THE RELATIONSHIPS BETWEEN PREGNANCY-RELATED WORRIES, CHILDHOOD MALTREATMENT HISTORY AND HPA-AXIS ACTIVITY IN PREGNANT WOMEN

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DECLARATION OF ORIGINALITY

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ABSTRACT

The Relationships Between Pregnancy-Related Worries, Childhood Maltreatment History and HPA-Axis Activity in Pregnant Women

Childhood maltreatment (CM) influences prenatal stress reactivity, such as the Hypothalamic-Pituitary-Adrenal (HPA)-axis, and maternal mood with other prenatal factors. Specifically, pregnancy-related worries (PRW) alter maternal mood and suggested be better predictors of maternal distress than general state anxiety (GSA). Present study investigates how CM is related to prenatal HPA-axis activity and whether this relationship is influenced by PRW. It is hypothesized that CM would predict prenatal HPA-axis activity through mediation by PRW, where CM increases PRW which alters HPA-axis; if not, PRW would moderate that relationship where CM predicts HPA-axis in relation to PRW. Participants were 77 pregnant women in their second-trimester (M = 31.80, (SD = 3.72) participating in the BABIP birth cohort from Istanbul, Turkey. CM, PRW, and GSA were assessed by Childhood Trauma Questionnaire, Cambridge Worry Scale, and State Anxiety Inventory-State Form, respectively. HPA-axis activity was measured from saliva as awakening cortisol, cortisol awakening response (CAR), and diurnal slope of cortisol (DS) across two days. Results showed that PRW did not mediate, but moderated the relationship between CM and HPA-axis. CM was associated with lower awakening cortisol, heightened CAR, and blunted DS in women with high PRW compared to women with low PRW. Unlike PRW, GSA did not moderate this relationship. These findings suggest PRW may have a more prominent role than GSA in exacerbating the impact of CM on prenatal HPA-axis. Future studies may focus on developing prevention and intervention programs towards PRW, particularly in at-risk groups like women with CM history to support maternal and infant health.

ÖZET

Hamile Kadınlarda Gebelikle İlgili Endişeler, Çocukluk İstismarı Geçmişi ve HPA-Eksen Aktivitesi Arasındaki İlişkiler

Çocukluk istismarı (Çİ) diğer prenatal faktörlerle birlikte prenatal stres reaktivitesini, Hipotalamik-Hipofiz-Adrenal (HPA)- eksen gibi sistemleri etkilediği bilinmektedir. Bu bağlamda, gebeliğe ilişkin endişelerin (GİE), genel durumluk kaygıya (GDK) göre anne sıkıntılarını daha iyi açıklayabileceği ileri sürülmektedir. Bu çalışma Çİ'nin doğum öncesi HPA-ekseni doğum öncesi HPA-ekseni aktivasyonuyla nasıl ilişkili olduğunu ve bu ilişkinin GİE'den etkilenip etkilenmediğini araştırmaktadır. Çİ'nin GİE'nin aracılığı ile doğum öncesi HPA-ekseni aktivitesini etkileyeceği, artan Çİ'nin artan GİE'yi tahmin edeceği varsayılmaktadır. Çİ, GİE'yi yordamadığı taktirde Çİ ve HPA-ekseni ilişkisi üzerinde GİE'nin düzenleyici bir etkisi olacağı varsayılmaktadır. Çalışmaya BABIP kohortundan ikinci trimesterinde olan (M = 31.80, SD = 3.72) 77 hamile kadın katıldı. Çİ, GİE ve GDK sırasıyla Çocukluk Çağı Travma Anketi, Cambdrige Endişe Ölçeği ve Durumluk-Sürekli Kaygı Envanteri-Durum Formu ile değerlendirildi. HPA-ekseni aktivasyonu tükürükten uyanma kortizolü, uyanıştaki kortizol tepkisi (UKT) ve günlük kortizol eğrisi (GKE) olarak iki gün boyunca ölçüldü. Sonuçlar GİE'nin Çİ ve HPA-ekseni aktivitesi arasındaki ilişkide aracılık etmediği, ancak düzenleyici bir etkiye sahip olduğunu gösterdi. Çİ, GİE'si yüksek olan kadınlarda düşük GİE'li kadınlara kıyasla daha düşük uyanma kortizolü, yüksek UKT ve daha az dik GKE ile ilişkili olduğu bulundu. GİE ile gözlenen bu düzenleyici etki, GDK ile gözlemlenmemiştir. Bu bulgular, GİE'nin Çİ ve prenatal HPA ekseni aktivitesi ilişkisi üzerindeki etkisinin GDK'dan daha belirgin bir rolü olabileceğini düşündürmektedir. Gelecekteki çalışmalar, özellikle anne ve bebek sağlığını desteklemek için Çİ tarihçesi olan risk altındaki gruplarda hamilelik sırasında görülen GİE'yi önleme ve müdahale programları geliştirmeye odaklanabilir.

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To a former geologist, Atife

and

a future astronaut, Arya...

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ABBREVIATIONS

11β-HSD2	11β-Hydroxysteroid Dehydrogenase Type 2
BDI	Beck Depression Inventory
BMI	Body Mass Index
CAR	Cortisol Awakening Response
CM	Childhood Maltreatment
CRH	Corticotrophin Releasing Hormone
CTQ	Childhood Trauma Questionnaire
CWS	Cambridge Worry Scale
DS	Diurnal Slope of Cortisol
HPA	Hypothalamic–Pituitary–Adrenal
MPF	Maternal-Placental-Fetal
MSPSS	Multidimensional Scale of Perceived Social Support
PRW	Pregnancy-Related Worries
PVN	Paraventricular Nucleus
SPSS	Statistical Package for the Social Sciences
STAI-X	State-Trait Anxiety Inventory X Trait
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

Childhood maltreatment (CM) is commonly defined as childhood exposure to stressors, such as abuse, neglect, and other traumatic experiences that result in actual or potential damage to one's mental and physical development (Carr, Martins, Stingel, Lemgruber, & Juruena, 2013). is generally categorized as abuse (sexual, physical, emotional) or neglect (physical, emotional) and different types are suggested to have different effects on mental and physical health (Carr et al., 2013; Norman et al., 2012; Van den Bergh et al., 2017). There exists a considerable body of literature on the influence of CM across the life span. It is a well-established risk factor for adulthood mental health problems and linked to various psychopathologies including drug abuse, suicide, risky sexual behavior, and depression (Heim & Binder, 2012; Heim, Entringer, & Buss, 2019; Norman et al., 2012; Spertus, Yehuda, Wong, Halligan, & Seremetis, 2003). It is suggested that CM is associated with these lifelong health problems by impairing the fundamental stress-related systems in the body, such as the Hypothalamic-Pituitary-Adrenal (HPA)-axis (Heim et al., 2019). Despite its well-established detrimental and long-term effects, CM, unfortunately, is quite common, with a global prevalence of 36% for emotional abuse, 23% for physical abuse, and 16% for neglect (WHO report, Butchart & Mikton, 2014). It is even more dramatic for women, with 30-40% of them reporting a history of at least one early life stressor (Buss et al., 2017). In the context of Turkey, lifetime prevalence of CM is above global averages, with 33% of children being affected by CM, especially with physical (43%) and emotional (51%) abuse (UNICEF Report, 2010), making it even more critical to understand its impact in Turkey.

Previous research suggests that this early life exposure starts even before childhood, with a more prominent impact of stressors during the perinatal period (Lupien, McEwen, Gunnar, & Heim, 2009), leading to long-term effects on the development and health of the offspring (Plant, Jones, Pariante, & Pawlby, 2017). Furthermore, long-term detrimental effects of CM on health is also documented for

women during the perinatal period, such as increased maternal anxiety and depressive symptoms and disorders (Biaggi, Conroy, Pawlby, & Pariante, 2016; Choi & Sikkema, 2016; Lang, Rodgers, & Lebeck, 2006), as well as reported worries during pregnancy (Chamberlain et al., 2019). Therefore, CM is a risk factor for both the mother and the offspring during pregnancy and may have persisting intergenerational effects. In order to break this intergenerational transmission of risk, it is crucial to identify prenatal factors that may influence the impact of CM on the mother and the offspring (Sawyer, Zunszain, Dazzan, & Pariante, 2018). Recent studies suggest that this intergenerational effect of CM may occur via changes in maternal endophenotypes (Sawyer et al., 2018) such as the stress responses (Drake, Tang, & Nyirenda, 2007) and immune markers (Miller, Chen, & Parker, 2011), psychosocial factors (Gluckman, Hanson, Cooper, & Thornburg, 2008) and epigenetic mechanisms (Oberlander et al., 2010). Following this framework, this study investigates whether CM is associated with changes in the endophenotype of HPA-axis activity during pregnancy and whether this change is mediated by maternal pregnancy-related worries.

1.1 Significance of childhood maltreatment on prenatal health

From Barker's "fetal origins" hypothesis to the "Developmental Origins of Health and Disease" (DOHaD) perspective (Heindel et al., 2016), researchers emphasized the developmental origins of various diseases by examining the associations between maternal prenatal factors and offspring health and development (Wadhwa, Buss, Entringer, & Swanson, 2009). It is suggested that due to the high plasticity of the offspring brain (Entringer, Buss, & Wadhwa, 2015), development is profoundly open to transformations during pregnancy and is primarily dependent on the intrauterine conditions (Buss, Entringer, & Wadhwa, 2012; Entringer et al., 2012; O'Donnell & Glover, 2015). In the context of maternal CM, it was previously linked to pregnancy complications (Leeners, Richter-appelt, Imthurn, & Rath, 2006), altered brain development (Wadhwa, Entringer, Buss, & Lu, 2011) and increased risk of

psychopathologies for the offspring (Plant, et al., 2017). It is suggested that CM may alter these risks through changes in the maternal-placental-fetal (MPF) biology, mainly in the stress, immune and metabolic systems during pregnancy (Sawyer et al., 2018; Entringer, Buss, & Wadhwa, 2010; Wadhwa et al., 2011). So far, various studies associated maternal differential stress response by increased vulnerability towards pregnancy complications, such as preterm birth (Buss et al., 2009). These studies underline the importance of fetal programming by MPF biology, emphasizing the significance of maternal environment and physiology on the offspring.

Several perspectives are proposed on the impact of maternal CM on maternal prenatal mood and mental health, such as anxiety, aggression, and depression. First of all, pregnancy itself is a set of major alterations, from psychosocial to biological changes (Buss et al., 2017; Choi & Sikkema, 2016), including hormonal, sensory, weight gain, among others. Since pregnancy consists of these immense and numerous changes (Lang, Rodgers, & Lebeck, 2006), it has been stated that the influence of CM could be more severe on pregnant women's mental health due to the rapid physiological and emotional changes women experience. In other words, during pregnancy, women who have a CM could suffer more about these pregnancy-related changes and perceive them to be more difficult than those without CM (Lang et al., 2006). It is also suggested that the transition to motherhood triggers the retrieval of childhood traumatic memories (Choi & Sikkema, 2016; Lang et al., 2006), creating a more vulnerable state of mind. Therefore, becoming a mother may trigger responses that are associated with her own childhood experiences and affect mental health (Choi & Sikkema, 2016). This effect could be visible not only in the mood itself but also on worries and concerns about pregnancy and becoming a parent (Chamberlain et al., 2019), where pregnant sexual abuse victims in particular reporting concerns about their children, indicating a link between CM and PRW. Overall, pregnancy and the changes in this period may be harder for women who experienced CM, it can also alter their mental state, trigger traumatic memories; hence, affect their mental health. Another proposed view is the impact of CM on perceived social support. In light of

the previous studies, it has been shown that those with CM may exhibit mistrust, feelings of unsafety (Lang et al., 2006), and vigilance for threat and aggression towards others that in return leads to poorer social relationships and less social support (Miller, Chen, & Parker, 2011), affecting health in various ways. Additionally, mothers who had CM also reported weaker social networks, less contact with friends, and lower perceived support (Bishop & Leadbeater, 1999), which are linked with physiological stress response in non-pregnant cohorts (Heaney, Phillips, & Carroll, 2010). Another possible mechanism on the heightened effects of CM during pregnancy may be through altering parenting style and attachment with the baby (Sawyer et al., 2018) that again influence the social environment of the mother and her offspring.

Considering these views, it can be deduced that maternal CM changes the maternal mood in a way that women exhibit higher worries and concerns about their pregnancy, their unborn child and their perceived social support, making it harder for them to overcome these challenges. These psychosocial factors may influence changes in MPF biology, such as in the HPA-axis stress response.

1.2 Childhood maltreatment and HPA-axis activity

One of the candidate systems that is affected by CM is the stress response system of the HPA-axis (Entringer, Buss, & Wadhwa, 2010). This neuroendocrine system is triggered in the presence of a stressor, leading to activation of the paraventricular nucleus (PVN) of the hypothalamus that secretes corticotrophin-releasing hormone (CRH) to stimulate the anterior pituitary to produce and release adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH then binds to the adrenal glands and from the adrenal cortex, glucocorticoids, mainly cortisol in humans are produced. The system is then shut down again by cortisol binding to its receptors and initiate a negative feedback loop. Cortisol is a very ubiquitous steroid hormone that is known to influence the various parts of the body in numerous pathways (Drake, Tang, & Nyirenda, 2007), including stress response, inflammation, and, sugar, fat, and salt

metabolisms. In humans, cortisol follows a diurnal rhythm, with a sharp peak shortly after awakening in the morning (i.e., Cortisol Awakening Response; CAR), followed by a gradual decrease towards the evening. This sharp increase usually occurs in the window between 15-45 minutes after awakening (Chida & Steptoe, 2009), and is typically observed around 30 minutes after awakening (Clow, Hucklebridge, & Thorn, 2010). The change from the morning to evening leads to a diurnal slope of cortisol (DS), which is defined as the change of cortisol across the day from awakening to evening (Ross, Murphy, Adam, Chen, & Miller, 2014). These different cortisol markers have been widely used to assess HPA-axis activity to detect possible dysregulations via biopsychosocial factors.

During the course of pregnancy, the release of the HPA-axis hormones are known to change immensely (Mastorakos & Ilias, 2003). For instance, starting the end of the first trimester, cortisol production proliferates (Sandman et al., 2006). In general, there is a 2 to 4 fold increase in the total maternal cortisol levels with increasing gestational age (De Weerth & Buitelaar, 2005). These changes in HPA-axis are mainly due to the doubled size of the pituitary gland and the growth of the placenta as an important endocrine gland (Davis & Sandman, 2012). Besides, this observed hypercortisolism is much higher towards the end of pregnancy due to the placental CRH (pCRH) production (Soma-Pillay et al., 2016). Another critical factor is a placental enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which oxidizes and inactivates the cortisol (Davis & Sandman, 2012), and thus, partially protects the fetus from increasing levels of maternal cortisol (De Weerth & Buitelaar, 2005) that may otherwise have adverse birth and fetal outcomes (Field et al., 2006; Kivlighan et al., 2008). Notably, although there are significant physiological changes and factors that influence HPA-axis during pregnancy, the diurnal rhythm of cortisol is still kept intact during the pregnancy (De Weerth & Buitelaar, 2005). This makes them suitable parameters of HPA-axis activity during pregnancy to be investigated in relation to maternal factors like CM.

In terms of CM and HPA-axis activity, the literature presents conflicting findings. As discussed in a recent review that focused on adulthood sample studies, concluded that CM has been associated with both hyper- and hypo-activity of the HPA-axis (Ceruso & Araminta, 2020). One line of research hypothesized that CM is positively correlated with HPA-axis activity and leads to a greater sensitivity of HPA-axis activity towards stressors in adulthood, hence a hypercortisolism is observed (Heim et al., 2000). For instance, CM has been associated with higher cortisol reactivity to an acute lab stressor compared to those without CM and this effect was even more prominent in depressed women with CM (Heim et al., 2000). CM was also associated with heightened diurnal cortisol levels in women with chronic pain compared to women without CM (Nicolson, Davis, Kruszeski, & Zautra, 2010) and enhanced CAR was observed in participants with CM compared to non-CM subjects, regardless of their depression status (Lu, Gao, Huang, Li & Xu, 2016). On the other hand, there are also studies indicating that CM could be associated with hypoactivity of the HPA-axis as well (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008) such that in a recent review lower awakening cortisol was associated with agency-referred CM instead of self-reports (Bernard, Frost, Bennet, & Lindhiem, 2017). Earlier studies showed that depressed women with an abuse history had lower baseline and stimulated cortisol compared to healthy subjects (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001) and enhanced suppression of cortisol response to dexamethasone suppression test was observed in sexually abused participants compared to the non-victimized women (Stein, Yehuda, Koverola, & Hanna, 1997). Recent studies also showed that CM is associated with both low daily saliva cortisol and hair cortisol (Hinkelmann et al., 2013) compared to people without CM.

