CRP levels. Results yielded presence of diabetes ($N = 4$) significantly affected CRP levels ($t$ (65) = -3.25, $p = .002$). When the participant with insulin resistance was also added to this group ($N = 5$), the results remained significant ($t$ (65) = -2.09, $p = .04$). Hence, having diabetes or insulin problems were considered as a covariate for the further analyses. Among the sicknesses and disorders, the ones who were found to be marginally associated with CRP were also taken as covariates in the further analyses (i.e. if $p$ value is between .05 and .1). These covariates were having eczema ($t$ (65) = 1.70, $p = .094$), major depression ($t$ (65) = 1.81, $p = .074$), feeling like having a psychological problem ($t$ (65) = 2.02, $p = .048$), vaginal bleeding ($t$ (65) = 1.83, $p = .072$), kidney disorder ($t$ (65) = -1.64, $p = .10$) and rheumatoid arthritis ($t$ (64) = -2.003, $p = .049$). Therefore, these disorders were taken as a covariate in the analyses of CRP.

Potential variation in CRP levels due to medicine usage was also checked by *t*-tests. Use of medicine (i.e. all medicines including vitamins), thyroid drugs, antidepressants, antibiotics, anticoagulants, other medicines (i.e. painkillers, etc.) and overall medicine usage excluding vitamins were examined. There was no effect of medicine usage on CRP levels (all *p*s > .1). Having anaemia, cystitis, asthma, allergy, migraine, anxiety, drug addiction, epilepsy, sexually transmitted disease or allergy were not found to modulate CRP levels as revealed by t-tests (all *p*s > .1). For presence of blood pressure problems (i.e. hypertension or hypotension), chronic disorder, thyroid problems, t-tests did not reveal significant difference between groups with regard to CRP levels (all *p*s > .1).

### 3.3 Analyses of sensitive period model

Bivariate associations between each all SES parameters and CRP level were checked controlling for the covariates that were significantly related to CRP. E-OSES: BN, E-OSES: PE and E-SSES were not correlated with CRP levels (all *p*s > .1). Therefore, these results did not support timing or sensitive period model with regard to the effect of early SES on CRP levels during prenatal period. In consideration of current SES parameters, C-OSES but not C-SSES were positively associated with CRP levels ($r(31) = .37$, $p = .03$). Hence, the findings provided a support for prenatal period as a sensitive period in which SES exerts its effects on CRP. Please see Table 10 for the summary of the statistics.

Table 10. Bivariate Correlations Between SES variables and CRP

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1. C-OSES | - | | | | | |
| 2. C-SSES | .30 | - | | | | |
| 3. E-OSES: PE | .14 | .03 | - | | | |
| 4. E-OSES: BN | .06 | -.04 | .40* | - | | |
| 5. E-SSES | -.24 | -.03 | .56* | .33 | - | |
| 6. CRP | .37* | .3 | .16 | .19 | -.09 | - |

Note: * $p < .05$ and ** $p < .01$.

3.4 Effects of subjective SES parameters

A set of multiple regression analyses was utilized to assess whether E-SSES and C-SSES are predicting CRP levels controlling for E-OSES: BN and COSES, respectively. First, I ran the analysis for E-SSES controlling for E-OSES: BN and the significant covariates of CRP. The covariates of CRP and E-OSES: BN were entered in the first stage of the model. E-SSES did not predict CRP levels ($\beta = -.17$, $t$ (32) = -.96, $p = .34$) controlling for E-OSES: BN and other covariates, although the model was significant ($R^2 = .45$, $F$ (8, 32) = 3.28, $p = .01$). The significant covariates in this model were pre-pregnancy BMI ($\beta = -.39$, $t$ (32) = -2.75, $p = .01$) and ever-smoking ($\beta = .33$, $t$ (32) = 2.32, $p = .03$). Further analysis with only these significant covariates and E-OSES: BN revealed non-significant results again.

