Université de Montréal

The social regulation and genetic and environmental underpinnings of cortisol: A longitudinal genetically-informed study

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Thèse présentée à la Faculté des études supérieures et postdoctorales en vue de l'obtention du grade de *Philisophæ Doctor (Ph. D.)* en criminologie

Août 2022

Université de Montréal

École de criminologie

Faculté des études supérieures et postdoctorales

Cette thèse intitulée

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Résumé

Contexte : Bien qu'il ait été proposé que l'exposition à un faible statut socioéconomique (SSE) familial altère l'activité de l'axe hypothalamo-pituito-surrénalien et sa production de l'hormone cortisol, les résultats actuels sont incohérents et suggèrent la présence de facteurs supplémentaires susceptibles de modifier ces associations. Pourtant, peu d'études à ce jour ont adopté une approche développementale sensible au timing, à la stabilité et aux changements au sein du SSE familial lors de l'étude de l'association liant le SSE au cortisol. En outre, peu de travaux empiriques ont évalué si cette association est non linéaire ou si elle est modulée par le soutien social. Enfin, rares sont les études qui ont examiné dans quelle mesure cette association est affectée par les facteurs génétiques et par les processus gène-environnement, notamment à l'adolescence. **Objectifs** : Ancré dans une perspective de psychopathologie développementale, l'objectif principal de cette thèse est d'examiner les processus gène-environnement impliqués dans les associations entre le SSE et divers indicateurs de sécrétion cortisolaire mesurés à l'adolescence. Cette thèse a également examiné dans quelle mesure ces associations sont affectées par le timing, la chronicité et les changements au sein du SSE familial et sont atténuées par le soutien social. **Méthodes :** Les participants proviennent de l'Étude des jumeaux nouveau-nés du Québec, un échantillon populationnel de jumeaux recrutés à la naissance. Le SSE familial a été recueilli au cours de la petite enfance (0-5 ans) et à la mi-adolescence (14 ans). Le soutien social a été rapporté par les jumeaux à l'âge de 14 et de 19 ans. Le cortisol diurne (n=569) a été mesuré à l'âge de 14 ans au réveil, 30 minutes plus tard, l'après-midi et le soir pendant quatre jours non consécutifs. Le cortisol capillaire (n=704) a été mesuré à l'âge de 19 ans. **Résultats :** Cette thèse est composée de trois articles. Les résultats des deux premiers articles indiquent que l'étiologie génétique du cortisol au réveil et capillaire fluctuent au long du continuum du SSE mesuré à la petite enfance. Les formes que prennent ces interactions gène-environnement sont toutefois distinctes pour ces indicateurs. De plus, nos résultats révèlent la présence d'associations uniques entre le SSE familial mesuré à la mi-adolescence et la plupart des indicateurs cortisolaire, soit suivant une relation linéaire, ou non linéaire. Nous avons également trouvé que l'association liant le SSE au cortisol capillaire n'est pas expliquée par une étiologie génétique commune, mais semble refléter les effets de l'environnement partagé par les jumeaux. Enfin, les résultats du troisième article suggèrent que l'effet synergique du SES familial mesuré à la petite enfance et à la mi-adolescence prédisent la sécrétion cortisolaire.

De plus, l'association concomitante entre le SSE et le cortisol au réveil est modulée par le soutien social. **Conclusions :** Collectivement, ces résultats soulignent l'importance d'adopter une approche développementale et génétiquement informative lors de l'étude de l'association liant l'adversité aux systèmes physiologiques de stress. Un tel examen pourrait contribuer à une meilleure compréhension des mécanismes sous-tendant les disparités socioéconomiques précoces documentées en matière de santé, d'apprentissage et de comportements.

Mots-clés : statut socioéconomique, stress, axe HPS, cortisol, héritabilité, interaction gène-environnement, soutien social, timing, sensibilité au stress, étude de jumeaux.

Abstract

Background: While exposure to lower family socioeconomic status (SES) has been proposed to induce alterations in hypothalamic-pituitary-adrenal (HPA) axis activity and its production of the hormone cortisol, existing findings are inconsistent and suggest the presence of additional factors that may modify these associations. Yet, few of the past studies have taken a developmental approach sensitive to the timing, stability, and change within family SES when investigating the association between SES and cortisol secretion. Furthermore, little empirical attention has been devoted to assessing the possibility that this association might be nonlinear or is modulated by youth's perceived availability of social support. Lastly, the extent to which this association is affected by genetic factors as well as gene-environmental interplays has seldom been investigated, particularly in adolescence. **Objectives:** Rooted in a developmental psychopathology perspective, the present thesis's main objective is to examine the gene-environment processes implicated in the associations of family SES with multiple indicators of cortisol secretion during adolescence. This thesis also investigated to what extent these associations are affected by the timing, chronicity and change in SES and buffered by perceived social support. **Methods**: Participants are from the Québec Newborn Twin Study, a population-based sample of twin pairs recruited at birth. Family SES was collected in early childhood (ages 0–5) and mid-adolescence (age 14). Perceived social support was reported by twins at aged 14 and 19. Diurnal cortisol (n=569) was measured at age 14 at awakening, 30 min later, in the afternoon and evening over four non-consecutive days. Hair cortisol (n=704) was measured at age 19. **Results:** This thesis is comprised of three articles. The results of the first two papers indicate that the genetic etiology of adolescence awakening cortisol and HCC fluctuated along the continuum of early childhood family SES. The patterns of these gene-environment interactions were, however, distinct for these indicators. Furthermore, our results pointed to unique associations between mid-adolescence family SES and most of the diurnal and hair cortisol indicators, either according to a linear or nonlinear function. We also found that the association linking mid-adolescence family SES to HCC is not explained by a common genetic etiology but appears to reflect shared environmental effects. Finally, the results of the third paper revealed that the synergistic effect of early childhood and mid-adolescence SES predicted cortisol secretion. Moreover, the concomitant association between SES and awakening cortisol was found to be modulated by mid-adolescence social support. **Conclusions:** Collectively, these findings

underscore the necessity of espousing a developmental and genetically sensitive approach in studies investigating the impact of adversity on stress physiological systems. Such investigations may pave the way to a fuller understanding of the mechanisms underlying the early roots of socioeconomic disparities in health, learning and behaviours.

Keywords : socioeconomic status, stress, HPA axis, cortisol, heritability, gene-environment interplay, social support, timing, stress-sensitization, twin study.

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List of acronyms and abbreviations

SES : Family socioeconomic status

HPA axis : Hypothalamic-pituitary-adrenal axis

CRH : Corticotropin-releasing hormone

AVP : arginine vasopressin

ACTH : Adrenocorticotropin hormone

CAR : Cortisol awakening response

GRs : Glucocorticoid

MRs : Mineralocorticoid

HCC : Hair cortisol concentration

MZ : Monozygotic

DZ : Dizygotic

A : Additive genetic effects

D : Non-additive genetic effects

C : Shared environmental influences

E : Unique environmental influences

GxE : Gene-environment interactions

*r*GE : Gene-environment correlations

QNTS : Québec Newborn Twin Study

LICOs : Low-income cut-offs

À mon grand-père, Jean E. Cantave

Je suis sûre que tu es fier de moi de là-haut.

Acknowledgments

On dit souvent que ça prend tout un village pour élever un enfant. C'est de même pour un doctorat, car ça prend l'effort de toute une communauté pour arriver jusqu'au bout. C'est avec beaucoup de plaisir et d'émotions que je prends ma plus belle plume pour vous dédier ces quelques mots.

Je tiens à remercier mes parents, particulièrement ma mère, pour son soutien et les nombreux sacrifices qu'elle a fait sans relâche, ce qui m'a permis d'entreprendre des études aussi longues. Je vous aime.

Je remercie énormément ma directrice, Isabelle, pour son soutien inconditionnel, sa disponibilité, sa supervision et son mentorat. Merci de m'avoir accompagné pendant ces sept dernières années, de m'avoir inclus dans tes projets, de m'avoir offert un environnement d'apprentissage stimulant et surtout d'avoir toujours cru en moi. You rock!

Un grand merci à ma codirectrice, Mara, pour ses nombreux conseils, sa supervision et son mentorat. Merci d'avoir dédié autant de temps et d'énergie à mes projets et d'avoir toujours apporté une perspective unique et complémentaire à celle d'Isabelle.

Je remercie également la capoeira, mon professeur, contra-mestre Buscapé et ma famille capoeiriste. Sans vous et la capoeira, je ne serais pas arrivée jusqu'au bout. Merci pour votre soutien durant cette pandémie. La petite formule suivante (s'entrainer 6 jours sur 7, petite conversation sur l'heure du midi, jeux en ligne le samedi soir) a été essentielle pour garder ma santé mentale. Vous êtes les meilleurs !

Je tiens à remercier mes deux collègues, Marie-Pier et Stéphanie, pour les nombreux 5 à 7. Merci les filles pour votre soutien, les fous rires, et de m'encourager à toujours viser plus haut.

Enfin, un grand merci à Hermeline, Standley et Glawdys pour votre soutien inconditionnel. Je me sens vraiment chanceuse d'avoir une si belle communauté qui me soutienne, me challenge, et qui croit en moi, même quand j'ai des doutes. Vous êtes tous incroyables.

Introduction

Family socioeconomic status (SES) is one of the most consistent and robust predictors of child development across the lifespan, with effects detected as early as in the prenatal period of development and extending well into adulthood (Bradley & Corwyn, 2002; Kim et al., 2018). Family SES is a multidimensional concept, reflecting disparities in family social position and access to wealth (Pluck et al., 2021). While family SES has been extensively studied over the years, there is a lack of consistency in the definition and operationalization of this concept (Farah, 2017). In past studies, family SES has been measured using a wide array of indicators, spanning from single indicators of wealth and prestige (e.g., family income, educational attainment, occupational prestige) to composite scores of objective, subjective (i.e., perceived), and relative (i.e., having less than other families) index of SES (Farah, 2017; Tarullo et al., 2020). Regardless, past research has consistently shown that a significant proportion of children in the world are growing up in families that face socioeconomic disadvantage, even in the world's richest countries (Cai & Smeeding, 2020; Duncan et al., 2017). For instance, it is estimated that approximately 11% and 7.5% of Canadian children were living in low income families in 2019 and 2020, respectively, while this prevalence was estimated to reach 8.3% and 6.6% in the same years in the province of Québec (Statistics Canada, 2015). Although the vast majority of children face transient experiences of socioeconomic disadvantage, nearly 8% to 10% are reported to experience chronic socioeconomic deprivation (Duncan et al., 2017; Mazza et al., 2017; Séguin et al., 2012). Recent data have, however, indicated that the Canadian poverty rate has significantly declined in 2020 (Employment and Social Development, 2022). This may be explained, in part, by temporary government initiatives implemented during the pandemic and, as such, many fear that this improvement may be short-lived when these exceptional measures are no longer in effect (Buheji et al., 2020; United Nations, 2021). As family socioeconomic disadvantage is known to have broad and long-lasting repercussions on child development, in itself or in synergy with other risk factors linked to SES disadvantage (Duncan et al., 2017; Kim et al., 2018), the early roots of social inequities constitute a major public health, human rights, and social concern.

Compelling evidence from decades of research has indeed revealed that children growing up in more disadvantaged households are more susceptible to manifest impaired cognitive,

socioemotional and behavioural development, in addition to achieving lower educational attainment and to show poorer mental and physical health later in life (Duncan et al., 2017; Kim et al., 2018). Moreover, these children are at greater risks of experiencing higher and more intense levels of stress (Evans, 2004), which may undermine key physiological systems responsible for maintaining successful adaptation to stress, such as the hypothalamic-pituitary-adrenal (HPA) axis (McEwen & Seeman, 1999; Shonkoff, Richter, et al., 2012). This has led many scholars to propose that family socioeconomic deprivation may induce enduring alterations in HPA axis activity, which may in turn increase later risks for psychopathologies (McEwen & Stellar, 1993; Shonkoff, 2010). Yet, findings from past investigations examining the association between family SES and HPA axis activity through its production of the stress hormone cortisol are inconsistent (Bryson et al., 2021; Dowd et al., 2009; Gray et al., 2018; Koss & Gunnar, 2018). This mixed pattern of evidence may be explained, among other things, by previous studies failure to exert control over several confounding variables or to explore the possibility that this association may be modulated by individual and psychosocial factors (Bryson et al., 2021; Dowd et al., 2009; Fogelman & Canli, 2018). Indeed, existing research bears several shortcomings that prevent from a more refine understanding of the association linking family SES to cortisol secretion. First, most of earlier research has focused on children. However, as important developmental changes in cortisol have been documented in adolescence (Gunnar et al., 2009; Shirtcliff et al., 2012), these findings may not generalize well to youth. Second, relatively few investigations have considered and tested the possibility that the association linking family SES to cortisol might be nonlinear. Third, only a limited number of studies have adopted a time-sensitive approach when examining the SES-cortisol association. Therefore, it remains unclear whether this association may be affected by the timing, chronicity, and changes occurring in family SES from early childhood to mid-adolescence. Fourth, despite its clinical relevance, little empirical attention has been given to social support as a resource that may buffer the expected wear and tear of the HPA axis following experiences of socioeconomic deprivation. Fifth, while mounting evidence attests to the partly inherited nature of cortisol secretion (Ouellet-Morin, Brendgen, et al., 2016; Rietschel et al., 2017; Tucker-Drob et al., 2017), most of the past studies have failed to acknowledge and consider the confounding effect of genetic factors as well as gene-environment processes when testing for this association.

Aiming to address these gaps in knowledge, the current thesis sought to examine the genetic and environmental processes underlying the associations of early childhood and mid-adolescence SES

with adolescence diurnal and hair cortisol secretion. Furthermore, we investigated to what extent these associations are affected by the timing, chronicity and change within family SES and buffered by perceived social support. This doctoral dissertation is divided into six chapters. The first chapter begins by discussing the short-and long-term effects of family SES on child development. Next, family socioeconomic deprivation is presented as a catalyst of stress that can alter HPA axis activity and the secretion of its end-product, the stress-hormone cortisol. We then propose four factors that may affect the magnitude and direction of the association linking family SES to cortisol and conclude with the theoretical underpinnings of the present thesis. The second chapter presents a detailed description of the sample, as well as the procedures, measures, and analytical strategies used to investigate the objectives of this thesis. The subsequent three chapters are dedicated to the three constitutive articles of the thesis. More specifically, in chapter 3, we examine whether family SES during early childhood (0–5 years old) and mid-adolescence (age 14 years) are linearly or nonlinearly associated with three diurnal cortisol indicators (cortisol at awakening, CAR and diurnal pattern of secretion), all measured at age 14. We also tested whether the relative contribution of genetic and environmental factors to these cortisol indicators fluctuates as a function of the timing of family SES. In chapter 4, we investigate whether early childhood and mid-adolescence SES are phenotypically related to age 19 HCC and to what extent these associations are explained by common underlying genetic factors. Also, we estimate whether the genetic and environmental etiology of HCC vary according to the timing of family SES. In chapter 5, we evaluate the role of stability and change in family socioeconomic deprivation, as evidenced by lower SES, in predicting diurnal and hair cortisol secretion and test whether social support moderates these associations. Lastly, Chapter 6 provides a general discussion of the thesis findings, in which the results of the three main articles are briefly outlined and then thoroughly discussed.

Chapter 1
Literature Review

1.1 The short-term and lifelong consequences of family socioeconomic deprivation

It is well established that family socioeconomic disadvantage posits a threat to children's basic development across many domains of functioning (Kim et al., 2018; Shonkoff, Richter, et al., 2012). Research in the past decades has consistently observed a linear gradient between SES and health, as evidenced by worsening health as a function of decreasing SES and vice versa (Bradley & Corwyn, 2002; Kim et al., 2018). For example, past studies have indicated that low SES children have a greater risk of being born prematurely, having a low birthweight and dying at birth (Bradley & Corwyn, 2002; Parker et al., 1994; Public Health Agency of Canada & Pan-Canadian Public Health Network, 2018; Savitz et al., 2004; Weck et al., 2008). Children raised in low SES households are also more likely to show worse overall physical health and experience chronic health problems (e.g., asthma attacks, convulsions, vision and hearing problems) during early childhood (Nikiéma et al., 2010, 2012).

Differences are also noted in other spheres of development beyond physical health. Children growing up in lower SES families show more developmental delays in transversal competences such as social skills, emotional maturity, language, cognitive development, reading, writing and general knowledge in comparison to their socioeconomically advantaged peers (Bradley & Corwyn, 2002; Duncan et al., 2017; Levesque et al., 2021; Public Health Agency of Canada & Pan-Canadian Public Health Network, 2018). This is cause for concern considering that transversal competences acquired during early childhood are the stepping stones upon which more complex and specialized competencies can subsequently be built on (Heckman, 2012). Indeed, it has been found that children from lower SES background in early childhood have lower scores of readiness for school in addition to being more prone to display internalizing and externalizing behaviour problems at school entry (Bradley & Corwyn, 2002; Dearing et al., 2006; Duncan et al., 2017; Roos et al., 2019).

A comparable pattern of findings has been reported in adolescence, whereby youth growing up in families lower on the SES hierarchy are more susceptible to display physical health problems and chronic conditions that limit their activities and require treatment by a physician (Chen et al., 2006, 2007; Kozyrskyj et al., 2010; Levesque et al., 2021). Furthermore, lower SES youth show unhealthier behaviours, including poorer eating habits (e.g., saltier and fattier diet with fewer fruits

and vegetables), are less physically active and have a higher prevalence of obesity and drug use (Daniel et al., 2009; Levesque et al., 2021; Min et al., 2018; Narciso et al., 2019; Stalsberg & Pedersen, 2010). These youth also lag behind those from more privileged families in regard to their cognitive abilities as tested in standardized tests (Lemos et al., 2011; von Stumm & Plomin, 2015) and academic achievement (Lacour & Tissington, 2011; Zhang et al., 2020) and have a higher rate of school dropouts (Archambault et al., 2017). Moreover, they show higher levels of socioemotional and behavioural problems (Comeau & Boyle, 2018; Najman, Hayatbakhsh, et al., 2010; Slopen et al., 2010), substance abuse, delinquency, and violent crimes (Duncan et al., 2010; Rekker et al., 2015; Sariaslan et al., 2014). In sum, strong evidence suggests that socioeconomic inequity in health arises at an early age, is observed in childhood and adolescence and is associated with higher problems in multiple domains of functioning.

Aside from the short-term burden related to socioeconomic disadvantage, a number of longitudinal studies have indicated that exposure to these adverse experiences during childhood and adolescence may have latent, protracted and harmful influences on adult health and health-related behaviours (Cohen et al., 2010; Duncan et al., 2017). Findings from the Dunedin Multidisciplinary Health and Development study have demonstrated a graded association between lower childhood and adolescence SES and numerous physical health outcomes (e.g., higher body-mass index, waist: hip ratio and lower cardiorespiratory health) when participants reached age 26 and age 32, respectively (Melchior et al., 2007; Poulton et al., 2002). These findings were documented above and beyond participants' concurrent socioeconomic position in adulthood. Another longitudinal study, which investigated the childhood SES-health association in a sample of graduated male physicians, provided evidence that those who experienced socioeconomic deprivation during childhood were twice more likely to suffer from coronary heart disease (CHD) at age 50 years, even after controlling for other CHD-related risk factors (Kittleson et al., 2006). These findings are important as they point to the enduring effect of SES on health outcomes beyond changes in life circumstances, depicted in that study among individuals who have achieved upward socioeconomic mobility in adulthood. Turning to the work of Duncan and colleagues (2010), boys exposed to socioeconomic deprivation during the first five years of life were twice more likely to be arrested in their 30s than those from more advantaged backgrounds (Duncan et al., 2010). Concomitantly, others have reported that children exposed to chronic socioeconomic deprivation in early childhood and adolescence, or in adolescence only, showed higher rates of aggressive and delinquent

behaviours as well as depression and anxious symptoms at age 21 years (Najman, Clavarino, et al., 2010).

Altogether, existing findings provide extensive evidence highlighting the onset of socioeconomic disparities in physical and mental health, cognitive development, education attainment, as well as in socioemotional adjustment and antisocial behaviours. Provisional evidence from longitudinal studies points to unique, pervasive and long-lasting effects of lower family SES during childhood and adolescence on child development, irrespective of socioeconomic status in adulthood (Cohen et al., 2010; Duncan et al., 2017; Shonkoff, Richter, et al., 2012). In addition to trying to reduce these socioeconomic inequalities, considerable efforts have been devoted to elucidating the pathways through which lower childhood SES levels may jeopardize development and functioning in many areas of life. This quest is further incentivized by the fact that knowledge of these mechanisms is critical to implement selective interventions aiming to promote healthy developmental trajectories among socioeconomically deprived children (Cohen et al., 2010; Levesque et al., 2021). While many explanations have been put forward to account for this association, one that has received widespread and persistent attention is the early-stress hypotheses. That is, family socioeconomic disadvantage experienced during childhood and adolescence is viewed as an early stressor that may persist over time (Duncan et al., 2017; Evans & Kim, 2007, 2013; Kim et al., 2018). Both the early onset of stressors (timing) and their chronicity (cumulative) are argued to be key factors by which socioeconomic inequality might be associated with poorer health and socioemotional and behavioural adjustment problems later on (Shonkoff, 2010). The next sections propose an outline of the concepts and mechanisms believed to be involved in these early-stress hypotheses.

1.2 Family socioeconomic deprivation as a catalyzer of stress

Stress is defined as a threat to homeostasis (i.e., the stability of dynamic physiological processes that preserve life). That is, situations that are uncontrollable, unpredictable, new or that threaten the ego (i.e., personality) or physical safety are expected to trigger a stress response (Lupien, 2010; Miller et al., 2007). However, stressful situations do not all have comparable effects. More particularly, when a stressful event is experienced over a limited duration, is met with the necessary internal and external resources to cope and leaves a sense of exhilaration and accomplishment and mastery, it can be referred to as a good stress (or eustress). Conversely, challenging events such as

severe or prolonged family socioeconomic disadvantage that involve a loss of control or agency, that become emotionally taxing to the child or their parents, that exhaust personal and external resources or support to cope, or that are accompanied by other stressors (e.g., perceived dangerousness of the neighborhood) may result in distress (bad stress or toxic stress; McEwen, 2007; Shonkoff, Richter, et al., 2012). Accordingly, there is substantial evidence suggesting that children from lower SES households disproportionately experience more diverse and severe levels of physical and psychosocial stress in their family environment, and elsewhere, than do those from more privileged backgrounds (Amso & Lynn, 2017; Evans, 2004; Kim et al., 2018; Steptoe & Feldman, 2001). For example, lower SES children tend to live in overcrowded, noisy, chaotic and substandard housing conditions (Duncan et al., 2017; Evans, 2004). They also have greater chances of being exposed to more harsh and conflictual relationships within the household, of experiencing family disruption or separation, and of having parents with poorer mental health or who are themselves experiencing higher levels of stress (Essex et al., 2002; Evans, 2004; Kim et al., 2018; Letourneau et al., 2013). Furthermore, these children are more likely to experience more punitive, harsh, inconsistent and insensitive parenting practices that are not adjusted to the developmental stage of the child (Duncan et al., 2017; Letourneau et al., 2013) reaching, for some, the intensity to fall under the definition of maltreatment (Herrenkohl & Herrenkohl, 2007).

The documented risk for lower SES children to be exposed to more stressors of higher intensity is further compounded by the fact that they are reported to receive lower levels of social support within their family environment (Evans, 2004; Evans & Kim, 2013). Taken together, these findings suggest that experiences of socioeconomic disadvantage may curtail children's and parents' accessibility to much-needed tangible and intangible resources (e.g., money, time, information, social support, access to health services) that are necessary, although not sufficient, to promote a healthy and nurturing family environment. This, in turn, may also be conductive to more stressful family environments (Vaghri et al., 2013).

Beyond the family context, children from more disadvantaged households are more inclined to reside in violent and more deprived neighborhoods, with decaying infrastructure, inadequate municipal services, and fewer retail facilities, such as supermarkets (Evans, 2004; Kim et al., 2018). In addition to attending lower quality daycares, they have a greater risk of being enrolled in underperforming schools characterized by less qualified teachers, higher teacher turnover rates,

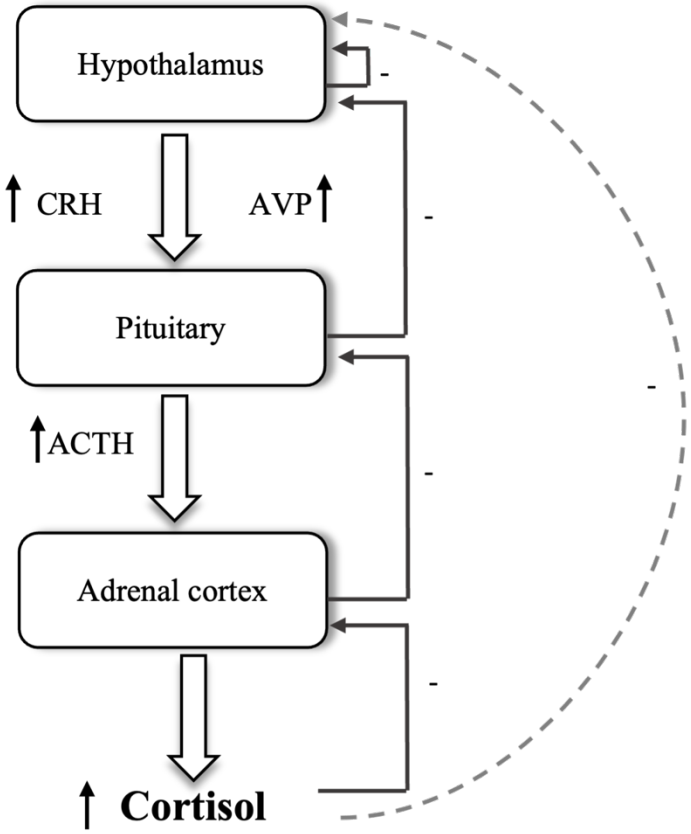
poorer infrastructure and school services, more inconsistent application of social norms regarding violence within their walls and overcrowding (Evans, 2004; Kim et al., 2018). In addition, these children are more susceptible to being exposed to peer victimization experiences (Tippett & Wolke, 2014). Aside from their greater exposure to stress, children whose families are lower on the SES hierarchy also show a greater vulnerability to the impact of stressors on their developmental trajectories than those from more fortunate backgrounds (Dohrenwend, 1974). Collectively, existent findings suggest that children from lower SES family environments may be more prone than those from wealthier backgrounds to be confronted to chronic and pervasive stressors, which has the potential to jeopardize their health and functioning in the long run (Koss & Gunnar, 2018; McEwen & Seeman, 1999; Shonkoff, Richter, et al., 2012). The question has thus moved toward *how* these lower SES-related stressful experiences may get under the skin and translate into risk for later developmental maladjustment.

1.2.1 Stress and normative physiological stress systems' activity and regulation

When an individual perceives a situation as uncontrollable, novel, unpredictable or threatening (e.g., incapacity to pay their bills or to buy food), their body coordinates the activation of multiple physiological systems, including the autonomic nervous system and the neuroendocrine system, during a short period of time in order to meet the metabolic needs of the organism (Flier et al., 1998; McEwen & Stellar, 1993). As such, brief activation of these physiological systems in the context of stressful situations is vital for survival (McEwen, 2007). The hypothalamic-pituitary-adrenal (HPA) axis is one of the core physiological systems implicated in the regulation of the body's response to stress (Koss & Gunnar, 2018; McEwen & Stellar, 1993). As its name implies, its main components include the hypothalamus, the pituitary gland and the adrenal cortex (see Figure 1). More specifically, the perception of stress triggers the activation of the HPA axis; neurons in the paraventricular nucleus of the hypothalamus release the corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which travel through the hypophysal portal circulation to the anterior pituitary gland. The latter reacts by releasing, in a pulsatile manner, the adrenocorticotropin hormone (ACTH), which is carried through the peripheral circulation to the adrenal glands. In response to ACTH, the adrenal glands synthesize and secrete the so-called glucocorticoid "stress hormone cortisol" (Gunnar & Vazquez, 2006; Miller et al., 2007). Cortisol

is notably responsible for mobilizing energy during stress and returning to baseline levels once the stressor subsides (Koss & Gunnar, 2018). Because of its liposoluble properties, cortisol can travel to the brain and bind to glucocorticoid receptors located in many brain structures, including in the pituitary gland, the hypothalamus, and the hippocampus to suppress stress reactivity (see the negative feedback loops in Figure 1). This, in turn, leads to a decrease in ACTH and CRH, and ultimately to a reduction to the baseline level of cortisol secretion (Koss & Gunnar, 2018; Lupien et al., 2006).

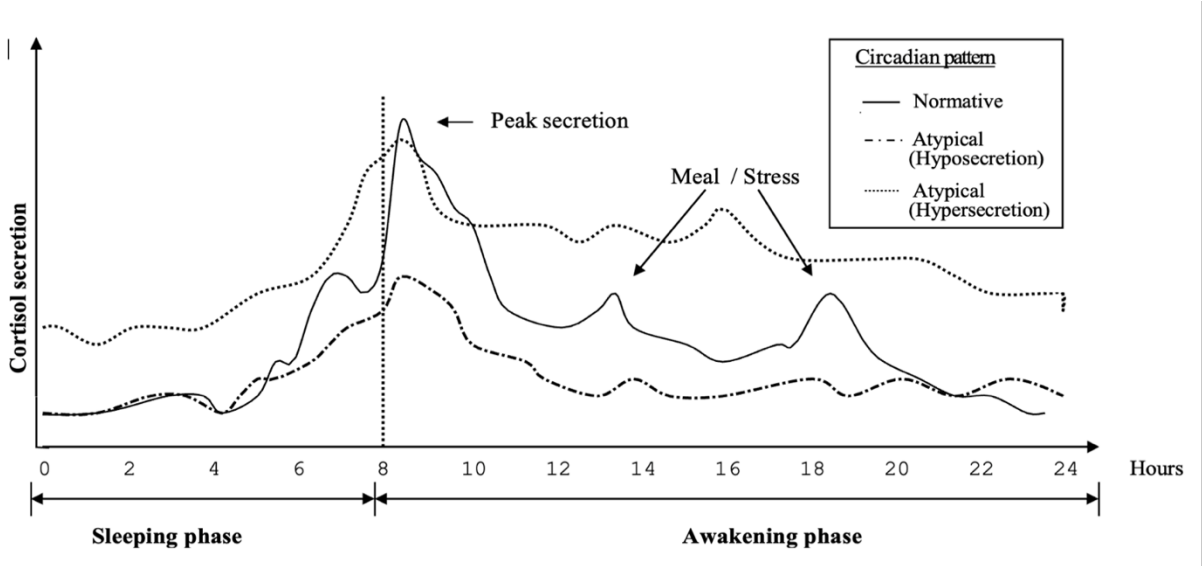
Figure 1. – Schematic overview of the Hypothalamic-Pituitary-Adrenocortical (HPA) axis



Aside from its secretion in response to stress, cortisol is released in the blood stream in a pulsatile manner at varying rhythms during the day. That is, cortisol typically follows a circadian rhythm (24 hours) characterized by a rise in cortisol levels after waking, reaching a peak 30 to 40 minutes later, following which a gradual decline is observed throughout the day until a minimum is reached

around midnight (see the normative circadian pattern in Figure 2; Koss & Gunnar, 2018). The peak cortisol observed 30 to 40 minutes after awakening is generally called the cortisol awakening response or CAR. Importantly, once released in circulation, cortisol binds to glucocorticoid (GRs) and mineralocorticoid (MRs) receptors (Koss & Gunnar, 2018). MRs are glucocorticoid-preferring receptors, and as such, are almost always occupied at low concentrations, which means at distinct degree throughout the day, except at the lowest point of the diurnal cycle. In contrast, GRs have a lower affinity to cortisol and are bound when cortisol levels increase in response to stress or is at the peak of the diurnal cycle (de Kloet & Meijer, 2019; Koss & Gunnar, 2018). As these receptors are available in almost all cells of the human body (Wilkinson & Imran, 2019), cortisol is implicated in the regulation of a wide range of physiological systems and functions that allow for successful adaptation to stress, including increasing the availability of glucose, reassigning energy to vital organs and functions (toward brain, muscles and away from unessential physiological processes such as digestion, physical growth, and reproduction), reducing inflammation, boosting attention to the immediate environment and facilitating defense-related learning and memory processes (Gunnar et al., 2015; Miller et al., 2007; VanZomeren, 2017). The widespread regulatory influence of cortisol on the body in both basal and stressful contexts is one of the overarching reasons why this hormone has received extensive research attention in the past decades (Miller et al., 2007; Nicolson, 2008).

Figure 2. – Normative and atypical profiles of cortisol secretion during a 24-hour cycle



Note. Figure reproduced from Étiologie des différences individuelles liées à la sécrétion cortisolaire à la petite enfance : une étude des facteurs génétiques et environnementaux by (Ouellet-Morin, 2008), © 2008, Isabelle Ouellet-Morin, edited with permission.

Over the last decades, cortisol activity and regulation have been assessed by various methods of collection, using different biospecimens, including blood, urine, saliva and, more recently, hair (Levine et al., 2007; Nicolson, 2008; Ryan et al., 2016). These assessments differ in a number of ways. Although blood and saliva cortisol measures are closely related and index shorter-span cortisol secretion, the former is indicative of total (i.e., protein-bound and unbound) cortisol production, while the latter is a measurement of free circulating (i.e., protein-unbound) cortisol release (Nicolson, 2008). In contrast, urine and hair samples provide integrated measures of long-term cortisol secretion, ranging from 12h or 24h (urine) to months (hair; Levine et al., 2007; Nicolson, 2008; Stalder et al., 2017).

Over the past decades, the use of salivary and hair samples to assess cortisol secretion has become more popular than the use of blood and urine samples (Koss & Gunnar, 2018). This may be explained by the relatively low cost of their related assays, but also by the simple and non-invasive nature of saliva and hair sampling procedures (Nicolson, 2008; Ryan et al., 2016). Another advantage of salivary cortisol over other biospecimen lies in its ability to measure the diurnal cortisol rhythm. Over the years, several approaches have been used to estimate the cortisol diurnal rhythm. At first, scientists used to collect a single or a few samples of saliva at specific time points during the diurnal cycle to measure individual differences in basal (i.e., nonstress) cortisol (Ryan et al., 2016). This indicator is usually termed according to the timeframe during which the sample was collected (e.g., morning, afternoon, evening, and bedtime cortisol). Increased funding, as well as methodological and statistical advances have led researchers to develop more refined indicators of diurnal cortisol secretion. That is, by collecting several saliva samples at key time points that are related to meaningful changes in cortisol circadian secretion (e.g., at awakening, 30 min later, in the afternoon and evening) investigators can reliably assess the cortisol diurnal rhythm. These saliva samples are typically measured over several (e.g., 3–4) days in order to obtain a more accurate and stable measurement of the cortisol diurnal rhythm (Nicolson, 2008; Ryan et al., 2016). Multiple diurnal cortisol indicators are commonly derived from these salivary samples, including (1) the awakening cortisol, reflecting cortisol levels after waking; (2) the CAR, representing the

magnitude of cortisol change observed from waking to about 30 minutes later, generally corresponding to the peak cortisol secretion in the morning; and (3) the diurnal slope, reflecting the degree of change across the day, from morning to evening (Koss & Gunnar, 2018; Ryan et al., 2016). Atypical patterns of diurnal cortisol secretion—as evidenced by a lower (i.e., hyposecretion, see Figure 2) or higher (i.e., hypersecretion) awakening cortisol, CAR and overall levels than expected (or the sample's mean) as well as a flatter diurnal slope—are considered to be indicators of a dysregulated diurnal cortisol secretion (Ryan et al., 2016).