As can be deduced, some studies associated CM with hypo- and some with hypercortisolism, which could be due to differential effects of CM both directly and indirectly. One of the main reasons for these different outcomes is that the influence of CM on the body includes various levels of changes including endocrine, immune

systems, and brain networks (Buss et al., 2017). These different systems that are affected by CM also influence each other (Gonzalez, 2013; Pariante, 2017); thus, these complex interactions could contribute to these conflicting findings. Other factors such as age, gender, and mood could also responsible for these contradictory results. Moreover, studies differ in their CM assessments in which many studies utilize different types of CM. For example, physical abuse and sexual abuse histories has been linked to flattened diurnal cortisol rhythms and elevated CAR in patients with fibromyalgia syndrome compared to patients without a trauma (Weissbecker, Floyd, Dedert, Salmon, & Sephton, 2006). Yet, a later children study showed that morning cortisol levels differ according to the different maltreatment (Bruce, Fisher, Pears, & Levine, 2009), underlining the varying nature of the adversity type. Additionally, how HPA-axis activity measures were collected is critical in this field. In other words, studies utilize different sampling methods than saliva such as plasma cortisol, hair cortisol and also different measuring paradigms such as acute stressors, awakening, daily output could yield varying results. As can be seen from the aforementioned studies, not all HPA-axis measures are correlated with each other and they may fed from other pathways. Therefore, utilizing varying measurement and assessment types could also feed the differences observed in the literature. Thus, these variables should be controlled and mentioned in studies focused on CM and HPA-axis measures.

1.3 CM and HPA-axis relationship in pregnancy cohorts

As mentioned above, CM has a high influence on health, especially during pregnancy, suggesting it would be also affecting HPA-axis activity in pregnant women. There is relatively a small number of studies focusing on CM and maternal HPA-axis activity, and most of them focusing particularly on sexual abuse. Yet still, the relationship between CM and different HPA-axis activity parameters and the mediators and moderators of this relationship is largely unknown (Swales et al., 2018).

One of the study is associated experiencing CM with lower morning saliva cortisol (Shea et al., 2007) where they recruited pregnant women at 28 weeks gestation and focused on sexual abuse. On the other hand, sexual abuse was associated with higher morning and evening saliva cortisol in advancing gestation following a stressful day (Bublitz & Stroud, 2013), when compared to women with non-sexual abuse or no abuse history. In their study, Bublitz &Stroud (2013) included the effect of current life stressors on their model which was moderating the relationship between sexual abuse and HPA-axis activity. Importantly, this study somehow underlines the importance of recent stressors on the CM and HPA-axis relationship, as a significant moderator in that relationship as well. Not only awakening cortisol, but sexually abused pregnant women also found to have different CAR (Bublitz & Stroud, 2012) over the 2nd and 3rd trimester, specifically at late pregnancy (35 week of gestation). They showed that women with child sexual abuse histories displayed increasing CAR at late pregnancy, compared to women with non-sexual child abuse histories or women who had never experienced abuse (Bublitz & Stroud, 2012). In a later study, they found that this pattern remained similar only if the women was perceiving poor family functioning (Bublitz, Parade, & Stroud, 2014), reporting family functioning as a significant moderator. Interestingly, Shea et al. (2007) found no associations between sexual abuse and CAR in their study. To wrap up, these two groups underline that in pregnant women, without the current adversities, CM is correlated mainly with lower morning cortisol and increased CAR (Thomas et al., 2018). There are several points to discuss here: first, vast majority of the studies focused on the sexual abuse in pregnancy cohort, second, these studies accentuate that not only the abuse type but how it has been compared and utilized could also alter findings, and third, there could be moderating factors between CM and HPA-axis relationship.

Not only studies focused on saliva cortisol, but other measurement methods were also utilized in pregnancy cohorts. A recent study found higher hair cortisol concentrations were associated with more traumatic events only in the CM group

where they focused on pregnant women at approximately 28 gestations weeks (Swales et al., 2018). Similarly, elevated hair cortisol was found in pregnant women with CM history around the 27th gestation week (Schreier, Enlow, Ritz, Gennings, & Wright, 2015). Furthermore, CM has been linked with an increase in placental CRH (pCRH) production (Moog et al., 2015), which underlines a different level in the HPA-activity. In addition, studies focused on the period after pregnancy could be also beneficial to understand how maternal HPA-axis is affected by CM. In postpartum studies, it has been shown that CM was linked with a steeper decline in cortisol in response to stress (Brand et al., 2010), higher CAR, and elevated morning cortisol levels (Gonzalez, Jenkins, Steiner, & Fleming, 2009), compared no or low abused groups. Overall, these findings may indicate a hypercortisolism in certain HPA-axis measures, such as increased CAR, flattened diurnal slope from studies utilizing saliva samples, and elevated hair cortisol, in pregnant women who have a history of CM (Thomas et al., 2018). It has been argued that early adversities like CM may lead to an augmented sensitivity of the HPA-axis towards later stressors and lead to this hypercortisolism observed in the adulthood (Thomas et al., 2018).

Although few studies examined the influence of CM with various HPA-measures, similar to the non-pregnant cohorts, pregnancy studies also exhibit contradictory findings and require further examination. As discussed above, there could be the effect of other systems such as immune or endocrine which leads to differential effects of CM on various HPA-axis measures. Moreover, age, gestation week, CM type, and methodological differences could contribute to these different results (Bernard et al., 2017). These underline the importance of studying various HPA-axis measures in one study to see the real effect of CM. By studying morning cortisol and CAR as well as diurnal cortisol levels could give a better understanding of the mechanism behind CM and other factors on HPA-axis activity.

1.4 Significance of prenatal timing on CM and HPA-axis relationship

During pregnancy, women's body greatly changes accordingly with advancing gestation that makes timing important in prenatal studies. Since HPA-axis activity also changes during the course of pregnancy, a recent review stated that trimesters are also informative about the effects of CM and HPA-axis during pregnancy (Van den Bergh et al., 2017). Various studies conducted at different times during the pregnancy suggest that the impact of CM on HPA-axis may be observed differently throughout the pregnancy. Studies focusing on late pregnancy found CM is associated with lower awakening cortisol (Shea et al., 2007), yet studies focusing on mid-late pregnancy found increased morning cortisol and elevated CAR across pregnancy (Bublitz & Stroud, 2012; 2013). In terms of neonatal adverse outcomes, the vast majority of the literature focused on the late pregnancy adversities (Hamada & Matthews, 2019; Kivlighan et al., 2008; Oberlander et al., 2010) such that they have found maternal distress is associated with preterm birth when assessed as higher pCRH concentrations (Wadhwa, 2005) and higher maternal cortisol (Giurgescu, 2009). However, other studies showed that maternal factors in the mid-pregnancy are also linked to maternal HPA-axis and infant outcomes (Baibazarova et al., 2013; Guendelman, Kosa, Pearl, Graham, & Kharrazi, 2008; Khashan, Everard, Mccowan, Dekker, & Baker, 2014), which may indicate there may be no specific time window and mid-pregnancy maternal factors should be addressed more (Hompes et al., 2013).

Additionally, it has been known that the human body undergoes significant changes especially in the first two trimesters (Deuschle et al., 2018); for instance, the fetal HPA-axis fully develops by mid-pregnancy and capable of generating a stress response by 20 weeks of gestation (Moisiadis & Matthews, 2014) which could interact with maternal HPA-axis. Notably, a recent study showed that maternal CM has been linked with amniotic BDNF when measured in mid-pregnancy, again making mid-pregnancy a critical period (Deuschle et al., 2018).

Interestingly, it has been discussed that exposure to adversities during the second trimester may trigger various maternal systems which then contribute to the

endocrine systems dysregulations that are observed during the third trimester (Shelton, Schminkey, & Groer, 2015). This study further discusses that distress in the second trimester may change the HPA-axis activity of the mother which leads to alternations in other systems and promote maternal risks in the third trimester and leads to negative health outcomes (Shelton et al., 2015). In support of these findings, it has been reported that women in their third trimester had higher evening cortisol if they were concerned about pregnancy complications during the second trimester (Obel, Hedegaard, & Henriksen, 2005), but not with morning cortisol (Obel et al., 2005). Nevertheless, these studies imply that the second trimester affects future outcomes, such as the later gestations, birth outcomes, or on the infant. In other words, these emphasize the importance of maternal distress during mid-pregnancy as a potential predictor for later outcomes, which could be prevented beforehand. Therefore, understanding these mechanisms especially in the mid-pregnancy may serve as precursors of further negative outcomes and may be used as precursors for the current and later maternal health.

1.5 Pregnancy-related worries, HPA-axis activity, and health

Considering the conflicting findings associating CM and HPA-axis activity, understanding the potential moderators and mediators of this relationship becomes crucial. Recent research suggests that pregnancy-related problems and anxieties are significant predictors of adverse maternal and offspring outcomes (Davis & Sandman, 2012; Wadhwa et al., 2011, Hompes et al., 2013), raising the question of whether they may contribute to the complex relationship between maternal CM and HPA-axis activity.

Pregnancy-related worry (PRW) is defined as the prenatal fears and beliefs of the mother about the birth and the overall health of her baby (Green, Kafetsios, Statham, & Snowdon, 2003). Importantly, these worries are suggested to be better measures of women's prenatal distress as they are more accurately related to the current mental state of the pregnant women, rather than general distress (Davis &

Sandman, 2012; Entringer et al., 2013; Hompes et al., 2013). Not only due to a higher relevance for the mother-to-be (Davis & Sandman, 2012), these specific worries may also be more influential since they describe the states of the pregnant women better than general measures (Buss, Poggi, Muftuler, Head, & Sandman, 2010; Davis & Sandman, 2010; Huizink et al., 2003). These effects are found to be still present even after adjusting for socioeconomic status, age, and even mothers' mood (Huizink et al., 2003), underlining the significance of the impact of PRW in pregnant women. Additionally, previous studies show that the frequency of different PRW types may change during pregnancy. For instance, PRW related to miscarriage or birth problems are typically more frequent at the earlier and later stages of gestation (weeks 16 and 35), and less frequent around mid-pregnancy (Öhman, Grunewald, & Waldenström, 2003; Statham & Kafetsios, 1997). However, there is no consensus about the reported frequencies across gestation. Contrary to the previous study, it has been also shown that higher worries were observed in the earlier gestation weeks that decreased towards the birth (Davis & Sandman, 2010). Therefore, studying PRW during mid-pregnancy and investigating the most frequently reported worries would be informative, particularly in relation to maternal mental health.

Additionally, worries are known to affect HPA-axis activity as well. In non-pregnancy cohorts, general worry was associated with elevated levels of cortisol followed by a higher increase (Mantella et al., 2008; Zoccola, Dickerson, & Yim, 2011), and in a pregnancy cohort, prenatal anxiety was linked with a steeper increase across gestation (Kane, Dunkel, Glynn, Hobel, & Sandman, 2014). On the other hand, high maternal anxiety was linked with lower baseline cortisol (Pluess, Bolten, Pirke, & Hellhammer, 2010) and lower awakening cortisol (Shea et al., 2007; Van den Heuvel, Assen, Glover, Claes, & Bergh, 2018). Yet, as mentioned, utilizing pregnancy-specific questionnaires may give a better idea about the mother's distress (Van den Heuvel et al., 2018), since these specific worries shape the emotional (Costa et al., 2017) and psychosocial distress of the mother which may in return alter stress

system activity. Notably, concerns about pregnancy were found to be associated with HPA-axis activity, where it was correlated with lower evening cortisol (Obel et al., 2005) at late pregnancy.

Overall, these pregnancy-specific worries and anxieties are argued to be the strongest predictors (Huizink et al., 2003) and most relevant factors that may be predicting the maternal stress; thus, suggested to be addressed more in pregnancy studies (Schetter, 2011). To the best of my knowledge, there is no study linking CM to maternal HPA-axis activity with a possible mediation, if not, a moderation of PRW on that relationship.

1.6 Present study

Considering the influence of CM and PRW on HPA-axis activity and maternal mental health during pregnancy, this study focuses on the relationship between these three factors in pregnant women participating in the ongoing BABIP prospective birth cohort from Istanbul, Turkey. I hypothesize that PRW would alter the effect of having CM history on different HPA-axis activity parameters (i.e. AC, CAR, DS) in pregnant women in their second trimester. For this purpose, first PRW will be tested as a mediator between CM history and HPA-axis activity. If it does not serve as a mediator, its potential role as a moderator will be investigated. The direction for the changes in the HPA-axis activity could not be hypothesized *a priori* due to contradictory findings in the literature.

CHAPTER 2

METHODS

2.1 Participants

Participants were 77 pregnant women (M = 31.8, SD = 3.7) recruited in the larger ongoing BABIP prospective birth cohort (Duman, Atesyakar, & Ecevitoglu, 2020). In this cohort, pregnant women are recruited at 20-26 weeks of pregnancy and complete 5 sessions up until 6 months after giving birth. Participants were recruited through doctor's offices, flyers, and online advertisements. Pregnant women were included if they are from Turkey, living in Istanbul, speaking Turkish, older than 18 years old, within a singleton intrauterine pregnancy, and not exhibiting any serious pregnancy complications or chronic diseases. Exclusion criteria were having multiple pregnancies and experiencing severe complications during pregnancy. For their participation in the whole project, women were compensated with educational booklets, videos, and online expert seminars about prenatal health as well as developmental reports and gifts for their infants at 4 months.

In this study, only questionnaires and diurnal salivary cortisol data from the first time point (T1) of the ongoing BABIP cohort were utilized. T1 lasted for approximately 2 hours. The flow diagram of participants for this session is given in Figure 1. From the 77 recruited participants of the BABIP cohort, 3 withdrew from the project, 2 did not complete the questionnaires, 7 did not complete the saliva collection procedure, 3 could not retrieve saliva samples, and 3 had insufficient amounts of saliva for analysis. Thus, in the end, 59 women successfully completed both the questionnaires and saliva samples for cortisol analysis.