Lastly, the relationship between C-SSES and CRP was investigated controlling for C-OSES and the significant covariates of CRP. C-SSES failed to predict CRP ($\beta = .13$, $t$ (31) = .80, $p = .43$) controlling for C-OSES and other covariates in a significant model ($R^2 = .44$, $F$ (8, 31) = 3.02, $p = .01$). However, in the first stage of the model in which the covariates were entered, C-OSES significantly predicted CRP levels ($\beta = .34$, $t$ (32) = 2.20, $p = .03$). In this model, the significant covariates were pre-pregnancy BMI ($\beta = -.34$, $t$ (32) = -2.29, $p = .03$) and ever-smoking ($\beta = .48$, $t$ (32) = 3.10, $p = .004$). The secondary analysis conducted with

these covariates only were non-significant. It should be noted that the same analyses were also repeated after removing participants with extreme CRP levels values (i.e. with disorders, such as diabetes and rheumatoid arthritis). However, the findings were again non-significant.

### 3.5 Analyses of pathway model

For the hypothesized model in which E-OSES: BN might explain CRP through C-OSES, a mediation analysis was conducted. The analysis included all covariates that were found to be significantly related to CRP. The indirect effects were tested by using bootstrapping. Furthermore, with the release of PROCESS 3.4, the mediation model (i.e. Model 4) also allows for the test of a potential interaction between IV and the mediator and their potential effect on DV. Hence, the interaction effect was also investigated.

The relationship between E-OSES: BN and CRP as well as its possible mediation by C-OSES was tested controlling for covariates of CRP. Direct effect of E-OSES: BN on C-OSES was non-significant ($b$ = .16, $t$ (34) = .42, $p$ = .68) in a marginally significant model ($R^2$ = .32, $F$ (7, 34) = 2.32, $p$ = .05). E-OSES: BN did not predict CRP levels controlling for C-OSES ($b$ = .18, $t$ (33) = 1.16, $p$ = .25) and C-OSES only marginally predicted CRP controlling for E-OSES: BN ($b$ = .14, $t$ (33) = 2.03, $p$ = .05) in a significant model ($R^2$ = .50, $F$ (8, 33) = 4.09, $p$ < .001). The test of interaction remained non-significant controlling for the covariates ($F$ (1, 32) = .82, $p$ = .37). The total effect of E-OSES: BN on CRP was found to be non-significant ($b$ = .20, $t$ (34) = 1.25, $p$ = .22) in a significant model ($R^2$ = .44, $F$ (7, 34) = 3.74, $p$ < .001). Furthermore, in this model, only significant covariates were pre-pregnancy BMI ($b$ = -22.9, $t$ (34) = -3.17, $p$ < .001) and ever-smoking ($b$ = .24, $t$ (34) = 2.72, $p$

= .01). Lastly, there was no mediational effect (Figure 3; Indirect = .02, *SE* = .07, 95% CI [-.12, .15]). Additional analysis was run with these covariates only. Results again showed non-significant associations and failed to find a mediational effect (Indirect = .03, *SE* = .06, 95% CI [-.09, .16]). Furthermore, here again, the analyses without the participants with high CRP levels led to non-significant findings.

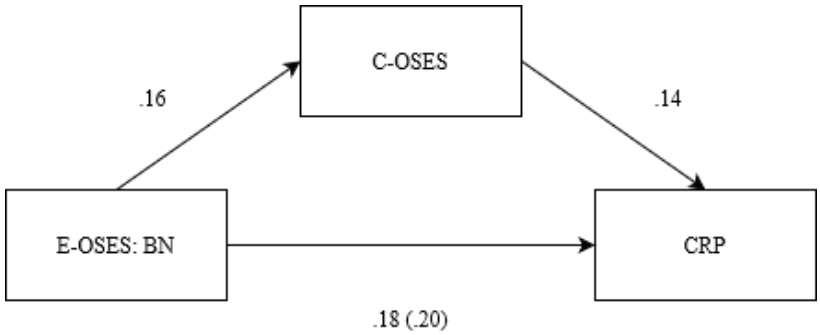


Fig 3. Proposed mediation model for the relationship between E-OSES: BN and CRP partially mediated by C-OSES controlling for covariates of CRP

# CHAPTER 4

# DISCUSSION

## 4.1 Relationship between SES parameters and CRP

The current study sought to provide an in depth investigation of how SES might "get under the skin" by investigating the unique associations between different SES parameters and inflammation (Hertzman, 1999; Kim et al., 2018). There is a paucity of research examining the multifaceted nature of SES and its link to inflammation during the prenatal period. The relationship between SES parameters and CRP especially merits research attention during this critical period due to its potential intergenerational effects. Researchers have put forward several theoretical models to account for impact of timing and/or duration of exposure to low SES on physiological systems (Cohen et al., 2010; Yang et al., 2017). In an attempt to fill the gap in the literature, the current study aimed to test timing or sensitive period model and pathway model in relation to CRP levels at the second trimester of pregnancy. The study also attempted to investigate whether SSES parameters are a better predictor of CRP levels in pregnant women than OSES measures.