In comparison to salivary cortisol, hair cortisol concentrations (HCC) provide a retrospective measure of cumulative cortisol secretion (Stalder et al., 2017). More specifically, cortisol is diffused into the cells of the hair follicle and is later stored in the hair shaft (Kirschbaum et al., 2009). Hair typically grows on average 1 cm per month at specific areas of the scalp. As such, the analysis of 3 cm long of hair segments allows capturing cortisol activity for the last 3 months prior to hair sampling, across a variety of contexts, including during daytime and nighttime diurnal secretion, as well as in response to minor, acute, repeated, or chronic stress and diurnal secretion (Kao et al., 2019; Kirschbaum et al., 2009; Stalder et al., 2017). Similar to indicators of diurnal cortisol secretion, both lower and higher HCC are expected to signal disruptions in HPA axis activity and regulation. Also, each of these diurnal and hair cortisol indicators are thought to capture specific, yet complementary, aspects of HPA axis functioning (Koss & Gunnar, 2018; Stalder et al., 2017). Thus, the examination of multiple cortisol indicators within the same participants offers a more comprehensive understanding of HPA axis activity in different contexts, timeframes and functions.

1.3 Impact of socioeconomic deprivation on HPA axis activity and regulation

As stated above, mounting evidence suggests that children growing up in more impoverished families are more susceptible to being exposed to higher levels of chronic stress within and outside of their family environment, which may bear consequences on their physiological stress systems (Evans, 2004; Kim et al., 2018; Shonkoff, Richter, et al., 2012). The Ecobiodevelopmental framework has identified three distinct profiles of physiological stress responses likely to be manifested in the context of stress—positive, tolerable, and toxic (Shonkoff, 2010; Shonkoff, Garner, et al., 2012). A positive stress response is defined by a brief and moderate activation of

physiological stress systems in response to normative stress (e.g., first day at school, giving an oral presentation in front of the class or taking an exam). A tolerable stress response represents a moderate to strong activation of these systems in response to threatening events (e.g., death of a parent, parental divorce, or community violence) that has the potential to instigate damages to physiological stress systems. However, these disruptions are circumvented by the protective effect of supportive relationships with adults that enable successful adaptation to stress. At last, a toxic stress response refers to strong, frequent, or prolonged activation of physiological stress systems triggered by challenging events, such as family socioeconomic deprivation, that occur in the absence of protective relationships with adults. Accordingly, this toxic stress response is expected to lead to the wear and tear of the HPA axis, as evidenced by atypical diurnal and hair cortisol concentrations (McEwen & Seeman, 1999; McEwen & Stellar, 1993; Shonkoff, 2010; Shonkoff, Garner, et al., 2012). This hypothesis, for which a brief review is proposed in the following sections, has gathered the attention of many scholars over the years. In order to facilitate the understanding of this great body of work, empirical findings will be first presented for diurnal cortisol indicators, followed by findings for HCC, the two cortisol indicators considered in the present thesis. Readers interested to learn more specifically about cortisol response to social stress are invited to consult (Dowd et al., 2009; Hooker et al., 2018; Malanchini et al., 2020).

Numerous studies, mostly cross-sectional, have offered evidence of altered HPA axis activity among children living in socioeconomically deprived households (Dowd et al., 2009; Koss & Gunnar, 2018), an association that has been detected as early as in infancy. For instance, Zalewski and colleagues (2012) documented a significant concurrent association between SES and cortisol measured in the morning in a sample of preschool children, whereby lower morning cortisol levels were found in children living in lower income households. These findings are not, however, consistent with several other studies that also measured morning cortisol secretion, but that reported higher levels of cortisol secretion among lower SES children (Gustafsson et al., 2006; Lupien et al., 2000, 2001). As an example, Lupien et al. (2000) assessed differences in morning cortisol level among Québec children from low, medium and high SES families. Their results revealed a higher morning cortisol secretion among low SES children in comparison to their more advantaged counterparts. Still, others have also documented nonsignificant findings (Cutuli et al., 2010; McLachlan et al., 2016).

A limited number of studies have additionally investigated the association between SES and the CAR, for which an inconsistent pattern of findings also emerged. More specifically, Saridjan and colleagues (2010) observed significant differences in the CAR of infant children as a function of their family income level, with children from lower income families exhibiting a higher CAR compared to those from higher-income families. However, the opposite pattern of results was reported in several other studies, which observed a lower CAR among children from lower SES families (Raffington et al., 2018; Zhu et al., 2019). Moreover, some studies failed to detect a significant association between SES and the CAR among children (Evans et al., 2020; Malanchini et al., 2020). Similarly, inconsistent findings have also been documented in studies assessing cortisol secretion in the later part of the day. While some investigations have provided evidence of a higher level of cortisol secretion in the afternoon, evening and at bedtime in lower SES children (Clearfield et al., 2014; Essex et al., 2002; Tarullo et al., 2020), others have reported null findings (Blair et al., 2011; Gustafsson et al., 2006; McLachlan et al., 2016; Zalewski et al., 2012). Turning to the work of those who have assessed the cortisol diurnal slope, one finds a remarkably similar depiction of findings. In a study of preschool children, Tarullo et al. (2020) found evidence of a flatter diurnal slope among 12-month-old children from less educated households. These findings stand in contrast with several other studies that did not detect significant associations between the diurnal slope and maternal education, family income and SES composite scores among infants and preadolescent children (Clearfield et al., 2014; Malanchini et al., 2020; Saridjan et al., 2010; Zalewski et al., 2012). Overall, available studies show a mixed pattern of results regarding the SES-cortisol association among children. These inconsistencies in results may be related to the great deal of variability noted in past studies in terms of the measurement of SES and cortisol indicators as well as the time of cortisol sampling (Dowd et al., 2009), with older studies being more likely to measure cortisol over one day and the more recent studies generally assessing cortisol over several days (2–4 days).

As previous studies have largely focused on children, little attention has been devoted to examining the SES-diurnal cortisol association in adolescents. This is surprising for many reasons. First, previous studies have shown important developmental changes in basal cortisol levels during the first two decades of life, characterized by lower cortisol secretions from toddlerhood to middle childhood, followed by a transition to higher secretions in adolescence (Gunnar et al., 2009; Shirtcliff et al., 2012). This developmental shift might be genetically influenced or induced by

environmental inputs. Second, adolescence is increasingly recognized as a period of heightened sensitivity of the HPA axis to environmental cues, both positive and detrimental (Koss & Gunnar, 2018). As such, experiences in adolescence may theoretically affect HPA axis functioning in itself, or else their impact might be exacerbated or reduced by the signal of earlier exposure to adversity (e.g., prenatally, early childhood). Third, past studies have documented a rapid increase of socioemotional and behavioural disorders in adolescence (Johnson & Wolke, 2013), which is presumed to be in part related to the higher exposure to stressors in adolescence combined with the above-mentioned higher sensitivity of the HPA axis (Kuhlman et al., 2017; Lupien et al., 2009).

Nevertheless, the few studies that have assessed this association in adolescence have also yielded inconclusive results. In an earlier study, Lupien and colleagues (2001) reported higher levels of morning cortisol in low SES children aged between 6 and 10 years compared to their high-SES peers. However, this association was not detected in adolescence in that same study, a finding that was later replicated by West et al. (2010) in a sample of 15-year-old youth. This suggests that morning cortisol measured during adolescence may be less sensitive to concurrent experiences of SES. In contrast, a handful of studies have provided evidence of a concurrent association between SES and evening cortisol, with youth from lower SES backgrounds evincing lower levels of evening cortisol (Chen & Paterson, 2006; Ford et al., 2021). Findings from a few longitudinal studies additionally revealed that family SES measured in childhood ***or*** adolescence may have long-lasting effect on diurnal cortisol secretion. For example, one study reported that childhood or adolescence SES significantly predicted diurnal cortisol secretion measured in early adulthood, with children and adolescents living in lower SES households showcasing a higher CAR and a flatter diurnal slope later on. Inversely, neither childhood or adolescence SES were found to predict awakening cortisol levels in early adulthood (Desantis et al., 2015). Another study documented a significant association linking SES measured in childhood and adolescence with higher morning cortisol in midlife, although this association disappeared after adjustment for adulthood SES (Li et al., 2007). Likewise, Gustafsson et al. (2010) found that adolescence SES was predictive of a higher CAR in midlife, only this time, this association remained significant even after adjusting for SES in adulthood. However, nonsignificant findings also exist (e.g., Franz et al., 2013). Taken together, available findings offer initial evidence of a dysregulated pattern of diurnal cortisol secretion taking the form of lower or higher concentrations in children and youth raised in lower SES households that seems to persist well into adulthood (Dowd et al., 2009).

Accumulating evidence from recent studies also points to an association between SES and HCC, with several studies reporting higher cumulative cortisol secretions among children raised in more disadvantaged households (Anand et al., 2020; Kao et al., 2019; Merz et al., 2019; Rippe et al., 2016; Ursache et al., 2017; Vaghri et al., 2013; Windhorst et al., 2017). For instance, a recent study found that children from lesser educated households exhibited a higher HCC (Merz et al., 2019). Other studies have also yielded contradictory findings, pointing to a nonsignificant association between SES and HCC in childhood (Alen et al., 2020; Bryson et al., 2019; Ertekin et al., 2021; Flom et al., 2017; Gerber et al., 2017; Hagaman et al., 2020; Karlén et al., 2013; Malanchini et al., 2020; Simmons et al., 2018) or a lower HCC among children with lesser educated fathers (Schloß et al., 2019). Although studies examining the SES-HCC association in samples comprising adolescents are scarcer, their results mirror those targeting exclusively children. In one study, a significant association emerged between SES and HCC, indicating higher HCC among children and adolescents from lesser educated families (Vliegenthart et al., 2016). Another study, however, reported lower HCC in children and adolescents from lower income families (White et al., 2017). Still other studies have reported null findings (Malanchini et al., 2020; Pluck et al., 2021). However, the majority of these studies focused on age heterogeneous samples, with the exception of Pluck et al., (2021).

In summary, evidence to date indicates an inconsistent pattern of findings, showing at times a nonsignificant association between SES and (salivary) diurnal and hair cortisol secretion, and revealing at other times altered cortisol secretion in children from lower SES contexts, taking the form of either higher or lower secretion than in children growing up in higher SES families (Bryson et al., 2021; Gray et al., 2018; Koss & Gunnar, 2018). Importantly, although there is currently no published meta-analysis on the SES-cortisol association, stronger evidence seems to emerge for both (salivary) diurnal and hair cortisol indicators measured in ***childhood***, while less convincing evidence emerged for cortisol measured during ***adolescence***. Collectively, these findings point to the possibility that living in lower SES family may exert a non-specific influence on HPA axis activity, affecting its activity across different timeframes, contexts and functions. However, the inconsistent patterns of association uncovered between SES and cortisol deserve more attention.

1.4. Factors that may affect the magnitude and directionality of the SES-cortisol association

The mixed pattern of findings observed for the associations linking SES to diurnal (salivary) cortisol and HCC seems to suggest a) that these associations are more complex than anticipated, b) that their magnitude and directionality may vary according to individual and psychosocial factors and c) that their robustness may be affected by confounding factors. In the next sections, we will delineate four groups of factors that have been argued to affect these associations, either as potential confounders or as moderators.

1.4.1 Methodological factors

The inconsistent findings uncovered for the SES-cortisol association may be the result of methodological differences between studies in regard to their sample characteristics (e.g., age, sex and ethnicity), the range of socioeconomic conditions captured in the study samples (e.g., at-risk versus population-based or privileged samples), the indicators of SES (e.g., single versus composite SES; dichotomized versus continuously distributed) and/or cortisol targeted (e.g., awakening cortisol, CAR, diurnal slope, HCC), the strategy used to measure them (e.g., one versus multiple collection days) and the study designs (e.g., cross-sectional versus longitudinal; Bryson et al., 2021; Chen et al., 2010; Ertekin et al., 2021; Fogelman & Canli, 2018). Discrepant findings may additionally arise because previous studies failed to consider nonlinear patterns of associations that may emerge between SES and cortisol secretion. Indeed, recent findings from a handful of studies suggest that the SES-cortisol association may not be adequately captured by linear functions (Deer et al., 2021; Ouellet-Morin, Cantave, Paquin, et al., 2021; Zalewski et al., 2016). For instance, Zalewski and colleagues (2016) reported that children from both higher and lower income families persistently showed lower levels of morning cortisol in comparison to those raised in families with an average income, who exhibited moderate levels of cortisol secretion. In another study, Deer et al. (2021) documented an inverted-U pattern of association between early childhood family income and mid-adolescence CAR, with children from lower income families exhibiting both lower and higher CAR. Although not the focus of the present dissertation, Ouellet-Morin et al. (2021) have also found evidence of a nonlinear pattern of association between HCC and peer victimization, with higher HCC found among boys exposed to both lower and higher experiences of peer victimization in comparison to those experiencing moderate levels of victimization from 6

to 15 years. Such findings suggest that a complete examination of any adversity-cortisol associations should comprise a test of nonlinear associations as well.

1.4.2 The timing, persistence, and change within family SES

The mixed pattern of findings observed for the SES-cortisol association may also emerge because previous studies omitted to examine the influence of time-related factors, such as the timing, chronicity, and changes in exposure to socioeconomic deprivation over time. While SES is often examined as a static construct, evidence suggests that SES may change over time as this concept is moderately stable (McFarland & Hayward, 2014; Serwinski et al., 2016; West et al., 2010). These methodological constraints may obscure the "real" magnitude or changing directionality of the SES-cortisol association. Accordingly, several theoretical models have provided arguments implying that time may play a central role in the SES-cortisol association (Cohen et al., 2010; Duncan et al., 2017). This includes several early-stress hypotheses, such as those related to the biological embedding of early stress, the cumulative effects of stress persisting during childhood, as well as the sensitization (or habituation) effects of early stress. According to the biological embedding hypothesis proposed by the Ecobiodevelopmental framework, the impact of socioeconomic deprivation on HPA axis activity is most pronounced when these experiences occur during childhood (Shonkoff, 2010; Shonkoff, Garner, et al., 2012). Indeed, the brain structures involved in the regulation of the HPA axis are rapidly maturing during childhood (Lupien et al., 2009; Shonkoff, 2010). As such, early adversity, such as socioeconomic disadvantage, is expected to affect the development of the HPA axis, hence the idea of biologically embedded traces left by these early experiences. Importantly, these traces could contribute to calibrating the axis as a means to adapt to an environment that may remain adverse over the life course (Shonkoff, 2010; Shonkoff, Garner, et al., 2012). According to this hypothesis, family socioeconomic deprivation experienced during childhood is expected to affect HPA axis functioning in adolescence, beyond (or irrespective of) concurrent family SES. While this hypothesis is widely known in the field and is an extension of the concepts of critical/sensitive periods of development, few investigations have formally tested it (Desantis et al., 2015; Li et al., 2007; Young et al., 2019). In an earlier study, Li and colleagues (2007) reported significant associations between childhood and adult SES in regard to morning cortisol secretion measured in adulthood. However, only adult SES had a unique effect when analyzed simultaneously with childhood SES. Likewise, Desantis and colleagues (2015) leveraged SES measured at several developmental periods (prenatal/birth, toddlerhood, middle childhood,

adolescence, and early adulthood) to find that childhood SES was not uniquely associated with awakening cortisol levels, the CAR and the diurnal slope beyond SES experienced at other time points. Importantly, however, they did not find evidence of unique associations between the cortisol indicators and SES measured at other developmental periods either (Desantis et al., 2015). To the best of our knowledge, only one study evaluated this hypothesis in regard to cortisol secretion measured in adolescence (McFarland & Hayward, 2014). Their results revealed unique associations between lower mid-adolescence awakening cortisol and family socioeconomic deprivation measured during infancy and mid-adolescence among girls. No associations, however, emerged with *childhood* family disadvantage or for adolescent boys. In short, to date, a pattern of findings opposite to the biological embedding hypothesis has emerged, pointing to significant associations between concurrent or more recent SES and cortisol. Yet, for the most part, none were observed for childhood SES. Moreover, it remains unclear whether these preliminary results might extrapolate to adolescence HCC, as past studies have primarily focused on diurnal cortisol indicators assessed in adulthood. Lastly, beyond the independent and cumulative impact of SES, it is also possible that childhood SES might interact with SES measured at a later developmental stage to predict cortisol. Yet, this alternative hypothesis was not tested in the aforementioned studies.

Some scholars have proposed the idea of interactive effects between adversity experiences encountered at distinct points over development (Desantis et al., 2015; Ellis et al., 2017; Gustafsson et al., 2010). Based on the sensitization hypothesis, applied to socioeconomic adversity, early socioeconomic deprivation may reprogram the HPA axis toward an upregulated pattern of (re)activity when exposed again to the same stressor later on (Daskalakis et al., 2013). According to this hypothesis, the impact of socioeconomic disadvantage in adolescence on higher cortisol secretion is expected to be exacerbated in children raised in more underprivileged households during childhood. Alternatively, the attenuation hypothesis posits that early adverse experiences may increase children's susceptibility of showing a dampened HPA axis activity when they encounter similarly stressful situations later on (Susman, 2006; Trickett et al., 2010). Based on this hypothesis, socioeconomic deprivation experienced during adolescence should be associated with attenuated cortisol secretion in youth who grew up in lower SES households during childhood. Evidence supporting either of these claims still awaits, as the only study to date that has investigated whether childhood SES modulated the association between later SES and adult

cortisol secretion has reported nonsignificant findings (Young et al., 2019). In sum, few studies have as of yet formally tested whether the timing, persistence and changes in SES can help uncover more robust associations between SES and cortisol, particularly in adolescence.

1.4.3 Perceived availability of social support resources within the youth network

Many theoretical frameworks have suggested that the impact of repeated or persistent stress may vary according to the degree of social support available within the youth's network of proximal relationships (e.g., parents, friends, siblings and teachers; Cohen & Wills, 1985; Gunnar & Hostinar, 2015; Shonkoff, 2010). Social support refers to the perception or experience of being loved, cared for, esteemed and valued by others and being a member of a network of reciprocal obligations (Cobb, 1976; Taylor, 2011). Generally, social support is assessed either according to the structure of the network of relationships (i.e., number of relationships the person has or the pattern of these social ties) and the functions served by network members (i.e., the perception of available resources from these relationships that might aid in adapting to stress; described below; Cohen & Wills, 1985; Gottlieb & Bergen, 2010; Taylor, 2011). As such, functional measures of social support are particularly relevant to the study of stress and will be the only one referred to in the following pages. Three broad dimensions of functional social support are commonly recognized: a) Information support refers to assistance in defining, understanding, and finding resources or acquiring knowledge to help coping with stress; b) Instrumental support designates the provision of tangible resources such as financial help, material resources and services; and c) Emotional support involves listening, caring and expressing the acceptance and esteemed value of the person for whom they are (Cohen & Wills, 1985; Taylor, 2011). Previous studies have shown that children can draw support from many members of their social network (Furman & Buhrmester, 1985). While parents are the primary sources of support during the early years of life, as children grow, they cultivate a wider network of social ties within which they gain additional support (Gottlieb, 1991). Therefore, a more detailed understanding of children and youth perceived social support requires to examine different relationships from which they may receive support, including parents, but also siblings, friends, romantic partners and teachers (Furman & Buhrmester, 1985).

It has been proposed that the perception of social support may help alleviate or eliminate the adverse impact of chronic stressors, such as socioeconomic deprivation, on physiological stress

systems (Cobb, 1976; Cohen & Wills, 1985; Shonkoff, 2010; Taylor, 2011). More specifically, social support is presumed to protect the HPA axis against the harmful impact of socioeconomic deprivation by facilitating the adoption of coping strategies that enable successful adaptation to stress. These expected protective effects are aligned with the stress-buffering hypothesis, which further contends that the shielding effect of social support on HPA axis activity is more likely to be expressed in high stress as opposed to low stress environments (Cohen & Wills, 1985; Taylor, 2011). Accordingly, the association linking lower family SES to cortisol is anticipated to be weaker (or nonexistent) among children receiving higher levels of social support, whereas the association should be more prominent in children who do not benefit from this support. Prior evidence, mostly coming from experimental studies conducted in laboratory settings, has offered some support to the stress-buffering hypothesis, as it has shown reduced cortisol reactivity to psychosocial stress among participants who received social support as part of the experiment in comparison to those who did not (Gunnar, 2017; Taylor, 2011). Although there is initial evidence of an association linking social support to diurnal (Heaney et al., 2010; Rickard et al., 2016; Sjögren et al., 2006) and hair cortisol (Iob et al., 2018), relatively few investigations have examined the stress-buffering role of social support in the association between SES and cortisol. To the best of our knowledge, only one study has examined this hypothesis, targeting young adults (Hooker et al., 2018). Their results revealed that, among participants with lower social support, those exposed to lower subjective SES had higher cortisol secretion during stress recovery from a psychosocial stress test than participants from higher subjective SES context. This association was not, however, significant among participants reporting higher social support (Hooker et al., 2018). Still, this pattern of findings did not extend to parental educational attainment. While not directly testing the stress-buffering role of social support, another study assessed the moderating effect of subjective and objective (i.e., parental educational attainment) SES in the association between daily social support and diurnal cortisol secretion and found nonsignificant results (Hooker et al., 2020). In sum, although many scholars have postulated that social support facilitates successful adaptation to stress, available evidence on its specific role in the SES-cortisol association rests on a handful of studies, with inconsistent findings. It is difficult to make strong inferences from these studies because they have measured distinct hypotheses, focused on divergent cortisol indicators, measured different social support components (daily versus trait-like perceived support) and only targeted parental educational attainment as an objective measure of SES. Additional studies

assessing distinct cortisol indicators within the same participants would provide a more in-depth understanding of the stress-buffering role of social support in these associations.

1.4.4 Genetic influences and gene and environmental interactions

Another factor that may modulate the SES-cortisol association that has received limited research interest over the years pertains to the partly inherited nature of cortisol secretion. That is, individuals of all ages differ significantly in their cortisol secretion (Smyth et al., 1997). Previous genetically informative studies (e.g., twin studies) posited that, ultimately, these individual differences in cortisol may be explained by environmental and by genetic influences (Bartels, Van den Berg, et al., 2003; Kupper et al., 2005). Twin-based study designs constitute a powerful tool to assess the heritability of cortisol secretion as they make it possible to disentangle the influence of genetic from environmental factors by comparing the similarity of monozygotic (MZ) twins to that of dizygotic (DZ) twins (Neale & Cardon, 1992a; Ouellet-Morin, Brendgen, et al., 2016). Moreover, genetic and environmental factors can be further divided into four possible latent (i.e., unmeasured) sources of variation. Genetic influences can be decomposed into additive genetic effects (A) and non-additive genetic effects (D). Additive effects refer to the independent effects of genes whereas non-additive influences denote the effects due to the interaction between alleles of the same locus (dominance) or located at different loci (epistasis). Environmental influences include environmental effects that are shared by members of a family (C) (e.g., family SES, neighborhood and school characteristics) and environmental effects that are unique to each member of a family (E) (e.g., friends and quality of relationships with parents and teachers, Bartels et al., 2003; Ouellet-Morin, 2013). Of note, given that the estimation of C and D both rely on the same information (i.e., difference between the MZ and DZ within-pair correlations), these parameters cannot be estimated within the same model in a typical twin reared together study design (Neale & Cardon, 1992a).

Evidence from a handful of twin studies suggests that both genetic and environmental factors contribute to individual differences in diurnal and hair cortisol secretion. Findings from an early meta-analysis have revealed that basal cortisol is strongly influenced by genetic factors, with heritability estimates accounting for 62% of the variation in twin cortisol levels (Bartels, Van den Berg, et al., 2003). Given that the factors that regulate cortisol secretion at different times of the day likely vary, subsequent studies took this into account while estimating their genetic and

environmental influences. In general, these studies found moderate genetic influences on cortisol levels in the early morning but low to nonsignificant genetic influences later in the day (Franz et al., 2010; Linkowski et al., 1993; Ouellet-Morin et al., 2009, 2016; Van Hulle et al., 2012; Wüst et al., 2000; Young et al., 2000). For instance, in a sample of twin pairs aged 9 to 16 years, a moderate influence of genetic factors on cortisol levels at awakening (28%) was observed, which reached about twice this magnitude for the CAR (60%), and was rather low in the evening (8%) (Gustafsson et al., 2011). Similarly, Schreiber and colleagues (2006) revealed that individual differences in evening cortisol were predominantly explained by shared environmental factors (i.e., 62%) in a sample of children and adults (Schreiber et al., 2006). Conversely, Steptoe and colleagues (2009) found that evening cortisol was more genetically influenced, with genetic contributions explaining 58% and nonshared environmental contributions accounting for 42% of the phenotypic variation in cortisol levels among children and adolescents (Steptoe et al., 2009). Altogether, available findings suggest that genes make a stronger contribution to individual differences in cortisol levels earlier in the day, whereas environmental factors seem to be the main source of influence during the rest of the day (Kupper et al., 2005). Later evidence further specified that the CAR is influenced by both dominant and additive genetic factors and is under stronger overall genetic influence than cortisol secreted at awakening (Ouellet-Morin et al., 2016). Furthermore, Ouellet-Morin et al. (2016) tested whether unique or common sources of genetic variation were present across these cortisol indicators. Specifically, although the contribution of genetic factors to the CAR was largely unrelated to awakening cortisol levels and diurnal slope levels, evidence of correlated nonshared environmental influences was documented for all three cortisol indicators. This was not the case for shared environmental influences, however (Ouellet-Morin et al., 2016). These findings fell in line with prior evidence suggesting that the CAR is under distinct regulatory processes from cortisol secreted in the remaining part of the diurnal cycle (Clow et al., 2004; Clow et al., 2010). The CAR is also argued to reflect the level of the body's preparedness to confront an upcoming period of activity or stress. During the rest of the day, however, the role of the HPA axis is primarily to maintain homeostasis and therefore may depend more on environmental stimuli (Gustafsson et al., 2011; Kupper et al., 2005).

Relative to diurnal cortisol, very little is known about the genetic and environmental etiology of HCC (Rietschel et al., 2017; Tucker-Drob et al., 2017). Yet, as this cortisol indicator encompasses extended periods of time and contexts, the etiological patterns documented for diurnal cortisol

indicators may not readily generalize to HCC. Initial evidence from the only two studies conducted on the matter so far suggests that HCC is more strongly influenced by genetic factors in comparison to the diurnal (salivary) cortisol indicators, even compared to the CAR. Indeed, approximately 65–72% of variation in HCC was found to be explained by inherited factors in children and youth (Rietschel et al., 2017; Tucker-Drob et al., 2017), which is consistent with the fact that HCC reflect more stable patterns of cortisol secretion. Overall, findings from twin studies revealed that diurnal and hair cortisol are shaped by both genetic and environmental influences, even though the magnitude of these influences varies according to each cortisol indicator. Nevertheless, there are caveats inherent to these studies that may obscure their interpretation, namely the presumption that genetic and environmental influences arise independently of each other, which implies that the estimates of the genetic and environmental contributions may be biased (Brendgen et al., 2012).

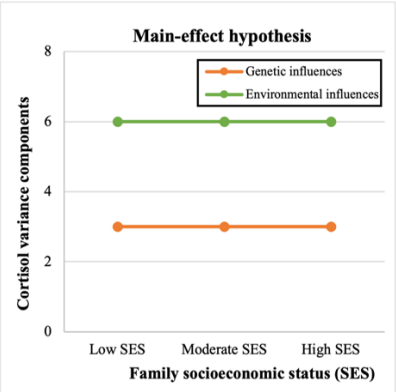
At a biological level, it is clear that genetic and environmental sources of variation do not combine additively but synergistically and dynamically for most complex phenotypes, including cortisol secretion (see Figure 3; Brendgen et al., 2012; Meaney, 2010). At a statistical level, genetic and environmental factors may be intertwined through at least two mechanisms: Gene-environment interactions (GxE) and Gene-environment correlations (*r*GE). Gene-environment interactions (GxE) refers to instances where the relative contribution of genetic factors to variation in cortisol varies according to environmental circumstances (e.g., family SES) or vice versa (Brendgen et al., 2012). At least two forms of gene-environment interactions can be expected. On the one hand, in line with the diathesis-stress hypothesis of GxE (see Figure 3, Panel B), the genetic factors related to cortisol may become expressed to a greater extent in stressful environments rather than in more favorable ones (Shanahan & Hofer, 2005). Evidence in favor of this hypothesis is found in a study where the heritability of morning cortisol was shown to be under stronger genetic influence (estimated heritability: 69%) among 6-month-old twins exposed to high family adversity, which encompassed several SES indicators (e.g., lower family income and maternal education). Morning cortisol levels were otherwise entirely accounted for by unique environments at the lower levels of family adversity (Ouellet-Morin et al., 2009). On the other hand, in line with a suppression hypothesis of GxE (see Figure 3, Panel C), inherited factors associated with cortisol may be reduced—or entirely silenced—in stressful environments in comparison to more advantaged ones (Shanahan & Hofer, 2005). A suppression pattern of GxE has been documented for cortisol responses to a novel social situation, whereby genetic factors explained 40% of the variance at

lower levels of family adversity, whereas shared and unique environmental effects accounted for all the variance in cortisol reactivity in children exposed to higher levels of adversity (e.g., low family income and maternal education; Ouellet-Morin et al., 2008). In contrast, the only study that has tested these GxE hypotheses in regard to HCC has documented a nonsignificant trend for larger genetic estimates in lower SES contexts (Tucker-Drob et al., 2017). Altogether, few studies have assessed these GxE hypotheses in regard to diurnal and hair cortisol secretion, notably in adolescence.

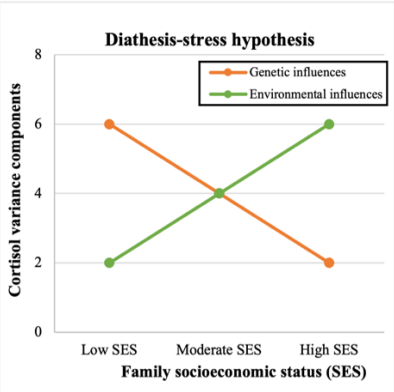
Gene-environment correlations (*r*GE) constitute another process of gene-environment interplay that may affect the SES-cortisol association. On the level of the species *r*GE may arise through natural selection, whereby environmental exposures shape the genotype. At an individual level, however, gene-environment correlations refer to genetically influenced exposure to environments (e.g., family SES, Brendgen et al., 2012). One way for gene-environment correlations to unfold is through passive *r*GE. More specifically, it has been proposed that parents' genetic predispositions influence the environments that they provide to their children (Moffitt, 2005). As a result, for example, some parents may pass down to their child genetic susceptibilities for atypical cortisol secretion, sensitivity to stress, or coping, while concomitantly providing a socioeconomically deprived family environment that may reflect their poor capacities to regulate stress (Moffitt, 2005). Although previous evidence from twins and genome-wide association studies have shown that SES is under low-to-moderate genetic influence (i.e., estimated heritability: 6–40%, Branigan et al., 2013; Hill et al., 2016; Marees et al., 2021), no studies to date, to our knowledge, have investigated whether SES and cortisol have a common genetic etiology.

Figure 3. – Overview of the theoretical additive and gene-environment interplay hypotheses

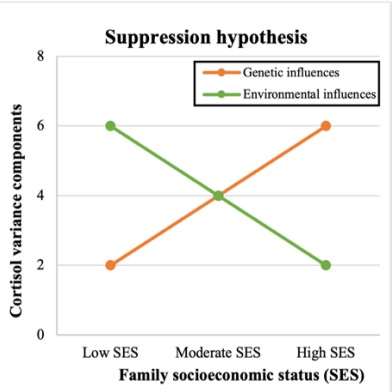
Panel A



Panel B



Panel C



In sum, little is known about the role of gene-environment etiology and interplay in the association linking SES to diurnal and hair cortisol. Moreover, the only available studies that have investigated GxE hypotheses have focused exclusively on young children (Ouellet-Morin et al., 2008, 2009) or an age-heterogeneous sample (aged 7.80 to 19.47 years; Tucker-Drob et al., 2017). As initial empirical observations suggest that the heritability of cortisol likely fluctuates with age (Tucker-Drob et al., 2017), the weak evidence for GxE in hair cortisol may not generalize to adolescence. Moreover, it is currently unknown whether these gene-environment processes may vary according to the timing of family SES (i.e., childhood versus adolescence) or whether gene-environment correlations may underlie the SES-cortisol association. It is critical to fill these gaps of knowledge to refine our understanding of the etiology of adolescence diurnal and hair cortisol secretion, first in light of the association between SES and these cortisol indicators, and second in regard to how this genetic and environmental etiology varies according to the SES continuum.

1.5 Problem statement and objectives

It has consistently been found that family SES experienced in early life has endemic and prolonged effects on mental and physical health as well as behavioural functioning (Cohen et al., 2010; Duncan et al., 2017; Kim et al., 2018). Lower family SES has been proposed to exert its lasting impact on later development, in part, through the dysregulation of HPA axis activity and cortisol secretion (Koss & Gunnar, 2018; McEwen & Seeman, 1999; Shonkoff, Garner, et al., 2012). Despite decades of research, the scientific evidence linking family SES in childhood and adolescence to diurnal and hair cortisol secretion remains unclear (Bryson et al., 2021; Gray et al., 2018; Koss & Gunnar, 2018). This mixed pattern of findings may be due, among other things, to past studies' failure to exert control over several confounding factors (Bryson et al., 2021; Fogelman & Canli, 2018) or to explore the possibility that these associations are modified by individual and psychosocial factors. Indeed, existing research bears several caveats that prevent a clearer understanding of the SES-cortisol association. First, past studies have mainly targeted children. As important developmental shifts in cortisol have been documented in adolescence (Gunnar et al., 2009; Shirtcliff et al., 2012), these earlier findings may not extrapolate to adolescence. Studies in adolescence should nevertheless be conducted because of (1) the higher prevalence of socioemotional and behavioural difficulties documented in adolescence as well as (2) the neuronal and neurophysiological reorganization puberty may bring about, which may

impact HPA axis activity (Johnson & Wolke, 2013; Koss & Gunnar, 2018). Second, preliminary findings have highlighted that the association between SES and diurnal and hair cortisol secretion may not be best modeled by linear functions (Zalewski et al., 2016). Yet, most of the previous investigations of the association that may emerge between SES and diurnal cortisol and HCC have ignored this possibility. Third, several theoretical models have surmised the critical role of time in the SES—cortisol association (Cohen et al., 2010; Daskalakis et al., 2013; Duncan et al., 2017; Shonkoff, Garner, et al., 2012). To date, however, few are the studies that have tested whether these associations differ according to the timing, chronicity, and changes in SES. Indeed, the majority of existing studies are cross-sectional. Fourth, most studies have shown a great heterogeneity in cortisol secretion among children living in lower SES households. It has been hypothesized that social support may act as a buffer, thereby preventing the expected wear and tear of the HPA axis following socioeconomic deprivation (Cobb, 1976; Cohen & Wills, 1985; Shonkoff, 2010; Taylor, 2011). Despite the relevance of this hypothesis for prevention research, relatively little is known about the stress-buffering role of social support in these associations. Fifth, findings from genetically informative studies have highlighted the inherited nature of diurnal and hair cortisol secretion (Ouellet-Morin, Brendgen, et al., 2016; Rietschel et al., 2017; Tucker-Drob et al., 2017). They have also suggested that the genetic etiology of cortisol may fluctuate according to environmental circumstances (Ouellet-Morin et al., 2008, 2009). Yet, most studies to date have failed to consider (or adequately controlled for) the confounding effect of genetic factors when testing for the magnitude and directionality of the SES-cortisol association. Moreover, it remains unclear (1) whether the SES-HCC association is partly explained by a shared genetic etiology and; (2) whether the relative strength of genetic influences on diurnal and hair cortisol is dependent on SES and its developmental timing.