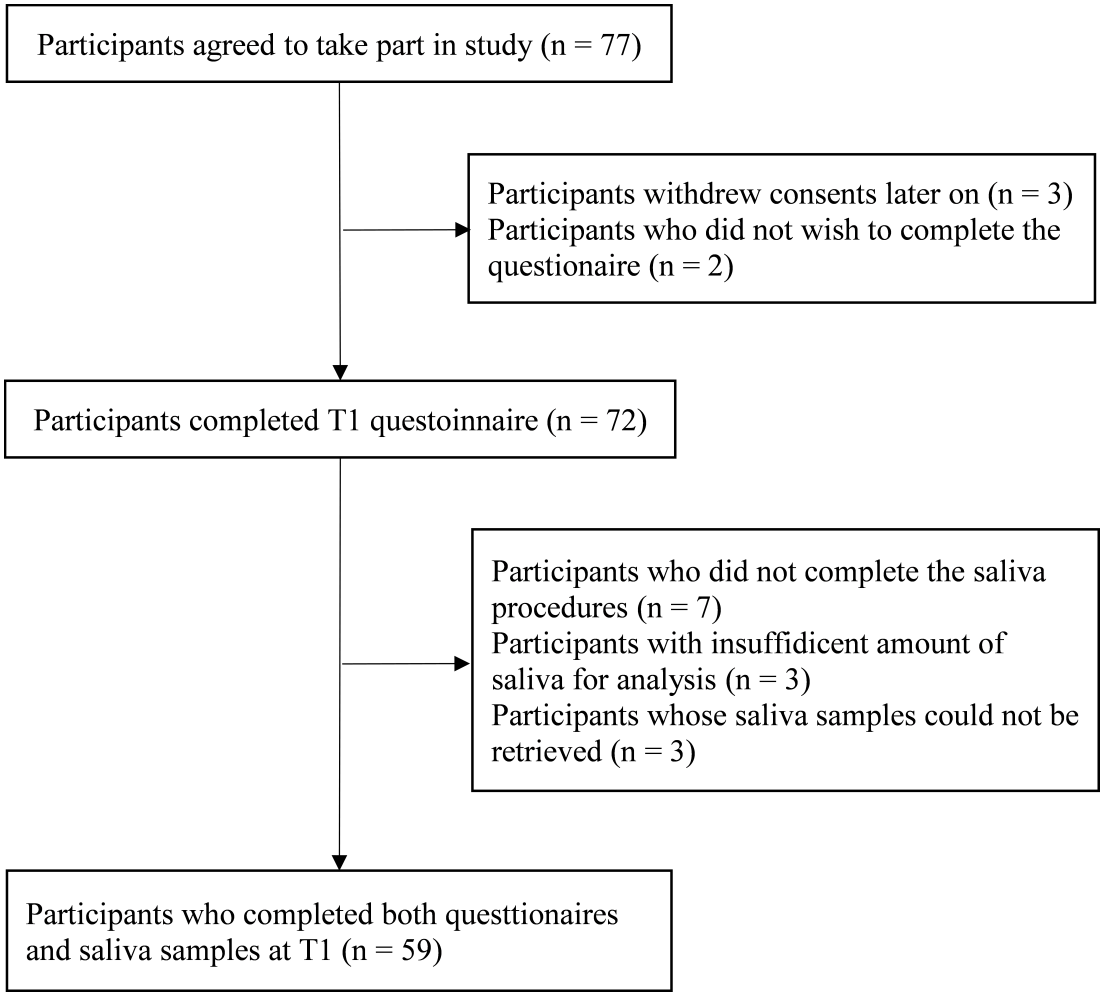


Figure 1. Participant flow diagram for the study.
Note: While 72 participants completed the questionnaires, saliva samples were available from 59 of these participants

Descriptive characteristics of the participants including pregnancy-related measures are summarized in Table 1. They were all married and had an average household income higher than 12,000 TL. In terms of education, all participants completed at least high school. Forty-seven point two percent completed an undergraduate degree and 44.4% completed a post-graduate degree.

Table 1. Descriptive Characteristics of Participants at T1

	M	*SD*	Range
Age	31.8	3.7	23 - 40
Gestation week	22.9	1.6	20 - 26
Monthly income (TL)	12241.9 TL	7044.6	3000 - 40000
	%		
Nulliparous	66.7%		
In vitro fertilization or intrauterine insemination	9.7%		
Wanted pregnancy	90.3%		
Smoker (last month)	1.4%		

Participants' health and medication history were determined by interviews. From 65 people who successfully answered the interview questions out of 77, the following pregnancy-related sicknesses were reported during pregnancy: 38 women had nausea, 26 experienced vomiting, 15 had diarrhea, 17 experienced vaginal bleeding, 20 had anemia and 15 women experienced cystitis. As chronic diseases, there were only 3 women who experienced pregnancy diabetes and using insulin shots as medication, and, only one woman who had hypertension. Furthermore, some participants reported having thalassemia (n = 1), hypotension (n = 1), sexually transmitted diseases (n = 2), a thyroid disease (e.g., Hashimoto's Thyroiditis, n = 9), insulin resistance (n = 1), epilepsy (n = 1), migraine (n = 2), eczema (n = 7), asthma (n = 1), drug addiction (n = 1), allergies (n = 25), food sensitivity (n = 10), and depression (n = 1), and anxiety disorders (n = 5), where one of these participants were on SSRIs. Of the participating women, 16.7% of them had previous pregnancy complications, such as miscarriage.

2.2 Measures

2.2.1 Questionnaires and interview measures.

As part of BABIP, participants completed various self-report questionnaires and interviews on demographic, health-related, and psychosocial factors. For this study, the main T1 demographic characteristics included women's age, gestation week,

monthly household income, education level, and marital status. Health-related factors are assessed through self-reports and interviews, including information on age, gestational week, current and pre-pregnancy BMI, health history, medication usage, and habits (e.g., sleep, smoking, and alcohol and substance use). For the present study, the psychosocial factors included CM, PRW, recent depressive symptoms, general state anxiety, and perceived social support.

As a measure of CM, the Turkish version of the Childhood Trauma Questionnaire (CTQ), a commonly utilized reliable measure of childhood maltreatment, was completed. CTQ is a 28-item questionnaire that assesses childhood maltreatment through five subcategories; emotional, physical, and sexual abuse and physical and emotional neglect (Bernstein et al., 1994; Turkish: Şar et al., 2012). Each subscale includes 5 items rated on a 5-point Likert scale (1: Never True, 5: Very Often True), and 3 items are used to test for denial of maltreatment (e.g. "I had the perfect childhood") which were not scored. In general, the emotional, physical, and sexual abuse items are about verbal mistreatments, physical assaults, and acts of sexual conduct, respectively. For emotional and physical neglect, items include failure of providing basic emotional needs and care, respectively (Carr et al., 2013). CTQ total scores range from 25 to 125, while subscale scores range from 5 to 25, with higher scores indicating higher maltreatment. The Turkish translation of the CTQ has been shown to be reliable and valid original (Şar, Öztürk, & Ikikardeş, 2012). Cronbach's α in this study was .911. Considering the importance of childhood sexual abuse on prenatal maternal health, sexual abuse subscale is separately investigated.

As the measure of PRW, the Cambridge Worry Scale (CWS) was utilized. CWS is a 17-item questionnaire that assesses pregnancy-related worries and concerns during pregnancy (Green, Kafetsios, Statham, & Snowdon, 2003; Turkish: Yigit Gunay & Gul, 2015). It has four suggested subtypes, such as socio-medical, socio-economic, health, and relationship worries (e.g. going to the hospital; the possibility of a miscarriage). In this original study, socio-medical factor included the

"Giving birth", "Going to the hospital", "Internal examinations" and "Coping with the new baby"; socio-economic factor contained "Money problems", "Housing", and "Employment problems"; health factor consisted of "Possibility of miscarriage", "Possibility of something wrong with the baby", "own health" and "health of someone else close"; lastly relationship factor included the two relationship items which are with friends/family and husband/partner. Items are rated on a 6-point Likert scale (0: No worry, 5: Major worry), with higher scores indicating higher worry. It was stated to be a reliable and valid instrument for the Turkish population (Yigit Gunay & Gul, 2015). In this study, the CWS total score and high vs. low PRW groups divided by a median split were utilized in statistical analyses, while subscales were determined by a principal component analysis (PCA). Cronbach's α of the scale in this study was .855.

Apart from CM and PRW, several psychosocial factors were assessed in relation to the study aims. Recent depressive symptoms in the last two weeks were assessed by Beck Depression Inventory-II (BDI-II), which is a 21-item questionnaire rated on a 4-point Likert scale (0 = Not at all to 3 = Severely) with items, such as "sadness" and "loss of appetite" (Beck, Steer, Ball, & Ranieri, 1996; Turkish version: Canel-Çinarbaş, Cui, & Lauridsen, 2011). Higher scores indicate higher recent depressive symptoms and it was utilized as total scores. Cronbach's α in this study for depressive symptoms was .861. Perceived social support was assessed by the Multidimensional Scale of Perceived Social Support (MSPSS), a 12-item questionnaire that includes subscales related to support from family, friends and significant other (Zimet, Powell, Farley, Werkman, & Berkoff, 1990; Turkish: Eker, Arkar, & Yaldız, 2001). It has items like "My family really tries to help me" for family, "My friends really try to help me" for friends, and "There is a special person who is around when I am in need" for significant other support. Scores range from 7 to 84 with items ranging from 1 = Very strongly disagree to 7 = Very strongly agree. Higher scores indicate higher perceived social support and it was utilized as total scores. Cronbach's α in this study for perceived social support was .859. General

state anxiety was measured by the State Anxiety Inventory X (STAI-X) – State form, which is a 20-item scale that measures current anxiety symptoms on a 4-point Likert scale (1=Almost never, 4=Almost always; Spielberger, Gorsuch, & Lushene, 1970; Turkish: Öner & Le Compte, 1985). Scores range from 20 to 80 with higher scores indicating higher state anxiety, it was utilized as total scores as well as high vs. low groups divided by a median split. Cronbach's α in this study for general anxiety was .922. Sleep quality and sleep patterns are assessed by a sleep diary based on previous research (Carney et al., 2012). Additional items were included concerning the measurement of HPA-axis activity (see Appendix A for English and Appendix B for Turkish version). Importantly, there were 5 participants whose self-report awakening and sampling times were missing, yet their call log information showed reliability and for these participants, the awakening time was taken as the first sampling time.

2.2.2 HPA-axis activity measures.

As an indicator of HPA-axis activity, salivary cortisol levels were utilized. Participants collected a total of 12 saliva samples at home for two consecutive weekdays at 0, 15, 30 and 45 minutes after awakening, and noon and 8 pm by Salivette synthetic rolls (Sarstedt, Germany). In this study, only 0 and 30 minutes after awakening samples and evening samples were utilized due to the observation of peak cortisol at 30 minutes after awakening, presence of missing samples from 15 and 45 minutes after awakening, and calculation of diurnal slope without the noon sample. Three parameters of salivary cortisol levels were utilized: 1) *Awakening cortisol* as the first saliva sample taken immediately after awakening, 2) *CAR* as the difference in cortisol between 30 minute and awakening samples, and 3) *DS* as the cortisol slope from awakening to evening samples, excluding the CAR (Ross et al., 2014), and by subtracting evening cortisol from morning cortisol.

Cortisol concentrations were determined by an electrochemiluminescence immunoassay at Centro Laboratories, Istanbul, using a Roche automated competitive system (Roche Diagnostics, Turkey). The minimum detection of the assay was 1.49

nmol/L. The intra-assay coefficient of variation (CV) was 1.31%, and the inter-assay CV was 2.85%. All cortisol values were utilized after converting from μg/dL to nmol/L by multiplying each value with 27.59, based on the molar mass of cortisol as 362.46 g/mol.

2.3 Procedure

All study procedures were approved by Bogazici University Human Research Ethics Committee. In this study, procedures of the BABIP birth cohort were followed (Duman et al., 2020). For T1, all participants were scheduled a visit at our collaborator Biruni Laboratories, Istanbul. First, oral and written consents were taken from participants, followed by a brief training on the collection of saliva samples at home with specific details about compliance. Afterwards, blood draws were performed by registered nurses. Sessions continued with completing self-report measures and interviews.

For saliva sample collection at home, participants were instructed to refrain from eating, drinking, tooth brushing, physical exercise, or any activities that could affect cortisol levels, during all morning samples and also 30 minutes before the evening (20:00) sample. They were also requested not to sleep after awakening or use the snooze feature of their alarms. They filled a form about their sleep quality, sleep patterns, and any difficulties such as night awakenings in the mornings, after the awakening sample. They were also given an information booklet including all necessary information to increase compliance (see Appendix C for English and Appendix D for Turkish version).

During the saliva collection days, participants who experienced minor illnesses (e.g., dental problems, flu) were rescheduled to the weeks following their recovery as suggested in the literature (Fries et al., 2009). Each participant was called the night before saliva collection to check any last-minute mishaps (e.g., infections, alcohol usage) and to be reminded about the instructions, timings, and booklets to increase compliance. In the morning, participants were instructed to take the samples

using Salivette rolls in the specified time points and rung the experimenter immediately after each collection. Sampling times are recorded by the experimenter as well.

Participants were instructed to keep all saliva samples in freezers (-20°C) until being picked up from their houses. These samples were transported on ice to our lab, centrifuged at 4°C, 1500g for 15 minutes, aliquoted and kept at -80 C until being analyzed at Centro Laboratories. All data were entered by two research assistants according to data entry guidelines and controlled by a third person.

2.4 Statistical plan

All statistical analyses were conducted by using IBM SPSS v23. For determining the PRW factor structure, a PCA was performed as previously reported (Green et al., 2003). Since the factors could be correlated with each other, an Oblimin rotation method with 4 factors was selected. Notably, Oblimin is an oblique rotation method in which factors are hypothesized to be correlated with each other.

For testing the hypotheses, several multiple regression analyses were utilized to investigate the associations between CM, PRW, and cortisol measures. Later, the effect of PRW on the relationship between CM and HPA-axis measures was examined similarly by multiple regressions. For revealing possible mediation analyses, Hayes' PROCESS module in SPSS was utilized (Model 4; Figure 2). If the results failed to yield an effect of CM on PRW, a moderation effect of PRW would be examined. For revealing the potential moderating effect of PRW, first, Model 1 by Hayes's PROCESS module was utilized, and second, PRW was dichotomized by median split and the effect of CM on HPA-axis measures was investigated for high and low PRW groups (Figure 3). The same was utilized with general state anxiety, high and low anxiety groups. In all the models, CM and PRW were taken as continuous variables unless stated otherwise. Sexual abuse as a type of CM was examined separately as a categorical variable (sexually abused vs. not abused) due to the low frequency of sexual abuse in the participant population.

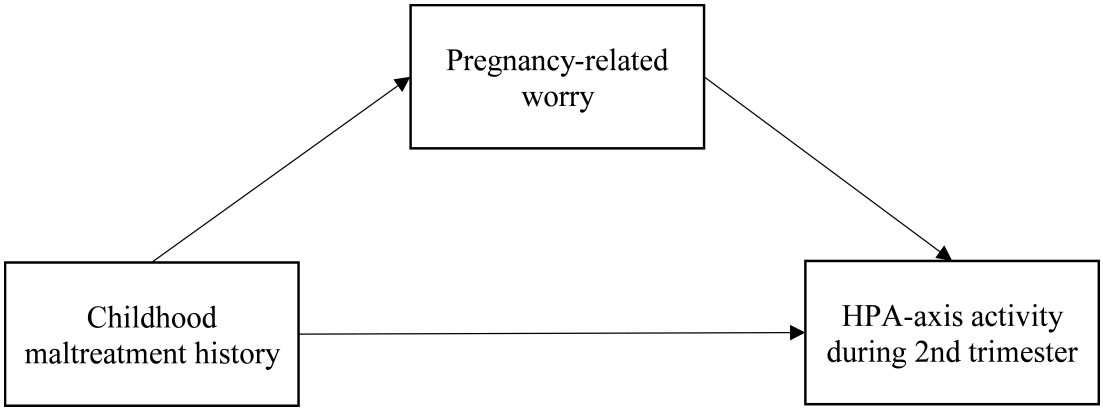


Figure 2. Proposed model of the relationship between history of CM and HPA-axis activity partially mediated by pregnancy-related worry

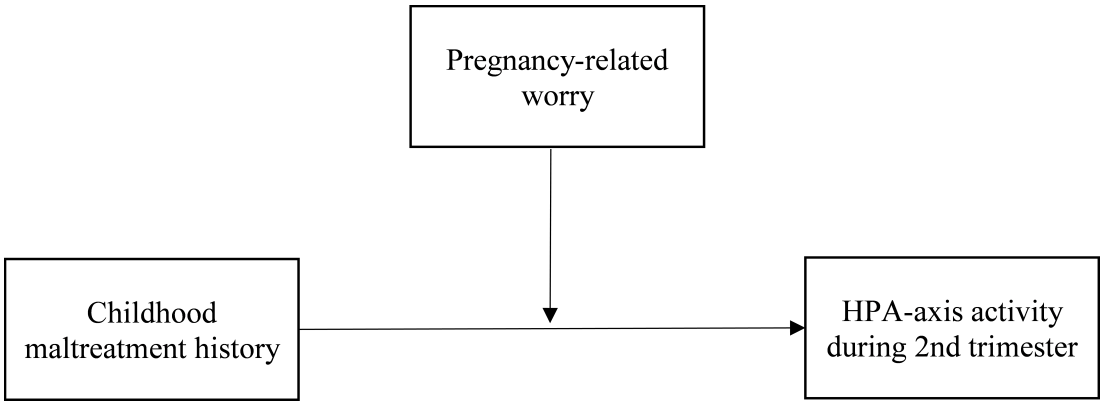


Figure 3. Proposed model of the relationship between history of CM and HPA-axis activity moderated by pregnancy-related worry

For this study, several covariates were considered. Self-report demographic characteristics (age, gestation week, current and pre-pregnancy BMI) were tested by t-tests between low and high CM groups, and psychosocial measures (depression and social support) were tested by Pearson correlations. Only the statistically significant variables were used as covariates in further analysis.