In terms of timing or sensitive period model, the current study first tested the effect of early environment as a critical period in which disadvantageous SES may "get under the skin" and influence adulthood physiology. However, E-OSES: BN, E-OSES: PE and E-SSES were not associated with CRP levels. Therefore, these findings opposed the timing or sensitive period model that regard early environment as a critical time frame. In consideration of E-OSES parameters, studies to date have mostly focused on E-OSES: PE and its relationship with inflammatory markers (Matthews et al., 2016; Packard et al., 2011; Taylor et al., 2006). There are only several studies on E-OSES: BN in relation to inflammation, but in the context of IL-6

(Carroll et al., 2011; Lockwood et al., 2018), reporting higher IL-6 levels when exposed to lower E-OSES independent of C-OSES. In this regard, lack of significant association between E-OSES parameters and CRP is not in line with these studies. However, findings in the studies of E-OSES should be interpreted carefully. That is because, research to date on E-OSES mostly differ on type (i.e. use of income, education or occupation) and timing (i.e. the first three years of life, at the age of ten or the first eighteen years of life) of E-OSES. Likewise, whereas some studies assessed E-OSES during several time points, others investigated E-OSES on a single time point. Therefore, the current findings on E-OSES: BN and E-OSES: PE in relation to CRP should be interpreted in this light as well. With regard to the relationship between E-SSES and CRP, the current study is the first to investigate E-SSES in relation to inflammatory status during prenatal period. Studies with non-pregnant samples in the literature point out a negative relationship between E-SSES and inflammatory markers (John-Henderson et al., 2015; 2016). However, here, the findings failed to show an association between E-SSES and CRP at the second trimester of pregnancy. Nevertheless, as the first study in the literature, the results of E-SSES in relation to CRP is unique, and thus it may not be compared with previous studies with non-pregnant adults.

In the current study, prenatal period was also evaluated as a critical time frame for CRP during pregnancy in the light of sensitive period or timing model. Therefore, C-OSES and C-SSES were also assessed in relation to CRP levels. The results indicated that higher C-OSES was linked to elevated CRP levels. This finding is contrary to the findings associating lower C-OSES with increased inflammatory markers (Gruenewald et al., 2009; Owen et al., 2003). Nevertheless, Steptoe, Owen, Kunz-Ebrecht and Mohamed-Ali (2002), for instance, also showed a non-linear

association between C-OSES and inflammatory status as measured by TNF-α, IL-1Ra and IL-6 although they hypothesized to find an inverse association between C-OSES and all inflammatory markers. They used grade of employment as a proxy for C-OSES and investigated its association with the inflammatory markers. Results revealed unique effects associated with each cytokine, suggesting that results from a single inflammatory marker should not be generalized. Thus, the findings in the current study with regard to CRP levels might as well point out a unique mechanism and should be evaluated carefully when comparing it with previous studies. More importantly, they found that, in women but not in men, the individuals with intermediate C-OSES exhibited lowest IL-6 levels compared to participants with low and high C-OSES. For, TNF-α and IL-1Ra, the link was again non-linear; the lowest values were observed in high C-OSES group, yet the intermediate and low C-OSES group did not differ from each other. Their findings of the lowest IL-6 levels being linked to intermediate C-OSES is in line with the findings in the present study as this study also linked increased CRP levels with higher C-OSES. The authors suggested that several explanations may account for their findings. To begin with, they claimed that previous findings in the literature might be due to presence of infectious illnesses in low C-OSES group at subclinical level. Furthermore, their inclusion criteria were strict, and thus their sample was generally healthy, which might also explain lower IL-6 levels compared to other studies (Steptoe et al., 2002). In the present study, the sample also consisted of generally healthy pregnant women with low CRP values. Hence, the explanation provided by the authors may also apply to the present study. Secondly, the authors argued that their sample size was indeed too small to observe grade of employment. Furthermore, the participants in their study were from middle-to-high C-OSES and they failed to include individuals with lowest C-OSES.