Aiming to address these gaps in knowledge, the current thesis sought to examine the genetic and environmental processes underlying the association of early childhood (0–5 years old) and mid-adolescence SES (age 14) with adolescence diurnal and hair cortisol secretion. Moreover, we tested to what extent these associations are modulated by the timing, chronicity and changes in SES and buffered by social support. Specifically, three objectives were pursued, each corresponding to the three articles that are at the core of the present thesis. First, we tested in the first article whether family SES during early childhood (0–5 years old) and mid-adolescence (age 14 years) are linearly or nonlinearly associated with three diurnal cortisol indicators (cortisol at awakening, CAR and

diurnal pattern of secretion), all measured at age 14. We also examined whether the relative contribution of genetic and environmental factors to these cortisol indicators fluctuated as a function of the timing of family SES. Second, we investigated in the second article whether early childhood and mid-adolescence SES are phenotypically related to age 19 HCC and to what extent these associations are explained by common underlying genetic factors. Also, we estimated whether the genetic and environmental etiology of HCC vary according to the timing of family SES. Thirdly, we evaluated in the third article the role of stability and changes in family socioeconomic disadvantage, as evidenced by lower SES, in predicting diurnal and hair cortisol secretion and tested whether social support moderates these associations.

This investigation may best be pursued in a developmental psychopathology framework considering the multilevel analysis approach to investigate the association between early childhood and mid-adolescence family SES on diurnal and hair cortisol. More specifically, this framework underscores the need for a multilevel assessment of risk and protective factors addressing biological (e.g., genetic factors), psychological and social (e.g., perceived social support) and contextual (family SES) factors—as well as their interaction—to understand individual differences in adaptive and maladaptive developmental outcomes (Cicchetti, 2016; Toth & Cicchetti, 2013). This theoretical framework also recognizes that environmental circumstances may lead to distinct biological outcomes across development and that earlier experiences may affect the response to later experiences, as well as their putative impact on developmental outcomes (Toth & Cicchetti, 2013). At last, this framework draws attention to the importance of investigating the impact of risk factors in conjunction with protective factors to better understand normative and atypical development (Cicchetti, 2016; Toth & Cicchetti, 2013). In sum, findings from this dissertation may contribute to narrowing knowledge gaps and may yield new insights in and refinements of early-life stress models and hypotheses, the entirety of which are anchored in a developmental psychopathology framework.

Chapter 2
Methodology

From a statistical standpoint, observing a significant association between family SES and diurnal and hair cortisol is far from sufficient in itself to provide a thorough and meaningful understanding of these associations. A more profound comprehension of these associations requires, among other things, to investigate the multilevel factors relative to the individual, their development as well as their psychosocial and contextual environment, likely to affect the SES-cortisol association. Therefore, the main objective of this dissertation is to examine the genetic and environmental processes underlying the association linking family SES to diurnal and hair cortisol indicators. In addition, we also evaluated to what extent these associations were affected by the timing, persistence and changes in SES and buffered by social support. This chapter begins with a brief description of the study sample, namely the Québec Newborn Twin Study (QNTS). Subsequently, the procedure and the measures are detailed, followed by a thorough description of the analytical approach adopted in each of the three constitutive articles of the thesis described in chapters 3 to 5.

2.1 Study sample

Participants were part of the QNTS, an ongoing prospective and repeated longitudinal follow-up of a birth cohort of twins born between 1995 and 1998 in the greater Montréal area. Twins were recruited from the Québec Newborn Twin registry, which identified all twin births occurring in the Province of Québec between April 1995 and December 1998. Names, addresses, and phone numbers of all the mothers of newborn twins were collected from the computerized birth records of the Québec Bureau of Statistics. Starting June 1st 1996, all parents of newly born twins in the registry living in the greater Montreal area were contacted by a letter and by phone to enroll in the QNTS. Of the 989 families contacted during the 3 years of recruitment, 662 (68%) agreed to participate in the first wave of data collection. Twins were first seen at 5 months of age and then prospectively assessed during preschool (at 5, 20, 32, 50, 64 months), kindergarten (6 years old), primary (ages 7, 9, 10 and 12 years old), secondary (ages 13, 14, 15 and 17), and postsecondary school (ages 19 and 23) on a variety of children characteristics (e.g., cognitive development, school achievement, social behaviours, and mental health symptoms) and environment (e.g., family income, parenting behaviours and peer relations).

Twins were comparable to a population-representative sample of single births in the province of Québec (Boivin et al., 2019). At the time of the twins' birth, 95% of parents lived together, 44% of them were the firstborn, 66% of mothers (Mean=40.47, *SD*=4.81, range=17-43) and 60% of fathers (Mean=33.08, *SD*=5.75, range=20-63) were between 25 and 34 years old, and 17% of mothers and 14% of fathers had not finished high school. Furthermore, 28% of mothers and 27% of fathers held a university degree, 83% of the parents were employed, 10% of the families received social welfare or unemployment insurance, while 30% of families had an income of <$30,000. During the twins' childhood and adolescence, between 16% and 28% of families reported income levels below the low-income cut-offs (LICOs), defined by Statistics Canada (2016) as an income-to-need threshold below which a family has to spend a larger proportion of its income on necessities in comparison to the average Canadian family (for more information, see Table 1). Most families were Whites (86%), 6% were Blacks, 6% were Asians and 0.3% were Native North Americans. Zygosity was assessed using 8–10 highly polymorphous genetic markers. Twins were diagnosed as monozygotic when concordant for all genetic markers. When genetic material was insufficient or unavailable (43% of cases), zygosity was determined based on physical resemblance questionnaires at 18 months and again at age 9 (Spitz et al., 1996). The comparison of both methods in a subsample of 237 same-sex pairs revealed a 94% correspondence rate (Forget-Dubois et al., 2003). Information on saliva samples at 14 years of age was available for 592 twin pairs [280 monozygotic (MZ), 204 same-sex dizygotic (DZ) and 108 mixed-sex DZ twin pairs; 52% girls] from whom most (74%) had collected saliva across each of the four collection days. Information on hair samples, collected when the twins were 19 years of age, was available for 422 twin pairs [161 MZ, 121 same-sex DZ, and 140 mixed-sex DZ twin pairs; 61% girls].

Table 1 - Description of the range of socioeconomic deprivation captured in the sample according to the low-income cut-offs provided by Statistics Canada.

Income assessments				
5 months (*1st wave*) ***Twins' birth years**	**1995**	**1996**	**1997**	**1998**

Low-income cut-offs for 4 persons (size of family unit) and Urban areas of 500, 000 and over (Statistics Canada, 2001) before tax	$31,753	$32,238	$32,759	$33,063
28.3% reported income levels below $30,000 and 44.7% reported income levels below $40,000.				
18 months (*2nd wave*)	**1996**	**1997**	**1998**	**1999**
Low-income cut-offs for 4 persons (size of family unit) and Urban areas of 500, 000 and over (Statistics Canada, 2001) before tax	–	–	–	$33,659
21.1% reported income levels below $30,000 and 34.8% reported income levels below $40,000.				
2.5 years (*3rd wave*)	**1997**	**1998**	**1999**	**2000**
Low-income cut-offs for 4 persons (size of family unit) and Urban areas of 500, 000 and over (Statistics Canada, 2001) before tax	–	–	–	$34,446
22.2% reported income levels below $30,000 and 35.2% reported income levels below $40,000.				
4 years (*4th wave*)	**1999**	**2000**	**2001**	**2002**
Low-income cut-offs for 4 persons (size of family unit) and Urban areas of 500, 000 and over (Statistics Canada, 2001) before tax	–	–	$35,313	$36,107
16.3% reported income levels below $30,000 and 27.2% reported income levels below $40,000.				
14 years (*13th wave*)	**2009**	**2010**	**2011**	**2012**
Low-income cut-offs for 4 persons (size of family unit) and Urban areas of 500, 000 and over (Statistics Canada, 2001) before tax	$41,307	$42,065	$43,292	$43,942
20.1% reported income levels below or equal to $40,000 and 29.9% reported income levels below or equal to $50,000.				

Note. This table shows the low-income cut-offs (LICOs) reported by Statistic Canada for the years during which family income was assessed in the QNTS. The LICOs are an income-to-need threshold below which a family must spend a larger proportion of its income on necessities in

comparison to the average Canadian family. The third line of the table shows the LICOS reported by Statistics Canada during the time when family income level was first assessed in the QNTS (i.e., between 1995 and 1998), whereas the subsequent grey line displays the proportion of families at the first assessment time reporting an income level below the LICOs. The same information is provided for the succeeding family income level assessment times.

2.2 Procedure related to saliva and hair samples for cortisol measurement

At age 14 years, letters detailing the objectives of the study were sent to the families, followed by a home visit. After informed consent from the parents and assent from the teenage participants were obtained, trained research assistants explained the saliva collection protocol, which consisted in sampling saliva at four-time points during the day (at awakening, 30 min later, late in the afternoon and bedtime) on four collection days (Tuesdays and Thursdays on two non-consecutive weeks) and recording the exact time at which samples were collected. The research assistants ensure that participants and their parents were familiar with the material and the collection protocol before leaving. Families were visited a second time to gather the saliva tubes and to administer interview-based questionnaires to parents and twins, which included several questions on factors likely to affect cortisol secretion (e.g., pubertal stage, medication intake, drug and alcohol consumption, physical health problems, etc.). Parents received $15 and each twin received $30 as a compensation for their complete participation to the data collection. Moreover, twins who provided all of their saliva samples were eligible to participate in a draw for a Wii Sports game console.

At age 19 years, twins were invited to our laboratory for a new data collection. Upon their arrival, participants were once more informed about the study procedures after which they provided their signed and informed consent. The visit, which lasted approximately 1h40 minutes, was conducted at the Ste-Justine Hospital Research Center and comprised the collection of several biological samples (i.e., mouth swabs, blood drops and hair samples) and the completion of self-reported questionnaires regarding twins psychological and physical health (for more information on all activities held during the lab visit, see Table 2). For those who showed reticence to the lab visit, a home visit (with trained research assistants) or postal participation were suggested. Approximately 15% (n=116) of the twins chose these latter alternatives, including 3.74% (n=28) who opted to

collect and mail their samples to the laboratory. Specifically, hair samples of at least 3 cm long and 1 cm wide were collected from the posterior vertex area of the participants' scalp by trained research assistants or according to a detailed illustrated guide for those who collected the sample independently (for more information, see Ouellet-Morin et al., 2016, 2021). The material and hair sample (placed in a Ziploc bag) were mailed back to our laboratory in a prepaid and pre-addressed envelope. In a previous validation study, we showed that no mean differences in HCC could be detected between cortisol levels measured from hair collected at home and the laboratory and that both strategies were strongly correlated (r=0.91, p<.001 ; Ouellet-Morin et al., 2016). Participants received $115 as compensation for their time and efforts. For those who came to the laboratory, additional compensation was given to reimburse travel, parking and other expenses. All instruments and study procedures were approved by the Ethics Committee of the Ste-Justine Hospital Research Center.

Table 2 - Procedure followed during the laboratory visit at 19 years

Tasks	Duration (min)	Subcomponents
Welcome & installation	05:00	
Mouth swabs x2	07:00	Epigenetics/Genotyping
Adult self-report (ASEBA)	23:00	Psychological
Health questionnaire	21:00	Health
Break (and snack if mouth swabs)	10:00 or more	
Blood drops	10:00	Metabolic markers
Pain questionnaire	05:00	Pain
Hair sample	09:00	Cortisol
Sleep questionnaire	06:00	Sleep
Conclusion	04:00	
Total	1:40:00	

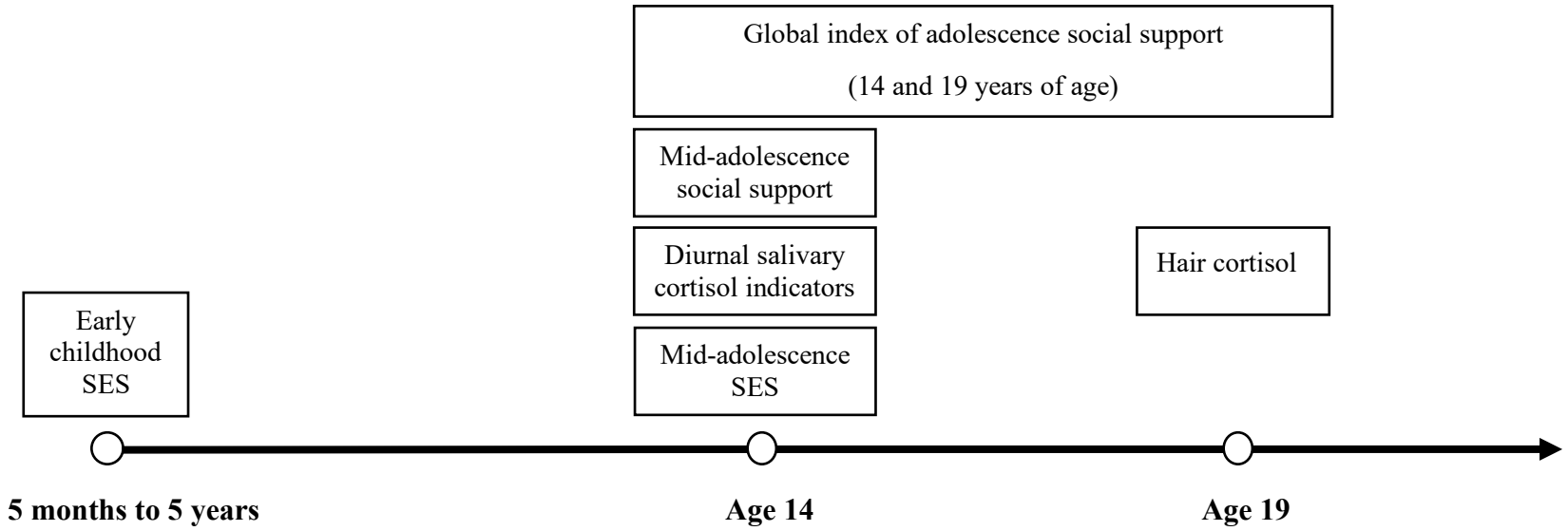
2.3 Measures

Early childhood and mid-adolescence family socioeconomic status (SES) were derived from questions enquiring information about the parents' highest educational level and family income during the twins' preschool years (several assessments between 5 months and 5 years of age), and once more at 14 years of age. Figure 4 presents an overview of these SES assessments in the context of the salivary diurnal (14 years) and hair (19 years) cortisol measures. An index capturing parents' highest educational level during the twins' early childhood and mid-adolescence, respectively, was computed for mothers and fathers. A score of 0 was attributed to those who had a high school diploma or less and a score of 1 was attributed to those with a postsecondary diploma. Family income was reported in categories ranging from 0 to ≥ $80,000 (i.e., 0 = "0 to $9,999," 1 = "$10,000 to $19,999," 2 = "$20,000 to $29,999," 3 = "$30,000 to $39,999," 4 = "$40,000 to $49,999," 5 = "$50,000 to $50,999," 6 = "$60,000 to $79,999," 7 = ">$80,000") during the twins' early childhood (i.e., 5 and 18 months, and again at 2.5, 4 years) and from 0 to ≥ $100,000 at age 14 (i.e., 1 = "$0 to $40,000," 2 = "> $40,000 to $60,000," 3 = "> $60,000 to $80,000," 4 = ">$80,000 to $100,000," 5 = ">$100,000"). The categorical response options were averaged to create an averaged family income during early childhood [Mean (SD) = 4.46 (1.92), corresponding to $40,000 to $49,999 on average] and mid-adolescence [Mean (SD) = 3.06 (1.49), corresponding to $60,000 to $80,000 on average]. Due to the negatively skewed distribution of family income, the distribution was then partitioned into five groups to lessen the distribution asymmetry and avoid cells with few participants, as this would generate biased estimates in the subsequent analyses. Information about the highest parental educational level and family income were included in a confirmatory factor analysis (CFA) to derive robust and cohesive indicators of latent early childhood (0–5 years old) and mid-adolescence (age 14) SES, respectively. Good model fit and parsimony indices are generally suggested by a nonsignificant chi-square statistic χ^2, a comparative fit index (CFI) ≥.9, a root mean square error of approximation (RMSEA) <.08 and a weighted root mean square residual (WRMR) ≤1 (Hooper et al., 2008). Adequate model fit was found in early childhood and mid-adolescence (see Figure 5). The early childhood and mid-adolescence standardized estimated SES factors [early childhood SES: Mean (SD) = -.05 (.53); mid-adolescence SES: Mean (SD) = -.03 (.71)] were saved to be included in the genetic modeling described below.

Perceived social support was self-reported using the Network of Relationships Inventory (NRI; Furman & Buhrmester, 1985) at age 14 and once again at age 19 (see Figure 4). The NRI is a widely used and reliable questionnaire that assesses relationship quality with different social agents according to seven dimensions (reliance alliance, enhancement of worth, affection, companionship, instrumental help, intimacy and nurturance of the other; Furman & Buhrmester, 1985, 1992). In the present study, three items were used to rate the participants' perceived emotional and instrumental support from their mother, father, close friend, cotwin and teacher at age 14 and from their romantic partner as well at age 19. The decision to not include items assessing perceived support from a romantic partner at age 14 was motivated by the high number of participants reporting not having a romantic partner at this age (i.e., proportion at age 14 = 89% and at age 19 = 44%). Of note, social support from teachers was not available at age 19. The social support subscale was thus comprised of 15 items at age 14 and age 19, respectively (e.g., *When you're feeling down or upset, how often do you depend on this person to cheer you up?, How often do you depend on this person for help, advice, or sympathy?, How often do you turn to this person for support with personal problems?*). Items were rated on a 5-point Likert-type scale ranging from "little or none" =1 to "the most" =5 and averaged to create a composite score of overall perceived social support at age 14 (mid-adolescence; Mean=2.74; SD=.84; $\propto$=.90) and at age 19 (late adolescence; Mean=2.93; SD=.81; $\propto$=.86), respectively. Owing to the moderate correlation between the mid- and late-adolescence social support scales (r=.38, p <.001), we averaged both scores into a global index of adolescence social support (Mean=2.84; SD=.73). Only the mid-adolescence (age 14) and the average adolescence social support were used in the subsequent analyses to examine the associations with salivary diurnal and hair cortisol indicators at 14 and 19 years of age, respectively.

Salivary diurnal cortisol (14 years). Participants were provided saliva tubes, instructions for collection and diaries to report the exact times the twins collected the samples (supervised by their parents). Saliva samples were first placed in the participants' refrigerator during data collection days.

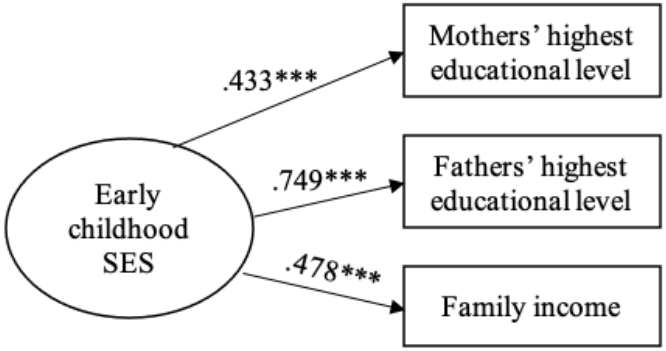
Figure 4. – Overview of the timeline of the main study variables



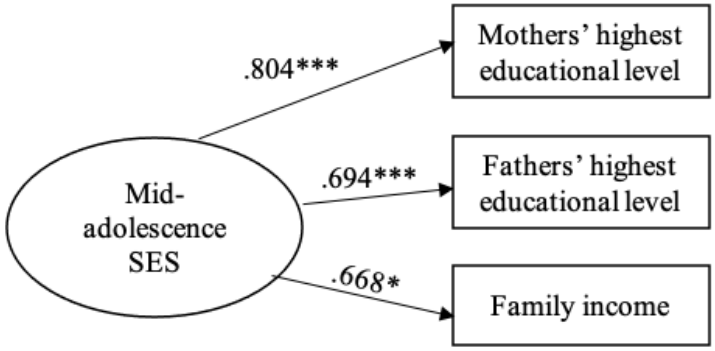
Note. Early childhood SES was computed using parents' highest educational level (3 assessments at 5, 30 and 60 months, respectively) and family income (4 assessments at 5, 18, 30 and 48 months) during the preschool years. Diurnal salivary cortisol was derived from saliva samples collected at four-time points during the day (at awakening, 30 min later, late in the afternoon and bedtime) on four collection days (Tuesdays and Thursdays on two consecutive weeks). The remaining measures were assessed once.

Figure 5. – Path diagram for early childhood (Panel A) and mid-adolescence (Panel B) SES

Panel A



Panel B



Note. Adequate model fit indices were found for SES in early childhood [$\chi^2(2) = .000$, p=.001; RMSEA=.00; CFI=1.000; TLI=1.000; WRMR=.004] and mid-adolescence [$\chi^2(1)=.000$, p=.001; RMSEA=.000; CFI=1.000; TLI=1.000; WRMR=.005].

After their collection, they were stored in -20ºC freezers until cortisol determination using a high sensitivity enzyme immune assay kit (Salimetrics® State College, PA, Catalog No. 1–3102). Frozen samples were brought to room temperature to be centrifuged at 15,000 × g (3000 rpm) for 15 min and were analyzed on 96-well plates. The range of detection for this assay was between 0.007–3 µg/dl (.19–82.76 nmol/L) and the intra- and inter-assay coefficients of variation were 4.8% and 8.2%, respectively. Of the possible 9472 saliva samples from 592 participants, 2037 (21.05%) were missing due to participants' lapses in saliva collection, insufficient saliva volume or technical problems (on average, 25.2% were missing at awakening, 17.7% at +30 min, 8.7% at the end of the afternoon and 25.95% in the evening). We identified 75 cortisol samples (1%) with a value greater than 3 times the SD above, which were winsorized (i.e., replacing outliers with the value closest to 3 SD the mean). Participants were considered "compliant" if their awakening and +30 min saliva samples were separated from at least 20 min and less than 40 min and that their awakening saliva collection was completed within the first 15 min following awakening and not distinct between the twins (≤8 min). A total of 8.61% of the samples were discarded due to noncompliance to the collection protocol. The final sample included 569 participants. Cortisol values were converted from µg/dl to nmol/L (i.e., multiplied by 27,588) and natural log-transformed prior to data analyses.

Three distinct indicators were derived from up to 16 cortisol time points to capture different aspects of cortisol function across the day: the CAR, the awakening and the diurnal change levels. As has been done previously (Adam et al., 2006; Badrick et al., 2007), the CAR was derived separately from the diurnal slope calculations because of previous reports suggesting that the CAR is regulated by different neurobiological and genetic mechanisms than cortisol secreted in the remaining part of the day (Clow et al., 2010; Ouellet-Morin et al., 2016). First, the CAR was calculated for each day of saliva collection by subtracting the awakening level from the one collected 30 min later. Second, growth curve analyses using mixed modeling for longitudinal data were carried in order to capture the cortisol diurnal rhythm at each collection day by estimating the mean level of cortisol at awakening (intercept) and the change that took place afterward (slope). To this end, an unspecified curve model was chosen to allow for slightly varying assessment times (i.e., time since awakening) between individuals and obtain an optimal estimate of change without imposing any particular shape of change across individuals (Duncan et al., 1997). The model contained both fixed and random estimates, corresponding to the parameters' mean and variance between individuals.

The fixed unstandardized beta estimate (means) of each collection day varied from 20.81 to 21.09 for the intercept and from -.89 to -.93 for the slope. The random unstandardized beta estimates (variance) of each collection day varied from 11.60 to 17.85 for the intercept and from .05 to .08 for the slope (see Ouellet-Morin et al., 2016 for additional information). Models were fitted in Mplus Version 6.11 using maximum likelihood estimation and the COMPLEX option adjusting standard error estimates to correct for the non-independence of observations. Growth curve models confirmed the expected progressive decrease of cortisol levels from awakening to evening (Brendgen et al., 2017). Third, we tested whether the estimates of the intercepts (awakening cortisol levels), slopes (diurnal change levels) and CAR were affected by a wide range of individual characteristics that have previously been identified to potentially affect diurnal cortisol secretion (e.g., sexual maturity, menstruation for girls, sex, medication use, awakening time, hours of sleep, sleeping problems, exercises and alcohol or drug consumption, and health-related characteristics such as cold, fever, allergies). Only a few (i.e., sex, awakening time, hours of sleep, sleeping problems, exercises and alcohol or drug consumption) were uniquely associated with at least one indicator and were thus statistically accounted for in the subsequent analyses. Fourth, the four intercept estimates (one for each collection day) were included in a CFA to derive an indicator free from day-specific variation. Similar CFAs were conducted for the slope and CAR estimates. The CFAs fit indices confirmed that the respective estimates derived from each collection day could be grouped into three global factors: CAR [χ^2 (2) = 1.95, p=.38; RMSEA=.00; CFI=1.00; SRMR=.03], intercept [χ^2 (1) = .002, p =.96; RMSEA=.00; CFI=1.00; SRMR=.00] and slope [χ^2 (1) = .007, p =.93; RMSEA=.00; CFI=1.00; SRMR=.00].

Hair cortisol (19 years). Washing and steroid extraction procedures were conducted at the Centre for studies on human stress (Montreal, Canada), according to a previously validated protocol (Kirschbaum et al., 2009). The first 3 cm hair segment was washed (i.e., not ground, cut, or pulverized) in a 15 millilitre (ml) tube with 2.5 ml of isopropanol before mixing. After decanting, the wash cycle was repeated and left to dry overnight. Pure methanol (1.5 ml) was added before being rotated for 24 hours. The samples were then spun down in a microcentrifuge and 1 ml was aliquoted. The methanol evaporated at 37 °C under a constant stream of nitrogen. Finally, 0.4 ml of phosphate buffer was injected in the tube before being vortexed for 15 seconds. The reconstituted sample was measured in duplicate using a luminescence immunoassay (detection range: .005–4 μg/dl; intra- and inter-assay coefficients of variation: 5.54 and 18.74, respectively). All samples

were assayed in duplicates and averaged. A total of 1.2% of the samples (*n*=9 participants) were discarded because of unusually high scores, with the highest outlier being greater than 14 SD. HCC were then 3-SD winsorized [1.6% of the samples, *n*=13, Mean (SD) = .07 µg/dl (.05)] and natural logarithmically transformed. Several factors previously identified to potentially affect HCC were reported by the twins (i.e., hair care: washing frequency, coloration, treatments, etc.; health-related characteristics: body mass index (BMI), drug and medication use, sleeping habits, cold, flu and allergies; health problems: cardiovascular problems, diabetes, head injuries, medications, etc.). Of those, only BMI, hair wash frequency, anxiolytic medication use, as well as cocaine and ecstasy consumption in the last three months were uniquely related to HCC. Standardized residuals were computed to statistically account for these potential confounders in subsequent analyses.

2.4 Statistical analyses

In this subsection are first discussed the attrition pattern of the QNTS cohort, the potential predictors of missingness as well as the technique used to handle missing data. Next, the analytical strategies used in each of the articles presented in chapters 3 to 5 will be described.

2.4.1 Attrition

One major methodological problem inherent to repeated data collection spread across many years, such as in the case of this 19 year-long twin study, is the longitudinal attrition due to participants' drop-out or nonresponse. Given that participants and nonparticipants may diverge on several characteristics relevant to the study outcomes, attrition may lead over time to sample biases, which could thus compromise the generalizability of the study findings (Gustavson et al., 2012; Twisk & de Vente, 2002). Prior to our main analyses, preliminary analyses were thus carried out to describe the pattern of attrition that occurred in the QNTS cohort over time, with a focus on our two main cortisol indicators sampled at 14 and 19 years, respectively. From the original 1324 participants, 800 twins took part in the age 14 data collection and 1007 twins participated in the age 19 data collection (Boivin et al., 2019), yielding an attrition rate of 40% and 24%, respectively. Such sample attrition rate is comparable to other longitudinal studies (Gustavson et al., 2012) and is to be expected considering the difficulties related to the longitudinal follow-up (e.g., lack of time, research fatigue, loss of contact and difficulty locating participants).

Since evidence of longitudinal attrition was found, we evaluated next whether the pattern of attrition of this cohort occurred randomly or was related to other variables. Three types of missing data mechanisms are generally discussed in the literature: (1) missing completely at random (MCAR: missing data is completely unrelated to both observable and unobservable data) (2) missing at random (MAR: missing data is dependent on observed data, but otherwise independent of unobserved data) (3) missing not at random (MNAR: missing data is related to unobserved data; Enders, 2013; Twisk & de Vente, 2002). The Little's MCAR test indicated that diurnal cortisol data was **not** missing completely at random [$\chi^2(7)=22.20$, $df=7$, $p=.002$], while HCC data was found to be missing completely at random [$\chi^2 = 20.60$, $df=19$, $p=.36$]. Further analyses were thus conducted to identify predictors of missingness of the diurnal cortisol data. Amongst a variety of demographic and psychosocial factors (i.e., sex, zygosity, young age of the mother at the twins' birth, early childhood and mid-adolescence SES, childhood and adolescent harsh and coercive parenting, the twins' depressive and anxious symptoms at age 12, 13 and 14), we found that DZ twins and those reporting higher levels of depressive symptoms at age 13 years were less likely to have participated in saliva collection at age 14 (awakening cortisol [$\chi^2(2)=45.65$, $p=.001$], CAR [$\chi^2(2)=36.42$, $p=.001$], diurnal slope [$\chi^2(2)=46.69$, $p=.001$]). In light of current recommendations of modern methods to account for missing data in developmental research (Enders, 2013), a maximum-likelihood estimation was used in all our analyses to handle attrition and generate more robust and accurate estimates and standard errors.

2.4.2 Analytical strategies of the 1st article entitled the phenotypic associations and gene-environmental underpinnings of socioeconomic status and diurnal cortisol secretion in adolescence.

This article has two main objectives. First, we tested whether early childhood (0–5 years old) and mid-adolescence (age 14) family SES are linearly or nonlinearly associated with three complementary indicators of diurnal cortisol secretion: cortisol at awakening, CAR, and the diurnal pattern of secretion, all measured at 14 years of age. Second, we examined whether the relative contribution of genetic and environmental factors to individual differences in these indicators varies according to family SES.

These research objectives were examined in four steps. First, we estimated bivariate correlations and conducted regression analyses to test the linear and nonlinear patterns of associations between

our main variables. Second, analyses of intra-pair correlations were carried out to obtain a rough estimation of the relative magnitude of latent genetic and environmental contributions to variation in the diurnal cortisol indicators. By comparing the degree of similitude (i.e., intra-pair correlations) between MZ twin pairs who share approximately 100% of their genetic background and between DZ twins who share, on average, 50% of their genetic makeup, and for whom all twin pairs grew up in the same families, the sources of variance of a phenotype can be partitioned in four types of estimate: additive genetic effects (A), non-additive or dominance genetic effects (D) as well as shared (C) and non-shared environmental effects (E) (Neale & Cardon, 1992a). Additive effects refer to the independent effects of genes, whereas non-additive influences denote the effects due to the interaction between alleles of the same locus (dominance) or located at different loci (epistasis). Environmental influences include shared environmental effects that make siblings alike (C) and nonshared environmental effects that make siblings dissimilar (E). Additive genetic effects are denoted by a MZ intra-pair correlation that is up to twice the DZ intra-pair correlation. Higher MZ intra-pair correlation may suggest dominance genetic effects. A crude estimate of the relative contribution of shared environmental factors can be evaluated by subtracting the MZ intra-pair correlation from twice the DZ intrapair correlation. Non-shared environmental effects are expected when the MZ intra-pair correlation is less than 1. Any measurement error is captured in the E variance component. Third, structural equation analyses using a maximum-likelihood function were conducted to obtain a more accurate estimation of the relative contribution of genetic and environmental parameters along with the statistical significance of these estimates tested via their respective confidence intervals. These analyses allow to partition the variance of a phenotype (i.e., hereby diurnal cortisol indicators) into its latent additive (A) or dominant (D) genetic influences and its shared (C) and nonshared (E) environmental influences. The estimated coefficients a, d, c, e provide information about the relative contribution of the latent factors A, D, C, E to the total variance of each phenotype P, with the variance of $P = a^2 + d^2 + c^2 + e^2$. Given that the estimation of c and d both rely on the same information (i.e., difference between the MZ and DZ within-pair correlations), it is not possible to estimate these parameters in the same model in a typical twin reared together study design (Neale & Cardon, 1992a). Therefore, we tested ACE and ADE models independently for each of the three cortisol indicators. Mixed-sex twin pairs were excluded from these analyses because their pattern of intra-pair correlations differed from that found for same-sex twin pairs (see Table 3). Using nested χ 2-difference tests, the full ACE (or ADE) model was

compared to more restrictive nested models, which allowed to determine the best fitting and more parsimonious models in addition to determine the significance and estimated values of the a, d, c and e parameters, as well as the significance of each nested model using the χ 2-difference tests. Non-significant χ 2-statistic, lower AIC and BIC and RMSEA <.08 indicate good models fit and parsimony (Hooper et al., 2008). Fourth, to examine whether SES interacted with the genetic and environmental estimated parameters, we expanded the univariate model to allow for each of the latent factor (A, C or D and E) to interact with early childhood and mid-adolescence SES (measured variable). These analyses were conducted separately for each cortisol indicator.

Table 3 - Intra-pair correlation estimates for adolescence diurnal cortisol indicators and hair cortisol according to zygosity

	Monozygotic twins	**Dizygotic twins**	**Mixed-sex twins**
Awakening cortisol	.47***	.27**	.43***
CAR	.43***	.15†	-.17
Diurnal change	.49***	.38***	.36**
Hair cortisol	.41***	.13	.007

Note. CAR = Cortisol awakening response; ***=$p \leq .000$; **= $p \leq .01$; †=$p \leq .10$

2.4.3 Analytical approach used in the 2nd article entitled association between the timing of family socioeconomic deprivation and adolescence hair cortisol among twins: A study of the genetic and environmental processes involved

In this second article, we first aimed to examine whether early childhood (ages 0–5 years) and mid-adolescence (age 14 years) SES are associated with HCC at age 19 years, and whether these associations may partially arise through a genetic pathway (*r*GE). Second, we estimated whether the genetic and environmental etiology of HCC varies according to family SES and the timing of these experiences (GxE), while controlling for potential *r*GE. To investigate these objectives, we

used a similar analytical strategy as the one conducted in the first article, to which we additionally included parameters to test the *r*GE and GxE between SES and HCC. The following steps were taken to evaluate these complementary hypotheses. To examine the *r*GE hypothesis, the best fitting univariate model was expanded to include the effect of SES on HCC's latent genetic factors, along with a direct effect of SES on HCC. A significant effect of SES on HCC's common latent genetic factor would suggest *r*GE. In addition, the GxE interaction hypothesis was examined by allowing each latent factor to interact with family SES. All models were estimated separately for early childhood and mid-adolescence SES.