For the cortisol measures, numerous covariates were checked for each cortisol sample (awakening, 30th minute, and evening on both days) and HPA-axis measures (e.g., CAR and DS). First, noncompliance for sample timing and missing values were detected and excluded. Second, the influence of demographic variables (age, gestation week, current and pre-pregnancy BMI) were checked with Pearson correlations. Third, health variables (alcohol usage in the last month, having a

chronic disorder, experiencing allergies, using drugs due to thyroid disorder) and sampling problems (toothbrushing, having a sickness during the day, bleeding) were checked by t-tests (yes vs. no). Fourth, features related to cortisol sampling (nightly awakening, daily mood, daily worry, expectations from today, and, overwhelmed due to saliva collection) and sleep variables (awakening time, sleep duration, sleep quality, and delay variables) were checked by Pearson correlations and regression analysis (Stalder et al., 2016). Some of these sleep measures were transformed before analysis: For awakening time, 04:00 was taken as a baseline since it was the earliest time of awakening among participants. Fifth, delay variables were constructed by comparing the expected vs. actual sampling time for 0 and 30 minutes after awakening and evening samples, and checked with regression analysis for each time point to see if they predict cortisol levels or not (p.c. Dr. Emma Adam). For awakening cortisol, the difference between awakening and first sample; for CAR, the difference between a 30th-minute sample and its correct sampling time based on the first sampling time; and for DS, evening sampling time was compared with 20:00. All these described delay variables were then divided into positive and negative values and then put in separate regressions for each cortisol data. In addition, awakening cortisol (Stalder et al., 2016) and the sampling time difference between morning and evening samples were controlled for CAR and DS measures, respectively. All these cortisol covariates were included only if they were statistically related to the HPA-axis measures and only included to the models if they were found to be statistically significant in the last regression model, or else they were removed. Importantly, covariates were considered as relevant if they show at least a trend towards significance ($p < .1$).

After data cleaning, for all outliers (z-scores higher than 3.29), winsorizing to the next maximum or minimum value that is not an outlier was utilized. All analyses were conducted after winsorizing. Each normality check was conducted for regression analysis according to the z-scores of skewness and kurtosis of each variable. The limit for z-scores was 3.29 (Kim, 2013), if z-scores do not exceed this

value, normality considered as not violated unless the scores would be transformed. Other assumptions for linear regression were also checked, such as linearity by scatter plots, and independence of residuals by Durbin-Watson.

CHAPTER 3

RESULTS

3.1 Descriptive statistics related to the psychosocial and health measures

CM was measured by CTQ total scores which was winsorized before analysis, and a median split yielded low and high CM groups with *M* = 27.7, *SD* = 2.1 (N_{low} = 38) and *M* = 40.0, *SD* = 7.7 (N_{high} = 34), respectively. Examining the specific abuse types (total CM subtype score = 5 for no-abuse and total CM subtype score $>$ 5 for abuse) yielded the following percentages: 56.9% reported emotional abuse, 16.7% reported physical abuse, 25% reported sexual abuse, 79.2% reported emotional neglect and 43.1% reported physical neglect. Sexual abuse was dichotomized as no-abuse (N = 54) vs. abuse (N = 18). For recent depressive symptoms, considering scores below the 20-point threshold for moderate depressive symptoms, 6.9% of our cohort experienced moderate to severe depressive symptoms. For general state anxiety, STAI scores were divided into low and high-anxiety groups by a median split, with *M* = 26.1, *SD* = 3.0 (N_{low} = 36) and *M* = 38.9, *SD* = 7.3 (N_{high} = 36), respectively. Other demographic and psychosocial measures are given in Table 2 below.

Table 2. Psychosocial Characteristics of Participants at T1

	M	*SD*	Range
Childhood maltreatment	33.5	8.2	25 – 58
Pregnancy-related worry	23.3	11.7	5 - 64
Depressive symptoms	8.1	6.2	0 – 29
Perceived social support	64.3	12.1	24 – 84
General state anxiety	32.5	8.5	20 – 58
Current BMI	24.9	3.2	19.9 – 32.2
Pre-pregnancy BMI	22.8	3.8	17.9 – 33.7

PRW was further divided into low and high worry groups by a median split, with *M* = 14.9, *SD* = 4.9 (N_{low} = 37) and *M* = 32.3, *SD* = 10.0 (N_{high} = 35), respectively. When the individual items were examined as suggested, the most commonly reported worries were “the possibility of something wrong with the baby” (94.4%), “giving birth” (93.1%), “relationship with the baby” (81.9%), “Money

problems" (80.6%) and birth complications such as the possibility of miscarriage (75%). On the other hand, "Partners presence at birth" was the least worried item, reported as "not a worry" in 67.6% of participants.

In the first PCA analysis, no rotation method was utilized with all the items in the questionnaire. It was shown that this factor analysis revealed 5 components with Eigenvalues higher than 1 and they explained 68.1% of the variance. However, to be comparable with the original studies' four-factor structure by Green et al (2003), and since the 5th component which was explaining only 6.9% percent with an Eigenvalue of 1.2, the 4-factor structure is selected. When PCA was utilized with 4 factors in the extraction, the components explained 61.2% of the variance cumulatively. In the same analysis, it was seen that item 7 ("The health of someone close to you") did not have a communality value higher than .4 after extraction (.3), and thus it was discarded from further analysis. Next, a PCA was repeated with Oblimin with Kaiser Normalization and with the Oblimin as rotation method with 4 factors. Again, when the communalities are examined, items 3 ("Problems with the law"), 5 ("Your relationship with friends and family"), and 15 ("Whether your partner will be with you for the birth") had the lowest commonalities. Only item 5 was kept in the analysis due to its relevance to the relationship factor. Item 3 was excluded due to low representation (51.4% reported this as "not a worry") and did not load into the suggested socio-economic factor. Item 15 was excluded due to the majority of participants reporting it as "not a worry" (67.5%).

With the remaining items, the PCA analysis again with Oblimin rotation and 4-factor extraction was repeated. This final PCA revealed that 4 components explain the 69.5% of the total variance with all components have Eigenvalues higher than 1. The loadings of each item and factor have been decided according to the loadings where the highest loading factor was utilized for each item. The pattern matrix was used as the main source of loadings and factors. Rotation converged in 22 iterations. The first component which explained 38.6% of the total variance was the "*health*" factor. The second component was the "*relationship*" component which explained the

12.9% of the total variance. The third factor was the "*socio-economic*" component which explained 9.8% of the total variance. The fourth factor was the "*socio-medical*" component that explained 8.3% of the total variance. These CWS subscales were constructed by taking the sum of each loading item. Please see Table 3 for subscales and their corresponding items, and Table 4 for the bivariate correlations between the PRW factors.

Table 3. Factor Structure and PCA Analysis for PRW

Items	Components				
	Factor 1 (Health)	Factor 2 (Relation-ship)	Factor 3 (Socio-economic)	Factor 4 (Socio-medical)	Eigenvalues (%variance)
6. Own Health	0.88				5.37 (38.6%)
9. Possibility of something wrong with baby	0.78				
16. Possibility of a miscarriage	0.643				
10. Going to the hospital	0.50				
11. Internal examinations	0.453				
4. Relationship with partner/ husband		0.88			1.80 (12.9%)
5. Relationships with family and friends		0.711			
1. Your housing		0.69			
14. Giving up work			0.89		1.373 (9.8%)
8. Employment problems			0.78		
2. Money problems			0.54		
12. Giving birth				-0.76	2.16 (8.3%)
13. Coping with the new baby				-0.62	
17. Labour too early				-0.52	

Table 4. Pearson Correlations Between PRW Subscales

	1	2	3	4	5
1. Total PRW	-	.86**	.65**	.80**	.59**
2. Health		-	.42**	.61**	.39**
3. Socio-economic			-	.35**	.29*
4. Socio-medical				-	.43**
5. Relationship					-
Note: * $p < .05$ and ** $p < .01$.					

3.1.1 Hypothesized covariates for psychosocial measures

In order to analyze these hypothesized demographics concerning CM and PRW, several t-tests were run. There was no difference between the two CM groups in terms of age, current and pre-pregnancy BMI. For gestation week, the low CM group (M = 22.5, SD = 1.6) were at a significantly lower gestation week than the high CM group (M = 23.4, SD = 1.6, p = .03), therefore, gestation week was included as a covariate in further analysis.

Furthermore, in order to study the relations between hypothesized psychological factors, a series of bivariate correlations were run with CM (Table 5). CM was associated negatively with perceived social support (r = -.34, p = .003), and positively associated with recent depressive symptoms (r = .29, p = .012) and general state anxiety (r = .36, $p < .001$). The analyses showed that social support, depressive symptoms, and gestation week were significant covariates in CM-related assessment within the proposed model, and thus considered as covariates for further analysis.

Table 5. Correlations Between Psychosocial Measures

	1	2	3	4	5
1. Childhood maltreatment	-	.11	.29*	-.34**	.36**
2. Pregnancy-related worry		-	.48**	-.17	.61**
3. Depressive symptoms			-	-.22	.52**
4. Perceived social support				-	-.24*
5. General state anxiety					-
Note: * $p < .05$ and ** $p < .01$.					

3.2 Descriptive statistics related to the HPA-axis activity and sleep measures

Before the statistical analysis, all saliva sampling logs were checked for compliance and missing data. First check was based on whether the collection was done during weekdays or weekends and done in two consecutive days or not. To this end, there were only 6 people who completed the sampling on a weekday (as opposed to a weekend) or two nonconsecutive days. An independent samples t-test showed no difference in any cortisol measures between these groups (ps $> .05$).

The second check was for compliance related to sample timing. The compliance threshold for CAR was selected as a 15-minute delay between awakening time and first sampling time, and 20 minutes delay for diurnal slopes, for each day separately (p. c. Dr. Emma Adam). For CAR, the 30th-minute sample threshold was taken as 50 minutes after awakening. Participants who exceed these thresholds were discarded from further analysis. Lastly, some participants had missing cortisol samples at awakening, 30th minute, or evening samples. Consequently, for Day 1, there were 12, 10, and 14 data points for awakening cortisol, CAR, and DS measures, respectively, that were discarded due to non-compliance. For Day 2, there were 14, 13, and 15 data points for awakening cortisol, CAR, and DS measures, respectively, were discarded due to non-compliance.

Cortisol values on Day 1 and Day 2 for awakening, 30th minute, evening, CAR, and DS are summarized in Table 6 and Figure 4. There was one outlier in Day 1 evening sample and another in Day 2 evening sample which were both treated with winsorizing. Awakening cortisol, CAR, and DS were normally distributed. Bivariate correlations between cortisol values at awakening, 30 minutes after awakening, and in the evening, CAR and DS without controlling for any covariates were summarized in Table 6. Cortisol levels at individual time points were significantly correlated across the two collection days (rs .47 - .51, $p < .001$), except for evening cortisol (r = .12, p $< .05$). Awakening cortisol at Day 1 and Day 2 were also correlated significantly (r = .47, p = .003). However, measures of CAR and DS were not significantly correlated between Day 1 and Day 2; thus, two Day 1 and Day 2 analyses conducted separately.

Table 6. Cortisol Values for Day 1 and 2 with Their Correlations Across Days

	Day 1				Day 2				
	M	*SD*	N	Range	*M*	*SD*	N	Range	*r*
Awakening	32.2	18.9	47	8.2 – 80.8	29.4	16.3	49	7.6 – 81.7	.47**
30th minute	46.0	23.7	46	8.1 – 111.5	36.7	19.5	45	11.6 – 92.4	.51**
Evening	7.7	5.5	48	1.5 – 24.6	7.1	5.3	44	1.5 – 23.2	.12
CAR	11.7	19.6	44	-30.4 – 67.3	6.9	11.5	45	-19 – 33.1	-.04
DS	24.3	17.6	45	-10.6 – 73.8	23.1	15.8	44	-13.4 – 71.8	.28

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

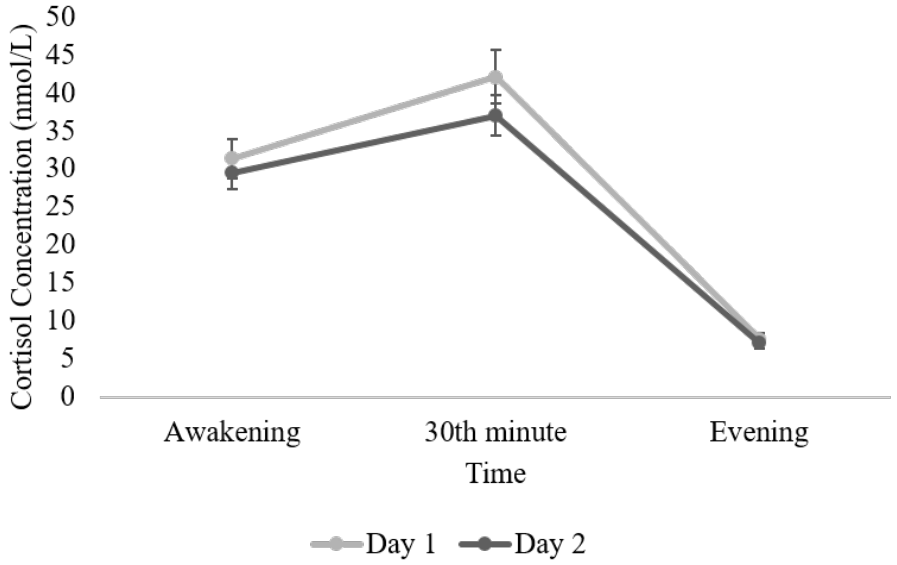


Figure 4. Cortisol diagram for two days including awakening, 30th minute and evening samples.
Note: There was no difference in cortisol values at the three time points across two days. Error bars indicate SEM

Lastly, differences between Day 1 and Day 2 were examined via paired sample t-tests for the following variables: awakening cortisol, 30th minute cortisol, evening cortisol, CAR, DS, number of nightly awakenings, sleep duration, awakening time, current mood, being overwhelmed due to saliva collection procedure, daily worry, expectations from the day, sample time difference between awakening and

evening, and, saliva collection problems. As a result, daily worries were significantly different (t (55) = 4.03, $p < .001$), where participants had higher worries in Day 1 (M = 1.6, SD = 1.4) than in Day 2 (M = .9, SD = 1.2). Moreover, current mood was also significantly different (t (54) = 2.1, p = .05), where participants had a better mood in Day 1 (M = 1.5, SD = 1.4) than in Day 2 (M = 1.1, SD = 1.9).

3.2.1 Hypothesized covariates for cortisol measures

To begin with, a series of Pearson correlations between demographic and cortisol variables were run as the second step of covariate analysis (Table 7). Results showed that none of the demographic variables were significantly correlated with cortisol measures.

Table 7. Correlations of HPA-axis Measures and Demographics for Days 1-2

	Day 1							Day 2						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7
1. AC	-	-.37*	.95**	.18	-.23	-.19	-.09	-	-.06	.95**	-.00	-.09	-.12	-.08
2. CAR		-	-.42**	.11	-.02	-.03	.11		-	-.01	.13	.12	.02	-.06
3. DS			-	.20	-.11	-.06	-.03			-	-.07	-.05	-.10	-.09
4. Age				-	.15	.22	.10				-	.15	.22	.10
5. BMI					-	.94**	.18					-	.94**	.18
6. P. BMI						-	.08						-	.08
7. GW							-							-

Note: AC = Awakening cortisol, P = Pre-pregnancy, GW = Gestation week;
* p <.05 and ** p <.01.