Likewise, the current study sample was drawn from the BABIP birth cohort which is the first longitudinal birth cohort study with extensive biological, physiological and psychological measures in Turkey (Duman et al., 2020). Furthermore, the sample consisted of individuals on average with a middle C-OSES background, which is suggesting that the individual with lower C-OSES might not fully represent or include individuals with lowest C-OSES in Turkey. In terms of participants' education level, for example, above 90 percent of women had at least a bachelor's degree in our study. Therefore, as opposed to the studies in the literature, the current analyses might have failed to capture the true continuum from low to high C-OSES and their predictor power on CRP levels. Altogether, the association between C-OSES and CRP revealed and supported prenatal period as a sensitive period during which high C-OSES may pose a risk factor for elevated CRP levels.

In consideration of C-SSES, only a recent study examined the link of C-SSES, in addition to C-OSES, to inflammatory markers during pregnancy (Scholaske et al., 2020). The results in the present study are in opposition to their findings. Their results linked lower C-SSES, rather than C-OSES, to increased inflammatory state. However, in the current study C-OSES but not C-SSES was associated with CRP. Here again, the explanation for the results regarding C-OSES and the ones offered by Steptoe et al. (2002) might also apply to C-SSES. That is, in consideration of the SES background of the participants in the current study, the continuum of C-SSES scores in our sample is also reflecting perception of individuals with middle-to-high C-OSES. Therefore, C-SSES scores might as well have failed to capture lower C-SSES levels - perhaps of individuals with lowest C-OSES. In contrast to Scholaske et al. (2020), this failure to capture lower C-SSES levels might have contributed to the non-significant results in the present study. Furthermore, it is also important to note

that Scholaske et al. (2020) utilized a composite score of IL-6, CRP and TNF-α. However, the current study only adopted CRP as a measure of inflammation. Discrepancy between the findings of C-SSES in the present study and that in Scholaske et al. (2020) might be also due to the type of MacArthur Scale of Subjective Social Status used. Whereas the nation version was used in the present study, Scholaske et al. (2020) utilized both nation and community version of the ladder. They concluded that community version is a stronger predictor of inflammatory status compared to nation version. Altogether these differences suggest that the C-SSES findings in the present study might have benefited from inclusion of participants with lower C-OSES background, adoption of several other inflammatory markers and utilization of community version of the ladder in addition to nation version.

Having attempted to investigate whether SSES parameters predicts CRP levels controlling for OSES parameters, the present study is to first to investigate E-SSES and C-SSES in relation to E-OSES: BN and C-OSES in pregnancy, respectively. The findings revealed that neither E-SSES nor C-SSES predicted CRP controlling for corresponding OSES parameters. These results are in contrast with previous findings suggesting SSES parameters as a better predictor of health than OSES parameters. More studies are definitely needed to investigate these associations in pregnant women in Turkey. The analysis of current SES parameters also supported previous findings of C-OSES in relation to CRP in the present study. Here again, higher C-OSES predicted elevated CRP levels at the first stage of regression model when entered with other covariates. Thus, the results, here, also showed prenatal period as critical time frame for adulthood physiology.

The present study also tested pathway model to assess whether the association between E-OSES: BN and CRP might be through C-OSES. Results did not reveal a mediational effect. Furthermore, the positive association between C-OSES and CRP was only at the marginal significance level controlling for E-OSES: BN and covariates of CRP. On the one hand, these results failed to provide a support for pathway model as the paths from E-OSES: BN to C-OSES and to CRP were non-significant. Also, the path from C-OSES to CRP was only marginally significant. On the other hand, the previous analyses in the current study established the association between higher C-OSES and increased levels of CRP. However, the strength of this association was reduced to a marginal significant value when controlled for E-OSES: BN in the pathway model. Therefore, although the pathway model did not find a support, the results of this model highlights multifaceted nature of SES parameters in predicting CRP levels. The results also suggest that studies should consider several SES parameters in relation to CRP to examine underlying mechanism.