2.4.4 Analytical approach used in the 3rd article entitled prospective and concurrent associations between family socioeconomic status, social support and diurnal and hair cortisol in adolescence

The objectives of this article were to examine the role of stability and changes in family socioeconomic disadvantage as indicated by low socioeconomic status (SES) in predicting multiple indicators of cortisol secretion and to test whether social support moderates these associations. These objectives were examined in 3 steps. First, preliminary missing data analyses were conducted and showed that 21% of participants with valid HCC data at age 19 had missing values on mid-adolescence SES (age 14). In order to increase the current study statistical power to test our interaction effects, participants' missing **mid-adolescence** SES values were imputed from their **early childhood** SES values. Following the imputation, between 0.4 and 4% of participants with valid diurnal and HCC data had missing values on mid-adolescence SES. Second, correlation analyses were conducted to analyse the prospective and concurrent associations between the main study variables. Third, the joint contributions of early childhood and mid-adolescence SES to cortisol as well as the mitigating effect of social support in these associations were evaluated using multilevel regression analyses. Multilevel regression analyses were used to account for the fact that twins might resemble each other on several characteristics due to sharing the same family environment. Failure to consider these similitudes may yield biased estimates of model parameters and false inference about the statistical significance of the predictors in the regression model. Multilevel regression allows to circumvent these pitfalls by accounting for the hierarchical structure of the data (i.e., twins are clustered within families in addition to being individuals as well), thereby providing more robust estimates and standard errors (Heck et al., 2013).

The multilevel regression analyses were conducted in two steps. First, we specified a null model in which variation in cortisol was partitioned into within (child-level)—and—between (family-level)—group components. This model contained one fixed-effect (intercept) and one random-effect (variation in intercepts across families) and allowed to estimate the intra-class correlation (ICC). The ICC represents the amount of variance in cortisol that is explained by the grouping variable (i.e., family-level; Heck et al., 2013). Higher ICCs indicate greater variability between families, thereby suggesting that the adoption of a multilevel approach is warranted. Second, the unique effects of the predictors as well as their joint (interaction) effects were introduced sequentially in the models as fixed-effects, while still accounting for random effects. Of note, the mid-adolescence social support scale (age 14) was included as a predictor of diurnal cortisol models (all variables measured at age 14), while the global index of adolescence social support (14 and 19 years) was included as a predictor of HCC models (age 19). A maximum-likelihood estimator was used to compare successive models. Model fit improvement after including additional predictors was tested using the likelihood ratio (deviance) test, with a lower deviance indicating a better fit. Sex was accounted for in all the regression models, while awakening cortisol was controlled for solely in the diurnal slope models. Post-hoc analyses of significant effects were probed using simple slope analyses, whereby the conditional effect of the predictor on the outcome was tested and plotted at -1 SD (lower), the mean (moderate) and +1SD (higher) of the moderator level. Analyses were run using SPSS, version 26. For ease of interpretation, all variables were Z-standardized before the analyses.

Chapter 3

Article 1:

The phenotypic associations and gene-environmental underpinnings of socioeconomic status and diurnal cortisol secretion in adolescence

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Article reference :

Cantave, C. Y., Brendgen, M., Paquin, S., Lupien, S., Dionne, G., Vitaro, F., Boivin, M., & Ouellet-Morin, I. (2021). The phenotypic associations and gene–environment underpinnings of socioeconomic status and diurnal cortisol secretion in adolescence. Development and Psychopathology, 1–11. https://doi.org/10.1017/S0954579421001048.

Abstract

Background: While converging evidence suggests that both environmental and genetic factors underlie variations in diurnal cortisol, the extent to which these sources of influence vary according to socioeconomic status (SES) has seldom been investigated, particularly in adolescence. **Objectives**: To investigate whether a distinct genetic and environmental contribution to youth's diurnal cortisol secretion emerges according to family SES and whether the timing of these experiences matters. **Method**: Participants were 592 twin pairs, who mostly came from middle-income and intact families and for whom SES was measured in early childhood and mid-adolescence. Diurnal cortisol was assessed at age 14 at awakening, 30 min later, in the afternoon and evening over four nonconsecutive days. **Results**: SES-cortisol phenotypic associations were specific to the adolescence period. Specifically, higher awakening cortisol levels were detected in wealthier backgrounds, whereas higher cortisol awakening response (CAR) and diurnal changes were present at both ends of the SES continuum. Moreover, smaller genetic contributions emerged for awakening cortisol in youth from poorer compared to wealthier backgrounds. **Conclusions:** The results suggest that the relative contribution of inherited factors to awakening cortisol secretion may be enhanced or suppressed depending on the socio-family context, which may help to decipher the mechanisms underlying later adjustment.

Keywords: Socioeconomic status, Cortisol, HPA-axis, Heritability, Gene-environment interactions

1. Introduction

A dysregulated hypothalamic-pituitary-adrenal (HPA) axis is often hypothesized as a key mechanism by which early stress exerts deleterious effects on physical and mental health (Koss & Gunnar, 2018; McEwen & Stellar, 1993). The HPA axis is one of the core biological stress systems responsible for mobilizing energy in stressful contexts in order to cope with stressors and return to baseline levels afterwards (Koss & Gunnar, 2018). Its action involves several neuromodulators and hormones, including the glucocorticoid stress hormone cortisol, of which the circadian rhythm is typically characterized by increased levels in the morning with a peak occurring 30 to 40 min after awakening (the cortisol awakening response or CAR) followed by a gradual decline throughout the day until a minimum is reached, around midnight (Koss & Gunnar, 2018). Substantial inter-individual disparities have, however, been noted regarding this circadian pattern of secretion (Smyth et al., 1997). Understanding the relative influence of genetic and environmental factors on individual differences in diurnal cortisol secretion may help to unravel its association and underlying mechanisms with a variety of stress-related psychopathologies (e.g., depression, anxiety and externalizing behaviours; Koss & Gunnar, 2018).

Exposure to stress early in life when the brain is ongoing key maturational changes has been proposed to induce long-lasting alterations in HPA axis secretion and regulation processes, as signaled by atypical patterns of diurnal cortisol secretion (Lupien et al., 2009; McEwen & Stellar, 1993). Aside from traumatic experiences (e.g., child maltreatment), living in socioeconomically deprived families is conceived as a form of stressful experience that aggregates with many stressful life events (Koss & Gunnar, 2018; Tarullo et al., 2020; Young et al., 2019; Zalewski et al., 2016). Previous studies have relied on a variety of indicators to measure socioeconomic status (SES), varying from composites of wealth and prestige (e.g., parents' education level and income) to wealth only (e.g., parents' income) or prestige only indicators (e.g., parents' education level and occupation). Nevertheless, converging evidence suggests that children whose families are lower on the SES hierarchy are more likely to experience greater and more intense levels of psychosocial and physical stress and to show a greater vulnerability to these stressors than their more advantaged counterparts (Dohrenwend, 1974; Evans & English, 2002). Low-SES households have thus been proposed to reflect a social environment typically encumbered with stressful life events that may induce dysregulations in stress-related neuroendocrine responses (McEwen & Seeman, 1999). To

date, however, scientific evidence linking socioeconomic strains in childhood or adolescence and diurnal cortisol secretion has been inconsistent, with studies reporting higher (Chen et al., 2010; Clearfield al., 2014; Essex et al., 2002; Lupien et al., 2001), lower levels of cortisol (Chen & Paterson, 2006; Desantis et al., 2015; Zalewski et al., 2016), as well as nonsignificant findings (Cutuli et al., 2010; McLachlan et al., 2016; West et al., 2010; Young et al., 2019). One reasons for such inconsistencies might be because previous studies have overlooked potential nonlinear patterns of association between these variables. Findings from a handful of studies suggest that the associations between gradients of socioeconomic strains and cortisol secretion may be nonlinear (Ouellet-Morin et al., 2020; Zalewski et al., 2016). For instance, Zalewski et al., (2016) found that children from both higher and lower income families consistently exhibited a low trajectory of morning cortisol, whereas those who grew up in families with an average income had a more moderate pattern of secretion. This suggests that both lower and higher SES backgrounds might feature factors that increase the risk for a dysregulated cortisol secretion among these children, even though these experiences might diverge (Zalewski et al., 2016). Alternatively, lower morning cortisol levels may suggest allostatic load among low-SES children, while indicating lower physiologic responsiveness among youth from wealthier families (Zalewski et al., 2016). Mixed findings may additionally arise because of variations in age range between samples, in how diurnal cortisol was measured, as well as in the nature (i.e., wealth and prestige SES indicators or wealth only or prestige only indicators) and the range of the socioeconomic contexts targeted in these studies, from the most disadvantaged to the wealthiest ones (Bernard et al., 2017; Bunea et al., 2017; Fogelman & Canli, 2018). Finally, most investigations have failed to acknowledge and adequately control for the confounding effect of the participants' genetic background when testing the presence and magnitude of these associations.

Substantiated evidence suggests that genetic and environmental factors both contribute to individual differences in cortisol secretion measured in basal and stressful contexts. Findings from an early meta-analysis of twin studies showed that basal cortisol levels are strongly influenced by genetic factors, with heritable factors accounting for 62% of variations in twin cortisol concentrations (Bartels et al., 2003). Given that the heritability of cortisol secretion likely fluctuates across the day, potentially reflecting distinct functions of cortisol as the day goes by, subsequent studies opted to describe the genetic and environmental contributions to cortisol secretion according to distinct indicators across the diurnal cycle. In general, moderate genetic influences

are evidenced in cortisol levels in the early morning, whereas stronger environmental influences emerge in the afternoon and evening (Gustafsson et al., 2011; Ouellet-Morin et al., 2016; Schreiber et al., 2006; Van Hulle et al., 2012). The CAR is, however, reported to be influenced by both dominant and additive genetic effects and has been found to be under stronger genetic influences than cortisol secreted at awakening and the diurnal slope (Ouellet-Morin, Brendgen, et al., 2016). Furthermore, Ouellet-Morin et al., (2016) documented specific and common sources of genetic variance across different indicators of diurnal cortisol secretion. Specifically, although the contribution of genetic factors to the CAR was largely uncorrelated with awakening cortisol levels and diurnal change levels, there was still evidence of a smaller genetic contribution to the CAR that was shared between these indicators. Evidence of an overlapping nonshared environmental influence was also documented for all three cortisol indicators, which was not the case for shared environmental influences (Ouellet-Morin, Brendgen, et al., 2016). These findings concord with prior evidence suggesting that the CAR is a distinct entity within the diurnal cycle and is under different regulatory processes than cortisol indicators capturing pre-and-post awakening cortisol secretion (Clow et al., 2004; Clow et al., 2010). Put together, studies investigating the SES-cortisol phenotypic association suggest that family SES during childhood and adolescence might play an environmentally-mediated role in diurnal cortisol secretion, whereas genetically-informed studies underscore the need to also consider participants' genetic background.

It is well established that genetic and environmental sources of influence do not combine additively but interact together to explain individual differences in diurnal cortisol secretion. For instance, interactions taking place at the DNA level interact with chemicals in the cellular environment (e.g., transcription factors). The presence of gene-environment interactions (GxE) can be investigated in a twin research design by examining to what extent the relative contributions of genetic and environmental factors vary according to environmental circumstances in which the twins evolve (e.g., family SES). At least two forms of gene-environment interactions could be expected. On the one hand, in line with the Diathesis-stress effect of GxE, the genetic factors related to diurnal cortisol secretion may become expressed to a greater extent in stressful environments rather than in more favorable ones (Shanahan & Hofer, 2005). Evidence in favor of this hypothesis is found in a study where the heritability of morning cortisol was shown to be under strong genetic influence (estimated heritability: 69%) among 6-month-old twins exposed to high family adversity, which encompassed several SES indicators. Morning cortisol levels were otherwise entirely accounted

for by unique environments at the lower levels of family adversity (Ouellet-Morin et al., 2009). On the other hand, in line with a suppression effect of GxE, inherited factors may be reduced—or entirely silenced—by environments thought to exert profound organizational effects on brain structures and connections involved in the regulation of the HPA axis activity, especially if these structures are still immature (Lupien et al., 2009; Shanahan & Hofer, 2005). Such a suppression pattern of GxE has been documented for cortisol responses to a novel social situation. Specifically, whereas genetic factors explained 40% of the variance at lower levels of family adversity (e.g., low family income, low maternal education and single parenthood), variations in cortisol reactivity were fully accounted for by shared and unique environmental effects in children exposed to higher levels of adversity (Ouellet-Morin et al., 2008). Collectively, these findings offer provisional evidence that the relative contributions of heritable and environmental factors to individual differences in cortisol secretion may vary as a function of the family environment.

Our understanding of the heritability of diurnal cortisol secretion, including GxE, is, however, limited by the fact that these hypotheses have mostly been tested among young children. It is currently unknown whether these initial GxE findings can be replicated in adolescence for three reasons. First, past studies have noted important changes in basal cortisol levels during the first two decades of life, with lower concentrations observed from toddlerhood to mid-childhood, followed by a transition to higher levels in adolescence (Gunnar et al., 2009; Shirtcliff et al., 2012). These processes may be genetically programed, as well as triggered by environmental cues. Second, adolescence is increasingly portrayed as a sensitive period during which embedded patterns of HPA axis activity resulting from earlier stressors can be recalibrated to more closely align with contemporary sources of influences, detrimental and positive ones (Koss & Gunnar, 2018). Third, a higher prevalence of emotional and behavioural disorders is noted in adolescence, for which the onset and recurrence are exacerbated by past and concomitant exposure to stress (Kuhlman et al., 2017; Lupien et al., 2009). A closer look at the genetic and environmental contributions to diurnal cortisol secretion in adolescence according to family SES is therefore warranted.

Another aspect that needs to be formally tested, among the same individuals, is whether the developmental timing of exposure to lower family SES (early childhood versus mid-adolescence) differentially affects adolescents' diurnal cortisol secretion and its genetic and environmental

contributions. Such an investigation requires the use of repeatedly measured income and education levels to test whether the timing of SES ought to be taken into consideration.

Aiming to address these gaps in knowledge, the present study tested whether early childhood (0–5 years old) and mid-adolescence (age 14) family SES are linearly or nonlinearly associated with three complementary indicators of diurnal cortisol secretion: cortisol at awakening, CAR, and the diurnal pattern of secretion, all measured at 14 years of age. Second, we examined whether the relative contribution of genetic and environmental factors to individual differences in these three indicators of diurnal cortisol secretion varies according to family SES, while controlling for the association between SES and cortisol. To best capture the socioeconomic context in which the twins are living, we opted to operationalize SES according to parents' education and income level.

2. Methodology

2.1. Participants

Participants were part of the Quebec Newborn Twin Study, a sample of twins recruited between 1995 and 1998 in the greater Montreal area. A total of 989 families with twins were contacted after the twins' birth, of which 662 agreed to participate (68%). Twins were first seen when they were 5 months of age and then prospectively assessed for a variety of children and family characteristics. The families were comparable to another sample of single births in the province of Québec. At the time of their children's birth, 95% of parents lived together, 44% of the twins were the firstborn children, 66% of mothers and 60% of fathers were between 25 and 34 years old and 17% of mothers and 14% of fathers had not finished high school. Also, 28% of mothers and 27% of fathers held a university degree, 83% of the parents were employed, 10% of the families received social welfare or unemployment insurance and 30% of families had an actual income of <$30,000. During the twins' preschool years and adolescence, between 16% and 28% of families reported income levels below the low-income cut-offs (LICOs), defined by Statistics Canada (2016) as an income-to-need threshold below which a family will have to spend a larger proportion of its income on necessities in comparison to the average Canadian family (For more information, see Table 1). Most families were Whites (86%), 6% were Blacks, 6% were Asians and 0.3% were Native North Americans. Zygosity was assessed by using 8–10 highly polymorphous genetic markers. Twins were diagnosed

as monozygotic when concordant for all genetic markers. When genetic material was insufficient or unavailable due to parental refusal (43% of cases), zygosity was determined based on physical resemblance questionnaires at 18 months and again at age 9 (Spitz et al., 1996). The comparison of both methods in a subsample of 237 same-sex pairs revealed a 94% correspondence rate (Forget-Dubois et al., 2003). The present study focuses on valid cortisol data collected at 14 years of age [Mean(SD)=14.0(.3)] and the SES indicators collected from 5 months to 14 years among 592 twin pairs [280 monozygotic (MZ), 204 same-sex dizygotic (DZ) and 108 mixed-sex DZ twin pairs] from whom most (74%) had collected saliva at each of the four collection days (for more information, see Ouellet-Morin et al., 2016).

2.2 Procedures

Letters detailing the objectives of the study were sent to the families, followed by a home visit. After informed consent from the parents and assent from the participants were obtained, the research assistants explained the saliva collection protocol, which consisted in sampling saliva at four-time points during the day (at awakening, 30 min later, late in the afternoon and bedtime) on four collection days (Tuesdays and Thursdays on two consecutive weeks) and the fulfillment of an interview-based questionnaire by the twins and their parents. The research assistants made sure that the participants and (their parents) were familiar with the material before leaving. The families were visited a second time to gather the saliva tubes. All instruments and study procedures were approved by the Ethics Committee of the Ste-Justine Hospital Research Center.

2.3. Measures

Early childhood and mid-adolescence family socioeconomic status (SES) were derived from questions enquiring information about the parents' highest educational level and family income during the twins' preschool years (several assessments between 5 months and 5 years of age) and once more at 14 years of age. An index capturing parents' highest educational level during the twins' early childhood and mid-adolescence, respectively, was computed for mothers and fathers. A score of 0 was attributed to those who had a high school diploma or less and a score of 1 was attributed to those with a postsecondary diploma. Family income was reported in categories when twins were 5 and 18 months, and again at 2.5, 4 and 14 years, and ranged from 0 to ≥ $80,000. The categorical response options were averaged to create an averaged family income during early

childhood [Mean (SD)=4.46 (1.92), corresponding to $40,000 to $49,999 on average] and mid-adolescence [Mean (SD)=3.06 (1.49), corresponding to $60,000 to $80,000 on average]. Due to the negatively skewed distribution of family income, the distribution was then partitioned into five groups to lessen the distribution asymmetry and avoid cells with few participants, as this would generate biased estimates in the subsequent analysis. Information about the highest parental educational level and family income were included in a confirmatory factor analysis (CFA) to derive robust and cohesive indicators of latent early childhood (0–5 years old) and mid-adolescence (age 14) SES, respectively. Good model fit and parsimony indices are generally suggested by a nonsignificant chi-square statistic χ^2, a comparative fit index (CFI) $\geq$.9, a root mean square error of approximation (RMSEA) $<$.08 and a weighted root mean square residual (WRMR) $\leq$1. Adequate model fit was found in early childhood [$\chi^2(2)$=.000, p=.001; RMSEA=.00; CFI=1.000; TLI=1.000; WRMR=.004] and mid-adolescence [$\chi^2(1)$=.000, p=.001; RMSEA=.000; CFI=1.000; TLI=1.000; WRMR=.005]. The early childhood and mid-adolescence standardized SES estimated factors [early childhood SES: Mean (SD)=-.05 (.53); mid-adolescence SES: Mean (SD)=-.03 (.71); see appendices, Supplementary Figures 1 & 2 for more information] were saved to be included in the genetic modeling described below.

Cortisol. Participants were provided saliva tubes, instructions for collection and diaries to report the exact times the twins collected the samples (supervised by their parents). Saliva samples were first placed in the participants' refrigerator during data collection days. They were then stored in freezers at -20^{o} C in the laboratory until cortisol determination completed using a high sensitivity enzyme immune assay kit (Salimetrics® State College, PA, Catalog No. 1–3102). Frozen samples were brought to room temperature to be centrifuged at 15,000 × g (3000 rpm) for 15 min and were analyzed on 96-well plates. The range of detection for this assay was between 0.007–3 µg/dl (.19–82.76 nmol/L) and the intra- and interassay coefficients of variation were 4.8% and 8.2%, respectively. Of the possible 9472 saliva samples from 592 participants, 2037 (21.05%) were missing due to participants lapses, insufficient saliva collection or technical problems (on average, 25.2% were missing at awakening, 17.7% at +30 min, 8.7% at the end of the afternoon and 25.95% in the evening). Systematic missing data analysis indicated that cortisol data was not missing completely at random [$\chi^2(7)$=22.20, p=.002]. Dizygotic twins and those reporting more severe depressive symptoms at age 13 years were less likely to have participated in saliva collection

(awakening cortisol [$\chi^2(2)=45.65$, $p=.001$], CAR [$\chi^2(2)=36.42$, $p=.001$], diurnal slope [$\chi^2(2)=46.69$, $p=.001$]). We identified 75 cortisol samples (1%) with a value greater than 3 times the SD above, which were then winsorized. Participants were considered "compliant" if their awakening and +30 min samples were separated from at least 20 min and less than 40 min, the awakening collection was completed within the first 15 min following awakening and not distinct between the twins ($\leq$ 8 min). A total of 8.61% of the samples were discarded due to noncompliance to the collection protocol. The final sample included 569 participants. Cortisol values were converted from µg/dl to nmol/L (i.e., multiplied by 27,588) and natural log-transformed prior to data analyses.

Creating aggregated indicators of cortisol secretion across several days is recommended when examining individual characteristics or experiences in relation to cortisol levels (Adam & Gunnar, 2001). To this end, three distinct indicators were derived: the CAR, the awakening and the diurnal change levels. As has been done previously (Adam et al., 2006; Badrick et al., 2007), the CAR was derived separately from the diurnal slope calculations because of previous reports suggesting that the CAR is regulated by different neurobiological and genetic mechanisms than cortisol secreted later in the day (Clow et al., 2010; Ouellet-Morin et al., 2016). First, the CAR was calculated for each day of saliva collection by subtracting the awakening level from the one collected 30 min later. Second, growth curve analyses using mixed modeling for longitudinal data were carried in order to capture the cortisol diurnal rhythm at each collection day by estimating the mean level of cortisol at awakening (intercept) and the change that took place afterward (slope). To this end, an unspecified curve model was chosen to allow for slightly varying assessment times between individuals and obtain an optimal estimate of change without imposing any particular shape of change across individuals (Duncan et al., 1997). Of note, the diurnal slopes were modeled according to time-since awakening. The model contained both fixed and random estimates, corresponding to the parameters' mean and variance between individuals. The fixed unstandardized beta estimate (means) of each collection day varied from 20.81 to 21.09 for the intercept and from -.89 to -.93 for the slope. The random unstandardized beta estimates (variance) of each collection day varied from 11.60 to 17.85 for the intercept and from .05 to .08 for the slope (see Ouellet-Morin et al., 2016 for additional information). Models were fitted in Mplus Version 6.11 using maximum likelihood estimation and the COMPLEX option adjusting standard

error estimates to correct for the non-independence of observations. Growth curve models confirmed the expected progressive decrease of cortisol levels from awakening to evening (Brendgen et al., 2017). Third, we tested whether the estimates of the intercepts (awakening cortisol levels), slopes (diurnal change levels) and CAR were affected by a wide range of individual characteristics that have previously been identified to potentially affect diurnal cortisol secretion (e.g., sexual maturity, menstruation for girls, sex, medication use and health-related characteristics such as cold, fever, allergies). Only a few (i.e., sex, awakening time, hours of sleep, sleeping problems, exercises and alcohol or drug consumption) were uniquely associated with at least one indicator and were thus statistically accounted for in the subsequent analyses. Fourth, the four intercept estimates (one for each collection day) were included in a CFA to derive an indicator free from day-specific variation. Similar CFAs were conducted for the slope and CAR estimates. The CFAs confirmed that the respective estimates derived from each collection day could be grouped into three global factors: CAR [χ^2 (2)=1.95, p=.38; RMSEA=.00; CFI=1.00; SRMR=.03], intercept [χ^2 (1)=.002, p =.96; RMSEA=.00; CFI=1.00; SRMR=.00] and slope [χ^2 (1)=.007, p =.93; RMSEA=.00; CFI=1.00; SRMR=.00].

2.4. Statistical analyses

2.4.1. Univariate Genetic modeling

Genetic modeling using twin design allows to examine the relative magnitude of latent genetic and environmental contributions to any given phenotype (Neale & Cardon, 1992b). By comparing the degree of similitude (i.e., intra-pair correlations) between MZ twin pairs who share approximately 100% of their genetic background and between DZ twins who share, on average, 50% of their genetic makeup, sources of variance in a phenotype can be partitioned in terms of additive genetic effects (A), non-additive or dominance genetic effects (D) as well as shared (C) and non-shared environmental effects (E) (Neale & Cardon, 1992b). Additive effects refer to the independent effects of genes, whereas non-additive influences denote the effects due to the interaction between alleles of the same locus (dominance) or located at different loci (epistasis). Second, environmental influences include shared environmental effects that make siblings alike (C) and nonshared environmental effects that make siblings dissimilar (E). Additive genetic effects are denoted by a MZ intra-pair correlation that is up to twice the DZ intra-pair correlation. Higher MZ intra-pair correlation may suggest dominance genetic effects. A crude estimate of the relative contribution of

shared environmental factors can be evaluated by subtracting the MZ intra-pair correlation from twice the DZ intra-pair correlation. Non-shared environmental effects are expected when the MZ intra-pair correlation is less than 1. Any measurement error is captured in the E variance component.

Structural equation modeling using a maximum-likelihood fit function allows a more precise estimation of the relative contribution of genetic and environmental parameters with their respective confidence intervals (CI), which enables the test of the statistical significance of these estimates (Neale & Cardon, 1992b). To this end, a two-group model is fitted to the data where (1) the latent genetic correlations between the twin pairs are constrained to 1.0 for MZ twins and to .50 (to estimate latent additive genetic effects) or to .25 (to estimate dominance genetic effects) for DZ twins; (2) correlations of latent shared environmental influences between the twins of the same pair are fixed to 1 for MZ and DZ twins; and (3) the nonshared environmental intra-pair correlation are fixed to zero for MZ and DZ twins. The estimated coefficients *a, d, c, e* provide information about the relative contribution of the latent factors A, D, C, E to the total variance of each phenotype P, with the variance of $P = a^2 + d^2 + c^2 + e^2$. Given that the estimation of c and d both rely on the same information (i.e., difference between the MZ and DZ within-pair correlations), it is not possible to estimate these parameters in the same model in a typical twin reared together study design (Neale & Cardon, 1992b). Therefore, we tested separate ACE and ADE models for each of the three cortisol indicators. Mixed-sex twin pairs were excluded from these analyses because their pattern of intra-pair correlations differed from that found for same-sex twin pairs (see Table 3). Using nested χ^2-difference tests, the full ACE (or ADE) model was compared to more restrictive models, which allowed to determine the best fitting and more parsimonious models in addition to the significance and estimated values of the a, d, c and e parameters, as well as the significance of the nested χ^2-difference tests. Non-significant χ^2-statistic, lower AIC and BIC and RMSEA $<.08$ indicate good models fit and parsimony.

2.4.2. Univariate models testing the genetic and environmental interaction (GxE)

To examine whether SES interacted with the genetic and environmental factors estimated for each of the cortisol indicator, taken separately, we expanded the **univariate** model to allow for each of the latent factor (A, C or D and E) to interact with SES (measured variable). As illustrated in Figure 6, the coefficients a, c (or d) and e represent the main effects of the latent factors A, C (or

D), E, respectively, whereas the coefficients β_aSES, $\beta_{c(or\ d)}$SES and β_eSES allow for the estimation of the interactions between SES and A, C (or D), E latent factors. The s coefficient represents the main effect of SES on a given cortisol indicator. Of note, model parameters from the best fitting univariate models were used as the starting point of the univariate GxE analyses. All of the genetic analyses were conducted in Mplus Version 8.1.6.

3. Results

3.1. Prospective and concurrent associations between the main study variables

As shown in Table 4, a moderate-to-strong correlation was noted between SES levels derived from information collected during early childhood and mid-adolescence, suggesting stability of this indicator over time, but also that changes occurred during this period. Furthermore, analyses revealed that early childhood SES was not significantly associated with adolescents' CAR, awakening cortisol or diurnal change levels. However, a significant correlation emerged between mid-adolescence family SES and awakening cortisol levels, indicating that adolescents living in wealthier families had higher awakening cortisol levels (see Figure 7, Panel A). While no linear associations were detected between mid-adolescence family SES and the CAR, nonlinear associations were observed with the CAR [R^2=.01, F=3.09, p=.05] and diurnal change levels [R^2=.02, F=5.50, p=.004]. As illustrated in Figure 7 (Panel B & C), adolescents growing up in *lower* or *higher* SES families both exhibited a higher CAR and a flatter diurnal slope in comparison to adolescents from families with average levels of SES (depicted by a standardized score of zero). The nonlinear associations linking mid-adolescence family SES to the CAR [R^2=.02, F=3.34, p=.02] and diurnal change levels [R^2=.02, F=3.36, p=.02] were observed over and above the effects of early childhood SES. As for the awakening cortisol levels, the previously detected linear association was significant at a trend level [R^2=.01, F=2.85, p=.06] once the putative effect of early childhood SES was controlled.

3.2. Do the genetic and environmental contributions to awakening cortisol levels vary according to early childhood or mid-adolescence SES?

Based on the AIC, the BIC and the χ^2-difference test, the nested univariate analyses suggested that individual differences in awakening cortisol levels were best characterized by an AE model (see Supplementary Table 1 in the appendices). The ACE model was nonetheless selected because the RMSEA was comparable in the ACE and AE models and the latent factor C explained a non-negligible portion of the variance of this phenotype (12%). The remaining part of the variance was accounted for by additive genetic (34%) and unshared environmental factors (54%; see Figure 8). This suggests that – beyond the moderate influence of genetic factors – environmental factors that either enhanced or reduced the twins' similarity in cortisol secretion at awakening were involved, albeit to a different degree.

As presented in Table 5, a significant interaction emerged indicating that the magnitude of additive genetic influences on awakening cortisol levels varied across the early childhood SES continuum. More specifically, Figure 9 (Panel A) shows that the contribution of the additive genetic factor to adolescents' awakening cortisol levels increased along the distribution of early childhood family SES, whereby lower genetic estimates were noted for children growing up in the most disadvantaged families, whereas heritability of this phenotype was greater in higher SES backgrounds. Figure 9 (Panel B) also illustrates that awakening cortisol levels were best explained by environmental factors [shared (17%) and unshared (76%)] than genetic factors (7%) among children from lower SES families. In comparison, among youth raised in wealthier families during their childhood years, the relative influences of shared and unshared environmental factors in awakening cortisol secretion appeared slightly less strong [shared (2%) and unshared factors (65%)], whereas the genetic estimated factors were nearly five times higher in magnitude (33%). The interaction between the latent additive genetic factors and mid-adolescence SES was also found to be significant (see Table 5) and depicted a similar pattern of findings as the one evidenced for early childhood SES (see Figures 9C and 9D), but no longer reached statistical significance once early childhood SES was controlled for.

Figure 6. – Univariate moderation model

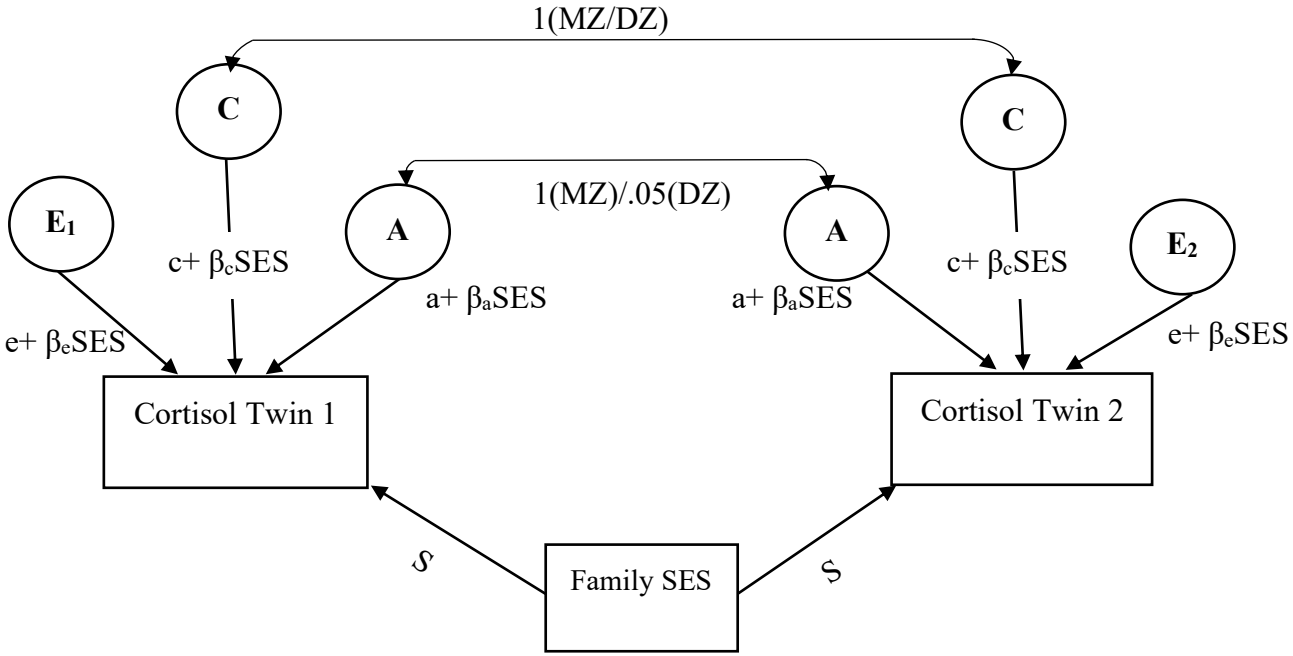


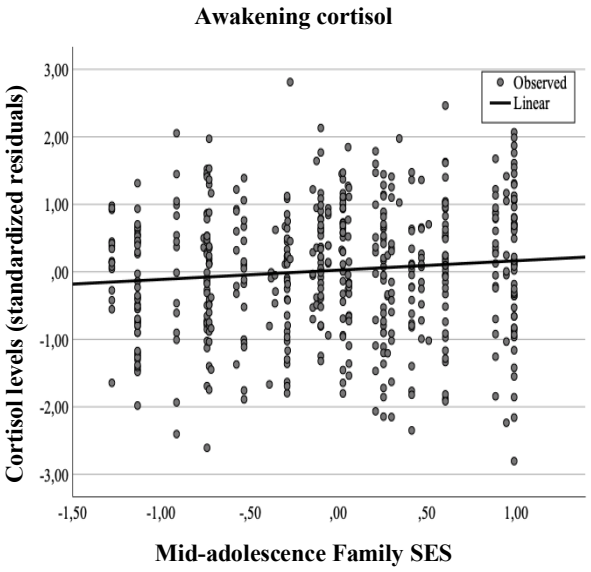
Table 4 - Phenotypic (linear) correlations between early childhood and mid-adolescence SES and the cortisol outcomes

	1	2	3	4	5
Early childhood SES	1	.52***	.03	.07	-.02
Mid-adolescence SES		1	-.01	.10*	-.09*
CAR			1	-.09*	.25***
Awakening levels				1	-.59***
Diurnal change					1

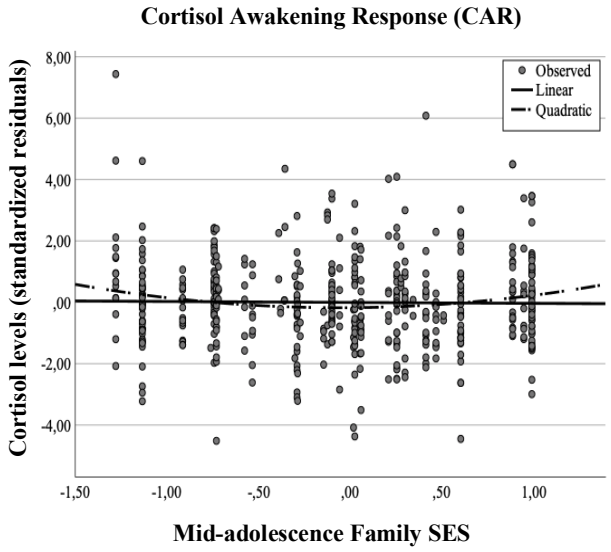
Notes. CAR = Cortisol awakening response; *** = $p \leq .000$; ** = $p \leq .01$; *=$p \leq .05$.