Then, psychosocial measures were correlated with each HPA-axis measure by using Pearson correlations (Table 8). This table showed that CMH was associated with awakening cortisol (r = -.30), CAR (r = .57) and DS (r = -.32) on Day 1; PRW with CAR on Day 2 (r = .30); depressive symptoms with awakening cortisol (r = -.34) on Day 1 and CAR (r = .32) on Day 2; and, general state anxiety with awakening cortisol (r = -.43), CAR (r = .40) and DS (r = -.44) on Day 1 (p <.05). Thus variables that were not predictors (CMH, PRW and general state anxiety) were used as covariates (e.g., depressive symptoms) for further analysis.

Table 8. Correlations of HPA-axis and Psychosocial Measures for Days 1-2

	Day 1					Day 2				
	4	5	6	7	8	4	5	6	7	8
1. AC	-.30*	-.17	-.34*	.13	-.43**	.16	.05	-.05	-.15	.10
2. CAR	.57**	.17	.10	-.034	.40**	.03	.30*	.32*	-.17	.07
3. DS	-.32*	-.12	-.25	.05	-.44**	.17	-.03	.00	-.24	.10
4. CM	-	.11	.29*	-.34**	.36**	-	.11	.29*	-.34**	.36**
5. PRW		-	.48**	-.17	.61**		-	.48**	-.17	.61**
6. BDI			-	-.22	.52**			-	-.22	.52**
7. MSPSS				-	-.24*				-	-.24*
8. STAI					-					-

Note: AC = Awakening cortisol * indicates p <.05 and ** indicates p <.001.

Next, differences between Day 1 and 2 related to cortisol values revealed that alcohol use in the last month (N = 6) influenced awakening cortisol at Day 1 (t (28) = -1.85, p = .075) and CAR at Day 2 t (26) = 2.08, p = .047) compared to participants with no alcohol use. Therefore, alcohol use was taken as a covariate in these cortisol measure analyses. For the chronic disorder, allergy, and using medication for thyroid variables, t-tests on each HPA-axis measure showed no difference between groups (ps $> .1$). For having a problem with cortisol sampling (e.g., toothbrush) only differed on awakening cortisol at Day 1 (t (45) = 2.32, p = .025) and on DS (t (43) = 2.17, p = .036) between having a problem and not groups. Thus, this variable was controlled for awakening cortisol and DS on Day 1. Next, sleep measures (Table 9) and mood were checked as the fourth step of covariate check by utilizing Pearson correlation s that are given in Table 10.

Table 9. Descriptive Statistics of Sleep Variables at for Days 1-2

	Day 1			Day 2		
	M	*SD*	Range	*M*	*SD*	Range
Awakening time	195.5	67.12	30 – 363	203.9	68.7	0 – 330
Sleep duration	438.2	100.8	106 – 720	454.8	89.9	255 – 670

Note: Times are in minutes, awakening time is standardized by 4am.

For Day 1, the Pearson correlations (Table 10) showed only sleep quality was significantly associated with awakening cortisol (r = .29, p = .053) but not the other sleep or mood variables. A regression analysis was conducted where all possible covariates entered as independent variables and awakening cortisol as output. This showed that worry was significantly predicting awakening cortisol (β = .39, p = .012) as well as the sleep quality (β = .47, p = .003), but not others. As a result, for Day 1 awakening cortisol, daily worry, and sleep quality have been decided to be taken as covariates for further analysis. For CAR, the correlation table showed no statistically significant correlations with any hypothesized covariates, except awakening cortisol as expected (r = -.37, $p < .05$). A regression analysis was applied again with the same variables, none of the hypothesized variables were predicting CAR, except awakening cortisol on that day (β = -.37, p = .013). Therefore, none was used as covariates except for the awakening cortisol in further analysis. Lastly, the Pearson correlations also showed that only daily worry was significantly associated with DS on Day 1 (r = .30, $p < .05$), but not the other sleep or mood variables. The influence of daily worry was supported by the regression analysis which showed that daily worry was significantly predicting awakening cortisol (β = .30, p = .047), but not others. This regression model also included the time difference between morning and evening samples which was also not significant.

Similarly, for Day 2, Pearson correlations showed that only awakening time was significantly associated with awakening cortisol which was also supported by the regression model (β = -.28, p = .056). For CAR, the correlation table showed no statistically significant correlations with any hypothesized covariates. To support, regression analyses were applied again with the same variables, none of the hypothesized variables were predicting CAR; therefore, none was used as covariates in further analysis. Lastly, for diurnal cortisol, the correlation table only showed that awakening time was significantly associated with DS (r = -.34, $p < .05$) but not the other sleep or mood variables. This finding was supported by the regression analysis which showed that awakening time was significantly predicting DS (β = -.34, p =

.027), but not others. The last regression again included the time difference between morning and evening, yielding a non-significant result. As a result, for Day 2 DS only awakening was taken as a covariate for further analysis .

Table 10. Correlations of HPA-axis Measures and Covariates on Days 1-2

	Day 1											Day 2										
	1	2	3	4	5	6	7	8	9	10	11	1	2	3	4	5	6	7	8	9	10	11
1. Awakening cortisol	-	-.37*	.95**	.09	.29	.18	.24	.18	-.16	.22	.07	-	-.06	.95**	.11	.06	-.28	-.21	.07	-.01	.01	.24
2. CAR		-	-.42**	.14	-.28	-.22	-.19	-.22	.09	-.01	.13		-	-.13	.05	-.17	-.09	.08	-.21	-.10	.13	.03
3. DS			-	-.01	.24	.19	.25	.15	-.20	.30*	.16			-	.15	.02	-.34*	-.29	.08	-.01	.03	.24
4. Nightly awakening				-	-.22	-.05	-.09	.05	.09	-.035	-.05				-	-.38**	.01	.01	-.03	.10	.19	.04
5. Sleep quality					-	-.15	.00	.60**	-.47**	-.34**	-.06					-	.07	.09	.54**	-.24	-.06	.03
6. Awaking time						-	.51**	-.11	.11	.01	.19						-	.62**	.16	-.10	.06	-.19
7. Sleep duration							-	.03	-.15	.03	-.04							-	.33*	-.14	-.07	-.16
8. Current mood								-	-.65**	-.24	-.16								-	-.37 **	-.02	.04
9. Overwhelmed due to saliva collection									-	.23	-.10									-	.36**	-.02
10. Daily worry										-	-.02										-	-.03
11. Expectation of today											-											-

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

As the final step of covariate analysis, the sampling times for each cortisol data are given in Table 11. From the regression analysis including the delay variables, I did not found a significant delay variable for awakening, CAR or DS for any of the days, except for the DS on Day 1 where positive delay at evening sample was found to be marginally significant ($p < .10$) and therefore, the evening positive delay variable was included in analyses for DS. As a result, for Day 1 DS measure, daily worry was taken as a covariate along with the positive delay variable for evening sample.

Table 11. Descriptive Statistics of Cortisol Sampling Times at Days 1-2

	Day 1			Day 2		
	M	*SD*	Range	*M*	*SD*	Range
Awakening	07:22	01:08	5:00 – 10:03	07:27	01:02	5:05 – 9:30
30th minute	07:54	01:08	5:30 – 10:33	07:59	01:02	5:35 – 10:03
Evening	20:09	00:38	18:35 – 23:00	20:12	00:43	18:18 – 21:58
Note: Times are given as hh:mm.						

3.3 CM, PRW, and HPA-axis measures: The models

3.3.1 CM and PRW relationship

The relationship between CM and total and subtypes of PRW were tested by a series of regression models including gestation week, depressive symptoms, and perceived social support. Results showed that there is no relationship between CM and total or subtypes of PRW ($p > .05$). On the other hand, depressive symptoms predicted PRW ($\beta = .47$, $t\ (67) = 4.15$, $p < .001$), and its socio-medical ($\beta = .46$, $t\ (67) = 4.10$, $p < .001$) and relationship subscales ($\beta = .46$, $t\ (67) = 4.31$, $p < .001$) while perceived support predicted only the relationship subscale ($\beta = -.27$, $t\ (67) = -2.52$, $p = .014$). These results suggest that in our sample, CM does not predict PRW. Therefore, instead of a mediation analysis, only moderation effect of PRW was examined on the CM and HPA-axis relationship.

3.3.2 CM and PRW on awakening cortisol

The effect of CM on awakening cortisol was tested for Day 1 and Day 2, taking PRW as moderator. In the first regression, the significant covariates which were daily worry, sleep quality, sampling problems, and alcohol usage entered as the initial step; and, second step was the predictors which were CMH and PRW. For Day 1, controlling for aforementioned covariates CM predicted awakening cortisol (β = -.32, t (37) = -2.32, p = .026), in a significant model (R^2 = .27, F (6, 37) = 3.89, p = .004) while explaining 27% of the variance in awakening cortisol. Next, moderation of PRW on CMH and awakening cortisol with significant covariates were tried with PROCESS, which did not yield a significant result ($p > .05$). Yet, with PRW moderation (high vs. low PRW), the results showed that the association between CM and lower awakening cortisol was significant only in the high PRW group (β = -.52, t (14) = -2.64, p = .019) in a significant model (R^2 = .61, F (5, 14) = 4.43, p = .012, N = 20), but not in the low PRW group (β = -.04, t (18) = -.21, p = .837; R^2 = .48, F (5, 18) = 3.32, p = .027, N = 24; see Figure 5). As can be seen, CMH was explaining 61% only in the high PRW group, indicating a moderation effect of PRW. In order to test whether this moderation is specific to pregnancy-related worries, general state anxiety was also tested as a moderator (high vs. low state anxiety). The results indicated that general state anxiety did not moderate the impact of CM on awakening cortisol (F (5, 15) = 2.33, p = .094 for low; F (5, 17) = 2.26, p = .095 for high anxiety groups), suggesting that the moderation was specific to PRW. When sexual abuse was investigated separately, there was no significant effect on awakening cortisol ($p > .05$). These effects were found to be specific to Day 1, but not Day 2 ($p > .05$).

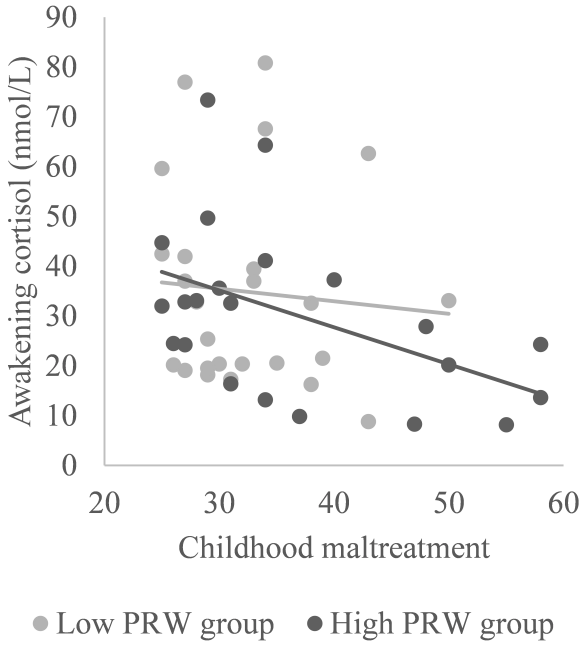


Figure 5. CM and awakening cortisol (nmol/L) relationship in low PRW (grey) and high PRW (black) groups.
Note: As CM increased, awakening cortisol significantly decreased only in the high PRW group (p = .027)

3.3.3 CM and PRW on CAR

For Day 1, a multiple regression was utilized where first step was the covariates, awakening cortisol, and second step as the predictors that are CMH and PRW resulted that CM significantly predicted CAR controlling for awakening cortisol (β = .50, t (40) = 3.92, $p < .001$) in a significant model, F (3, 40) = 8.58, $p < .001$, R^2 = .39), explaining 39% of the variance in CAR. Similar to awakening cortisol, moderation analysis by PROCESS did not produce a significant result ($p > .05$); however, when PRW was considered as a moderator, controlling for awakening cortisol and recent depressive symptoms, CM predicted heightened CAR only in the high PRW group (β = .74, t (17) = 5.02, $p < .001$) in a significant model (R^2 = .72, F (3, 17) = 14.34, $p < .001$, N = 21), explaining 72% of the variance in CAR. This was not true in the low PRW group (R^2 = .14, F (3, 19) = 1.04, p = .397, N = 23), indicating a moderation of PRW, see Figure 6. Moreover, this moderation was again specific to PRW, as general state anxiety (high vs. low groups) did not moderate the relationship between CM and CAR (both CM coefficients' ps $< .05$). For the specific

effect of sexual abuse, it was shown that sexual abuse significantly predicted CAR (β = .50, t (40) = 4.02, $p < .001$; F (3, 40) = 8.89, $p < .001$, R^2 = .40), explaining 40% of the variance in CAR. When influence of sexual abuse on CAR was compared between low and high PRW groups, sexual abuse was predicting CAR in both, implying a more robust effect of sexual abuse on CAR (ps <.05 for both PRW groups). Similar to awakening cortisol, these results were observed only for Day 1, but not for Day 2. On day 2, only relationship subscale of PRW predicted higher CAR (β = .38, t (42) = 2.62, p = .012; F (2, 42) = 3.45, p = .041).

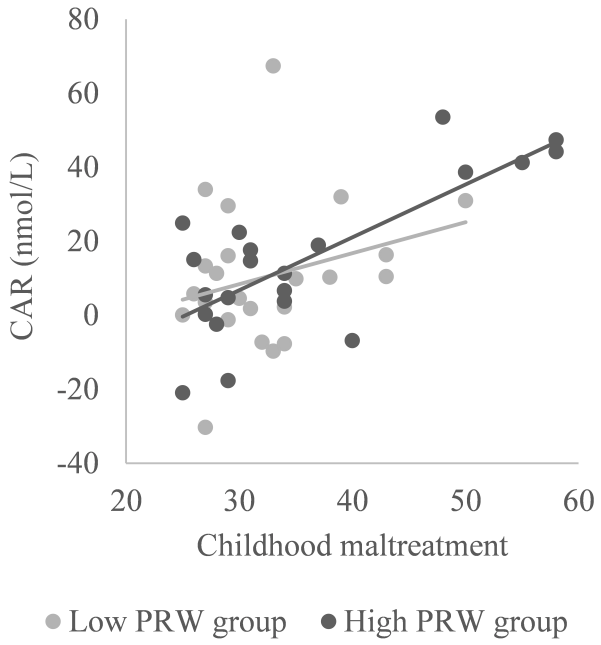


Figure 6. CM and CAR (nmol/L) relationship in low PRW (grey) and high PRW (black) groups.
Note:As CM increased, CAR significantly increased only in the high PRW group (p <.001)

3.3.4 CM and PRW on DS

For Day 1, a multiple regression was utilized where covariates which are daily worry, sampling problems, depressive symptoms and positive delay at evening sample entered as the first step; and, predictors (CM and PRW) as the second step of analysis. Here, CM marginally predicted DS while controlling for the aforementioned covariates (β = -.26, t (33) = -1.89, p = .067), in a significant model (F (6, 33) = 3.91,

p =.005, R^2 = .42), where 42% of the variability in DS was explained. Similar to awakening cortisol and CAR, when PRW was considered as a moderator by utilizing PROCESS, it did not produce any significant results ($p > .05$); however, when taken as high-low PRW groups, CM predicted blunted DS only in the high PRW group (β = -.60, t (11) = -3.09, p = .010) in a significant model (R^2 = .63, F (5, 11) = 3.82, p = .030, N = 17), while explaining 63% of variance of DS. This effect was not found in the low PRW group (β = -.04, t (17) = -.19, p = .849; R^2 = .516, F (5, 17) = 3.62, p = .021, N = 23; see Figure 7). Besides, this moderation was again specific to PRW, as general state anxiety (high vs. low groups) did not moderate the relationship between CM and DS (both models ps $> .05$). For the specific effect of sexual abuse, no effect was found ($p > .05$). These results were only specific to Day 1, but not Day 2.