## 4.2 Strengths and limitations

As the first longitudinal birth cohort in Turkey (Duman et al., 2020), this study is the first to establish the unique associations between SES parameters and inflammatory status as measured by CRP levels in pregnant women in Turkey. Hence, the findings are of the utmost importance in deciphering adverse effects of both early and current SES background on physiology, here inflammatory profile, of pregnant women in Turkey. Furthermore, as stated earlier, this study is the first to investigate the role of E-SSES on CRP levels during prenatal period along with its relationship to other SES parameters. Therefore, it fills the gap in the literature and the findings set an important ground for comparison with other international birth cohorts.

The current study has several methodological strengths. First of all, the participant pool consisted of pregnant women with lower incidence of poor health, medication use and psychological disorder history. Therefore, investigation of the relationship between SES parameters and CRP levels benefitted from absence of such confounding factors. Similarly, participants mostly did not have any pregnancy complication. Furthermore, all participants were married; hence, calculation of monthly household income did not need any adjustment. Likewise, the participants' parents were mostly not separated from age 0 to 18. Thus, calculation of E-OSSES and E-SSES was not influenced by any potential bias due to separation from a parent or recalling bias that might stem from poor memory of a parent. In addition, all participants live in Istanbul, Turkey; therefore, it minimizes any potentially confounding factor that might stem from differential levels of opportunities and challenges presented in different cities in Turkey. Lastly, all participants were from Turkey, which reduces the risk of any potential modulation of the association between SES parameters and CRP by race (Lam, Chiang, Chen, & Miller, 2021).

In addition to strengths, the current study also has drawbacks. First, as stated earlier, C-OSES level of the participant pool mostly represented a continuum from middle-to-high SES. Therefore, the pregnant women in the current study reflects a narrow population living in Istanbul. Thus, in order to represent a full spectrum of pregnant women in Turkey, there is a need for recruiting participants from lower SES background. Then, with the inclusion of individuals with lower C-OSES, the direction of the association between C-OSES and CRP would be tested again. Furthermore, the current study only utilized CRP as a proxy for inflammatory status. However, adoption of several other inflammatory markers, such as IL-6 and TNF-α, and assessing their unique effects in addition to their composite effect would be more

informative. In addition, it would make the comparison with other international birth cohorts easier.

An important point to consider is retrospective nature of SES parameters used in the current study. First, retrospective recalling of early environment is always open to recall bias. For instance, participants with higher depressive symptoms might be more likely to perceive their early environment badly. Although we examined and controlled for depressive symptoms, it might not be enough. In this regard, for instance, Baldwin, Reuben, Newbury, and Danese (2019) showed the discrepancy between retrospective and prospective measures in measuring childhood maltreatment. They suggested that retrospective and prospective measures should be treated separately when investigating its link to health and disease. Furthermore, as mentioned earlier, a recent meta-analysis (Milaniak & Jaffee, 2019) revealed that although low E-OSES pose a risk factor for increased inflammatory status in adulthood controlling for C-OSES, longitudinal studies with prospective measures failed to find such association. Although the current study utilized retrospective measures of E-OSES: BN and E-SSES, these measures were not linked to CRP. As it is a birth cohort study, it would be also impossible to measure E-SES measures prospectively. However, in the current study, all early SES parameters (i.e. E-OSES: BN, E-OSES: PE and E-SSES) were associated with CTQ. This, in turn, provides strong evidence for the strength of the early SES parameters in reflecting early life adversity in the present study. Therefore, the lack of significant findings with regard to early SES parameters is not due to the power of early SES parameters utilized. Future studies may benefit from considering minimal age at exposure to low E-OSES. In this regard, for instance, Raymond et al. (2021) revealed that exposure to early adversity for the first time between 3 and 7 years of age predicted decreased

cortisol reactivity and increased cortisol awakening response in comparison to participants who were exposed to early life adversity for the first time before 3 or after 7 years of age. Similarly, future studies may examine specific timing of low E-OSES exposure in relation to CRP. For example, parental job loss, overcrowding at home or moving to a low SES area during a specific time period in early life might be interesting topics of investigation.