Figure 7. – Linear and nonlinear associations between mid-adolescence family SES and awakening cortisol (Panel A), CAR (Panel B), and diurnal change (Panel C)

Panel A



Panel B



Panel C

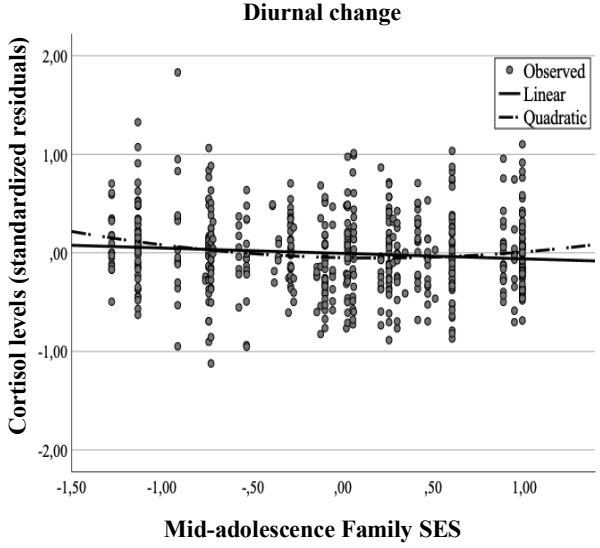


Figure 8. – Proportion (%) of variance explained by the dominance genetic, additive genetic, shared environmental and nonshared environmental factors for the CAR, awakening cortisol levels and cortisol diurnal change

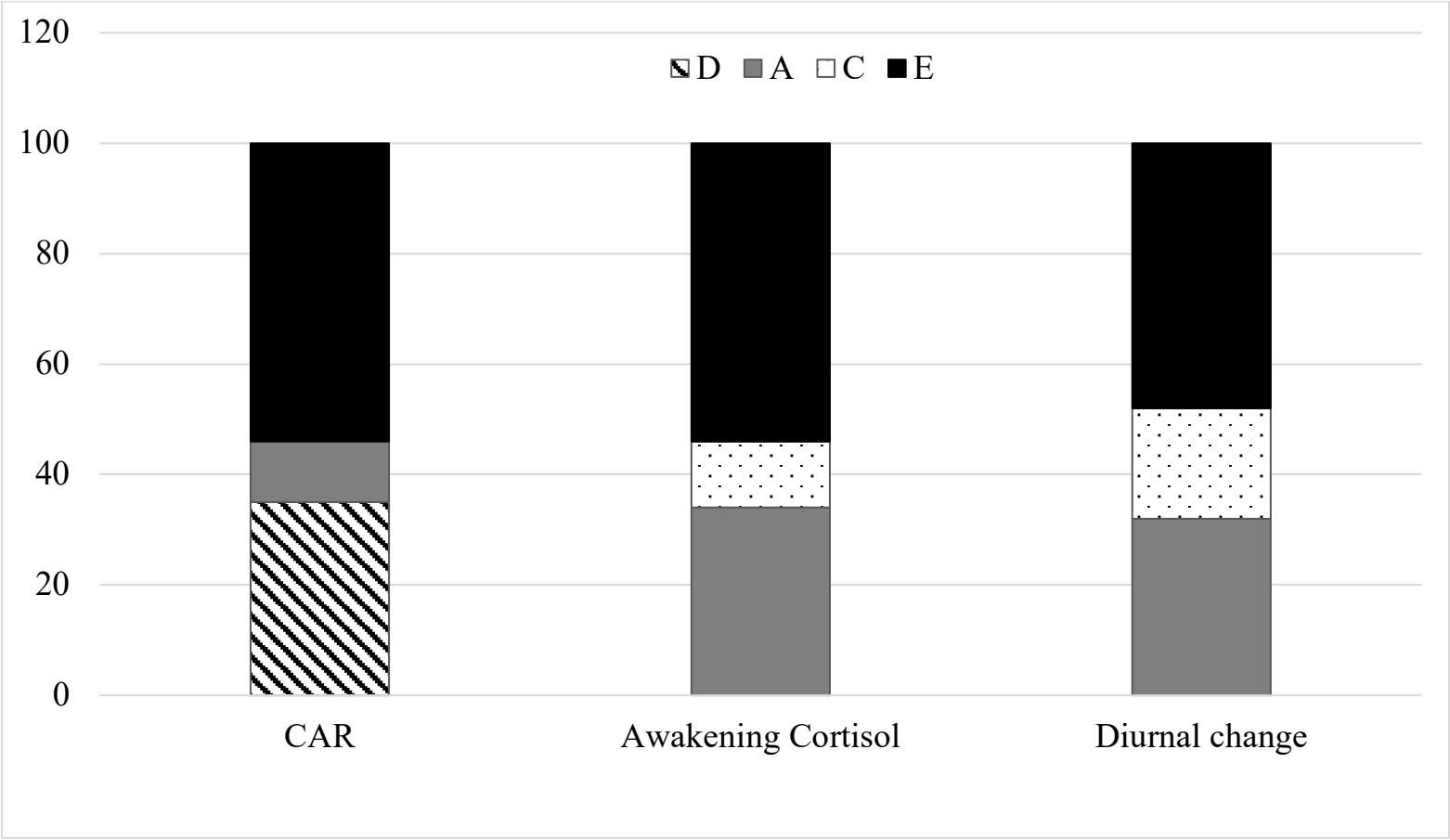


Table 5 - Results of the univariate models including the interactions

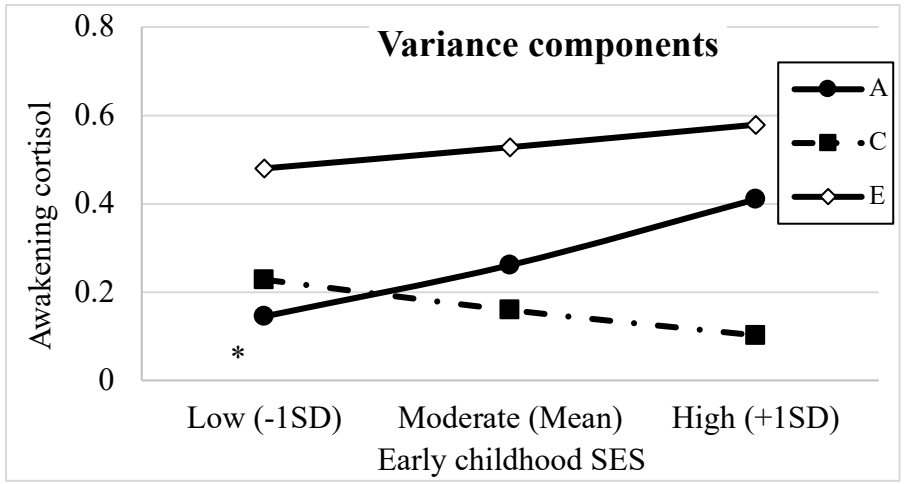
		Early childhood SES		Mid-adolescence SES	
	Parameter	Estimate	95%CI	Estimate	95% CI
CAR		-2LL (np)= -508.693(8)		-2LL (np)= -546.608(8)	
	a	.44†	[-.16; .70]	.30	[-.14; .66]
	d	.46†	[-.11; .73]	.58**	[.00; .76]
	e	.73***	[.63; .81]	.72***	[.63; .81]
	SES	.08	[-.05; .21]	-.01	[-.12; .10]
	β_aSES	.08	[-.19; .34]	-.11	[-.36; .12]
	β_dSES	-.17	[-.34; .10]	.11	[-.10; .34]
	β_eSES	.06†	[-.02; .12]	.03	[-.04; .12]
Awakening levels		-2LL (np)= -546.283(8)		-2LL (np)= -578.764 (8)	
	a	.41*	[.03; .68]	.47***	[.13; .66]
	c	.44**	[.00; .62]	.37**	[.00; .58]
	e	.72***	[.63; .80]	.72***	[.64; .80]
	SES	0.06	[-.06; .19]	.13*	[-.02; .24]
	β_aSES	.32**	[.03; .53]	.20*	[.00; .36]
	β_cSES	-.13	[-.32; .13]	-.15†	[-.29; .02]
	β_eSES	.02	[-.06; .10]	.04	[-.04; .11]
Diurnal change		-2LL (np)= -551.974(8)		-2LL (np)= -586.552 (8)	
	a	.51**	[.00; .73]	.53**	[.00; .72]

	c	.42**	[.00; .65]	.39*	[.00; .62]
	e	.69***	[.59; .76]	.67***	[.59; .75]
	SES	-.003	[-.12; .10]	-.12*	[-.23; -.02]
	β_aSES	.16	[-.17; .48]	.05	[-.20; .33]
	β_cSES	-.10	[-.23; .12]	-.06	[-.31; .17]
	β_eSES	-.01	[-.08; .10]	-.02	[-.10; .08]

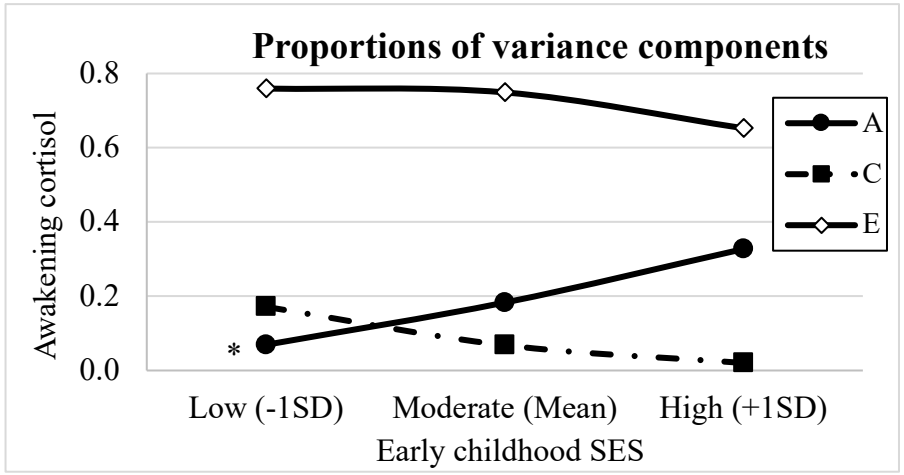
Note. The β coefficients represent the interactions between each genetic and environmental latent factor and SES. LL=log-Likelihood; np = number of parameters. *** = $p \leq .001$; ** = $p \leq .01$; *=$p \leq .05$; † = $p \leq .10$.

Figure 9. – Genetic, shared and nonshared raw and proportional variance components of awakening cortisol as a function of early childhood (Panels A & B) and mid-adolescence SES (Panels C & D)

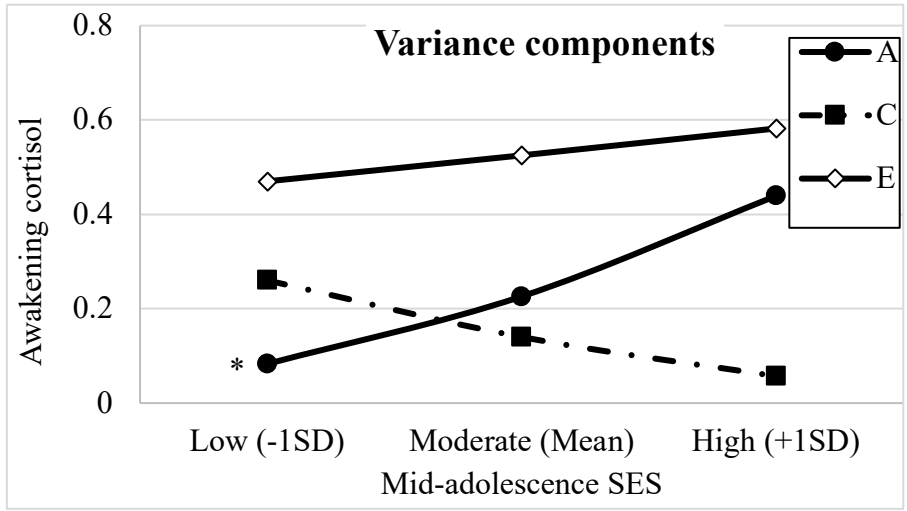
Panel A



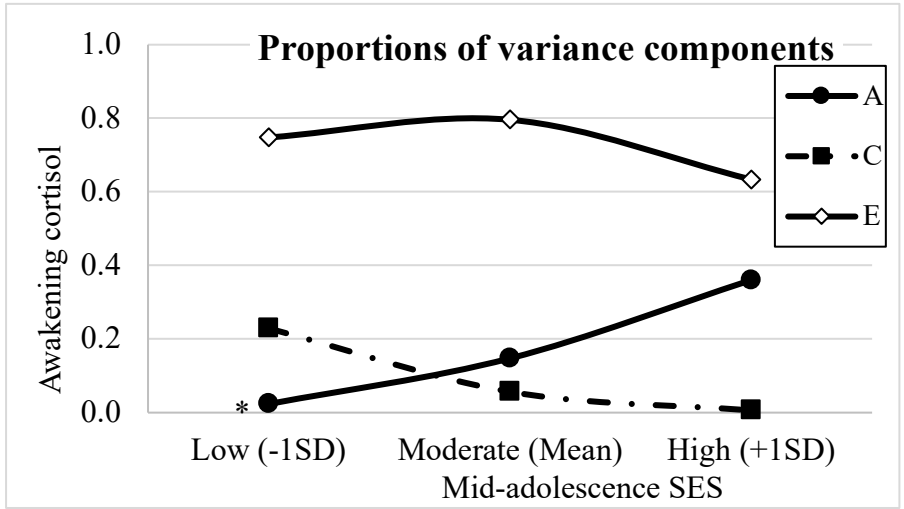
Panel B



Panel C



Panel D



Note. The input of the additive genetic factor to awakening cortisol levels was not significant at lower [*aa*1=.01; *SE*=.09; *p*=.94] and moderate [*aa*3=.17; *SE*=.12; *p*=.17] levels of early childhood SES, but a significant contribution emerged at higher levels of early childhood SES [*aa*5=.53; *SE*=.21; *p*=.01]. Awakening cortisol was under significant genetic influences at higher [*aa*5=.44; *SE*=.17; *p*=.01] and moderate [*aa*3=.22; *SE*=.11; *p*=.04] levels of mid-adolescence SES, but no longer had an effect at lower mid-adolescence SES level [*aa*1=.07; *SE*=.09; *p*=.43].*= interaction between SES and the A parameter significant at $p \leq .05$

3.3. Do the genetic and environmental contributions to the CAR vary according to early childhood or mid-adolescence SES?

The univariate genetic analyses revealed that the variation in the CAR was best explained by a DE model, as indexed by a nonsignificant χ^2-difference test, as well as lower AIC, BIC and RMSEA indices (see Supplementary Table 1 in the appendices). The ADE model was nonetheless selected given its comparable RMSEA value with the DE model and because the additive genetic factors accounted for a non-negligible 11% of variation of the CAR (see Figure 8). Altogether, 46% of the CAR variance was explained by (additive and dominance) genetic factors, with the remaining 54% due to unshared environmental factors. Examination of the CIs of the interaction terms (presented in Table 5) indicated that the relative influence of genetic and environmental factors on individual differences in the CAR of 14-year-old adolescents was not moderated by the family socioeconomic context experienced early in life or concurrently.

3.4. Do the genetic and environmental contributions to cortisol diurnal change levels vary as a function of early childhood or mid-adolescence SES?

The univariate genetic analyses indicated that individual differences in cortisol secretion change across the day was best described by an ACE model (see Supplementary Table 1 in the appendices). Additive genetic factors accounted for 32% of the variance of this phenotype, another 20% was explained by shared environmental factors, and the remaining variance (48%) was related to unshared environmental factors. As reported in Table 5, none of the interactions between the latent factors A, C and E and early childhood (or mid-adolescence) SES reached statistical significance, implying that the genetic and environmental influences on diurnal cortisol levels in adolescence are independent of (i.e., not moderated by) the youth's family SES in early childhood or mid-adolescence. Of note, nonlinear interactions were tested between early childhood and mid-adolescence SES and each cortisol indicator. None were found to be significant (available upon request).

4. Discussion

Anchored in a developmental perspective, this study provided a unique opportunity to test whether the genetic and environmental contributions to three indicators of diurnal cortisol secretion assessed at age 14 varied according to family SES and whether these findings were contingent on

the timing of these socio-family experiences. As done previously (Chen et al., 2007; Young et al., 2019), family SES was measured during the first 5 years of life and again at age 14, reflecting both continuity and changes occurring between these developmental periods and accounting for the high covariance estimated from infancy to early childhood. Our data revealed that the phenotypic associations between early childhood SES and all three indicators of adolescence diurnal cortisol secretion were not significant. In contrast, there were significant associations between the SES factor assessed contemporaneously (in mid-adolescence) and the salivary cortisol measures, either according to a linear or nonlinear function. These associations were observed, for the most part, even when controlling for early childhood SES. Moreover, the findings provided evidence of an interaction (GxE) between genetic effects on cortisol measured at awakening and early childhood (and also to a lesser extent mid-adolescence) family SES. In contrast, the genetic and environmental contributions of the CAR and cortisol changes across the day did not vary by SES.

4.1 Prospective and concurrent associations between SES and diurnal cortisol indicators

At the phenotypic level, the results indicated that adolescents living in wealthier families concurrently had higher awakening cortisol levels. In contrast, a nonlinear pattern of correlation emerged for the CAR and diurnal change levels, revealing that youth raised in either *higher* or *lower* SES households both exhibited a higher CAR and a flatter diurnal slope in comparison to those who grew up in more average SES families according to this study sample. These findings did not, however, extend to early childhood SES. This suggests that adolescence diurnal cortisol secretion is influenced more by the current family socioeconomic environment than by the family SES documented in twins' early childhood. Although the magnitude of these phenotypic associations was small, our results concord with those from other studies that indicators of diurnal cortisol levels measured in adolescence may vary according to the family concurrent living contexts and that nonlinear patterns of associations may exist (Ouellet-Morin et al., 2020; Zalewski et al., 2016). Thus, Zalewski et al. (2016) reported a flatter diurnal slope among adolescents from richer *and* poorer families when compared to those growing up in average-income families, similarly to what was found in the present study sample. Building on this evidence, we speculate that youth growing up in families subjected to more socioeconomic constraints – as well as those growing up in the most affluent families – may be exposed to several experiences that may collectively relate to a higher CAR and a flatter diurnal slope, even though the nature of these

experiences may differ. This hypothesis is consistent with other reported phenotypic associations between diurnal cortisol and SES in a handful of cross-sectional and prospective studies (Chen et al., 2010; Clearfield et al., 2014; Essex et al., 2002; Gustafsson et al., 2006; Lupien et al., 2001; Lupien et al., 2000). However, according to the present set of findings, it is not possible to discern whether a higher CAR or a flatter diurnal slope signal increases vulnerability to socioemotional, academic and behavioural difficulties in the long run or, inversely, may be indicative of positive adaptation to the social environment. To better understand the role played by diurnal cortisol secretion in the adolescence gradients of socioeconomic inequity, future studies ought to systematically test nonlinear patterns of associations and examine whether these indicators of cortisol diurnal secretion predict unique risks and strengths in youth from a variety of backgrounds and across a wide range of domains of functioning.

4.2 Genetic and environmental contributions to adolescence diurnal cortisol indicators

As reported before for this cohort (Brendgen et al., 2017; Ouellet-Morin et al., 2016), awakening cortisol levels, the CAR and diurnal change levels were found to be moderately influenced by genetic factors. This result is consistent with earlier findings in behavioural genetic studies conducted among children and adolescents (Bartels et al., 2003; Gustafsson et al., 2011; Van Hulle et al., 2012; Wüst et al., 2000), as well as with prior evidence from genome-wide association studies (GWAS) and candidate gene studies (Chen et al., 2009; Utge et al., 2018; Velders et al., 2011; Wüst et al., 2004). The findings are, however, partly inconsistent with previous studies indicating that afternoon and evening cortisol secretion were uniquely explained by shared and nonshared environmental factors (Schreiber et al., 2006; Wüst et al., 2000), whereas diurnal change from morning to evening was shown to be under both genetic and environmental influences. These divergent findings may be partly due to the examination of cortisol change during the day from morning to evening in the present study, instead of cortisol changes that occurred from afternoon to evening. Additionally, distinct findings may arise because we considered stable indicators of diurnal cortisol derived from saliva sampled over four collection days. Notwithstanding these putative explanations for divergent findings, we found a moderate contribution of genetic factors to cortisol diurnal change from morning to evening, as was also reported in another study that estimated a stable indicator of diurnal cortisol change from morning to afternoon (i.e., genetic factors [32%]; Van Hulle et al., 2012). Collectively, our findings indicated that adolescence diurnal

cortisol secretion is largely influenced by twins' unique environmental experiences and to a lesser part by their shared experiences. These cortisol indexes might thus be particularly useful for investigating the influences of past and concurrent experiences – whether good or bad – on adolescents' patterns of cortisol secretion, especially in youth from lower SES families. The latter findings emphasize the need for environmentally-rooted prevention strategies to recalibrate cortisol secretion among these adolescents, as individual differences are mainly attributable to environmental forces. Taken together, the CAR seems to be the most heritable indicator of diurnal cortisol secretion and the genetic influences on the CAR do not overlap, for the most part, with those of awakening cortisol and the diurnal change (Ouellet-Morin, Brendgen, et al., 2016). The possibility that the genetic and environmental contributions to cortisol secretion vary across the day makes a compelling case for systematically investigating the associations between childhood stress, cortisol, and stress-related psychopathologies according to multiple, yet distinct and complementary, indicators of diurnal cortisol secretion.

4.3 Gene-environment interactions between SES and diurnal cortisol indicators

We found that the contribution of genetic factors to awakening cortisol varied according to early and – to some extent – mid-adolescence SES, such that lower genetic influences were observed among children from more deprived families in comparison to those from wealthier backgrounds. Incidentally, this means that individual variation in awakening cortisol secretion among youth from lower SES families seems to be mainly due to shared and nonshared environmental factors. It is noteworthy that this pattern of GxE was observed within the range of SES captured in the present sample, which was mainly composed of families from moderate-to-wealthy backgrounds – with approximately a quarter of families reporting an income of less than CAN$30K (≈US$24K). This indicates that lower heritability of awakening cortisol may not arise only in the context of extreme poverty. Our findings are thus consistent with the idea that adverse environments, such as growing up in more socioeconomically deprived families, may exert a profound organizational influence on the developing brain that supersedes the effects of genetic factors, especially in cerebral structures implicated in the regulation of the HPA axis activity (Lupien et al., 2009; Shonkoff, 2010). The observation of smaller genetic influences on awakening cortisol among youth from lower SES households concord with evidence from singleton studies emphasizing the relevance of low-SES conditions, especially during childhood and adolescence, to diurnal cortisol secretion (Chen et al.,

2010; Chen & Paterson, 2006; Lupien et al., 2001; Zalewski et al., 2016). Our results additionally contend that GxE processes cannot be overlooked when ascertaining the cortisol-adversity association, as genetic liability may not be uniformly distributed across the environment continuum.

One noteworthy implication of the present findings is that interventions aiming to normalize HPA axis diurnal activity may differ in effectiveness according to SES levels and genetic background. Children from middle to higher SES households may benefit to some extent from interventions contributing to recalibrate awakening cortisol secretion. However, these interventions may be more fruitful for children from lower SES backgrounds, because environmental forces explain individual differences in secretion to a greater extent in this context. This is consistent with findings from a previous study that the effect of a social skills intervention on the recalibration of children's diurnal cortisol secretion varies according to family income, with greater effects observed among children from low-income families (Larose et al., 2019). Additional experimental research is needed to test whether this putative enhanced impact of interventions on awakening cortisol level of adolescents from lower SES backgrounds predicts lower risk for emotional and behavioural problems later on.

Although the concurrent measure of SES was phenotypically associated with the CAR and with diurnal cortisol change, the relative role of genetic influences on these two cortisol indexes appeared to be unaffected by current or past family SES backgrounds. It is possible that genetic (and environmental) influences on these cortisol indicators are differentially affected by other adverse experiences, such as peer victimization (Brendgen et al., 2017) or maltreatment rather than by sociodemographic aspects of the familial context, such as family SES. Alternatively, gene-environment interplay with respect to the CAR and with diurnal cortisol change may be more readily detectable when including more severely deprived families than those participating in the present study. Future genetically-informed studies investigating a wider range of adverse socioeconomic and psychosocial contexts could test these alternative hypotheses.

4.4 Limitations and Future Directions

Our findings should be interpreted in light of some limitations. First, due to our sample size, we were unable to examine whether the contribution of genetic and environmental factors to variations in diurnal cortisol was different for boys and girls. As sex and gender differences have been

reported in regard to cortisol secretion (Doom et al., 2013) and hormonal coupling (Phan et al., 2020), future work with larger samples is needed to examine this hypothesis. Second, the phenotypic associations between family SES and each indicator of diurnal cortisol were tested without exerting adequate control over shared genetic influences. Hence, it is not possible to decipher whether these reported associations emerge from environmental- and/or genetically-mediated processes. In a twin design, only environmental measures that vary within a twin pair allow for such a level of control, which is not the case for family SES. Third, because the participants of this population-based study were mostly Whites and came from middle-to-higher socioeconomic backgrounds, our findings may not generalize to adolescents from other ethnic and socioeconomic backgrounds, in addition to clinical populations. Finally, the influence of non-compliance to the collection protocol was examined through written records provided by the participants instead of the use of electronic devices. Nevertheless, mean sampling times reported by the participants mostly complied with the protocol, to which we exerted additional statistical control to minimize potential bias due to non-compliance in our analyses.

5. Conclusion

Using a genetically-informed and longitudinal study design, this study provided a unique insight into the specific patterns of gene-environment interplay noted to distinct indicators of adolescence diurnal cortisol secretion in the context of early childhood and mid-adolescence family SES. Our findings suggested that the contribution of genetic and environmental factors to cortisol secreted at awakening was contingent on family SES, while it was not the case for the CAR and diurnal changes. This suggests that genetically-informed studies are needed to refine our understanding of the hypothesized association between early-life experiences and the HPA axis. This undoubtedly constitutes the building blocks by which we would bring a new light into the mechanisms by which early adversity is expected to increase risks for physical and mental health.

Chapter 4

Article 2 :

Association between the timing of family socioeconomic deprivation and adolescence hair cortisol among adolescent twins: A study of the genetic and environmental processes involved

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Article reference :

Cantave, C. Y., Brendgen, M., Lupien, S., Dionne, G., Vitaro, F., Boivin, M., & Ouellet-Morin, I. (2022). Association between the timing of family socioeconomic deprivation and adolescence hair cortisol among adolescent twins: A study of the genetic and environmental processes involved. Psychoneuroendocrinology, 144, 105889. https://doi.org/10.1016/j.psyneuen.2022.105889.

Abstract

Background: While evidence shows that lower socioeconomic status (SES) is related to dysregulated hair cortisol concentration (HCC), the genetic and environmental processes underlying this association remain understudied. **Objectives**: (1) to examine whether early childhood and mid-adolescence SES are phenotypically related to late adolescence HCC and to what extent these associations are explained by common underlying genetic factors (2) to estimate whether the genetic and environmental etiology of HCC varies according to SES and the timing of these experiences. **Methods**: Participants were 422 twin pairs for whom SES was measured in early childhood (ages 0–5 years) and mid-adolescence (age 14 years). Hair cortisol was assessed at age 19. **Results:** Additive genetic factors explained 39% of variability in HCC, whereas nonshared environmental factors accounted for the remaining 61%. A significant negative association emerged between HCC and family SES assessed in mid-adolescence (β=-.11,p=.02), which was entirely explained by common underlying environmental influences. We also found evidence of stronger genetic contributions to HCC among youth who lived in more disadvantaged households during early childhood in comparison to those from wealthier backgrounds. **Conclusions:** This study provides first-time evidence that the association between adolescence SES and HCC is environmentally-explained and that genetic influences underlying HCC are not uniformly distributed across the family SES continuum measured during early childhood. These findings may pave the way for a fuller understanding of the impact of early adversity on HPA axis activity.

Keywords: Socioeconomic status; Hair cortisol; Hypothalamic-pituitary-adrenal (HPA) axis; Timing; Heritability; Gene-environment interactions

1. Introduction

Family socioeconomic deprivation has consistently been shown to be related to higher risk for health problems and behavioural difficulties (Poulain et al., 2020). Moreover, children from lower socioeconomic backgrounds (SES) are disproportionately exposed to chronic stressors in their daily lives (Evans & English, 2002), which may wear out their physiological stress systems and increase later risks for psychopathologies (McEwen & Stellar, 1993; Shonkoff, Garner, et al., 2012). The hypothalamic-pituitary-adrenal (HPA) axis is a key biological stress system contributing to upholding adaptation to stressors through short-term variations in the secretion of the glucocorticoid hormone cortisol (Koss & Gunnar, 2018). Cortisol follows a diurnal rhythm, with higher levels in the morning and a peak occurring 30 to 40 min after awakening, followed by a gradual decline throughout the day (Koss & Gunnar, 2018). Cortisol has been traditionally measured in saliva to measure short-term changes in circulating cortisol levels. Conversely, hair cortisol concentration (HCC) is increasingly used to capture prolonged systemic differences in cortisol secretion across multiple contexts, including during daytime, nighttime, and in response to acute or chronic stress (Koss & Gunnar, 2018; Stalder et al., 2017).

Mounting evidence indicates that family socioeconomic deprivation may trigger enduring alterations in HPA axis activity (Gray et al., 2018; Koss & Gunnar, 2018), particularly when it occurs during sensitive periods of neurobiological development (Lupien et al., 2009; Shonkoff et al., 2012). Numerous studies, mostly using cross-sectional designs, have reported a dysregulated HPA axis activity among children from low-SES households, for the most part characterized by higher HCC (Anand et al., 2020; Kao et al., 2019; Rippe et al., 2016). However, lower HCC has also been documented in similar contexts (White et al., 2017), in addition to null findings (Bryson et al., 2019; Malanchini et al., 2020; Wagner et al., 2019). This overall mixed pattern of findings may be partly explained by differences in sample characteristics (e.g., age, sex, ethnicity), the nature and diversity of the SES indicators used (e.g., single measure vs. composite scores), as well as the range of socioeconomic deprivation captured in the samples (e.g., at-risk vs. population-based samples). Inconsistent findings may also arise because underpowered studies are more vulnerable to false positive or negative results (e.g., Ertekin et al., 2021; Pluck et al., 2021). However, there is a more pervasive confounder that has been mostly overlooked in previous studies: the partly genetic nature of individual differences in cortisol secretion.

Twin studies have shown that individual differences in cortisol secretion are genetically and environmentally influenced. An early meta-analysis found that 62% of variation in basal cortisol levels is explained by genetic factors (Bartels, Van den Berg, et al., 2003). Subsequent twin studies have further shown that cortisol heritability varies according to the circadian rhythm, with higher heritability estimates observed in the morning as opposed to later in the day (Ouellet-Morin, Brendgen, et al., 2016). To date, however, few investigations have reported on how these etiological patterns generalize to HCC, as this stress index encompasses extended periods of time and contexts. Initial evidence from the only two studies conducted on the matter suggests that HCC is more strongly related to genetic factors than salivary cortisol levels, even compared to morning samples. Approximately 65–72% of variation in HCC is reportedly explained by inherited factors (Rietschel et al., 2017; Tucker-Drob et al., 2017), which is consistent with the fact that HCC reflects more stable patterns of cortisol secretion. As these two studies were conducted among age-heterogeneous samples (from 7 to 31 years of age, Rietschel et al., 2017; Tucker-Drob et al., 2017), replication in age-homogeneous samples is needed to obtain a more robust estimation of HCC etiology, notably in adolescence. Studies conducted in adolescence should be prioritized because of the substantial increases in the prevalence of socioemotional and behavioural disorders, presumably related to the increasing levels of daily stressors encountered during adolescence (Anniko et al., 2019; Kuhlman et al., 2017).

Despite initial finding underscoring the heritability of HCC as well as SES (Hill et al., 2016; Marees et al., 2021), little is known about the gene-environment processes implicated in the association between SES and HCC. More specifically, it is currently unknown whether the SES-HCC association could arise, to some extent, because of a common genetic etiology underlying SES and HCC. Finding such genetically-explained effects would provide evidence of a gene-environment correlation (*r*GE). It is also possible that the role of genetic factors in the etiology of HCC varies according to family socioeconomic conditions, suggesting a gene-environment interaction effect (GxE; Meaney, 2010). This GxE interaction could unfold through different processes. According to the suppression model, the expression of genetic factors underlying variation in HCC may be reduced (or silenced) in stressful environments in comparison to more advantaged ones (Ouellet-Morin et al., 2008). Alternatively, and converging with the diathesis-stress model, genetic influences linked to HCC might be more readily expressed in stressful environments (e.g., low-SES families; Ouellet-Morin et al., 2009). To the best of our knowledge,

only Tucker-Drob et al. (2017) have tested these hypotheses in regard to HCC, revealing a nonsignificant trend for larger genetic estimates in lower-SES contexts. However, several limitations constraint the generalization of these findings. First, the study failed to account for potential *r*GE involved in this association. Failure to consider *r*GE may lead to biased estimates of GxE underlying variation in HCC (Brendgen et al., 2012). Second, the genetic etiology of salivary cortisol in mid-adolescence is reported to be more contingent on family SES measured during early childhood than in mid-adolescence (Cantave et al., 2021b). Hence, the timing of exposure to socioeconomic strain may differently affect HCC's etiology. Addressing these issues in an age-homogenous sample is critical to refining our knowledge of HCC's etiology.

This investigation aimed to extend our current understanding of the genetic-environmental etiology of HCC in late adolescence. First, we examined whether early childhood (ages 0–5 years) and mid-adolescence (age 14 years) SES are phenotypically associated with HCC at age 19 years, and whether these associations may partially arise through a genetic pathway (*r*GE). Second, we estimated whether the genetic and environmental etiology of HCC varies according to family SES and the timing of these experiences (GxE), while controlling for potential *r*GE.

2. Methodology

2.1. Participants

Participants were part of the Quebec Newborn Twin Study (QNTS), a sample of twins recruited between 1995 and 1998 in the greater Montreal area. Of the 989 families with twins contacted after the twins' birth, 662 agreed to participate (68%). Twins were first seen at 5 months of age and then prospectively assessed for a variety of children and family characteristics every one or two years on average. Twins were comparable to a population-representative sample of single births in the province of Québec (Boivin et al., 2019). At the time of the twins' birth, 95% of parents lived together, 44% of them were the firstborn, 66% of mothers and 60% of fathers were between 25 and 34 years old, and 17% of mothers and 14% of fathers had not finished high school. Furthermore, 28% of mothers and 27% of fathers held a university degree, 83% of the parents were employed, 10% of the families received social welfare or unemployment insurance, while 30% of families had an income of <$30,000. During the twins' childhood and adolescence, between 16% and 28% of families reported income levels below the low-income cut-offs (LICOs),

defined by Statistics Canada (2016) as an income-to-need threshold below which a family has to spend a larger proportion of its income on necessities in comparison to the average Canadian family (for more information, see Cantave et al., 2021b). Most families were Whites (86%), 6% were Blacks, 6% were Asians and 0.3% were Native North Americans. Zygosity was assessed using 8–10 highly polymorphous genetic markers. Twins were diagnosed as monozygotic when concordant for all genetic markers. When genetic material was insufficient or unavailable (43% of cases), zygosity was determined based on physical resemblance questionnaires at 18 months and again at age 9 (Spitz et al., 1996). The comparison of both methods in a subsample of 237 same-sex pairs revealed a 94% correspondence rate (Forget-Dubois et al., 2003). The present study focused on participants with valid HCC data collected at age 19 [Mean (Standard Deviation or SD) = 19.10 (.26)]. Information was available for 422 twin pairs [161 monozygotic (MZ), 121 same-sex dizygotic (DZ), and 140 mixed-sex DZ twin pairs; 61% girls]. Little's MCAR test was nonsignificant [χ^2 = 20.60, *df*=19, *p*=.36], suggesting that information on HCC was missing completely at random.