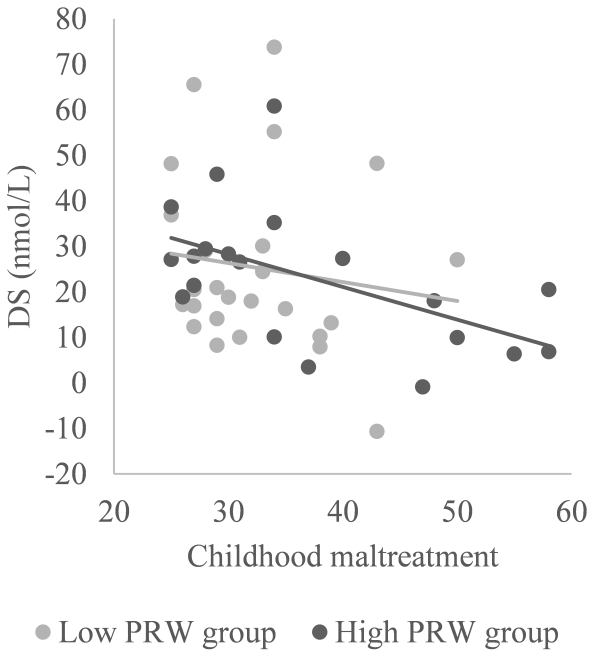


Figure 7. CM and DS (nmol/L) relationship in low PRW (grey) and high PRW (black) groups.
Note: As CM increased, DS was blunted only in the high PRW group (p = .010)

Overall, results show that CM was associated with several HPA-axis measures, awakening cortisol, CAR, and DS, and this relationship was stronger in the high PRW group, compared to the without moderation analyses (Table 12).

Table 12. β values of CM on HPA-axis measures with and without PRW moderation

	βs without moderation	βs with PRW moderation
Awakening cortisol	-.32	-.52
CAR	.50	.74
DS	-.26	-.60

CHAPTER 4

DISCUSSION

The initial aim of this study was to investigate whether maternal CM was associated with HPA-axis activity during pregnancy and whether this relationship would be mediated by PRW. For the first part, I found a significant association between CM history and HPA-axis activity as hypothesized. Results revealed that CM is associated with a lower awakening cortisol, a heightened CAR, and a blunted DS during mid-pregnancy.

Regarding awakening cortisol, as reviewed recently, many non-pregnancy cohorts find lower morning cortisol with CM (Bernard et al., 2017), especially from the studies of agency-referred samples instead of self-reports. Similarly, a pregnancy study that recruited sexually abused women during their 28th week of gestation also found lower awakening cortisol compared to sexually non-abused women (Shea et al., 2007). Here, the results are in line with these findings, where CM is associated with lower awakening cortisol. However, another non-pregnancy study utilizing women with violent criminal behavior found no associations between CM and awakening cortisol (Brewer-Smyth, Burgess & Shults, 2004) possibly due to living in a prison environment. In relation to CAR, I found that CM is associated with heightened CAR as shown in the literature numerous times, especially for CM (Fogelman & Canli, 2018). For example, enhanced CAR has been associated with CM (Lu et al, 2016) and also with physical and sexual abuse histories (Weissbeck et al., 2006). Similar results were found in postpartum studies recruiting women with CM (Gonzalez et al., 2009), again in support of the present findings. Regarding the pregnancy studies, one group who recruited sexual abuse victims from mid-late pregnancy found increased CAR at late pregnancy (Bublitz & Stroud, 2012); however, Shea et al. (2007) failed to find such an association between sexual abuse and CAR. In their study, they focused on a later gestation week than ours (28 weeks of gestation) and their participants reported higher levels of depression (50% assigned as depressed according to the Edinburgh Postnatal Depression Scale or

Montgomery–Asberg Depression Rating Scale cutoffs), which may be the reason behind the difference between results. Regarding DS, I found a flatter slope with CM, which is supported by non-pregnancy cohorts that found flatter DS with specifically physical (Weissbecker et al., 2006); and sexual abuse histories (Weissbecker et al., 2006; Nicolson et al., 2010). These results are also somehow in line with pregnancy cohorts that report higher evening cortisol in sexual abuse victims during mid-late pregnancy (Bublitz & Stroud, 2013). However, a post-partum study found steeper DS with CM (Brand et al., 2010), which indicates pregnancy and post-partum HPA-axis activities and how CM influencing them may differ in terms of cortisol DS.

Considering the relevance of sexual abuse especially among pregnant women who experienced CM (Chamberlein et al., 2019), I also found significant associations with CAR where higher CAR was observed with sexually abused women. Although there is one pregnancy study that failed to find such a relationship with CAR (Shea et al., 2007), our results are somehow in line with another pregnancy study with sexual abuse victims (Bublitz & Stroud, 2012), as described above. Combining all these findings suggest that the impact of CM is reflected in HPA-axis activity during pregnancy, in a way that may impact maternal and fetal health. Yet, there could be several mediator or moderator factors that could aid in understanding this relationship better.

4.1 Relationship between CM, PRW, and HPA-axis measures

The second aim of this study was to test the mediation or moderation effect of PRW on the CM and HPA-axis activity relationship. Regarding the possible mediation by PRW, the results failed to find any association between CM and PRW or its subscales, and only recent depressive symptoms were related to certain subtypes of PRW, along with perceived social support on relationship worries. These findings indicate that CM is not directly influencing PRW in this cohort, but recent mood and support as measured by depressive symptoms and perceived social support were more relevant to PRW. Regarding the well-established influence of CM on anxiety and concerns

(Choi & Sikkema, 2016), this is opposed to what was expected. Here, one of the candidate reasons could be the attachment between the mother and the unborn fetus. It is a well-known fact that CMH could affect attachment and this effect could be more salient in the course of pregnancy as discussed before (Choi & Sikkema, 2015). Thus, one explanation for this non-significant association between CM and PRW could be the attachment style of the mother-to-be. Studying the attachment style and the internal representations of it could give a better understanding of this CM and PRW relationship. Additionally, we did not find a direct prediction of PRW on HPA-axis measures as well, opposed to one pregnancy study which found lower awakening cortisol with higher anxieties (Van den Heuvel et al., 2018). There could be numerous explanations for these results, such as fewer reported cases of CM in our cohort compared to percentages provided by UNICEF (2010) about the prevalence of CM; or, any history of mood disorders or genetic factors.

Considering the non-significant association between CM and total and subtypes of PRW, and the non-significant mediation of PRW on cortisol measures, we failed to support the hypothesized mediation. However, when PRW was taken as a moderator, results showed that CM was predicting lower awakening cortisol, heightened CAR, and blunted DS with a significant moderation by PRW such that this effect was only observed in the high PRW group, but not in the low PRW group. Furthermore, this moderation effect was only present with PRW, but not with general state anxiety, suggesting a unique effect of PRW. This finding suggests that for pregnant women, CM and HPA-axis relationship is moderated by PRW rather than general state anxiety. These results are supporting the arguments by previous studies utilizing pregnancy-specific or related worries/anxiety over the general ones (Buss et al., 2010; Davis & Sandman, 2010; Huizink et al., 2003), which assert that PRW would be better predictors for pregnant women due to its higher maternal relevance (Hompes et al., 2013; Van den Heuvel et al., 2018). Considering previous studies that reported moderating effects current traumatic experiences (Swales et al., 2018) and perceived family functioning (Bublitz, Parade, & Stroud, 2014) on CM and HPA-axis

activity, my findings also increase our understanding about the possible moderators on this well-known relationship. The overall results here indicate that the proposition of PRW being a better predictor of distress is also present in the mid-pregnancy on the relationship between CM and various HPA-measures, enhancing its importance, especially in pregnant cohorts. Hence, future studies recruiting pregnant women would benefit from taking these specific worries into account.

An important point to discuss is the difference in the findings between the two sampling days. Contrary to finding expected differences in Day 1, there were no significant findings on Day 2. As similar day-to-day differences were previously reported in the literature (Gonzalez et al., 2009), it is possible to suggest that there may be different state factors or participant characteristics between the sampling days. From such data collected, it is shown that mood and daily worries differed significantly across the two days, which may contribute to the differences observed in this study. Interestingly, the results did not change when these variables were controlled, indicating possible indirect effects of mood and worry on the HPA-axis which may then lead to a difference between the days. Considering the fact that HPA-axis activity is also affected by mood, worries, depressive symptoms, and perceived social support (Stalder et al., 2016), these factors could mediate or moderate this relationship further. With the growing number of participants in the BABIP cohort, to further analyze this difference, multi-level modeling approaches could be utilized in the future with larger sample size. It is also possible that the differences are a result of differences between the participant characteristics each day since some participants had missing samples on Day 1 or Day 2.

In summary, this study showed that CM is associated with lower awakening cortisol, a higher CAR, and a blunted DS in pregnant women with high PRW. The direction of this effect did not specify a hypo- or hypercortisolism since lower awakening cortisol is signaling hypocortisolism but heightened CAR and blunted DS points a hypercortisolism, yet it indicates that it is a more complex system (Ceruso & Araminta, 2020) with more support towards the hypercortisolism from the present

findings. This study is one of first that showing the moderating effect of PRW on the relationship between total CM, as well as by utilizing several HPA-axis measures. As a result, it is a unique study by emphasizing the relevance and importance of PRW instead of general anxieties, especially on the complex relationship between CM and HPA-axis activity, thus, supporting its significance in pregnant women.

4.2 Strengths and limitations

This thesis produced from the BABIP birth cohort, the first longitudinal birth cohort from Turkey that includes biopsychosocial and physiological measures (Duman et al., 2020). Therefore, the findings are primarily critical in understanding the investigated relationships in Turkey's context and pregnant women's characteristics. Moreover, considering the limited number of studies on this topic, the study results are also important to be compared with similar international cohorts.

Regarding the factor structure of PRW, the results showed similar patterns with the original study and the Turkish version (Green et al., 2003; Yigit Gunay et al., 2015). The studies following the original one utilized a similar four-factor structure, yet with small differences, as in ours. For example, in the German version, socio-economic and relationship factors were merged and the health subscale was divided into the health of the baby and the mother/others (Petersen, Paulitsch, Guethlin, Gensichen, & Jahn, 2009). In terms of frequency, in the present study, the most frequently reported worries were about birth and baby (e.g. "the possibility of something wrong with the baby", "giving birth" and "relationship with the baby"). This was an expected finding since Gunay et al. (2015) also reported "giving birth" as the highest-ranked worry, followed by baby/birth outcomes and money problems (Gunay et al., 2015), similar to ours. These results increase the relevance and appropriateness of PRW in our cohort. Yet, it should be noted that this PCA was conducted with 72 people, which is a relatively low number of participants for this type of an analysis.

As methodological factors, the present study recruited participants from a specific trimester that is mid-pregnancy. Considering the enormous changes occurring in maternal HPA-axis throughout the pregnancy, and the importance of prenatal timing (Sandman & Davis, 2012), this part also decreases the possible variabilities due to differing gestation weeks and strengthens the interpretations about mid-pregnancy maternal factors. Moreover, this study also utilized cortisol samples from two consecutive days at multiple time points throughout the day, making it possible to investigate and compare different HPA-axis activity parameters (awakening cortisol, CAR, DS) together in one study. As discussed earlier, utilizing several HPA-axis measures helps us understand CM and HPA-axis relationship better. In terms of cortisol data collection and analysis, compliances of the sampling times were checked by both self-reports and call logs, which increases the reliability of the sample timing. This again strengthens the definitions of cortisol measures, increases the precisions of especially awakening cortisol and CAR. Besides, several mood and sleep measures were collected on the sampling days, as well as, many sampling problems (e.g., toothbrush) and disorders (e.g., chronic diseases) were controlled, in order to again enhance the power and clarification of the findings. Controlling for many factors that can influence cortisol measures enhances the power of the findings presented here.

Moreover, the present study participants were highly similar in terms of not having depression symptoms or related medication use, which may aid in observing the effect of CM and PRW on HPA-axis activity without the influence of any psychopathology or medication. Similarly, all participants in this study were married, making it possible to study the relationship between CM – PRW and HPA-axis without any major relationship differences, such as being a single mother compared to having a partner. These rather homogenous characteristics of participants in potentially confounding variables is a strength for comparing the hypothesized relationships.

Despite these strengths, the study also had several limitations to consider. First of all, our cohort was mainly from a middle-to-high socioeconomic background, especially in terms of education. In this sense, it represents a rather limited population in Istanbul, and in Turkey in general. Although observing the aforementioned findings in a sample that reported relatively low CM reports with a middle-to-high socioeconomic background, findings associations between CM, PRW, and HPA-axis activity indicates how strong these effects might be. However, having participants from a larger range of CM and socioeconomic status would aid in increasing the representativeness of the population. Furthermore, considering the minimum and maximum scores of the PRW and general state anxiety scales, our cohort had relatively low levels of worries and anxieties since no one reported scores close to the maximum score. Once again, though having extremes may trigger the addition of more participants with disorders or medication, it could still be enlightening to see whether the observed effects would change with more severe cases. Besides, inclusion of partner factors (e.g., paternal factors) may increase our understanding about the maternal health and may be beneficial towards the infant outcomes as well (Lamb, 2004). Lastly, the sample size was relatively small for studying mediation/moderation effects since a power analysis calculated by G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) with 2 main predictors suggest that 76 participants to obtain an 85% power, thus, recruiting more participants may expand the power of the findings.

Combining the significance of the findings and the limitations, there are several future steps that may be considered. First, the inclusion of lower socioeconomic status participants and those with higher CM may be beneficial to see how having participants along the full spectrum would influence the reported relationships. Second, there were many women reporting morning sickness which made it harder for them to provide saliva samples. Utilizing different methods for cortisol collection could be beneficial for future studies to both ease the procedures and eliminate the effect of confounding factors. Furthermore, combining the cortisol

data with biomarkers of other related systems, such as immune/inflammatory system markers may provide more insight into the mechanisms altered by CM. Considering the glucocorticoid sensitivity and other pathways between the endocrine and immune systems, it a well-known fact that they substantially interact with each other (Pariante, 2017). Relatedly, considering the influence of CM on immune system, depressive symptoms, HPA-axis and its interactions with immune markers (Pariante, 2017), the inclusion of proinflammatory cytokines, *per se*, may reveal a bigger picture of how CM and PRW influence health. Lastly, this study emphasized the relationship between CM and HPA-axis during mid-pregnancy. Following the participants of the present, BABIP cohort at their late pregnancy and collection of baby outcomes will complement these findings in the near future.

The results of this study critically emphasize the relevance and significance of PRW that pregnant women experience, suggesting that it may have the potential to exacerbate the relationship between CM and HPA-axis activity. The findings are in line with studies that show the highest interleukin-6 levels, a critical immune system marker, in the interaction of CMH with stress (Gouin, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012) and depressive symptoms at 2nd trimester (Walsh et al., 2016). Similarly, Pawlby et al. (2011) reported a greater risk of developing psychopathology in children born to mothers with a history of both CM and prenatal depression as well. In our study, we see a similar pattern for women with a history of CM and high PRW on HPA-axis activity that is not observed in those with low PRW or with general state anxiety. Furthermore, PRW had an aggravating effect on CM and stress systems as well. In support of this finding, a review from Turkey which focuses on maternal depression and its risk factors also reported fear of birth having an adverse influence on maternal health, signaling the importance of PRW in Turkish pregnant population as well (Çalık & Aktaş, 2011). Thus, future prevention and intervention strategies should consider PRW as a risk factor for pregnant women.

Regarding the association of sexual abuse history and CAR also implies that this specific abuse type may alter mother's concerns about their baby (Chamberlain et

al., 2019), and implications towards this specific group could be also valuable with consideration of PRW. Therefore, having a screening for PRW during pregnancy, particularly in women at risk, such as having a history of CM or specifically sexual abuse, may be an important addition to prenatal assessments, to support future maternal and offspring health. Yet, it should be noted that these results do not mean the only maternal factors have an impact on future health, yet, it is a more complex and the role of family and society is highly critical as well (Richardson et al., 2014).