Given the strengths and limitations of the current study as well as findings in the literature, future studies might benefit from inclusion of several other factors. For instance, in addition to immune system, HPA-axis reactivity is known to be influenced by SES parameters during prenatal period (Bosquet Enlow et al., 2019). Moreover, studies in the literature mostly either focus on HPA-axis or inflammatory markers. However, investigating their separate and combined effects in the same study sample would be more informative about the MPF biology and its modulation by SES parameters. In addition, future studies should also adopt neuroimaging methods to examine potential neural changes or brain region specific alterations in relation to SES parameters. For example, Gianaros et al. (2007) showed that participants with low C-SSES have a reduced gray matter volume in the perigenual area of the anterior cingulate cortex, which contributes in to the regulation of emotional states and reactivity to stress. Similary, Gianaros et al. (2008) documented that E-SSES during childhood and adolescence was associated with amygdala reactivity in response to angry faces, controlling for their C-SSES, suggesting neurodevelopmental pathways underlying disadvantaged SES and emotional reactivity. Thus, here again, combination of neuroimaging data with inflammatory measures would provide a huge insight into the mechanism by which SES parameters might lead to psychological disorders in offspring. That is because,

researchers posit that there is a crosstalk between inflammatory system and neural circuits controlling processes linked to threat, reward and executive control. Furthermore, dysfunction in these systems due to adversity, especially early in life, might increase vulnerability to psychosocial disorders related to threat, reward and executive control (Nusslock & Miller, 2016).

Lastly, with regard to the birth outcomes and offspring's psychosocial development and health, BABIP study is in the process of collecting such measures. Thus, in near future, it will be possible to investigate the current variables of interest in relation to birth and developmental outcomes. As a result, particularly, prevention and intervention methods might be developed. Vulnerability of those with high C-OSES to elevated levels of CRP merits research attention. It could be that achieving higher C-OSES might be related to a stressful work-life, a sedentary life-style and less time spent with family, friends and relatives. Therefore, it might lead to increased inflammatory status during prenatal period. In this regard, specific intervention methods, such as encouraging work-life balance, might be a solution.

APPENDIX A

NATION VERSION OF THE MACARTHUR SCALE OF SUBJECTIVE SOCIAL STATUS (ENGLISH)

**Think of this ladder as representing where people stand in the United States.** At the top of the ladder are the people who have the most money, most education, and most respected jobs. At the bottom are the people who have the least money, least education, and least respected jobs or no job. The higher up you are on this ladder, the closer you are to the people at the very top, and the lower you are, the closer you are to the people at the very bottom.

**Where would you place yourself on this ladder?** Please, place an **"X"** on the rung where you think you stand at this time in your life, relative to other people in the United States.

APPENDIX B

NATION VERSION OF THE MACARTHUR SCALE OF SUBJECTIVE SOCIAL STATUS (TURKISH)

**Sağ taraftaki merdivenin, insanların Türkiye'de nerede durduklarını temsil ettiğini düşününüz.**


**Merdivenin tepesinde** en fazla paraya, yüksek eğitim seviyesine ve saygın işlere sahip insanlar bulunmaktadır.

**Merdivenin en altında** ise en az paraya, eğitim seviyesine ve en az saygı duyulan işe sahip olan veya hiç işe sahip olmayan insanlar bulunmaktadır. Bu merdivende ne kadar yüksekte olursanız, en üstteki insanlara o kadar yakınsınız demektir. Aynı şekilde, ne kadar aşağıda olursanız, en alttaki insanlara o kadar yakınsınız demektir.

**Bu merdivende kendinizi (*ailenizle birlikte düşünürseniz*) Türkiye'deki diğer insanlara kıyasla nereye yerleştirirsiniz?** Lütfen, şu anki yaşamınızı göz önünde bulundurarak, durduğunuzu düşündüğünüz **basamağa çarpı "X" koyunuz.**

# APPENDIX C

# ETHICS COMMITTEE APPROVAL

**T.C. BOĞAZİÇİ ÜNİVERSİTESİ**
**İnsan Araştırmaları Kurumsal Değerlendirme Kurulu (İNAREK)**

06.02.2018

Yrd. Doç. Dr. Elif Ayşimi Duman
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Sayın Araştırmacı,

"Türkiye Anne-Bebek İlişkisi Çalışması" başlıklı projeniz ile yaptığınız Boğaziçi Üniversitesi İnsan Araştırmaları Kurumsal Değerlendirme Kurulu (İNAREK) 2018/02 kayıt numaralı başvuru 06.02.2018 tarihli ve 2018/1 sayılı kurul toplantısında incelenerek etik onay verilmesi uygun bulunmuştur.

Saygılarımızla,

Doç. Dr. Arzu Çelik Fuss (Başkan)
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