2.2 Procedures

Twins were invited to our laboratory for the data collection. For those who showed reticence to the lab visit, a home visit (with research assistants) or postal participation were suggested. Approximately 15% (*n*=116) of the twins chose these latter alternatives, with about 3.74% (*n*=28) opting to collect and mail their samples to the laboratory. Hair samples of at least 3 cm long and 1 cm wide were collected from the posterior vertex area of the participants' scalp by trained research assistants or according to a detailed illustrated instruction guide for those who collected the sample by themselves (for more information, see Ouellet-Morin et al., 2016, 2021). The material and hair sample (stored in a Ziploc bag) were mailed back to our laboratory in a prepaid and pre-addressed envelope. Importantly, there were no mean differences in HCC and we noted a strong correlation between cortisol measured from hair collected at home and laboratory (*r*=0.91, *p*<.001; Ouellet-Morin et al., 2016). All participants provided active written consent. All instruments and study procedures were approved by the Ethics Committee of the Sainte-Justine Hospital Research Center.

2.3. Measures

Early childhood and mid-adolescence SES were derived from parents' highest educational level and family income during the twins' preschool years (3–4 assessment time points between 5 months and 5 years of age) and once again at 14 years of age. Parents' highest educational level was attributed a score of 0 for those who had a high school diploma or less and a score of 1 to those with a postsecondary diploma, based on information collected in early childhood and mid-adolescence, respectively. Family income was reported in categories ranging between 0 and ≥ $80,000. The scores were averaged to create a mean family income during early childhood [Mean (SD) = 4.46(1.92), corresponding to a $40,000-to-$49,999 average] and mid-adolescence [Mean (SD) = 3.06(1.49), corresponding to a $60,000-to-$80,000 average]. Due to the negatively skewed distribution of family income, each score was partitioned into five groups to reduce skewness for subsequent analyses. Information about the highest parental educational level and family income were included in a confirmatory factor analysis (CFA) to derive robust and cohesive SES latent indicators in early childhood (0–5 years old) and mid-adolescence (age 14). Good model fit and parsimony are generally suggested by a non-significant chi-square statistic χ^2, a comparative fit index (CFI) ≥.9, a root mean square error of approximation (RMSEA) <.08 and a weighted root mean square residual (WRMR) ≤1. Adequate model fit was found in early childhood [$\chi^2(2)$ = .000, *p*=.001; RMSEA=.00; CFI=1.000; TLI=1.000; WRMR=.004] and mid-adolescence [$\chi^2(1)$ =.000, *p*=.001; RMSEA=.000; CFI=1.000; TLI=1.000; WRMR=.005]. The standardized SES estimated factors [early childhood: Mean (SD) = -.05 (.53); mid-adolescence: Mean (SD) = -.03 (.71); see Cantave et al., 2021b) for more information] were saved and included in the genetic modeling described below.

HCC. Washing and steroid extraction procedures were conducted at the Centre for studies on human stress (Montreal, Canada), according to a previously validated protocol (Kirschbaum et al., 2009). The first 3 cm hair segment was washed (i.e., not ground, cut, or pulverized) in a 15 millilitre (ml) tube with 2.5 ml of isopropanol before mixing. After decanting, the wash cycle was repeated and left to dry overnight. Pure methanol (1.5 ml) was added before being rotated for 24 hours. The samples were then spun down in a microcentrifuge and 1 ml was aliquoted. The methanol evaporated at 37 °C under a constant stream of nitrogen. Finally, 0.4 ml of phosphate buffer was injected in the tube before being vortexed for 15 seconds. The reconstituted sample was measured in duplicate using a luminescence immunoassay (detection range: .005-4 μg/dL; intra- and inter-assay coefficients of variation: 5.54 and 18.74, respectively). All samples were assayed

in duplicates and averaged. A total of 1.2% of the samples (*n*=9 participants) was discarded because of unusually high scores, with the highest outlier greater than 14 SD. HCC was then 3 SD winsorized [1.6% of the samples, *n*=13, Mean (SD) = .07 µg/dl (.05)] and natural logarithmically transformed. Several factors previously identified to potentially affect HCC were reported by the twins (i.e., hair care: washing frequency, coloration, treatments, etc.; health-related characteristics: body mass index (BMI), drug and medication use, sleeping habits, cold, flu and allergies; health problems: cardiovascular problems, diabetes, head injuries, medications, etc.). Of those, only BMI, hair wash frequency, anxiolytic use, as well as cocaine and ecstasy consumption in the last three months were uniquely related to HCC. Standardized residuals were computed and later used to statistically account for these potential confounders.

2.4. Statistical analyses

2.4.1. Univariate genetic modeling

Structural equation modeling using a maximum-likelihood fit function allows a more precise estimation of the relative contribution of genetic and environmental parameters with their respective confidence intervals (CI), which enables the test of the statistical significance of these estimates (Neale & Cardon, 1992b). By comparing the degree of similitude (i.e., intra-pair correlations) between MZ twin pairs who share approximately 100% of their segregating genes and DZ twins who share, on average, 50% of their genetic makeup, the sources of variance in a phenotype can be partitioned in additive genetic (A), non-additive or dominance genetic effects (D), and shared (C) and non-shared environmental effects (E) (Neale & Cardon, 1992b). Additive effects refer to the independent effects of genes, whereas non-additive influences denote interactions between genes of the same locus (dominance) or at different loci (epistasis). Environmental influences include shared environmental effects that make siblings alike (C), whereas nonshared environmental effects capture environments that make siblings dissimilar, plus measurement error (E). Additive genetic effects can be approximated by twice the difference between the MZ intra-pair correlation and the DZ intra-pair correlation. An MZ intra-pair correlation that is considerably higher than twice the size of the DZ intra-pair correlation may indicate dominance genetic effects. A crude estimate of the relative contribution of shared environmental factors can be evaluated by subtracting the MZ intra-pair correlation from twice the

DZ intra-pair correlation. Non-shared environmental effects are expected when the MZ intra-pair correlation is less than 1.

Using the Mplus package version 8.1.6 (Muthén & Muthén, 2018), univariate structural equation models using a maximum-likelihood fit function were performed to estimate the relative contribution of genetic and environmental factors to variation in HCC. To this end, a two-group model was fitted to the data whereby (1) the latent genetic correlations between the twin pairs were constrained to 1.0 for MZ twins and to .50 (to estimate latent additive genetic effects) or to .25 (to estimate dominance genetic effects) for DZ twins; (2) correlations of latent shared environmental influences between the twins of the same pair were fixed to 1 for MZ and DZ twins; and (3) the nonshared environmental intra-pair correlations were fixed to zero for MZ and DZ twins (see Figure 10). The estimated coefficients *a, d, c, e* provide information about the relative contribution of the latent factors A, D, C, E to the total variance of each phenotype P, with the variance of P = $a^2 + d^2 + c^2 + e^2$. Measurement error is also included in e^2. Given that the estimation of c and d both rely on the same information (i.e., difference between the MZ and DZ within-pair correlations), it is not possible to estimate d and c parameters simultaneously in a typical twins-reared-together study design (Neale & Cardon, 1992b). Therefore, ACE and ADE models were tested separately. More restrictive nested models (e.g., AE, CE) were compared using nested χ^2-difference tests. A nonsignificant χ^2-statistic, lower AIC and BIC, and RMSEA $<.08$ indicate good model fit and parsimony. While we observed sex differences in the variance of HCC [$\chi^2(2) = 7.19$, p=.03], sex-limited analyses were not performed as they require over 1000 twin pairs to be robustly estimated (Verhulst, 2017). HCC was thus standardized within sex groups to account for these differences ($\chi^2(2) = .50$, p=.78]. Mixed-sex DZ twin pairs were excluded from these analyses because their intra-pair correlation tended to differ from that of same-sex DZ twin pairs ($\chi^2(4) = 8.54$, p=.07; rSame-sexDZ=.13, p=.12; *r*Mixed-sexDZ=.007, p=.48].

2.4.2. Bivariate models testing the genetic and environmental correlations (*r*GE) and interactions (GxE)

To test whether the expected phenotypic associations between family SES and HCC arise partially through a genetic pathway (*r*GE), the best fitting univariate model was expanded to include the effect of SES on HCC's latent genetic factor, along with a direct effect of SES on HCC. A significant effect of SES on HCC's common latent genetic factor would suggest *r*GE. In addition,

we examined whether SES interacted with the genetic and environmental HCC's estimates by allowing each latent factor to interact with family SES to assess potential GxE. All models were estimated separately for early childhood and mid-adolescence SES. The power to test the current study primary research question (i.e., the GxE hypothesis) was calculated using Monte Carlo power analyses in Mplus. These analyses revealed that the bivariate model was well powered to estimate a small interaction effect between SES and the genetic (β=.20, 89.6% power) and environmental etiology of HCC (β=.15, 97.2% power).

3. Results

3.1. Concurrent and prospective associations

Early childhood family SES was moderately associated with SES measured in mid-adolescence (r=.52, $p\leq$.001), indicating moderate stability of SES across these developmental periods. To examine whether individual differences in each of these SES indicators were uniquely associated with HCC, indirectly capturing our developmental timing hypothesis, both early childhood and mid-adolescence SES were included simultaneously in a regression model predicting HCC. Only mid-adolescence SES was associated with HCC (mid-adolescence SES: β=-.12, p=.02; early childhood SES: β=.06, p=.29), suggesting that twins raised in lower SES households at age 14 years had higher HCC at the end of adolescence (age 19) once early childhood SES was statistically accounted for. Given the moderate continuity of family SES from early childhood to mid-adolescence, additional analyses were carried out to test the possibility that the presumed association between early childhood SES and HCC might be mediated by mid-adolescence SES. The mediation model was tested with the SPSS macro Process v4.0 and indeed revealed a significant indirect effect (β=-.06, bootstrap 95%CI=-.11 to -.01), indicating that mid-adolescence SES fully mediated the association between early childhood SES and HCC (total effect, β=-.01, 95%CI=-.18 to .16).

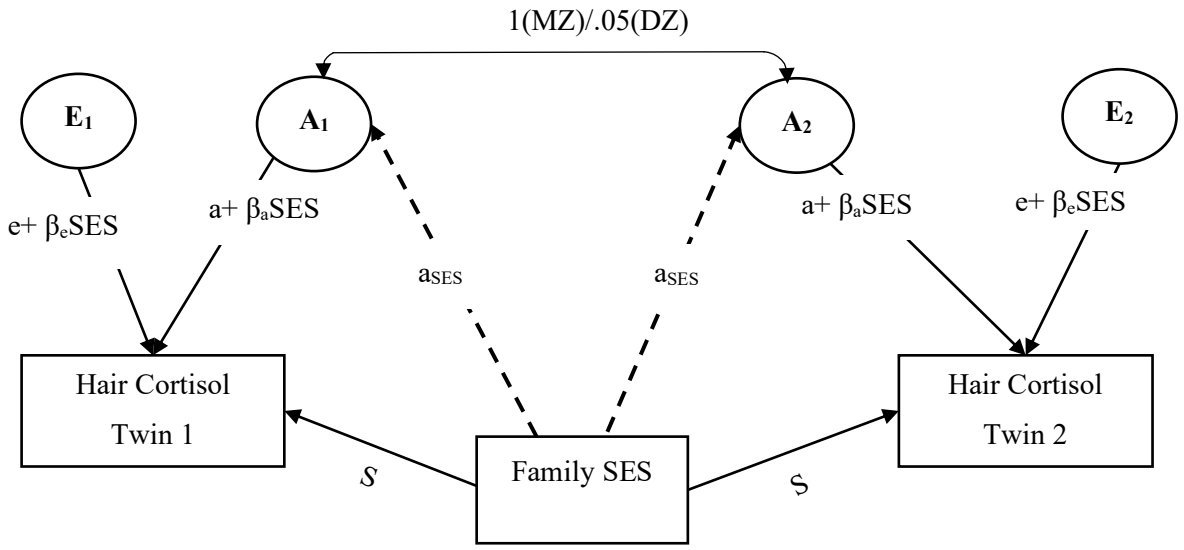
3.2. Gene-environment processes linking early childhood and mid-adolescence SES to HCC

Table 6 summarizes the estimated parameters, as well as fit and parsimony statistics from the univariate analyses. Individual differences in HCC were best explained by an AE model, as

Table 6 - Univariate models for hair cortisol concentration

	A	C or D	E	A^2	C^2 or D^2	E^2	RMSEA	AIC	BIC	-2ll (np)	$\Delta\chi^2$	Δ *df*	*P*
Hair Cortisol													
ACE	.64 [.00;.76]	.001 [.00;.64]	.80 [.70;.90]	39%	.00%	61%	0.03	1334.03	1348.49	-663.02 (4)	3.60	2	.17
AE	**.64 [.49;.76]**	**—**	**.80 [.69;.90]**	**39%**	**—**	**61%**	**0.00**	**1332.04**	**1342.87**	**-663.02 (3)**	**3.60**	**3**	**.31**
CE	—	.59 [.38;.72]	.84 [.73;.93]	—	33.5%	66.5%	0.04	1333.91	1344.75	-663.96 (3)	5.47	3	.14
E	—	—	1 [.95;1.09]	—	—	100%	0.14	1353.15	1360.38	-674.57 (2)	27.06	4	.00
ADE	.63 [.00;.74]	.10 [.00;.74]	.80 [.69;.89]	38%	1%	61%	0.03	1334.04	1348.49	-663.02 (4)	3.60	2	.17
DE	—	.64 [.49;.76]	.79 [.69;.90]	—	40%	60%	0.01	1332.48	1343.32	-663.24(3)	4.04	3	.26

Figure 10. – Bivariate moderation model



Note. The coefficients a and e refer to the main effects of the latent factors A and E on HCC. The coefficient S represents the main effect of SES on HCC. The coefficient a_{SES} represents the association between SES and HCC via genetic pathways, indicating *r*GE. Finally, the coefficients β_aSES and β_eSES provide estimates of the interactions between SES and the A and E latent factors to test whether the relative contributions of genetic and nonshared environmental factors vary according to family SES.

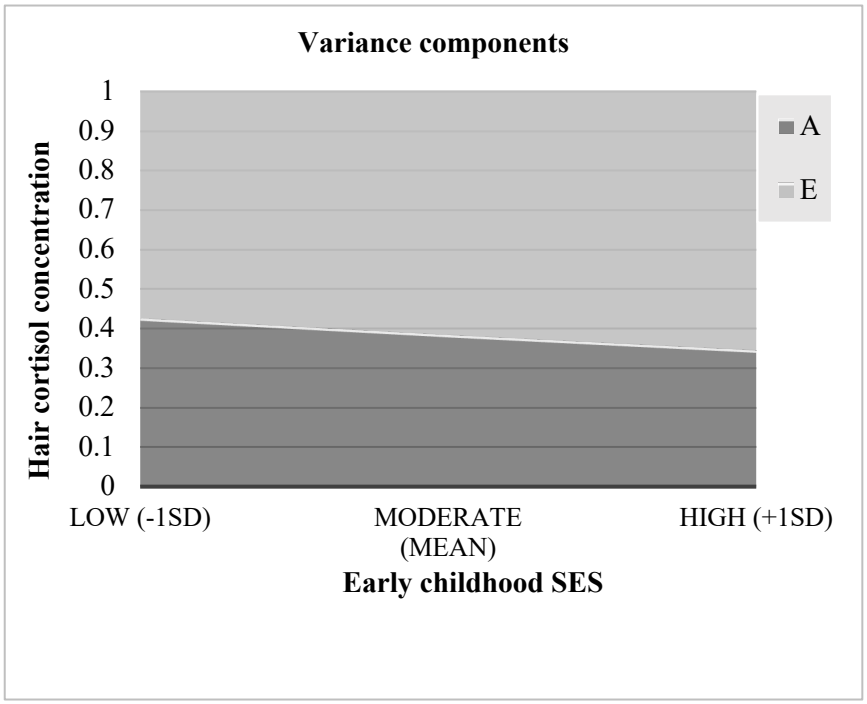
Table 7 - Results of the bivariate models including the gene-environment correlations (*r*GE) and gene-environment interactions (GxE)

		Early childhood SES		**Mid-adolescence SES**	
	Parameter	Estimate	95% CI	Estimate	95% CI
HCC		-2LL (np)=-610.057(7)		-2LL (np)= -539.127(7)	
	a	-.62***	[-.65; .59]	.70***	[.57; .83]
	e	.81***	[.72; .90]	.77***	[.66; .88]
	SES[1]	.78	[-1.57; 3.14]	.01	[-1.26; 1.26]
	a_{SES}	-1.21	[-2.49; 4.91]	-.01	[-1.83; 1.81]
	β_aSES	**.03*** **	[.01 ; .06]	.07	[-.05; .19]
	β_eSES	.01	[-.07; .08]	-.01	[-.11; .08]

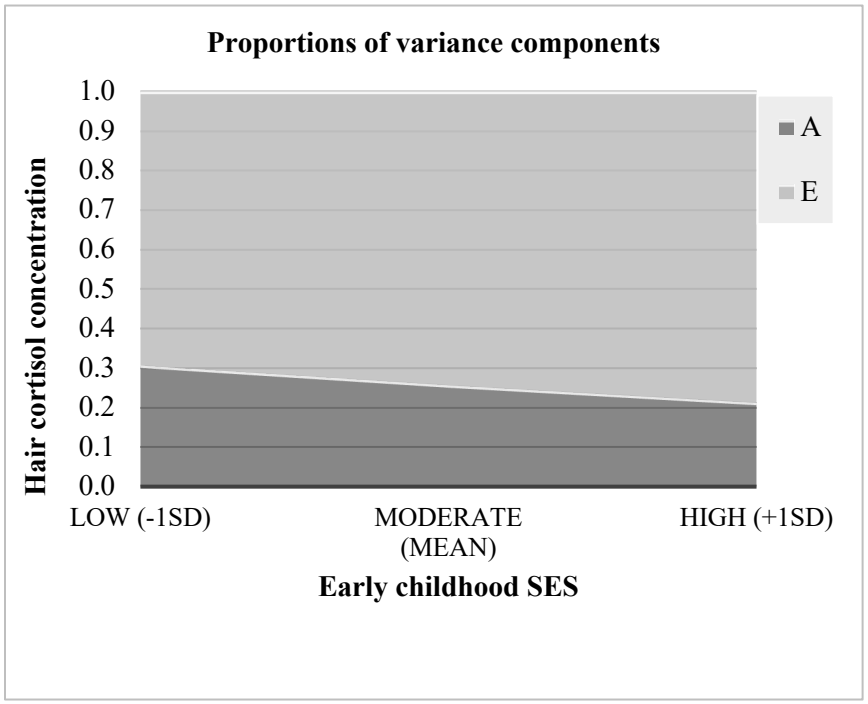
Note. The a_{SES} coefficient represents the gene-environment correlation between the latent factor A and SES. The β_aSES or β_sSES coefficients represent the interactions between SES and the genetic and environmental latent factors, respectively. LL=log-Likelihood; np = number of parameters. ***=$p \leq .001$; **= $p \leq .01$; *=$p \leq .05$; [1]=Z-standardized values.

Figure 11. – Genetic, shared and nonshared raw (Panel A) and proportional (Panel B) variance estimates of hair cortisol as a function of early childhood SES

Panel A



Panel B



indicated by a nonsignificant χ^2-difference test compared to the full ACE model, as well as lower AIC, BIC and RMSEA indices compared to alternative models. Additive genetic factors explained 39% of the variance in HCC, whereas nonshared environmental factors accounted for the remaining 61%.

Next, we extended the univariate model to investigate potential *r*GE and GxE between HCC and family SES. The estimated model is illustrated and defined in Figure 10. The genetic correlations between early childhood (or mid-adolescence) SES and HCC (a_{SES}) were not significant (see Table 7), suggesting that the previously reported phenotypic association likely represents a "true" environmental association between mid-adolescence SES and HCC. However, a significant interaction was observed between the latent factor A and early childhood SES, indicating that the relative strength of genetic underpinnings of HCC varied depending on the level of early childhood SES. As illustrated in Figure 11 (Panel A), additive genetic factors played a lesser role in HCC as early childhood SES increased. Specifically, 31% and 69% of inter-individual differences in HCC at age 19 were accounted for by genetic factors and nonshared environmental factors, respectively, among youth from lower (-1SD) SES families (see Figure 11, Panel B). In contrast, among those from more advantaged (+1SD) SES backgrounds, genetic factors accounted for only 21% of the variance of HCC, with the rest explained by nonshared environmental factors (79%). The genetic and environmental contributions of HCC did not fluctuate according to mid-adolescence SES (see Table 7).

4. Discussion

This study is the first to test whether the genetic and environmental etiology of chronic cortisol secretion varied as a function of family SES in an age-homogeneous sample of adolescents, and whether these interactions differed according to the timing of these experiences. Analyses indicated that individual differences in HCC were moderately accounted for by heritable factors (39%), and substantially associated with environmental experiences unique to each individual (61%). These findings corroborate those from a burgeoning scientific literature which supports the heritability of HCC. Nevertheless, our heritability estimate is considerably lower than what has been previously reported (72% and 65% by Rietschel et al., 2017; Tucker-Drob et al., 2017, respectively). These differences might reflect the current study's focus on HCC in late adolescence among age-homogeneous twins [M_{age} (SD) = 19.10 (.26)], as opposed to the previous studies' inclusion of

younger twins (Rietschel et al., 2017 [M_{age} (SD) = 14.5 [2.4], range=10.1-31.1]; Tucker-Drob et al., 2017, [M_{age} (SD) = 12.42 [2.78], range=7.80-19.47]). Consistent with this hypothesis, Tucker-Drob et al. (2017) provided evidence of gradually reducing genetic contributions to HCC with age. Notwithstanding these differences, our findings revealed that variations in late adolescence HCC are substantially explained by uniquely-experienced environmental factors. As the unshared environmental estimate refers to experiences that increase twins' dissimilarities in addition to randomness and measurement errors, it may index a multitude of experiences (e.g., peer victimization, uncontrollable life events, social support) that go beyond the family socioeconomic context and timing, as SES in mid-adolescence may correlate with (unmeasured SES) at age 19 years, when HCC has been measured. These findings nevertheless converge with the hypothesis of an enhanced sensibility of the HPA axis to environmental influences in adolescence, positive or detrimental (Koss & Gunnar, 2018).

Our results further revealed that participants raised in lower SES households at age 14 showed higher HCC at age 19. These findings concur with previous cross-sectional observations of higher HCC among lower SES children (Anand et al., 2020; Kao et al., 2019; Rippe et al., 2016; Vaghri et al., 2013) and support the view that youth growing up in lower SES families may be exposed to more frequent, severe, and persistent stressors, both within and beyond the family environment (Evans & English, 2002). Higher exposure to stress has been proposed to induce repeated activation of the HPA axis, which may lead to long-lasting alterations indexed through the measure of hair cortisol collected in late adolescence (McEwen & Seeman, 1999; Shonkoff, Garner, et al., 2012). Prior to the present study, however, few investigations formally tested the alternative hypothesis that the SES-cortisol association could, to some extent, be driven by shared genetic liabilities passed down from parents to their offspring. In other words, it was assumed that this association was environmentally-explained. A formal test of these competing hypotheses requires the use of a genetically-informed design that allows to disentangle genetic from environmental sources of influence. Our finding suggests for the first time that the association between mid-adolescence SES and HCC does not arise because of common underlying genetic factors, but in all likelihood is due to environmental processes (e.g., instability and turmoil, low-quality housing, violence; Evans & English, 2002)

In contrast, we found that early childhood SES made no direct contribution to late adolescence chronic cortisol secretions, but indirectly affected the latter through its effect on mid-adolescence SES. This underscores the sensitivity of late adolescence HPA axis activity to early and contemporaneous experiences of family socioeconomic deprivation. These findings additionally suggest that alterations in HCC are related to the continuation of SES-related experiences from early childhood to mid-adolescence, but not only, as our results revealed that novel SES-related experiences during mid-adolescence may also affect HCC. The fact that early childhood SES was still associated with HCC 14 years later, even if indirectly, emphasizes the importance of implementing psychosocial interventions aiming to recalibrate youth's HPA axis activity following early adversity or to prevent the effects of later adversity on HCC. While these findings ought to be replicated and shown to remain beyond a concurrent measure of SES with HCC (in this study at age 19 years), they nonetheless shed light on the potential importance of taking a developmental approach sensitive to the timing of adversity when investigating its association with HPA axis activity.

Results also revealed that the magnitude of additive genetic influences on HCC decreased along the continuum of early childhood SES, with slightly larger heritability estimates among lower-SES families in comparison to wealthier households. However, the moderating role of SES in the etiology of HCC was relatively weak, as the contribution of heritable factors to HCC remained moderate in magnitude across the distribution of early childhood family SES. Our GxE findings nevertheless lend support to the diathesis-stress model (Shanahan & Hofer, 2005). Our findings also parallel, albeit partially, those from a previous research revealing a nonsignificant trend for stronger genetic heritability of HCC in the context of family socioeconomic disadvantage (Tucker-Drob et al.,2017). Tucker-Drob et al. (2017), however, did not consider the developmental timing of SES. Our results are congruent with another study pointing to variation in the relative contribution of genetic factors to salivary awakening cortisol in mid-adolescence across the early childhood SES distribution (Cantave et al., 2021b). Notably, however, an opposite pattern of GxE was noted, whereby lower heritability estimates emerged in socioeconomically more disadvantaged families in comparison to more privilege ones. As salivary awakening cortisol and HCC capture different HPA axis functions, index distinct contexts and time windows, and were measured at two different time points (age 14 vs. age 19), it is difficult to distinguish whether these distinct patterns of GxE are the result of age-related differences in sensitivity to SES and/or the

reflection of regulatory mechanisms involved in these two indicators of HPA axis activity. What is striking and new, however, is that these different patterns of GxE interplay emerge across distinct indicators of adolescence cortisol secretion. Altogether, these GxE findings underline the complex and dynamic nature of the interactions taking place between genetic and environmental sources of influence across development, pertaining to our understanding of individual differences in HPA axis activity.

4.1 Strengths and Limitations

This study has several strengths, including the use of a prospective genetically-informative design, which allowed us to unravel the influence of genetic and environmental inputs on HCC and to consider the developmental timing of exposure to family deprivation. However, several limitations must also be acknowledged. First, due to insufficient statistical power, we did not conduct sex-limited analyses. Although preliminary findings found no sex-specific differences in regard to HCC's etiology (Tucker-Drob et al., 2017), replication in larger samples are needed before further conclusions can be derived. Second, hair samples were collected only once in this study. Future studies with multiple measures of HCC may provide a more complex understanding of the impact of SES timing on HCC. Third, the generalizability of our findings is limited by the racial and ethnic homogeneity of our sample, which mostly consisted of White, European descent participants. Moreover, we did not consider whether the participants' gender and sexual orientation could modify the pattern of reported findings. Additional studies are needed to examine whether these findings can be generalized to more diverse populations (O'Brien et al., 2013). Finally, the majority of our sample came from middle-to-higher income families, with approximately a quarter of them reporting an income of less than CAN$30K [≈US$24K]. While it is remarkable that the presence of GxE interaction was detected within the range of SES captured in this population, future genetically-informed studies are needed to establish whether these findings extend to less-advantaged youth.

5. Conclusions

Using prospective data from an age-homogeneous twin sample, the present study expands our understanding of the etiology of HCC in late adolescence according to socioeconomic contexts measured in early childhood and mid-adolescence. This study additionally allowed to reject the alternative possibility that the phenotypic association between mid-adolescence SES on HCC is

partially or entirely explained by common genetic factors, supporting the hypothesis of an environmentally-explained effect. Genetically-informed studies are essential to complement robust investigations of the early roots of health inequalities, in which stress systems such as the HPA axis are expected to play a crucial role because of their malleability and embedded effects on a wide range of physiological and psychological processes over time (Shonkoff, Garner, et al., 2012).

Chapter 5

Article 3

Prospective and concurrent associations between family socioeconomic status, social support and diurnal and hair cortisol in adolescence

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Unpublished article

Abstract

Background: Although exposure to socioeconomic hardship is hypothesized to induce dysregulation in hypothalamic-pituitary-adrenal (HPA) axis activity and cortisol secretion, evidence remains inconsistent. Yet, few studies have investigated this association according to a developmental approach sensitive to the social context likely to mitigate this association. **Objectives**: 1) To examine the role of stability and changes in family hardship as indicated by low socioeconomic status (SES) in predicting multiple indicators of cortisol secretion; 2) To test whether social support moderates these associations. **Method**: Participants were part of a population-based sample of twin pairs recruited at birth. Family SES was collected in early childhood (ages 0–5) and mid-adolescence (age 14). Perceived social support was assessed at aged 14 and 19. Diurnal cortisol (n=569) was measured at age 14 at awakening, 30 min later, in the afternoon and evening over four non-consecutive days. Hair cortisol (n=704) was measured at age 19. **Results**: Youth experiencing lower SES levels throughout childhood and adolescence had a flatter diurnal slope and higher hair cortisol levels in comparison to those who experienced upward socioeconomic mobility from early childhood to mid-adolescence and those with persistently higher SES levels. Moreover, youth who experienced downward socioeconomic mobility showed higher hair cortisol levels, except for those who were raised in higher SES households during early childhood. Finally, participants from lower SES households who reported receiving higher social support in mid-adolescence had lower awakening cortisol secretion. **Conclusions**: This study supports the hypothesis that early socioeconomic adversity may sensitize HPA axis activity to later socioeconomic disadvantage, which may bear consequences for socioemotional and behavioural functioning.

Keywords: Socioeconomic status, Cortisol, HPA-axis, Social support, Stress-sensitization.

1. Introduction

Over the last decades, an extensive body of work has identified family socioeconomic deprivation as one of the most consistent and robust predictors of children's future health problems, with effects detectable as early as in prenatal development and persisting well into adulthood (Bradley & Corwyn, 2002; Kim et al., 2018). Research has also documented that children raised in more socioeconomically impoverished households (e.g., lower income and less educated parents) experience a higher prevalence of cognitive and socioemotional difficulties later in life in comparison to those growing up in more affluent families (Bradley & Corwyn, 2002; Kim et al., 2018). These children are also more likely to face chronic stressors within and outside of their family environment (e.g., low-quality housing, parental separation, noisy and crowded households, and community violence), which may exacerbate the negative effects of family socioeconomic disadvantage and further tax their capacity to adapt to future stress (Evans & English, 2002; Kim et al., 2018). This led many researchers to propose that early stressors, such as family socioeconomic deprivation, jeopardize later functioning in part through the dysregulation of the body's neurophysiological stress systems (McEwen & Seeman, 1999; Shonkoff, 2010).

The hypothalamic-pituitary-adrenal (HPA) axis is one of the main physiological stress systems responsible for maintaining adaptation to stress in changing, novel, unpredictable, uncontrollable, or threatening environments through a cascade of peptide and hormonal secretion, including the glucocorticoid stress hormone cortisol (Koss & Gunnar, 2018). Cortisol secretion follows a diurnal cycle characterized by higher levels after awakening reaching a peak approximately 30 to 40 minutes later—together depicting the cortisol awakening response or CAR—followed by progressive declining levels during the day. Past studies have usually captured this diurnal rhythm using saliva and blood samples as they reflect shorter-span (minutes to hours) variation in circulating cortisol levels (Koss & Gunnar, 2018). In contrast, cortisol concentration measured in hair (HCC) is proposed to indicate prolonged cortisol production (over the past 2–3 months) across a variety of contexts, including during daytime and nighttime diurnal secretion, as well as in response to minor, acute, repeated, or chronic stress (Koss & Gunnar, 2018; Stalder et al., 2017). As these cortisol indicators are proxies for distinct, yet complementary HPA axis dynamics, they should be examined within the same individuals to refine our understanding of how lower family socioeconomic status (SES) is linked to altered HPA axis functioning and identify factors that may moderate this association.

Previous research has shown that socioeconomic deprivation often co-occurs with dysregulation in HPA axis activity (Koss & Gunnar, 2018). Yet, important discrepancies exist regarding the magnitude and direction of this association. Indeed, prior studies have reported both lower and higher diurnal and hair cortisol secretion among children and youth living in more impoverished households (Chen et al., 2010; Gray et al., 2018; Koss & Gunnar, 2018; Tarullo et al., 2020), in addition to nonsignificant findings (Bryson et al., 2019; Malanchini et al., 2020; McLachlan et al., 2016; Young et al., 2019). Inconsistency in findings might be influenced by many methodological factors, including sample characteristics (e.g., age, sex and ethnicity), which cortisol and/or SES indicators were selected (e.g., awakening cortisol, CAR, diurnal slope, HCC; single vs. composite SES; dichotomized vs. continuously distributed), the range of socioeconomic conditions captured in the study samples (e.g., at-risk vs. population-based samples), and the study designs (e.g., cross-sectional vs. longitudinal; Bryson et al., 2021; Chen et al., 2010; Ertekin et al., 2021; Fogelman & Canli, 2018). Another potential source of confound that has received scant attention in previous research—despite its central role in several theoretical models such as the Ecobiodevelopmental framework (Garner et al., 2012; Shonkoff, 2010; Shonkoff, Richter, et al., 2012) and the Life cycle model of stress (Lupien et al., 2009)—is the dynamic nature of adversity. Indeed, the association of socioeconomic disadvantage with diurnal cortisol and HCC may be more complex than originally presumed, as the timing, persistence, and changes in these experiences may play an important role (Cantave et al., 2021b; Desantis et al., 2015; Kim et al., 2018).

While SES is reported to be moderately stable (Cantave et al., 2021b), prior studies largely restricted their investigation to the concurrent association with cortisol (Desantis et al., 2015). Yet, failing to consider the occurrence of (past and future) changes in SES may obscure a clearer depiction of the magnitude and direction of its associations with diurnal cortisol secretion or HCC, as well as the factors that may modify them (Cantave et al., 2021b; Desantis et al., 2015; Gustafsson et al., 2010). In particular, accounting for stability and change in SES across childhood and adolescence may help clarify whether these experiences have cumulative (i.e., additive) or synergic (i.e., interaction) effects on cortisol secretion in youth. Based on the stress-sensitization model (Daskalakis et al., 2013), experiences of adversity occurring early in life, such as socioeconomic deprivation, may sensitize HPA axis activity to later socioeconomic adversity. According to that model, family socioeconomic deprivation experienced during early childhood may prime a stronger response to similar contexts in adolescence, taking the form of a stronger association

between SES and cortisol secretion for youth who grew up in more impoverished households during early childhood (Young et al., 2020). While some studies have examined the association between trajectories of SES (i.e., repeated measurements) and diurnal cortisol (Gustafsson et al., 2010; Lê-Scherban et al., 2018) and HCC in late adolescence or adulthood (Ouellet-Morin, Cantave, Lupien, et al., 2021; Serwinski et al., 2016), only one study has tested whether early childhood exacerbated (i.e., moderated) the association between later SES and cortisol secretion (Young et al., 2019). In that study, neither of these measures of SES—whether independently or jointly—covaried with adult diurnal cortisol levels (Young et al., 2019). However, because the study sample only included middle-aged adults, it remains unknown whether these findings also apply to adolescents. Indeed, HPA axis' responsiveness to social environments is expected to be heightened during adolescence in part due to pubertal changes (Gunnar et al., 2019; Koss & Gunnar, 2018). Family socioeconomic strain may more readily affect cortisol secretion in adolescence, especially for those who also grew up in a lower socioeconomic environment in early childhood.