APPENDIX A: SALIVA SAMPLING LOG SHEET (ENGLISH)

SALIVA SAMPLING LOG SHEET (ENGLISH)

BABIP PARTICIPANT NO: _____ T1 / T2 / T3 _

DAY 1 – FOLLOW UP (Date: / /)

	Tube 1: 1.Day	Tube 2: 1.Day 15Min	Tube 3: 1.Day 30Min	Tube 4: 1.Day	Tube 5: 1.Day 12:00	Tube 6: 1. Day 20:00
Sample Collection Time						
Sample to FREEZER						

How do you feel right now?

Happy	Very little 1–2–3–4–5–6–7	Very much
Nervous	Very little 1–2–3–4–5–6–7	Very much
Alone	Very little 1–2–3–4–5–6–7	Very much
Awake	Very little 1–2–3–4–5–6–7	Very much

ATTENTION!
Please do not forget to fill in the scale behind this form after taking the Day 1 – 0. Min Tube, Tube 1

IF YOU HAVE A QUESTION, PLEASE CALL US.

Do you have a different expectation from today? (An important job, etc.)
◯ **Yes** ◯ **No**

BABIP PARTICIPANT NO: _____ T1 / T2 / T3 TEL: _____

2. DAY FOLLOW UP (Date: / /)

	Tube 7: 2.Day	Tube 8: 2.Day 15Min	Tube 9: 2.Day 30Min	Tube 10: 2.Day	Tube 11: 2.Day 12:00	Tube 12: 2. Day 20:00
Sample Collection Time						
Sample to FREEZER						

How do you feel right now?

Happy	Very little 1–2–3–4–5–6–7	Very much
Nervous	Very little 1–2–3–4–5–6–7	Very much
Alone	Very little 1–2–3–4–5–6–7	Very much
Awake	Very little 1–2–3–4–5–6–7	Very much

ATTENTION!
Please do not forget to fill in the scale behind this form after taking the Day 2 – 0. Min Tube, Tube 7

IF YOU HAVE A QUESTION, PLEASE CALL US.

Do you have a different expectation from today? (An important job, etc.)
◯ **Yes** ◯ **No**

BABIP PARTICIPANT NO: _____ T1 / T2 / T3 _

1. DAY Sleep Diary

1. What time did you sleep last night?	_____:_____
2. Have you woken up and slept two or more times during the night?	◯ Yes ◯ No ◯ I do not know
3. How would you rate your sleep quality tonight?	Very bad O—O—O—O—O Very good (-2, 0, +2)
4. What time did you wake up this morning?	_____:_____
5. What time did you get out of bed?	_____:_____
6. How was the sound level of the environment where you slept last night?	Too quite O—O—O—O—O Very noisy (-2, 0, +2)
7. How was the light level of the environment you woke up this morning?	Too dark O—O—O—O—O Too bright (-2, 0, +2)
8. How much rest did you feel when you woke up?	Very little O—O—O—O—O Too much (-2, 0, +2)
9. How easily did you wake up this morning?	Too easy O—O—O—O—O Too hard (-2, 0, +2)
10. How is your current mood?	Too bad O—O—O—O—O—O—O—O—O Very good (-4, 0, +4)
11. How overwhelmed are you feeling right now?	Not at O—O—O—O—O—O Very (0, 5)
12. How worried are you today's saliva collection process?	Not at O—O—O—O—O—O Very (0, 5)

Your notes on the saliva collection process:

BABIP PARTICIPANT NO: _____ T1 / T2 / T3

2. DAY Sleep Diary

1. What time did you sleep last night?	_____:_____
2. Have you woken up and slept two or more times during the night?	◯ Yes ◯ No ◯ I do not know
3. How would you rate your sleep quality tonight?	Very bad O—O—O—O—O Very good (-2, 0, +2)
4. What time did you wake up this morning?	_____:_____
5. What time did you get out of bed?	_____:_____
6. How was the sound level of the environment where you slept last night?	Too quite O—O—O—O—O Very noisy (-2, 0, +2)
7. How was the light level of the environment you woke up this morning?	Too dark O—O—O—O—O Too bright (-2, 0, +2)
8. How much rest did you feel when you woke up?	Very little O—O—O—O—O Too much (-2, 0, +2)
9. How easily did you wake up this morning?	Too easy O—O—O—O—O Too hard (-2, 0, +2)
10. How is your current mood?	Too bad O—O—O—O—O—O—O—O—O Very good (-4, 0, +4)
11. How overwhelmed are you feeling right now?	Not at O—O—O—O—O—O Very (0, 5)
12. How worried are you today's saliva collection process?	Not at O—O—O—O—O—O Very (0, 5)

Your notes on the saliva collection process:

APPENDIX B

SALIVA SAMPLING LOG SHEET (TURKISH)

BABIP KATILIMCI NO: _____ T1 / T2 / T3

1. GÜN TAKİP KAĞIDI (Tarih: / /)

	Tüp 1: 1.Gün 0Dk	Tüp 2: 1.Gün 15Dk	Tüp 3: 1.Gün 30Dk	Tüp 4: 1.Gün 45Dk	Tüp 5: 1.Gün 12:00	Tüp 6: 1. Gün 20:00
Örneği toplama saati						
Örneği BUZLUĞA koyma						

Şu an kendinizi nasıl hissediyorsunuz?

Mutlu	Çok az 1–2–3–4–5–6–7	Çok fazla
Gergin	Çok az 1–2–3–4–5–6–7	Çok fazla
Yalnız	Çok az 1–2–3–4–5–6–7	Çok fazla
Uyanık	Çok az 1–2–3–4–5–6–7	Çok fazla

DİKKAT!
Lütfen 1. Gün 0 Dk. Tüp 1 örneğini aldıktan sonra bu formun arkasındaki ölçeği doldurmayı unutmayınız.

BİR SORUNUZ OLURSA BİZİ ARAYABİLİRSİNİZ.

Bugünden farklı bir beklentiniz var mı? (Önemli bir iş vb.)
◯ **Evet** ◯ **Hayır**

BABIP KATILIMCI NO: _____ T1 / T2 / T3 TEL: _____

2. GÜN TAKİP KAĞIDI (Tarih: / /)

	Tüp 7: 2.Gün 0Dk	Tüp 8: 2.Gün 15Dk	Tüp 9: 2.Gün 30Dk	Tüp 10: 2.Gün 45Dk	Tüp 11: 2.Gün 12:00	Tüp 12: 2. Gün 20:00
Örneği toplama saati						
Örneği buzluğa koyma saati						

Şu an kendinizi nasıl hissediyorsunuz?

Mutlu	Çok az 1–2–3–4–5–6–7	Çok fazla
Gergin	Çok az 1–2–3–4–5–6–7	Çok fazla
Yalnız	Çok az 1–2–3–4–5–6–7	Çok fazla
Uyanık	Çok az 1–2–3–4–5–6–7	Çok fazla

DİKKAT!
Lütfen 1. Gün 0 Dk. Tüp 1 örneğini aldıktan sonra bu formun arkasındaki ölçeği doldurmayı unutmayınız.

BİR SORUNUZ OLURSA BİZİ ARAYABİLİRSİNİZ.

Bugünden farklı bir beklentiniz var mı? (Önemli bir iş vb.)
◯ **Evet** ◯ **Hayır**

BABIP KATILIMCI NO: _____ T1 / T2 / T3 _

1. GÜN Uyku Günlüğü

1. Dün gece saat kaçta yattınız?	_____:_____
2. Gece boyunca iki veya daha fazla defa uyanıp geri uyudunuz mu?	◯ Evet ◯ Hayır ◯ Bilmiyorum
3. Bu geceki uyku kalitenizi nasıl değerlendirirsiniz?	Çok kötü O—O—O—O—O Çok iyi -2 0 +2
4. Bu sabah saat kaçta uyandınız?	_____:_____
5. Saat kaçta yataktan çıktınız?	_____:_____
6. Dün gece uyuduğunuz ortamın ses düzeyi nasıldı?	Çok sessiz O—O—O—O—O Çok gürültülü -2 0 +2
7. Bu sabah uyandığınız ortamın ışık seviyesi nasıldı?	Çok karanlık O—O—O—O—O Çok aydınlık -2 0 +2
8. Uyandığınızda kendinizi ne kadar dinlenmiş hissediyordunuz?	Çok az O—O—O—O—O Çok fazla -2 0 +2
9. Bu sabah ne kadar kolaylıkla uyandınız?	Çok kolay O—O—O—O—O Çok zor -2 0 +2
10. Şu anki ruh haliniz nasıl?	Çok kötü O—O—O—O—O—O—O—O—O Çok iyi -4 0 +4
11. Şu anda kendinizi ne kadar bunalmış hissediyorsunuz?	Hiç O—O—O—O—O—O Çok 0 5
12. Bugünkü tükürük toplama süreci sizi ne kadar endişelendirdi?	Hiç O—O—O—O—O—O Çok 0 5

Tükürük toplama süreciyle ilgili notlarınız:

BABIP KATILIMCI NO: _____ T1 / T2 / T3

2. GÜN Uyku Günlüğü

1. Dün gece saat kaçta yattınız?	_____:_____
2. Gece boyunca iki veya daha fazla defa uyanıp geri uyudunuz mu?	◯ Evet ◯ Hayır ◯ Bilmiyorum
3. Bu geceki uyku kalitenizi nasıl değerlendirirsiniz?	Çok kötü O—O—O—O—O Çok iyi -2 0 +2
4. Bu sabah saat kaçta uyandınız?	_____:_____
5. Saat kaçta yataktan çıktınız?	_____:_____
6. Dün gece uyuduğunuz ortamın ses düzeyi nasıldı?	Çok sessiz O—O—O—O—O Çok gürültülü -2 0 +2
7. Bu sabah uyandığınız ortamın ışık seviyesi nasıldı?	Çok karanlık O—O—O—O—O Çok aydınlık -2 0 +2
8. Uyandığınızda kendinizi ne kadar dinlenmiş hissediyordunuz?	Çok az O—O—O—O—O Çok fazla -2 0 +2
9. Bu sabah ne kadar kolaylıkla uyandınız?	Çok kolay O—O—O—O—O Çok zor -2 0 +2
10. Şu anki ruh haliniz nasıl?	Çok kötü O—O—O—O—O—O—O—O—O Çok iyi -4 0 +4
11. Şu anda kendinizi ne kadar bunalmış hissediyorsunuz?	Hiç O—O—O—O—O—O Çok 0 5
12. Bugünkü tükürük toplama süreci sizi ne kadar endişelendirdi?	Hiç O—O—O—O—O—O Çok 0 5

Tükürük toplama süreciyle ilgili notlarınız:

APPENDIX C

SALIVA SAMPLING GUIDELINE (ENGLISH)

This guide has been prepared to guide you step by step and remind you as you collect your saliva samples. You have 12 blue capped tubes that you will use for 2 days, and a yellow paper containing the sleep diary and sample hours for each day. Samples will be collected for 2 days at the following times:

Immediately after wake up, 15, 30 and 45 minutes after waking up, 12:00 noon and 20:00 pm.

When collecting samples, please continue your normal daily life, just make sure to follow the specified times and the following guidelines.

As detailed below, for each example, respectively: 1- We ask you to collect the sample on time, 2- Enter the time on yellow paper 3- Ring the phone, 4- Put the sample in the freezer and enter the time. Many thanks for your support in advance!

DAY BEFORE DAY SAMPLES:

o Please refer to Day 1 Tube 1 in the Day 1 bag provided, which is 0 Min. Put the tube (tube 1), yellow paper, this guide and a pencil on your bedside table at night.

o Please do not use lip balms, colds, allergies or sleeping pills and do not drink alcohol the day before. If you have used or have used one of the above, please inform us when we call you in the evening. We will call you between 20:30 and 21:30 as agreed with you the night before collecting Day 1 samples.

o If you wake up at a time other than the time you planned in the morning, it's okay, whenever you wake up, you can start collecting samples at that time.

o Please turn off the snooze / snooze feature of your alarm.

Please DO NOT within 45 minutes after waking up (during the FIRST 4 samples):

o Do not sleep back after waking up.

o Do not eat anything, smoke, drink or drink. Do not brush your teeth. You can drink water.

o Do not do activities that will physically tire yourself.

o If your gum is bleeding, do not collect the saliva sample.

Day 1- 0. Minute Sample (Tube 1)

When you wake up, when you wake up in the bed and put your feet on the ground, collect your saliva sample with the 1st Day - 0 Min tube.

o Open the tube by twisting the blue cap to the side.

o Put the cotton in the tube into your mouth without touching it and keep it under your tongue for 2 minutes. Please do not chew!

o Put the cotton back into the tube without touching it with your hands and close the blue cap tightly.

o Set your alarm 15 minutes later and keep it close to you.

o Put the 1st tube in the locked bag in the FREEZER section of refrigerator.

o Fill in the hour information and sleep diary on Day 1 yellow paper.

o Ring the lab phone given to you long so that we know that you have taken your first saliva sample. We will not open your call and we will get back to you with a message.

o Do not forget to follow the instructions on yellow paper for 15 minutes (no eating-drinking, smoking, brushing teeth, heavy physical activity).

Day 1 - 15. Minute Sample (Tube 2)

o Day 1 0 Min. When your alarm sounds 15 minutes after the sample, make sure to follow the instructions

o From Day 1 bag, Day 1 15 Min. Take the (Tube 2) tube. Keep the cotton under your tongue for 2 minutes, as in the previous example, and put it back in the tube and tightly close the blue cap.

o Set your alarm 15 minutes later and keep it close to you.

o Put the second tube in the locked bag in the freezer.

o Enter the time information on the yellow paper.

o Ring us over the phone long so we know that you have taken the sample

Day 1 - 30th Minute Sample (Tube 3)

o Day 1 30 Min. When your alarm sounds 15 minutes after the sample, be sure to follow the instructions.

o From Day 1 bag, Day 1 30 Min. Take the tube that says (Tube 3), keep the cotton under your tongue for 2 minutes, put it back in the tube and tightly close the blue cap.

o Set your alarm 15 minutes later and keep it close to you.

o Put the third tube in the locked bag in the freezer.

o Enter the time information on the yellow paper.

o Ring us over the phone long so we know that you have taken the sample

Day 1 - 45th Minute Sample (Tube 4)

o Day 1 30 Min. When your alarm sounds 15 minutes after the sample, be sure to follow the instructions.

o From Day 1 bag, Day 1 45 Min. Take the tube that says (Tube 4), keep the cotton under your tongue for 2 minutes, put it back in the tube and tightly close the blue cap.

o Set your alarm at 12:00 and keep it close to you.

o Put the 4th tube in the locked bag in the freezer.

o Enter the date and time information on the yellow paper.

o Make us ring over the phone.

Day 1 - 12:00 & 20:00 Samples: (Tube 5 & 6) 30 minutes before taking the saliva sample:

o Do not eat. Do not brush your teeth.

o Do not consume caffeinated or sugary foods and beverages and dairy products (such as tea, coffee, milk, cola, cheese, chocolate).

o Do not do activities that will physically tire yourself.

o Take samples as close as possible to 12:00 and 20:00, as in previous examples, and ring us for each sample.

Day 1 12:00 Sample (Tube 5)

o Please try to give saliva sample as soon as possible to 12:00 without having your lunch. Make sure to follow the instructions

o Take the tube from Day 1 bag, tube Day 1 12:00 (Tube 5), hold the cotton under your tongue for 2 minutes, put it back in the tube and tightly close the blue cap.

o Set your alarm at 20:00 and keep it close to you.

o If you are at home, place the sample in the freezer next to the other samples in Day 1 bag. Enter the time on the yellow paper and ring us.

o If you are out, put the tube in the extra locked bag provided to you, ring us. When you go home in the evening, place the tube next to the other samples in the freezer and enter the time to put it in the freezer on the yellow paper.

Day 1 - 20:00 Sample (Tube 6)

o Please try to collect samples as soon as possible at 20:00.

o Be sure to follow the instructions (no eating-drinking, smoking, brushing teeth, medication, heavy physical activity).

o Take the 1st Day 20:00 (Tube 6) tube from the 1st Day bag. Hold the cotton under your tongue for 2 minutes, put it back in the tube and close the blue cap tightly.

o Put the 6th tube in the locked bag in the freezer.

o Enter the time information on the yellow paper.

o Ring us over the phone long so we know that you have taken the sample

You have completed the 1st day samples, congratulations!