The magnitude of the association between SES and cortisol may also depend on the degree of social support available within youth's proximal network of relationships. Growing evidence suggests that perceived social support can buffer or offset the link between stressful environments, such as family socioeconomic deprivation, and HPA axis activity (Cohen & Wills, 1985; Hostinar & Gunnar, 2015; Shonkoff, 2010). Many studies supporting this claim have been conducted in laboratory settings and have reported reduced cortisol responses to psychosocial stress among participants who received social support as part of the experiment in comparison to those who did not (Gunnar, 2017; Taylor, 2011). While emerging findings from observational studies point to an association of social support with diurnal (Heaney et al., 2010; Rickard et al., 2016; Sjögren et al., 2006) and hair cortisol secretion (Iob et al., 2018), evidence corroborating the putative buffering role of social support in the SES-cortisol association is scarce. To the best of our knowledge, only one study has examined this hypothesis, targeting young adults (Hooker et al., 2018). Their results revealed that, among participants with lower social support, those exposed to lower SES had higher cortisol secretion during stress recovery than participants from higher SES context. This association was not, however, significant among participants reporting higher social support (Hooker et al., 2018). While these results offer provisional evidence for the stress-buffering role of social support, another study which assessed the moderating role of SES in the association between

social support and diurnal cortisol secretion reported nonsignificant results (Hooker et al., 2020). Further investigation of whether social support buffers the association between family socioeconomic deprivation and diurnal cortisol or HCC is warranted. This is especially true in adolescence, a period that is increasingly recognized for the heightened plasticity of neurophysiological systems and structures regulating stress, emotion and behaviours (Koss & Gunnar, 2018). By examining the potential moderating role of social support, the present study also contributes to further our understanding on how social support may help support resilience.

Building from previous work that examined the association between early childhood (0–5 years old), mid-adolescence (age 14) family SES, and either diurnal (age 14; Cantave et al., 2021b) or hair cortisol secretion (age 19; Cantave et al., 2022), the current study tested the hypothesis that lower childhood family SES exacerbates the hypothesized association of lower mid-adolescence SES with dysregulation in these cortisol indicators. We also examined whether social support buffered these associations.

2. Methodology

2.1. Participants

Participants were a convenience sample drawn from the Québec Newborn Twin Study (QNTS), a sample of twins recruited between 1995 and 1998 in the greater Montreal area. Twin samples have been used in the past to address research questions where the examination of genetic influences or the twin relationship are not specifically targeted (Brendgen, 2016; Malanchini et al., 2020; Vucetic et al., 2021). This sample of twins was comparable to a population-representative sample of single births in the province of Québec in terms of their family context at birth (Boivin et al., 2019; Ouellet-Morin, Cantave, Lupien, et al., 2021; Seguin, 2005). Of the 989 families with twins contacted, 662 agreed to participate (68%). Participants were first seen at 5 months of age and then prospectively assessed for a variety of children and family characteristics every one or two years on average. At the time of the participants' birth, 95% of parents lived together, 44% of them were firstborn, 66% of mothers and 60% of fathers were between 25 and 34 years old, and 17% of mothers and 14% of fathers had not graduated from high school. Furthermore, 28% of mothers and 27% of fathers held a university degree, 83% of the parents were employed, and one in 10 families received social welfare or unemployment insurance. Approximately a third of the families (30%) had an annual income of less than $30,000. During the participants' early childhood and mid-

adolescence, between 16% and 28% of families reported income levels below the low-income cut-offs (LICOs), defined by Statistics Canada (2016) as a threshold below which a large proportion of the income is spent on necessities in comparison to the average Canadian family (for more information, see Cantave et al., 2021b). Most families were Whites (86%), 6% were Blacks, 6% were Asians, and 0.3% were Native North Americans. This study focused on a subsample of participants with valid cortisol data collected from saliva at age 14 years [Mean(Standard Deviation or SD)=14.0(.3)] or from hair at age 19 years [Mean(SD)=19.1(.3)]. Information on saliva samples was available for 569 participants [52% girls] from whom most (74%) had collected saliva across each of the four collection days (for more information, see Ouellet-Morin et al., 2016). Information on hair samples was available for 704 participants [61% girls; see section 2.4 for analyses examining attrition].

2.2 Procedures

At age 14, letters detailing the objectives of the study were sent to the families, followed by a home visit. After informed consent (parents) and assent (youth) were obtained, the research assistants explained the saliva collection protocol, which consisted in sampling saliva at four-time points during the day (awakening, 30 min later, late in the afternoon and bedtime) on four collection days (Tuesdays and Thursdays on two consecutive weeks) and the completion of an interview-based questionnaire with the youth and their parents. During the home visit, the research assistants ensured that participants and their parents were familiar with the collection material. Families were visited a second time to gather the saliva tubes. At age 19, youth were invited to our laboratory, which included the collection of a hair sample of at least 3 cm long and 1 cm wide from the posterior vertex area of the participants' scalp by trained research assistants. For those who showed reticence to the lab visit, a home visit (with research assistants) or postal participation were suggested. Approximately 15% (n=116) of the participants chose these latter alternatives, with about 3.74% (n=28) opting to collect a sample of their hair themselves (with the help of a parent or co-twin). In such cases, the material and a detailed illustrated guide of how to perform the hair collection, were sent by mail and returned to our laboratory in a prepaid and pre-addressed envelope (for more information, see Ouellet-Morin et al., 2016, 2021). In a previous validation study, we showed that no mean differences in HCC could be detected between samples measured from hair collected at home and laboratory and that these distinct protocols yielded highly correlated

measures (r=0.91, p<.001; Ouellet-Morin et al., 2016). At age 19 years, only the participants provided active written consent. All instruments and study procedures were approved by the Ethics Committee of the Sainte-Justine Hospital Research Center.

2.3 Measures

Early childhood and mid-adolescence SES were derived from the parents' highest educational level and family income measured during the twins' preschool years (see Figure 4) and again at 14 years of age. Parents' highest educational level was attributed a score of 0 for those who had a high school diploma or less and a score of 1 to those with a postsecondary diploma. Family income was reported in categories ranging between 0 and ≥ $80,000. The scores were averaged to create a mean family income in early childhood [Mean(SD)=4.46(1.92), corresponding to a $40,000-to-$49,999 average] and mid-adolescence [Mean(SD)=3.06(1.49), corresponding to a $60,000-to-$80,000 average]. Due to the negatively skewed distributions of family income at both time points, each score was partitioned into five groups to reduce the impact of this asymmetric distribution on subsequent analyses. Information about the highest parental educational level and family income were included in a confirmatory factor analysis (CFA) to derive robust and cohesive SES latent indicators in early childhood (age 0–5 years) and mid-adolescence (age 14 years). Good model fit and parsimony are generally suggested by a non-significant χ^2 statistic, a comparative fit index (CFI) ≥.9, a root mean square error of approximation (RMSEA) <.08 and a weighted root mean square residual (WRMR) ≤1. Adequate models fit was found in early childhood [$\chi^2(2)$=.000, p=.001; RMSEA=.00; CFI=1.000; TLI=1.000; WRMR=.004] and mid-adolescence [$\chi^2(1)$=.000, p=.001; RMSEA=.000; CFI=1.000; TLI=1.000; WRMR=.005; see (Cantave et al., 2021b), for more information].

Social support was self-reported using the Network of Relationships Inventory (NRI; Furman & Buhrmester, 1985) at age 14 and once again at age 19. The NRI is a widely used questionnaire that assesses relationship quality with different social agents from which youth typically draw support from (Gottlieb, 1991). In the present study, three items assessing perceived emotional and instrumental support (i.e., *When you're feeling down or upset, how often do you depend on this person to cheer you up? How often do you depend on this person for help, advice, or sympathy?, How often do you turn to this person for support with personal problems?*) were used to rate the participants' support from their mother, father, close friend, co-twin and teacher at age 14 and age

19, as well as from their romantic partner (if any) at age 19.The decision to not include items assessing perceived support from a romantic partner at age 14 was motivated by the high number of participants reporting not having a romantic partner at this age (i.e., proportion at age 14: 89% and at age 19: 44%). Of note, social support from teachers was not available at age 19. The social support measure used in the present study was thus comprised of 15 items at age 14 (i.e., three items for each potential source of support) and at age 19, respectively. Of note, we also estimated a social support scale without the three items measuring participants' perceived support from a romantic partner at age 19 and found that it was highly correlated with the one that included these items (r=.97, p<.001). Items were rated on a 5-point Likert-type scale ranging from 1 (little or none) to 5 (the most) and averaged to create a total score at age 14 (mid-adolescence; Mean=2.74; SD=.84; ∝=.90) and at age 19 (late adolescence; Mean=2.93; SD=.81; ∝=.86), respectively. Owing to the moderate correlation between the mid- and late-adolescence social support scales (r=.38, p<.001), we also averaged both scores into a global index of adolescence social support (Mean=2.84; SD=.73). The mid-adolescence (age 14) social support was used in the subsequent analyses of cortisol measured at age 14 and the global index of (i.e., averaged age 14 and 19) social support were used for analyses of cortisol at 19 years so that associations could be examined according to a clear temporal sequence.

Diurnal cortisol. At age 14, we provided saliva tubes to the participants along with instructions for collection and diaries to report the exact times the samples were collected (supervised by their parents). Saliva samples were first placed in the participants' refrigerator during data collection days. After their collection, research assistants brought them back to our laboratories and stored in -20^{o} C freezers until cortisol determination using a high sensitivity enzyme immune assay kit (Salimetrics® State College, PA, Catalog No. 1–3102). Frozen samples were brought to room temperature to be centrifuged at 15,000 × g (3000 rpm) for 15 min and analyzed on 96-well plates. The range of detection for this assay was between 0.007–3 µg/dl (.19–82.76 nmol/L) and the intra- and inter-assay coefficients of variation were 4.8% and 8.2%, respectively. Of the possible 9472 saliva samples from 592 participants, 2037 (21.05%) were missing due to participants lapses, insufficient saliva collection or technical problems (on average, 25.2% were missing at awakening, 17.7% at +30 min, 8.7% at the end of the afternoon and 25.95% in the evening). We identified 75 cortisol samples (1%) with a value greater than 3 times the SD above, which were winsorized. Participants were considered "compliant" if their awakening and +30 min saliva samples were

separated from at least 20 min and less than 40 min and that their awakening saliva collection was completed within the first 15 min following awakening and not distinct from the co-twin (≤8 min). A total of 8.61% of the samples were discarded due to noncompliance to the collection protocol. The final sample included 569 participants. Cortisol values were converted from µg/dl to nmol/L (i.e., multiplied by 27,588) and natural log-transformed prior to data analyses.

Three distinct indicators were derived from up to 16 cortisol time points to capture different aspects of cortisol function across the day: the CAR, the awakening and the diurnal change levels. As done previously (Adam et al., 2006; Badrick et al., 2007), the CAR was derived separately from the diurnal slope calculations because of evidence suggesting that the CAR is regulated by different neurobiological and genetic mechanisms than cortisol secreted in the remaining part of the day (Clow et al., 2010; Ouellet-Morin et al., 2016). First, the CAR was calculated for each day of saliva collection by subtracting the awakening level from the one collected 30 min later. Second, growth curve analyses using mixed modeling for longitudinal data were performed to estimate, at each collection day, the mean level of cortisol at awakening (intercept) and the change that took place afterward (slope). To this end, an unspecified curve model was chosen to allow for slightly varying assessment times (since awakening) between individuals and obtain an optimal estimate of change without imposing any particular shape of change across individuals (Duncan et al., 1997). The model contained both fixed and random estimates, corresponding to the parameters' mean and variance between individuals. The fixed unstandardized means estimate of each collection day varied from 20.81 to 21.09 for the intercept and from -.89 to -.93 for the slope. The random unstandardized variance estimates of each collection day varied from 11.60 to 17.85 for the intercept and from .05 to .08 for the slope (see Ouellet-Morin et al., 2016, for additional information). Models were fitted in Mplus Version 6.11 using maximum likelihood estimation and the COMPLEX option adjusting standard error estimates to correct for the non-independence of observations. Growth curve models confirmed the expected progressive decrease of cortisol levels from awakening to evening (Brendgen et al., 2017). Third, we tested whether the cortisol indicator estimates were affected by several potential confounders (see Cantave et al., 2021b) and found that awakening time, hours of sleep, sleeping problems, exercises and alcohol or drug consumption were uniquely associated with at least one cortisol indicator and were thus statistically accounted for in the subsequent analyses. Fourth, the four intercept estimates (one for each collection day) were included in a CFA to derive an indicator free from day-specific variation. Similar CFAs were

conducted for the slope and CAR estimates. The CFA fit indices confirmed that the respective estimates derived at each collection day could be grouped into three global factors: CAR [χ^2 (2)=1.95, p=.38; RMSEA=.00; CFI=1.00; SRMR=.03], intercept [χ^2 (1)=.002, p =.96; RMSEA=.00; CFI=1.00; SRMR=.00] and slope [χ^2 (1)=.007, p =.93; RMSEA=.00; CFI=1.00; SRMR=.00].

Hair cortisol. Washing and steroid extraction procedures were conducted at the Centre for studies on human stress (Montreal, Canada), according to a previously validated protocol (Kirschbaum et al., 2009). The first 3 cm hair segment was washed (i.e., not ground, cut, or pulverized) in a 15 millilitre (ml) tube with 2.5 ml of isopropanol before mixing. After decanting, the wash cycle was repeated and left to dry overnight. Pure methanol (1.5 ml) was added before being rotated for 24 hours. The samples were then spun down in a microcentrifuge and 1 ml was aliquoted. The methanol evaporated at 37 °C under a constant stream of nitrogen. Finally, 0.4 ml of phosphate buffer was injected in the tube before being vortexed for 15 seconds. The reconstituted sample was measured in duplicate using a luminescence immunoassay (detection range: .005-4 µg/dL; intra- and inter-assay coefficients of variation: 5.54 and 18.74, respectively). All samples were assayed in duplicates and averaged. A total of 1.2% of the samples (n=9 participants) were discarded because of unusually high scores, with the highest outlier greater than 14 SD. HCC was then 3 SD winsorized [1.6% of the samples, n=13, Mean(SD)=.07 µg/dl(.05)] and natural logarithmically transformed. Several factors previously identified to potentially affect HCC were reported by the twins (i.e., hair care: washing frequency, coloration, treatments, etc.; health-related characteristics: body mass index (BMI), drug and medication use, sleeping habits, cold, flu and allergies; health problems: cardiovascular problems, diabetes, head injuries, medications, etc.). Of those, only BMI, hair wash frequency, anxiolytic medication use, as well as cocaine and ecstasy consumption in the last three months were uniquely related to HCC. Standardized residuals were computed to statistically account for these potential confounders in subsequent analyses.

2.4 Statistical analyses

Preliminary analyses indicated that diurnal cortisol data was not missing completely at random [χ^2(7)=22.20, p=.002] and that DZ twins and those reporting more severe depressive symptoms at age 13 years were less likely to have participated in saliva collection (awakening cortisol [χ^2(2)=45.65, p=.001], CAR [χ^2(2)=36.42, p=.001], diurnal slope [χ^2(2)=46.69, p=.001]). HCC

data was found to be missing completely at random [χ^2=20.60, *df*=19, *p*=.36]. However, 21% of participants with valid HCC data at age 19 had missing values on mid-adolescence SES (age 14). Considering the strong correlation between early childhood and mid-adolescence SES (see Table 8), participants' missing mid-adolescence SES values were imputed from their early **childhood** SES values. Following the imputation, between 0.4 and 4% of participants with valid diurnal and HCC data had missing values on mid-adolescence SES, whereas between 11% and 13% had missing values on early childhood SES. Moreover, our analyses revealed significant mean differences in social support between boys and girls at mid-adolescence [*t*(798)=-7.70, *p*<.001; Mean=2.51 for boys and Mean=2.95 for girls] and from age 14 to age 19 (i.e., global index of adolescence social support) [*t*(1011)=-11.36, *p*<.001; Mean=2.59 for boys and Mean=3.08 for girls], with boys receiving fewer support than girls. Sex effects were therefore controlled in subsequent analyses.

To account for the hierarchical structure of the data (i.e., twins are clustered within families), we used multilevel regression analyses. The main analyses were conducted in two steps. First, we specified a null model in which variation in cortisol was partitioned into within (individual-level) and between (family-level) components. This model contained one fixed-effect (intercept) and one random-effect (variation in intercepts across families) and allowed us to estimate the intra-class correlation (ICC). The ICC represents the amount of variance of cortisol that is explained by the grouping variable (i.e., family; Heck et al., 2013). Higher ICCs indicate greater variability between families, thereby suggesting that the adoption of a multilevel approach is warranted. Second, the unique effects of the predictors as well as their joint (interaction) effects were introduced sequentially in the models as fixed effects, while still accounting for random effects. Of note, the mid-adolescence social support scale was included as an independent variable in the diurnal cortisol models (all variables measured at age 14), whereas the global index adolescence social support (averaged 14 and 19 years) was included as a predictor of HCC models (age 19). A maximum likelihood estimator was used to compare successive models. Model fit improvement after including additional predictors was tested using the likelihood ratio (deviance) test, with a lower deviance indicating a better fit. Analyses were run using SPSS, version 26. For ease of interpretation, all variables were Z-standardized before the analyses.

3. Results

3.1 Prospective and concurrent associations between the main study variables

As shown in Table 8 and reported, in part, elsewhere (Cantave et al., 2021b, 2022), a moderate-to-strong association was observed between early childhood and mid-adolescence SES, indicating stability and change in youth's family SES across these developmental periods. Childhood SES did not predict social support, nor (salivary) diurnal or HCC. In contrast, mid-adolescence SES significantly covaried with mid-adolescence social support (14 years) and the global index of adolescence social support (average 14 and 19 years). This reveals that youth from wealthier households reported receiving higher levels of concurrent and later emotional and instrumental support from their proximal network of relationships. As reported previously (Cantave et al., 2021b), adolescents living in higher SES families exhibited concurrently higher awakening cortisol levels and a steeper decreasing diurnal slope. No other associations were detected between SES and cortisol indicators. However, youth with higher social support in mid-adolescence had higher awakening cortisol levels. While the diurnal (salivary) cortisol indicators (14 years) all covaried, none were associated with HCC (19 years). Considering the strong association between awakening cortisol and diurnal change, awakening cortisol was accounted for in all diurnal slope regression models.

3.2 Independent and joint contributions of early childhood and mid-adolescence SES to cortisol

Model 1 presented in Table 9 indicated a significant variation in the CAR explained by both between- (Z=4.05, p<.001) and within-family (Z=9.89, p<.001) differences. More specifically, the ICC indicated that around 31% of the total variation in awakening cortisol is accounted for by differences between families (i.e., between twin pairs), while the remaining 69% is explained by differences within families (i.e., within twin pairs). Similar findings were observed for the other cortisol indicators. Altogether, these findings suggest that a considerable portion of the variation in diurnal (salivary) and (hair) cortisol secretions lie between families, which ought to be controlled for to reliably test the associations presumed to be present at the individual level.

Next, we tested the additive effect of early childhood and mid-adolescence SES on cortisol by including these variables as fixed effects (Model 2). After adjusting for sex, random intercept effects (and awakening cortisol for diurnal slope models), early childhood and mid-adolescence

SES were not uniquely associated with adolescents' CAR, awakening cortisol or diurnal change levels. In contrast, lower mid-adolescence SES predicted higher chronic cortisol secretion at age 19.

The interaction term between both SES indicators included in model 3 showed that the strength of the association linking mid-adolescence SES to HCC significantly varied as a function of early childhood SES levels. Simple slope analyses revealed that lower mid-adolescence SES predicted higher HCC for twins who were raised in lower (-1 SD) [*b*=-.20(*SE*=.07), *p*=.004] and moderate (average level) [*b*=-.11(*SE*=.05), *p*=.03] SES households during early childhood, whereas no significant association between mid-adolescence SES and HCC was noted for those raised in wealthier families (+1 SD) during early childhood [*b*=-.02(*SE*=.07), *p*=.82]. To further illustrate this moderation, the conditional effect of mid-adolescence SES on HCC was plotted at lower (-1SD), moderate (mean) and higher (+1SD) levels of early childhood SES (see Figure 12, panel A). Among youth who grew up in lower SES households during early childhood, those who continued to live in disadvantage families at age 14 showed higher HCC at age 19 in comparison to those for whom family SES increased (to moderate and higher SES) during mid-adolescence (i.e., upward social mobility). A similar pattern of findings was uncovered for twins who grew up in the sample's average SES in early childhood. Notably, no association emerged between mid-adolescence SES and HCC for those who were raised in higher SES households during early childhood. These results suggest that growing up in favourable socioeconomic circumstances during early childhood may shield children from the adverse impact of downward socioeconomic mobility during mid-adolescence on later HCC.

We observed a similar interaction between early childhood and mid-adolescence SES for (salivary) cortisol diurnal change measured at age 14, albeit at a trend level (see Table 9, Model 3). Simple slope analyses as well as the graphical illustration of this interaction (see Figure 12, panel B) revealed a pattern that was partially consistent with the one found for HCC. Specifically, a flatter diurnal slope was noted in youth growing up in lower SES families in mid-adolescence, but only among those who had experienced socioeconomic disadvantage in early childhood (i.e., - 1 SD) [*b*=-.14(*SE*=.07), *p*=.043].

3.2 Adolescence social support as a potential moderator to the associations between SES and cortisol

Our findings revealed that the bivariate association previously observed between mid-adolescence social support and awakening cortisol remained significant after adjusting for SES, sex and random intercept effects (see Table 10, Model 2). Moreover, a significant interaction effect emerged between mid-adolescence SES and social support (Table 10, Model 3). As depicted in Figure 13, youth who were living in more impoverished households in mid-adolescence concurrently had lower awakening cortisol levels in comparison to those growing up in average-to-higher SES families, but this association was only significant among participants who reported higher levels (+1 SD) of social support [*b*=.19(*SE*=.08), *p*=.02]. In contrast, no significant association could be detected between mid-adolescence SES and awakening levels for youth who reported lower (-1 SD) [*b*=-.01(*SE*=.07), *p*=.95] or moderate (i.e., average) [*b*=.09(*SE*=.06), *p*=.13] levels of support.

We also investigated the possibility that the association of social support with awakening cortisol could differ at different levels of mid-adolescence SES. Our findings revealed that this association was only significant at moderate (i.e., mean [*b*=.14(*SE*=.05), *p*=.003]) and higher levels (+1 SD [*b*=.23(*SE*=.07), *p*=.001]) of mid-adolescence SES. Specifically, among youths from moderate to higher SES backgrounds, higher social support was concurrently associated with higher awakening cortisol (see Figure 13). In contrast, awakening cortisol levels were consistently low in youth from lower SES (-1 SD) environments during mid-adolescence, regardless of the level of social support they received [*b*=-.04(*SE*=.07), *p*=.53]. Of note, models including only age 19 social support (measured concurrently with HCC) as the moderator resulted in similar findings as those reported for the global index of social support (averaged ages 14 and 19; available upon request). Social support did not moderate the associations between SES and the other cortisol indicators.

Table 8 - Linear correlation estimates between SES, social support and salivary and hair cortisol indicators

	1	2	3	4	5	6	7	8
1. **Early childhood SES (5 months - 5 years)**	–	.49***	.02	.05	.04	.08†	-.02	.01
2. **Mid-adolescence SES (14 years)**		–	.11**	.12*	-.02	.10*	-.08*	-.02
3. **Mid-adolescence social support (14 years)**			–	.85***	.02	.12**	-.07†	.01
4. **Global adolescence social support (14 & 19 years)**				–	-.003	.12**	-.08†	.03
5. **CAR (14 years)**					–	-.09*	-.59***	.002
6. **Awakening cortisol (Intercept; 14 years)**						–	.25***	-.01
7. **Diurnal cortisol (slope; 14 years)**							–	.03
8. **HCC (19 years)**								1

Note. ***$p \leq .001$, **= $p \leq .01$, *= $p \leq .05$. CAR = Cortisol awakening response; HCC = Hair cortisol concentration.

Table 9 - Multilevel regression models linking early childhood and mid-adolescence SES to the salivary and hair cortisol indicators

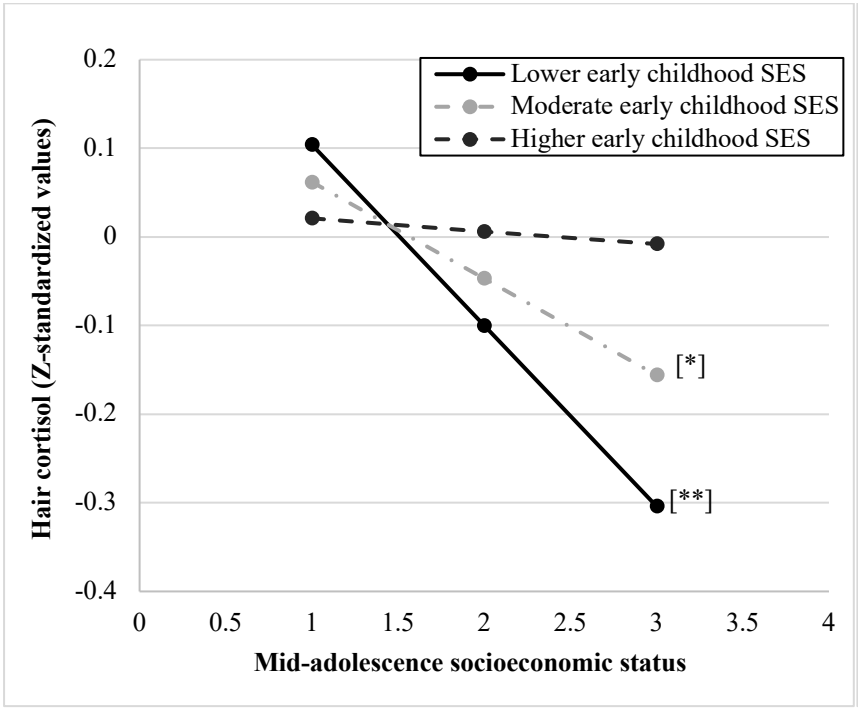
	CAR (14 years)			**Awakening cortisol (14 years)**			**Diurnal slope (14 years)**			**HCC (19 years)**		
	β(*SE*)	*p*	*ICC*	*β*(*SE*)	*p*	*ICC*	*β*(*SE*)	*p*	*ICC*	*β*(*SE*)	*p*	*ICC*
Model 1			.31			.41			.43			.24
Intercept	.03(.05)	.56	–	.01(.06)	.82	–	-.03(.05)	.53	–	.003(.05)	.96	–
Random intercept	**.31**	–	–	**.43**	–	–	**.40**	–	–	**.25**		–
Model 2			.30			.41			.37			.23
Intercept	-.21(.16)	.20	–	-.14(.16)	.39	–	.16(.12)	.21	–	.003(.15)	.85	–
Early childhood SES	.06(.06)	.31	–	.03(.06)	.67	–	.09(.05)	.07	–	.06(.05)	.29	–
Mid-adolescence SES	-.04(.06)	.50	–	.09(.06)	.12	–	-.04(.05)	.36	–	**-.10(.05)**	**.044**	–
Sex	.16(.10)	.12	–	.10(.10)	.34	–	-.12(.08)	.11	–	-.01(.09)	.89	–
Awakening cortisol	–	–	–	–	–	–	**-.55(.04)**	**<.001**	–	–	–	–
Model 3			.29			.41			.37			.22
Early childhood SES * Mid-adolescence SES	.07(.06)	.21	–	-.06(.06)	.39	–	**.09(.05)**	**.058**	–	**.09(.05)**	**.037**	–

Note. SES=socioeconomic status, CAR = Cortisol awakening response; HCC = Hair cortisol concentration, *β*=Standardized regression coefficient, *SE*=Standard error, *Df*=Degree of freedom, *ICC*=Intra-class correlation. Significant parameters are indicated in boldface. Significant parameters are indicated in boldface. Due to space limitations, the random intercepts parameters were not included in Models 2 and 3 notations. Of note, significant variability was evidenced across families for the CAR, awakening cortisol, the diurnal change levels and HCC (Z=4.05, p<.001; Z=5.80, p<.001; Z=6.05, p<.001 and Z=3.65, p<.001, respectively), in addition to within family

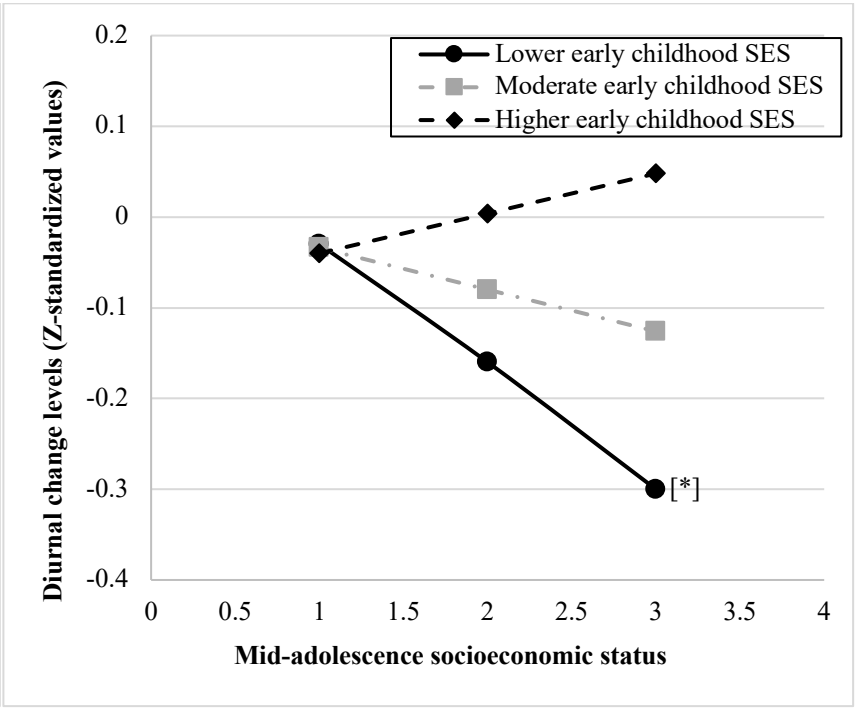
differences (Z=9.89, p<.001; Z=10.69, p<.001; Z=10.74, p<.001 and Z=11.27, p<.001, respectively). Comparing models 2 to 1 and models 3 to 2 for HCC [model 2 deviance reduction (dr)=8.19, number of parameters (np)= 3, p=.04; model 3 dr=8.71, np=1, p=.003] and cortisol diurnal change [model 2 dr=401.46, np= 4, p=.001; model 3 dr=7.18, np=1, p=.01] showed that, in both cases, model 3—which contained the interaction between early childhood and mid-adolescence SES—was the best fitting model, as evidenced by a lower deviance estimate.

Figure 12. – Associations between mid-adolescence SES and HCC (Panel A) and (salivary) diurnal cortisol (Panel B) according to early childhood SES.

A.



B.



Note. **= $p \leq .01$, *= $p \leq .05$.

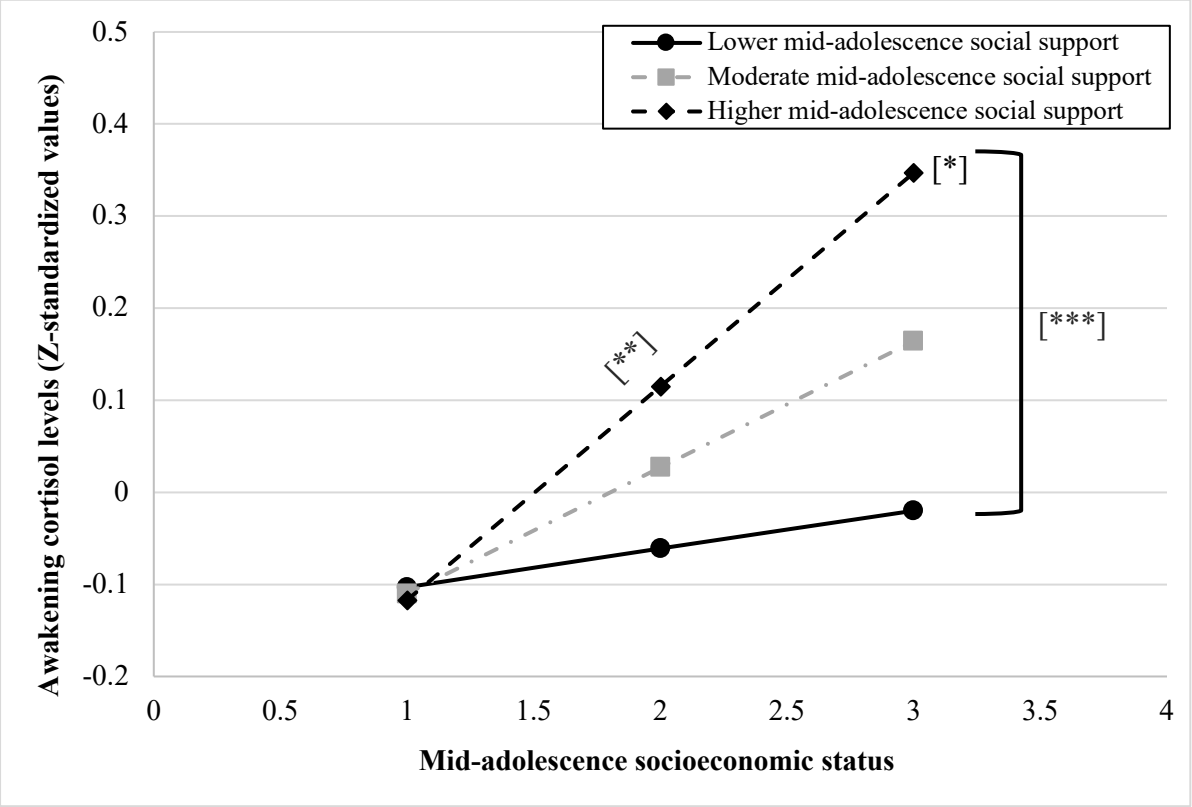
Table 10 - Multilevel regression models linking early childhood, mid-adolescence SES and social support to the cortisol indicators

	CAR (14 years)			Awakening cortisol (14 years)			Diurnal slope (14 years)			HCC (19 years)		
	β(*SE*)	*p*	*ICC*	*β*(*SE*)	*p*	*ICC*	*β*(*SE*)	*p*	*ICC*	*β*(*SE*)	*p*	*ICC*
Model 1			.31			.41			.43			.27
Intercept	.03(.05)	.56	–	.01(.06)	.82	–	-.03(.05)	.53	–	.004(.05)	.94	–
Random intercept	**.31**	–	–	**.43**	–	–	**.40**	–	–	**.28**	–	–
Model 2			.30			.42			.37			.26
Intercept	-.22(.17)	.19	–	-.02(.16)	.89	–	.19(.13)	.13	–	.003(.16)	.99	–
Childhood SES	.06(.06)	.31	–	.03(.06)	.61	–	.09(.05)	.07	–	.05(.06)	.35	–
Adolescence SES	-.04(.06)	.51	–	.08(.06)	.18	–	-.04(.05)	.33	–	**-.10(.05)**	**.044**	–
Social support	-.01(.05)	.78	–	**.14(.05)**	**.002**	–	.04(.04)	.26	–	-.01(.05)	.88	–
Sex	.16(.10)	.11	–	.02(.10)	.87	–	-.14(.08)	.07	–	.01(.09)	.95	–
Awakening cortisol	–	–	–	–	–	–	**-.55(.04)**	**<.001**	–	–	–	–
Model 3			.29			.42			.36			.25
Childhood SES * Adolescence SES	.07(.06)	.24	–	-.06(.06)	.35	–	**.09(.05)**	**.053**	–	**.11(.05)**	**.016**	–
Childhood SES * Social support	.10(.06)	.09	–	-.01(.06)	.92	–	-.00(.04)	.95	–	.06(.06)	.33	–
Adolescence SES * Social support	-.07(.05)	.21	–	**.10(.05)**	**.047**	–	-.02(.04)	.58	–	-.02(.05)	.74	–

Note. SES=socioeconomic status, CAR = Cortisol awakening response; HCC = Hair cortisol concentration, *β*=Standardized regression coefficient, *SE*=Standard error, *Df*=Degree of freedom, *ICC*=Intra-class correlation. The mid-adolescence social support scale was included in diurnal cortisol models, while the global index of social support (14- and 19-years average) was included in HCC models to account for the measures' timeline. Significant estimates are indicated in boldface. Due to space limitations, the random intercepts

parameters were not included to Models 2 and 3 notations. Comparisons between models 1–3 for awakening cortisol [model 2 *dr*=28.68, *np*= 4, *p*=.001; model 3 *dr*=11.50, *np*=3, *p*=.01] indicated that model 3—which included the interaction between mid-adolescence SES and social support—significantly improved model fit, offering additional support for the reported moderation finding.