We will call you again for the second day as soon as possible.

Day 2 Samples (Tube 7-12):

For Day 2, you can follow the same instructions on Day 1.

Use the tubes in the 2nd day bag and fill the 2nd day yellow paper.

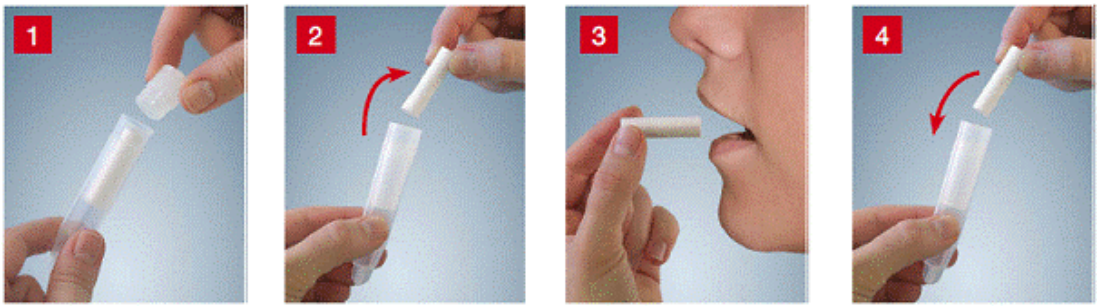
On Day 2, ring us at each sampling and keep the samples in the freezer.

Please follow the sequence below:

1. Day 2 0. Minute Tube (Tube # 7), Day 2 Sleep Diary
2. Day 2 15. Minute Tube (Tube # 8)
3. Day 2 30th Minute Tube (Tube # 9)
4. Day 2 45th Minute Tube (Tube # 10)
5. Day 2 12:00 Tube (Tube # 11)
6. Day 2 20:00 Tube (Tube # 12)

After completing the 2nd day samples in the freezer and filling the yellow paper, you have completed this stage of the experiment, thank you very much!

Keep the bags in the freezer. We will receive these samples and forms from you as soon as we have agreed together.



FREQUENTLY ASKED QUESTIONS

1. I forgot to collect the sample at the specified time, what should I do?

For the first 4 examples in the morning (wake up, after 15, 30 and 45 minutes):

If less than 2 minutes have passed, you can collect the sample IMMEDIATELY. Please write down how much time has passed on the note on the yellow paper. If more than 2 minutes have passed since you had to collect, call and inform us by phone, and we'll guide you.

For 12:00 noon and 20:00 in the evening:

You can take the samples within 1 hour of 12:00 and 20:00 according to your eating and drinking time:

For the example of 12:00, between 11:00 and 13:00.

For the example of 20:00, between 19:00 and 21:00.

2. I fell asleep after collecting the first sample in the morning, what should I do?

Do not collect the remaining samples and inform us by phone. Let's set up a new date for you to collect samples with.

3. I have eaten / smoked or smoked / brushed my teeth / engaged in heavy physical activity during the sample collection period, what should I do?

Whether it matters please inform us by phone so we can guide you. Note this situation on your yellow paper.

4. Can samples in the locked bag remain in the freezer with other food?

Yes, as long as his mouth is closed, there is nothing wrong with it.

PLEASE CONTACT US FOR COMPILING WITH THE INSTRUCTIONS GIVEN AND SUPPORTING OUR RESEARCH.

1. . Gün 0. Dakika Örneği (Tüp 1)

Uyandığınız anda yatağın içinde doğrulup ayaklarınızı yere bastığınızda, hemen önceki gece başucunuza koyduğunuz, **1. Gün 0 Dk.(Tüp 1)** tüpü ile tükürük örneğinizi toplayınız:

- Tüpün mavi kapağını yana doğru bükerek açınız.
- Tüpün içindeki pamuğu elinize çok değdirmeden ağzınıza atınız ve **2 dakika** boyunca dilinizin altında tutunuz. **Lütfen çiğnemeyiniz!**
- Elinize çok değdirmeden pamuğu tüpe geri koyunuz ve mavi kapağı sıkıca kapatınız.
- Alarmınızı **15 dakika** sonrasına kurunuz ve yakınınızda tutunuz.
- 1. tüpü kilitli poşet içinde buzdolabınızın **BUZLUK** kısmına koyunuz.
- 1. Gün **sarı kağıdındaki saat bilgilerini** ve **uyku günlüğünü** doldurunuz.
- Size verilmiş lab telefonunu uzunca çaldırınız ki ilk tükürük örneğinizi aldığınızı bilelim. Çağrınızı açmayacağız ve size mesajla geri döneceğiz.
- 15 dakika boyunca sarı kâğıttaki yönergelere uymayı unutmayınız (yeme-içme, sigara, diş fırçalama, ağır fiziksel aktivite olmadığına).

1. Gün 15. Dakika Örneği (Tüp 2)

- 1. Gün 0 Dk. örneğinden 15 dakika sonra alarmınız çaldığında, yönergelere uyduğunuza emin olunuz
- 1. Gün poşetinden **1. Gün 15 Dk. (Tüp 2)** tüpünü alınız. Önceki örnekte olduğu gibi pamuğu **2 dakika** dilinizin altında tutunuz, ve tüpe geri koyup, mavi kapağı sıkıca kapatınız.
- Alarmınızı 15 dakika sonrasına kurunuz ve yakınınızda tutunuz.
- 2. tüpü de buzluktaki kilitli poşetin içine koyunuz.
- **Sarı kağıda** saat bilgilerini giriniz.
- Bizi telefonla uzunca çaldırınız ki örneği aldığınızı bilelim.

1. Gün 30. Dakika Örneği (Tüp 3)

- 1. Gün 30 Dk. örneğinden 15 dakika sonra alarmınız çaldığında, yönergelere uyduğunuza emin olunuz.
- 1. Gün poşetinden **1. Gün 30 Dk. (Tüp 3)** yazan tüpü alınız, pamuğu **2 dakika** dilinizin altında tutunuz, tüpe geri koyunuz ve mavi kapağı sıkıca kapatınız.
  - Alarmınızı 15 dakika sonrasına kurunuz ve yakınınızda tutunuz.
- 3. tüpü de buzluktaki kilitli poşetin içine koyunuz.
- **Sarı kağıda** saat bilgilerini giriniz.
- Bizi telefonla uzunca çaldırınız ki örneği aldığınızı bilelim.

1. Gün 45. Dakika Örneği (Tüp 4)

- 1. Gün 30 Dk. örneğinden 15 dakika sonra alarmınız çaldığında, yönergelere uyduğunuza emin olunuz.
- 1. Gün poşetinden **1. Gün 45 Dk. (Tüp 4)** yazan tüpü alınız, pamuğu **2 dakika** dilinizin altında tutunuz, tüpe geri koyunuz ve mavi kapağı sıkıca kapatınız.
  - Alarmınızı 12:00'ye kurunuz ve yakınınızda tutunuz.
- 4. tüpü de buzluktaki kilitli poşetin içine koyunuz.
- **Sarı kağıda** tarih ve saat bilgilerini giriniz.
- Bizi telefonla uzunca çaldırınızız.

1. Gün 12:00 & 20:00 örnekleri: (Tüp 5 & 6)

Tükürük örneğini almadan 30 dakika önce:

- Yemek yemeyiniz. Dişlerinizi fırçalamayınız.
- Kafeinli veya şekerli yiyecek ve içecekler ve süt ürünleri tüketmeyiniz (çay, kahve, süt, kola, peynir, çikolata gibi).
- Kendinizi fiziksel olarak yoracak aktiviteler yapmayınız.
- Örnekleri, önceki örnekler gibi 12:00 ve 20:00 saatlerine olabildiğince yakın zamanlarda alınız ve bizi her örnek için çaldırınız.

1. Gün 12:00 Örneği (Tüp 5)

- Lütfen öğlen yemeğinizi yemeden saat 12:00'ye en yakın zamanda örnek vermeye çalışınız. Yönergelere uyduğunuza emin olunuz
- 1. Gün poşetinden **1. Gün 12:00 (Tüp 5)** yazan tüpü alınız, pamuğu **2 dakika** dilinizin altında tutunuz, tüpe geri koyunuz ve mavi kapağı sıkıca kapatınız.
  - Alarmınızı 20:00'ye kurunuz ve yakınınızda tutunuz.
- *Eğer evdeyseniz,* örneği 1. Gün poşetindeki diğer örneklerin yanına buzluğa koyunuz. Sarı kağıda zamanı giriniz ve bizi uzunca telefonla çaldırınız
- *Eğer dışardaysanız,* tüpü size verilen ekstra kilitli poşet içine koyunuz, bizi uzunca çaldırınız.
  Akşam eve gittiğinizde tüpü diğer örneklerin yanına buzluk kısmına koyunuz ve sarı kağıda buzluğa konma saatini giriniz.

1. Gün 20:00 Örneği (Tüp 6)

- Lütfen saat 20:00'ye en yakın zamanda örnek toplamaya çalışınız.
- Yönergelere uyduğunuza emin olunuz (yeme-içme, sigara, diş fırçalama, ilaç, ağır fiziksel aktivite olmadığına).
- 1. Gün poşetinden 1. Gün 20:00 (**Tüp 6)** tüpünü alınız. Pamuğu **2 dakika** dilinizin altında tutup tüpe geri koyunuz ve mavi kapağı sıkıca kapatınız.
- 6. tüpü de buzluktaki kilitli poşetin içine koyunuz.
- Sarı kağıda saat bilgilerini giriniz.
- Bizi telefonla uzunca çaldırınız ki örneği aldığınızı bilelim.
- **1. Gün örneklerini tamamladınız, tebrikler! ☺ İkinci gün için size en kısa zamanda tekrar arayacağız.**

2. Gün Örnekleri (Tüp 7-12):

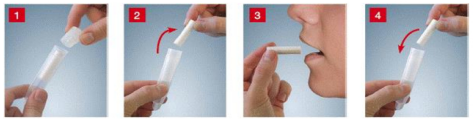
- 2. Gün için de 1. Gün'deki aynı yönergeleri takip edebilirsiniz.
- 2. Gün poşetindeki tüpleri kullanıp, 2. Gün sarı kağıdını doldurunuz.
- 2. Gün de her örnek alımınızda bizi çaldırınız ve örnekleri buzlukta saklayınız.

Lütfen aşağıdaki sırayı izleyiniz:

1. 2. Gün 0. Dakika Tüpü (Tüp #7), 2. Gün Uyku Günlüğü
2. 2. Gün 15. Dakika Tüpü (Tüp #8)
3. 2. Gün 30. Dakika Tüpü (Tüp #9)
4. 2. Gün 45. Dakika Tüpü (Tüp #10)
5. 2. Gün 12:00 Tüpü (Tüp #11)
6. 2. Gün 20:00 Tüpü (Tüp #12)

- **2. Gün örneklerini buzluğa koyup, sarı kağıdını doldurduktan sonra** deneyin bu aşamasını tamamlamış oluyorsunuz, **çok teşekkürler!** ☺

- Lütfen sizden teslim alınana kadar 2 günün poşetlerini de buzlukta tutunuz. Sizden bu örnekleri ve formlarınızı birlikte kararlaştırdığımız en yakın zamanda teslim alacağız.



- Notlar:

SIKÇA SORULAN SORULAR

1. **Belirtilen zamanda örneği toplamayı unuttum, ne yapmalıyım?**

Sabahki ilk 4 örnek için (uyanınca, 15, 30 ve 45 dakika sonra):
Eğer üzerinden 2 dakikadan az geçtiyse **HEMEN** örneği toplayabilirsiniz. Lütfen üzerinden ne kadar zaman geçtiğini sarı kâğıttaki not kısmına yazınız. Eğer toplamanız gereken zamanın üzerinden 2 dakikadan fazla zaman geçtiyse bizi telefonla arayıp bilgilendiriniz, sizi yönlendirelim.

Öğlen 12:00 ve Akşam 20:00 örnekleri için:
Örnekleri yeme-içme saatinize göre 12:00 ve 20:00'nin 1 saat yakınında alabilirsiniz:
12:00 örneği için 11:00-13:00 arasında.
20:00 örneği için 19:00-21:00 arasında.

2. **Sabah ilk örneği topladıktan sonra geri uyuyakalmışım, ne yapmalıyım?**

Geri kalan örnekleri toplamayınız ve bizi telefonla bilgilendiriniz. Sizinle örnekleri toplamanız için yeni bir tarih ayarlayabilelim.

3. **Örnek toplama süresi içerisinde bir şey yedim/içtim ya da sigara içtim/dişlerimi fırçaladım/ağır fiziksel aktivitede bulundum, ne yapmalıyım?**

Farkeder farketmez lütfen HEMEN bizi telefonla bilgilendiriniz ki sizi yönlendirebilelim. Sarı kağıdınıza bu durumu not düşünüz.

4. **Kilitli poşetteki örnekler buzlukta diğer yiyeceklerle kalabilir mi?**

Evet, ağzı kapalı oldukça, kalmasında hiçbir sakınca yoktur.

VERİLEN YÖNERGELERE UYDUĞUNUZ VE ARAŞTIRMAMIZA DESTEK OLDUĞUNUZ İÇİN TEŞEKKÜR EDERİZ.BİR SORUNUZ VEYA YÖNERGELERE UYAMADIĞINIZ BİR DURUM OLURSA, YARDIMCI OLABİLMEMİZ İÇİN LÜTFEN BİZİ ARAYINIZ:

TEL: _____

TÜKÜRÜK TOPLAMA KILAVUZU

Bu kılavuz tükürük örneklerinizi toplarken size adım adım yol göstermek ve hatırlatmalarda bulunmak için hazırlanmıştır. Elinizde 2 gün boyunca kullanacağınız 12 adet mavi kapaklı tüp ve her gün için uyku günlüğü ve örnek saatlerini içeren bir sarı kâğıt bulunmaktadır. **Örnekler 2 gün boyunca aşağıdaki saatlerde toplanacaktır:**
Uyanır uyanmaz, Uyandıktan 15, 30 ve 45 dakika sonra, Öğlen 12:00 ve Akşam 20:00.

Örnekleri toplarken lütfen *normal gündelik hayatınıza devam ediniz*, sadece belirtilen zamanlara ve aşağıdaki yönergelere uyduğunuza emin olunuz.

Aşağıda detayları verildiği üzere her bir örnek için sırasıyla:
1- Zamanında örneği toplama, **2-** Sarı kağıda zaman girme **3-** Lab telefon çaldırma, **4-** Örneği buzluğa koyma ve zaman girme işlemlerini yapmanızı rica ediyoruz.
Şimdiden desteğiniz için çok teşekkürler! ☺

1. GÜN ÖRNEKLERİNDEN ÖNCEKİ GÜN:

- Lütfen size verilen 1. Gün poşetindeki **1. Gün 0 Dk. (Tüp 1)** tüpünü, sarı kâğıdı, bu kılavuzu ve bir kalemi gece yatarken başucunuza koyunuz.
- Lütfen gece yatarken dudak kremi, soğuk algınlığı, alerji ya da uyku ilacı kullanmayınız ve alkol almayınız.
  Eğer yukarıda belirtilenlerden birini kullandıysanız ya da kullanmak zorundaysanız lütfen akşam sizi aradığımızda bizi bilgilendiriniz.
- 1. Gün örneklerini toplamanızdan önceki gece sizinle kararlaştırıldığı üzere 20:30-21:30 arası sizi arayacağız.
- Eğer sabah planladığınız saatten başka bir saatte uyanırsanız sorun değildir, ne zaman uyanırsanız, o saatte örnekleri toplamaya başlayabilirsiniz.
- Lütfen alarmınızın snooze/erteleme özelliğini kapatınız.

Lütfen uyandıktan itibaren 45 dk (İLK 4 örnek boyunca):

- **Uyandıktan sonra geri uyumayınız.**
- **Hiçbir şey yemeyiniz, sigara ve içecek içmeyiniz, ilaç almayınız. Dişlerinizi fırçalamayınız. Su içebilirsiniz.**
- **Kendinizi fiziksel olarak yoracak aktiviteler yapmayınız.**
- **Diş etinizde kanama olursa tükürük örneğini toplamayınız.**

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