Figure 13. – Association of mid-adolescence SES with awakening cortisol levels according to mid-adolescence social support (age 14).



Note. **= $p \leq .01$,*= $p \leq .05$.

4. Discussion

Taking advantage of the prospective longitudinal design of the present study, the current study assessed whether early childhood SES moderated the association between mid-adolescence SES and diurnal (salivary) or chronic (hair) cortisol indicators. This allowed testing the putative impact of stability and changes in SES over time on these cortisol indicators. We also evaluated whether social support moderated the associations between SES and these cortisol indicators. Four findings merit further attention.

First, we found that youth living in lower SES households at age 14 had higher HCC at age 19. This finding is consistent with other studies reporting higher HCC in lower SES children, but that did not specify the relative contribution of earlier vs. later family socioeconomic disadvantage in that association (Bryson et al., 2021; Kao et al., 2019; Merz et al., 2019; Rippe et al., 2016; Tarullo et al., 2020; Ursache et al., 2017; Vaghri et al., 2013; Windhorst et al., 2017). Because family SES is only moderately stable in the first 15 years following the birth of children (Cantave et al., 2021b), this variable cannot be assumed to be constant. Our findings indirectly support the idea that lower SES children disproportionally experience more chronic stress within their environment (e.g., parental separation, harsh and coercive parental practices, noisy and crowded households, and community violence; Evans & English, 2002; Kim et al., 2018), which may be intertwined in the reported association between family SES and HPA axis activity over time (McEwen & Seeman, 1999; Shonkoff, 2010).

Second, the repeated assessments of family SES, from early childhood to mid-adolescence, enabled to use a time-sensitive analytical approach to formally test the sensitization role that early childhood family SES may play in the association between mid-adolescence SES and cortisol secretion. Two out of the four cortisol indicators assessed, namely HCC and the diurnal slope, suggested that this might indeed be the case. Specifically, youth raised in more impoverished households during early childhood and who were still exposed to lower family SES in mid-adolescence (i.e., chronic exposure) had higher HCC at age 19 years and a trend for flatter (salivary) diurnal slope at age 14 years. In contrast, individual differences in SES in mid-adolescence did not correlate with these cortisol indicators among youth who grew up in wealthier families during early childhood. Altogether, these findings are in line with the stress-sensitization hypothesis, which proposes that early exposure to adversity may enhance HPA axis sensitivity to stress experience

later in time (Daskalakis et al., 2013; Young et al., 2019). Furthermore, we found that youth raised in lower SES families during childhood but who experienced upward social mobility during mid-adolescence had lower HCC as well as a more dynamic diurnal slope than those who experienced chronic socioeconomic disadvantage. This finding echoes another feature of the stress-sensitization hypothesis; future stress ought to be present to trigger the embedded diathesis brought about by early family socioeconomic disadvantage. Contrastingly, youth who were exposed to downward social mobility (i.e., from moderate early childhood SES (or the sample's average) to lower mid-adolescence SES) also showed higher HCC. This is in line with findings from a previous investigation revealing that middle-aged women who experienced deterioration of income during a 4-year period showed higher HCC in comparison to those who experienced no change or an improvement in income during this period (Serwinski et al., 2016). Our study extends this prior evidence by showing that downward social mobility from early childhood to mid-adolescence is not predictive of age 19 HCC among children who grew up in wealthier families during early childhood. This finding offers support to the long-term benefit associated with growing up in a higher SES context in early life and underscores the importance of strategies aiming to increase the socioeconomic welfare of young families.

Third, it is noteworthy that the synergistic effect of early childhood and mid-adolescence SES was only detected for HCC, and to a lesser extent, the diurnal slope. These two cortisol indicators were measured 5 years apart, in different biospecimens (saliva vs. hair) and reflect distinct HPA axis dynamics. Crucially, these two indicators did not significantly covary and, yet, a similar pattern of findings was observed for both. Notably, HCC and the diurnal slope both reflect patterns of cortisol secretion during a protracted period, although the duration of that period varies (Koss & Gunnar, 2018). Accordingly, we argue, similar to others (Malanchini et al., 2020), that these two cortisol measures may reflect more accurately the impact of chronic exposure to socioeconomic adversity on HPA axis activity than more acute measures of diurnal secretion, such as the awakening cortisol and the CAR. Taken together, these results underline the importance of investigating distinct and complementary indicators of HPA axis activity in future studies to provide much-needed insights into the pathways by which early adversity disrupts HPA axis activity. However, such studies ought to investigate associations prospectively using repeatedly measured diurnal and hair cortisol indicators. This would help acquire a more nuanced understanding of the mechanisms affecting the

onset of disrupted patterns of cortisol secretion following experiences of chronic SES disadvantage and SES mobility as well as their long-term impact on health.

Fourth, we found that youth from more disadvantaged backgrounds in mid-adolescence reported lower levels of emotional and instrumental support from their proximal network of relationships, whereas this association did not emerge in regard to early childhood SES. These results are consistent with several lines of evidence suggesting that socioeconomic disadvantage may constrain lower SES individuals' access to social support (Belle, 1983). Relatedly, youth growing up in higher SES contexts in mid-adolescence had higher awakening cortisol levels when they perceived higher levels of social support. Contrary to our expectations, this pattern of finding is opposite to the stress-buffering model, as the SES-awakening cortisol association was magnified for those who reported higher social support, whereas awakening cortisol levels in youth from lower SES backgrounds remained at similar (low) levels regardless of the level of social support received from others. It is possible that social support does not exert a strong stress-buffering effect in socioeconomically deprived contexts, as provisions of social resources in such contexts tend to co-occur with stress contagion, negative interactions, reciprocal obligations as well as unequal reciprocity, which may lead to higher stress (Belle, 1983; Cattell, 2001; Moskowitz et al., 2013; Stringhini et al., 2012; Tigges et al., 1998). In line with the biological sensitivity to context theory (Boyce & Ellis, 2005) and the adaptive calibration model (Del Giudice et al., 2011), the higher awakening cortisol level detected in youth from higher SES families who reported higher social support might be associated with a heightened responsiveness to environmental cues in the morning, thus enabling these youth to benefit more from the social resources and positive opportunities available within such context during the day. In contrast, the low awakening cortisol levels observed among lower SES youth – regardless of their levels of social support – might be indicative of a lower sensitivity to prolonged exposure to stressful cues during the day, which are much more prevalent in lower SES contexts (Boyce & Ellis, 2005; Del Giudice et al., 2011; G. W. Evans, 2004; Fries et al., 2005; Susman, 2006). Regardless, these phenotypes might still be associated with pathological developmental outcomes, as it has been shown that both higher and lower awakening or morning cortisol are related to socioemotional and behavioural difficulties in adolescence (Dietrich et al., 2013; Goodyer et al., 2009; Halligan et al., 2007; Murray-Close et al., 2008)

4.1 Strengths and limitations

This study had several strengths, including its large sample size, the assessment of multiple indicators of cortisol as well as the access to repeated measurement of family SES at key developmental periods (early years and adolescence). The current study also has several limitations. First, given that the sample of this study is largely composed of Whites from middle-to-higher SES families, with about a quarter of families reporting an income less than CAN$30K (≈US$24K), our findings may not readily generalize to more diverse or socioeconomically deprived populations. Second, perceived social support was only measured during adolescence, which precluded from investigating the potential buffering impact of childhood social support on the SES-cortisol association. Future studies examining this possibility may help better understand the buffering role of social support in the context of socioeconomic disadvantage, in all its complexity. Finally, the influence of noncompliance to the saliva collection protocol was verified through written records provided by the participants instead of information drawn from electronic devices. Nevertheless, mean sampling times reported by the participants mostly complied with the protocol, to which we exerted additional statistical control to minimize potential bias due to noncompliance in our analyses.

5. Conclusion

Using a prospective longitudinal study design, the present study found evidence that early childhood family SES exacerbated the association between mid-adolescence SES and HCC and, to a lesser extent, its association with the (salivary) diurnal slope. More research is needed to examine whether these findings represent a mechanism underlying vulnerability or resilience. Furthermore, higher perceived social support magnified the association between mid-adolescence family SES and awakening cortisol favoring youth growing up in wealthier families. Collectively, the present findings highlight the relevance of examining patterns of stability and change in youth's social context for a deeper understanding of the association between adversity and HPA axis activity, as well as the factors that may modulate this association.

Chapter 6 – Discussion

Anchored in a developmental psychopathology perspective (Toth & Cicchetti, 2013), the main objective of this thesis was to examine the gene-environment processes implicated in the link between family SES and variation in multiple cortisol indicators during adolescence. Findings from the first two thesis articles pointed to unique associations between family SES in mid-adolescence and indicators of diurnal cortisol (CAR and diurnal slope), as well as HCC. These associations varied either according to a linear or nonlinear function. Conversely, the linear association linking mid-adolescence SES to awakening cortisol only approached statistical significance once the effect of early childhood SES was controlled. Evidence from this thesis indicated that these associations further varied as a function of the timing of SES experiences and, to some extent, of the level of perceived social support during mid-adolescence. Contrary to expectations, the association between family SES in mid-adolescence and HCC was not accounted for by a common genetic etiology, but instead reflected shared environmental effects. The first two thesis articles also provided first time evidence that the genetic effects on adolescents' awakening cortisol and HCC varied depending on early childhood family SES (GxE). There was also an interaction between mid-adolescence SES and the genetic effects on awakening cortisol, that no longer reached statistical significance once early childhood SES was accounted for. The specific GxE patterns were, however, distinct for awakening cortisol and HCC. Whereas a suppression pattern of GxE was detected for awakening cortisol, a diathesis-stress pattern of GxE was documented for HCC. In contrast, the genetic effects on the CAR and the diurnal slope did not vary according to early childhood or mid-adolescence family SES.

To further discuss the scientific implications of our findings, we will focus on four key results in the next sections. First, we will review the phenotypic SES-cortisol association in light of prior scientific evidence. Second, we will examine whether time-related hypotheses—i.e., the biological embedding of early stress and the sensitization (or habituation) effects of early stress—proposed to explain the developmental impact of early adversity on physiological stress systems and health may help refine our understanding of the SES-cortisol association. Third, we will discuss the findings relative to the genetic and environmental etiology of cortisol, especially in regard to GxE. Fourth, we will address the role of social support on awakening cortisol in lower SES contexts. We will then propose an adaptation of the Ecobiodevelopmental framework (Shonkoff, 2010), one of

the most well-known developmental models to explain the early roots of later health inequalities. Several of the hypotheses investigated in the present thesis are anchored within this theoretical model. Next, we will present the strengths and limitations of the thesis, along with directions for future research. We will conclude with the practical implications of our research findings.

6.1 Evidence of a fairly consistent pattern of associations between mid-adolescence family SES and diurnal and hair cortisol indicators

Our findings suggest that the family socioeconomic context during mid-adolescence has a nonspecific, widespread influence on adolescence HPA axis functioning. This was observed across both diurnal and hair cortisol indicators, although awakening cortisol was only shown to be related to SES at a trend level of significance. This is noteworthy because these indicators have distinct, but nevertheless overlapping and complementary triggers for secretion, regulating processes, and functions (Bates et al., 2017; Koss & Gunnar, 2018; Malanchini et al., 2020). As family SES represents a distal factor indexing disparities in family social position and access to wealth (Pluck et al., 2021), its effect on the HPA axis is unlikely to be direct. One of the pathways through which SES may affect HPA axis activity is via its effect on youth's exposition to risk and protective factors within their environment (Dowd et al., 2009; Duncan et al., 2017). It has been reported that children living in more disadvantaged households are more likely to experience greater and more intense levels of stress while also having access to fewer resources than their wealthier counterparts (Duncan et al., 2017; Evans, 2004). These lower SES-related stressful experiences, which occur both within (e.g., noisy, chaotic and substandard living conditions, unpredictable family routines and parent-child interactions, coercive and harsh parenting practices, childhood maltreatment experiences) and outside of the youth family environment (e.g., residing in violent and deprived neighbourhood, attending underperforming schools, exposure to peer victimization, Duncan et al., 2017; Evans, 2004) are hypothesized to lead to the dysregulation of the HPA axis (McEwen & Seeman, 1999; Shonkoff, 2010). This proposition is consistent with our observation of a lower awakening cortisol, higher CAR and a flatter diurnal slope, in addition to higher HCC among lower SES youths.

The seemingly uniform pattern of associations observed between family SES and diurnal and hair cortisol contrasts with the broader scientific literature on socioeconomic adversity in psychoneuroendocrinology and developmental psychobiology, which rather points to a mixed

pattern of evidence (Bryson et al., 2021; Dowd et al., 2009; Koss & Gunnar, 2018). This begs the question as to which methodological factors (e.g., participants' characteristics) or analytical strategies (e.g., sample size, targeted hypotheses) may explain this departure from previous findings. First, past studies have largely focused on children or age-heterogeneous samples. Yet, normative developmental changes in basal cortisol have been noted at several periods during the first 20 years of life (Gunnar et al., 2009; Shirtcliff et al., 2012), including during adolescence. This may have contributed to additional variance unrelated to the hypothesis under study or related to age-dependent changes in sensitivity to adversity, leading to reduced power to detect the SES-cortisol association. In contrast, associations were examined within an age-homogeneous sample in this thesis, which may have facilitated the detection of associations between SES and cortisol. Still, studies that assessed this association mostly in adolescence (albeit using age-heterogeneous samples) have also yielded conflicting results (Chen & Paterson, 2006; Ford et al., 2021; Lupien et al., 2001; Malanchini et al., 2020; Pluck et al., 2021; Vliegenthart et al., 2016; West et al., 2010; White et al., 2017), which suggests that other factors may also be at play.

Another potential explanation for these inconsistent results may lie in the failure of past studies to investigate potential nonlinear associations between family SES and cortisol. If this possibility had not been assessed in the present thesis, the nonlinear associations between mid-adolescence SES and the CAR and the diurnal slope, respectively, would not have been detected. Specifically, the first article of this thesis revealed that youth raised in either higher or lower SES families both showed a higher CAR and a flatter diurnal slope compared to those living in more averaged SES households. These findings concord with preliminary evidence from a handful of studies highlighting nonlinear associations between early adverse experiences and cortisol secretion (Deer et al., 2021; Ouellet-Morin, Cantave, Paquin, et al., 2021; Zalewski et al., 2016). For instance, similar to our findings, Zalewski et al. (2016) reported a flatter diurnal slope among adolescents from poorer and richer households compared to those from average-income families. In a recent study, Deer et al. (2021) found an inverted-U pattern of association between early childhood family income and mid-adolescence CAR, with children from more disadvantaged families exhibiting both a lower and higher CAR. Altogether, these results suggest that the SES-cortisol association is not always well captured by linear functions and that potential nonlinear associations ought to be systematically investigated to refine our understanding of this association.

It is tempting to assert that the significant findings across our four indicators of cortisol secretion may be due to the larger size of our sample (i.e., CAR [*n*=506]; awakening cortisol [*n*=542]; diurnal slope [*n*=565]; HCC [*n*=704]), which offers more statistical power to detect small overall phenotypic associations between mid-adolescence SES and cortisol (Akobeng, 2016). However, the majority of past investigations of the SES-cortisol association in youth also used rather large sample sizes (i.e., ranging from *n*=300 to *n*=2800 participants, Chen & Paterson, 2006; Ford et al., 2021; Lupien et al., 2001; Malanchini et al., 2020; West et al., 2010) and still reported nonsignificant findings (Lupien et al., 2001; Malanchini et al., 2020; West et al., 2010). Thus, other factors besides statistical power may explain the inconsistency in the reported findings. We propose that other methodological strengths of this thesis may have contributed to its capacity to uncover significant associations. Namely, for articles 1 and 3, we assessed stable patterns of diurnal cortisol secretion measured at four-time points during the day over 4 days. This enabled us to account for intra-individual variability in cortisol to estimate individuals' mean cortisol secretion over several days using distinct cortisol indicators. Furthermore, this thesis accounted for many covariables (e.g., awakening time, hours of sleep, exercises, alcohol and drug consumption and hair wash frequency) related to either diurnal and hair cortisol, which allowed for a robust examination of the SES-cortisol association. Finally, relying on multiple assessments of family SES during early childhood and in mid-adolescence provided the opportunity to examine unique associations between SES and each of the cortisol indicators, which will be discussed in the next section.

6.2 The importance of taking a time-sensitive, developmental approach when investigating the SES-cortisol association

The thesis results revealed that the SES-cortisol association was affected by the timing of SES experiences. While the first article showed that mid-adolescence SES was concurrently associated with (salivary) diurnal cortisol indicators, early childhood SES did not directly contribute to any of these cortisol indicators. This finding suggests that diurnal cortisol is more related to ongoing family SES experiences than those encountered during early childhood. However, a partially distinct result emerged for HCC in the second thesis article. Although an association with mid-adolescence SES was still detected, we also uncovered an indirect effect of early childhood SES on HCC at the end of adolescence through its association with mid-adolescence SES. These findings suggest that alterations in HCC are related to the continuation of SES-related experiences

from early childhood to mid-adolescence, but novel SES-related experiences during mid-adolescence may also affect HCC. Overall, these findings concord partially with previous studies reporting unique associations between concurrent or more recent SES with youth and adult diurnal cortisol secretion, over and above the impact of early childhood SES (Li et al., 2007; McFarland & Hayward, 2014). However, these results contradict the biological embedding of early stress hypothesis. Namely, this hypothesis suggests that the HPA axis is particularly sensitive to stress during early life when brain structures implicated in the regulation of the axis are undergoing maturational changes. As such, exposure to adversity early in life is expected to trigger long-lasting changes in HPA axis activity, affecting its functioning throughout life (Lupien et al., 2009; Miller et al., 2011; Shonkoff, 2010; Shonkoff, Garner, et al., 2012). Based on this hypothesis, early experiences of socioeconomic deprivation should affect HPA axis activity during adolescence, irrespective of concurrent experiences of SES. However, our findings offer limited support for the biological embedding of early stress hypothesis, as no (direct) associations emerged between early childhood SES and adolescence diurnal and hair cortisol. Conversely, the family socioeconomic environment during mid-adolescence was found to be related to diurnal and hair cortisol secretion. A potential explanation for these results may be that family SES might hold greater importance for adolescents than for children's self-perceptions (McFarland & Hayward, 2014; Mcleod & Owens, 2004). As children mature, they develop higher-order cognitive competences allowing them to appraise their social environment and to become aware of their family position on the SES hierarchy (Bukatko & Daehler, 2004; Mcleod & Owens, 2004). Considering that social comparison and peer acceptance and relationships become increasingly important in adolescence (Bukatko & Daehler, 2004), ongoing or recent experiences of family socioeconomic deprivation might be more stressful during adolescence than early childhood and thus may be more impactful on adolescents' HPA axis activity (McFarland & Hayward, 2014). Future studies examining the role of social-evaluative processes in the SES-cortisol association during childhood and adolescence could offer a more comprehensive understanding of the developmental impact of family SES on HPA axis activity.

The third thesis article additionally showed that the associations linking mid-adolescence SES to HCC and the diurnal slope were modulated by early childhood SES, although this interaction was only significant at a trend level for cortisol diurnal change. Specifically, the study found that youth raised in more impoverished households during early childhood and who were still exposed to

lower family SES in mid-adolescence (i.e., chronic exposure) had higher HCC at age 19 years and a trend for flatter (salivary) diurnal slope at age 14 years. In contrast, individual differences in SES in mid-adolescence did not correlate with these cortisol indicators in youth who grew up in more privileged families during early childhood. Altogether, these findings offer some support for the stress-sensitization hypothesis, which proposes that early exposure to adversity may increase HPA axis sensitivity to stress experienced later in time (Daskalakis et al., 2013; Young et al., 2019). However, this is inconsistent with the habituation hypothesis, which expects children exposed to early adverse experiences to manifest lower HPA axis activity when they encounter similar situations later in life (Susman, 2006; Trickett et al., 2010). Additionally, the study revealed that youth raised in lower SES families during early childhood but who experienced upward social mobility during mid-adolescence (i.e., living in moderate or higher SES households at age 14) had lower HCC as well as a more dynamic diurnal slope than those who experienced chronic socioeconomic disadvantage. This finding is consistent with another point highlighted by the stress-sensitization hypothesis, namely that future stress needs to be present to prompt the embedded diathesis brought forth by early family socioeconomic disadvantage. In contrast, youth who were exposed to downward social mobility (i.e., from moderate early childhood SES to lower mid-adolescence SES) also showed higher HCC. However, downward social mobility from early childhood to mid-adolescence was not predictive of age 19 HCC among children who grew up in wealthier families during early childhood. This suggests that growing up in a higher SES household during the first five years of life may buffer against the potential impact of later socioeconomic adversity on cumulative cortisol. Altogether, these findings make a compelling case for the consideration of stability and changes in family SES when assessing the association between family SES and cortisol. Such investigations may provide a more nuanced comprehension of the mechanisms underlying the onset of dysregulated patterns of HPA axis activity following experiences of chronic deprivation and SES mobility as well as their expected associations with health.

It is noteworthy that HCC was the only indicator related to family SES via three different time-related pathways. That is, article 2 found evidence of a direct effect of mid-adolescence SES as well as an indirect effect of early childhood SES via mid-adolescence SES on HCC, whereas article 3 documented the synergistic effect of early childhood and mid-adolescence SES on HCC. This begs the question as to why these results were specific to HCC. HCC is a cumulative index

that captures HPA axis activity over several months and across different contexts (i.e., during daytime and nighttime diurnal secretion, as well as in response to minor, acute, repeated, or chronic stress and diurnal secretion; Kao et al., 2019; Kirschbaum et al., 2009; Stalder et al., 2017). In comparison, diurnal cortisol indexes variation in cortisol secretion over a more limited time window, as a function of the circadian rhythm and naturally occurring acute stressful life events (Stalder et al., 2017). Accordingly, we argue that HCC may more readily capture the impact of stable (or persistent) experiences of adversity of lower intensity—such as those experienced by the chronically deprived children within this population-based sample—on HPA axis activity. Moreover, HCC may be better suited than diurnal cortisol to document the potential impact of gradual changes in the family SES (i.e., mobility) occurring from early childhood to mid-adolescence on HPA axis activity. Taken together, the thesis findings suggest that the association between SES and HPA axis functioning is complex. Moreover, they draw attention to the fact that cross-sectional studies are not well suited to dissect the independent, indirect, and combined effects of the socioeconomic environment on youth's HPA axis activity at different developmental stages. Yet, investigating these time-relevant hypotheses is crucial to gain greater insights into the developmental impact of family SES on youth's stress system activity (Dowd et al., 2009).

6.3 Evidence of GxE interplay between early childhood SES and awakening cortisol and HCC

Articles 1 and 2 found that the contribution of genetic factors to mid-adolescence awakening (salivary) cortisol and late adolescence HCC varied along the continuum of family SES. Consistent with the suppression of genetic influences by environmental factors (GxE), lower genetic contributions to awakening cortisol emerged in youth from lower SES families compared to those from higher SES households during early childhood and, to some extent, in mid-adolescence. In contrast, the pattern of GxE observed for HCC was congruent with a diathesis-stress pattern, with higher genetic effects on HCC in youth from lower SES households compared to those raised in more socioeconomically advantaged families during early childhood. Interestingly, these contrasting GxE results echo those of two previous studies conducted with this sample when the twins were 6 and 19 months old. In the first study, Ouellet-Morin and colleagues (2009) observed that morning cortisol was under strong genetic influences (69%) among 6-month-old twins exposed to high family adversity, which included several SES indicators (e.g., lower family income and

maternal education). In contrast, morning cortisol levels were entirely (100%) explained by environmental influences unique to each child in toddlers exposed to lower (or no) family adversity (Ouellet-Morin et al., 2009). In the second study, Ouellet-Morin and colleagues (2008) found that (shared and unique) environmental effects accounted for all the variance in cortisol reactivity in 19-month-old children exposed to higher levels of family adversity, whereas cortisol reactivity was to a significant part (40%) explained by genetic influences in those exposed to lower family adversity. Collectively, these results suggest that the modulating role of family SES in the genetic etiology of cortisol secretion varies depending on the nature and timing of the assessed cortisol indicators. However, it is impossible to distinguish these two potential sources of influence, as each of the targeted cortisol indicators were measured at different time points, both in the present thesis and in previous findings from this sample.

Beyond these factors, these opposing GxE findings might be influenced by several developmental changes that occurred between mid-and-late adolescence, including pubertal maturation. That is, awakening cortisol was measured at age 14 (mid-adolescence), whereas HCC was measured at age 19 (late adolescence). During mid-adolescence, youth are still undergoing pubertal maturation, notably boys (Rogol et al., 2002), and this has been found to affect HPA axis functioning (Koss & Gunnar, 2018). Past studies have indeed revealed notable differences in cortisol secretion as youth advance through puberty, with typically higher overall cortisol secretion, higher afternoon secretion and a flatter diurnal slope as youth progress through puberty (Gunnar et al., 2009; Netherton et al., 2004; Shirtcliff et al., 2012). Moreover, higher cortisol reactivity to stress has also been reported among mid-adolescent boys and girls, suggesting that this period is characterized by higher basal cortisol secretion superpose by a more reactive stress system (Gunnar et al., 2009). This has led several researchers to propose that puberty is related to an enhanced sensitivity of the HPA axis to environmental influences (Koss & Gunnar, 2018). This proposition is in line with our findings showing strong environmental influences on diurnal cortisol indicators at age 14. They are also consistent with the observation of higher environmental influences on awakening cortisol secretion in the context of lower SES. Additional genetically-informed studies investigating the genetic and environmental etiology of cortisol as a function of youth pubertal stage will further enhance our understanding of adolescence cortisol secretion.

It is noteworthy that genetic influences on both awakening cortisol and HCC varied according to family SES measured during the first five years of life. This specificity for early childhood SES concord with arguments from several early life stress models purporting that the influence of the early life environment on development is conditional on the child's genetic endowment (Miller et al., 2011; Shonkoff, 2010). Moreover, the suppression pattern of GxE documented for awakening cortisol is congruent with arguments that the influence of life stressors on stress systems may be greater and surpass those of genetic influences (also referred to as programming effects; Miller et al., 2011; Shonkoff, 2010). The additionally observed diathesis-stress pattern of GxE does not undermine the importance of early environments to the genetic etiology of HCC. Indeed, it signals that lower SES during early childhood may potentiate the influence of inherited factors on chronic cortisol secretion. More generally, our findings partly echo accumulating evidence that highlights the modulating role of common polymorphisms located within the glucocorticoid receptor gene and other genes implicated in HPA axis regulation in the association between stress and cortisol (Cicchetti et al., 2011; Coulon et al., 2016; Gerritsen et al., 2017; Kohrt et al., 2015; Peter et al., 2022; Starr et al., 2019; Willner et al., 2014).

From a population genetic perspective, our results suggest that family socioeconomic conditions in early childhood and mid-adolescence may modify the strength of the contribution of genetic factors to individual differences in awakening and HCC during adolescence. This finding may inform GWAS and candidate genes association studies attempting to identify genetic polymorphisms (SNPs) associated with stress biomarkers, as these associations may not necessarily be uniform across study participants living in distinct SES contexts. From a psychopathology developmental perspective, our findings suggest that the interplay between genes and environments ought to be considered, as the influence of genetic factors may not be uniformly distributed across the environmental continuum.

6.4 The stress-buffering role of social support in the association linking SES to cortisol

Evidence from the third thesis article revealed that social support modified the association between mid-adolescence SES and concurrent awakening (salivary) cortisol. More specifically, youth living in more impoverished households in mid-adolescence concurrently had lower awakening cortisol levels than those from average-to-higher SES families, but this association was only significant

among participants who reported higher levels of social support. This finding is at odds with the stress-buffering hypothesis of social support (Cohen & Wills, 1985; Taylor, 2011), as the SES-awakening cortisol association was magnified—not mitigated—for those who reported higher social support. This finding also contrasts with evidence from an extensive body of scientific work reporting reduced cortisol reactivity to acute psychosocial stress (e.g., public speaking and mental arithmetic) among participants receiving higher social support (Gunnar, 2017; Gunnar & Hostinar, 2015; Hostinar & Gunnar, 2015; Taylor, 2011). It is also inconsistent with the only study so far that has examined the modulating role of social support in the SES-cortisol association (Hooker et al., 2018). In that study, the association between lower SES and higher cortisol secretion during stress recovery from a psychosocial stress test was significant among participants with lower—but not in those with higher—social support (Hooker et al., 2018). However, previous studies targeted the cortisol response to psychosocial stress and it is unclear whether their findings should generalize to diurnal (salivary) and chronic (hair) cortisol secretion, which were examined in this thesis. Future studies using multiple cortisol indicators may provide further insight as to whether the stress-buffering role of social support is distinct for different cortisol outputs and whether it is restricted to the context of acute psychosocial stress.

Several scholars have also noted that social support is not a panacea and its impact is likely to vary according to individual, developmental and contextual factors (Cobb, 1976; Colten & Gore, 1991). For example, it has been suggested that emotional and informational support may be beneficial in a wide range of stressful situations, whereas instrumental support may be effective only when its closely aligned with the specific demand elicited by the stressor (i.e., hereby, sharing resources in a lower SES context; Cohen & Wills, 1985; Taylor, 2011). The social support scale used in the third thesis article assessed the overall level of perceived emotional and instrumental support provided by distinct members of participants' proximal relationship network. We did not, however, test the possibility that the buffering effect of social support on the SES-cortisol association would be contingent on the nature of social support targeted (i.e., emotional vs. instrumental support). Additional work assessing the role of distinct dimensions of social support in the association between SES and cortisol are needed to further our understanding of the stress-buffering role of social support.

Incidentally, it is also possible that perceived social support from different sources may differentially affect the association linking mid-adolescence SES to awakening cortisol. It is well known that peer relationships take on a prominent role and are a source of social support during adolescence (Brown & Braun, 2013). Accordingly, perceived availability of support from friends may play a more dominant protective role during this developmental period than perceived support from other members of youth's proximal network of relationships. This hypothesis was partially tested in a recent study, the results of which supported the buffering role of perceived social support from mothers in the association linking peer victimization experiences in college with HCC (Brendgen et al., 2022). Perceived social support from friends and fathers were otherwise not found to modulate this association. As this hypothesis was not examined within the present thesis, it remains unknown whether a distinct pattern of findings would have emerged had we investigated the buffering role of perceived social support from different relationships. Future studies assessing this hypothesis may help specify whether support from friends may play a stronger buffering role in this association during adolescence in comparison to support from other social agents.

The effectiveness of perceived social support in protecting against the harmful impact of socioeconomic adversity on HPA axis functioning may also be contingent upon youth's early life experiences. That is, perceived social support has its roots in early childhood caregiving experiences and is viewed as an observable manifestation of attachment styles (Blain et al., 1993). Youth's beliefs about their self-worth and the availability and responsiveness of others are formed within the context of their relationship with their caregiver. When children develop an insecure attachment style, they tend to adopt negative beliefs about self and others that may lead them to perceive less support from their network of relationships (Blain et al., 1993). Early caregiving experiences through its impact on children attachment style may thus erode the expected buffering role of social support later in life. Given that youth early life experiences and attachment styles were not considered in the present thesis, it remains unknown if the pattern of results reported for social support may have been influenced by these confounders. Additional empirical work examining the developmental impact of early life experiences on later perception of social support is needed to increase our understanding of the stress-buffering role of social support during adolescence.

Relatedly, the third article showed that youth from lower SES families generally reported lower levels of social support, which is consistent with previous evidence that socioeconomic deprivation might constrain access to social support (Belle, 1983; Cattell, 2001). Moreover, the beneficial effect of social support on adjustment has been shown to be reduced in highly stressful environments such as socioeconomically deprived households, as social support tends to co-occur with stress contagion, negative interactions, reciprocal obligations as well as unequal reciprocity, which may lead to higher stress (Belle, 1983; Cattell, 2001; Moskowitz et al., 2013; Stringhini et al., 2012; Tigges et al., 1998). Accordingly, the apparent absence of the stress-buffering role of social support in the cortisol-SES association may point to the lower levels (or reduced variance) of support among youth living in lower SES families. It is also possible that exposure to additional (unaccounted for) stressors occurs more often in socioeconomic disadvantaged contexts, which may cancel out any protective effect of social support.

On the flip side, the higher awakening cortisol level in youth who live in higher SES families *and* receive higher social support could be tentatively interpreted in the context of the biological sensitivity to context theory (Boyce & Ellis, 2005) and the adaptive calibration model (Del Giudice et al., 2011). Higher awakening cortisol secretion among these youth may indeed signal a heightened sensitivity to environmental cues that allows them to benefit from an enhanced level of biological preparedness to the anticipated stressors of the day. Additional tests are needed to determine whether higher awakening cortisol levels in these youth relate to benefitting more from the social resources and positive opportunities encountered during the day, which, in turn, may translate into more positive socioemotional and behavioural outcomes. In contrast, the lower awakening cortisol levels among lower SES youth—which appear to be unaffected by their perceived social support—might indicate a lowered sensitivity to developmentally promotive, protective (or detrimental) environments during the day (Belle, 1983; Boyce & Ellis, 2005; Del Giudice et al., 2011; G. W. Evans, 2004; Fries et al., 2005; Susman, 2006). Importantly, although the lower and higher awakening cortisol levels may reflect an adaptation to the youth's socioeconomic living conditions, they might still be associated with pathological developmental outcomes. Indeed, both higher and lower awakening or morning cortisol have been related to socioemotional and behavioural difficulties in adolescence (Dietrich et al., 2013; Goodyer et al., 2009; Halligan et al., 2007; Murray-Close et al., 2008).

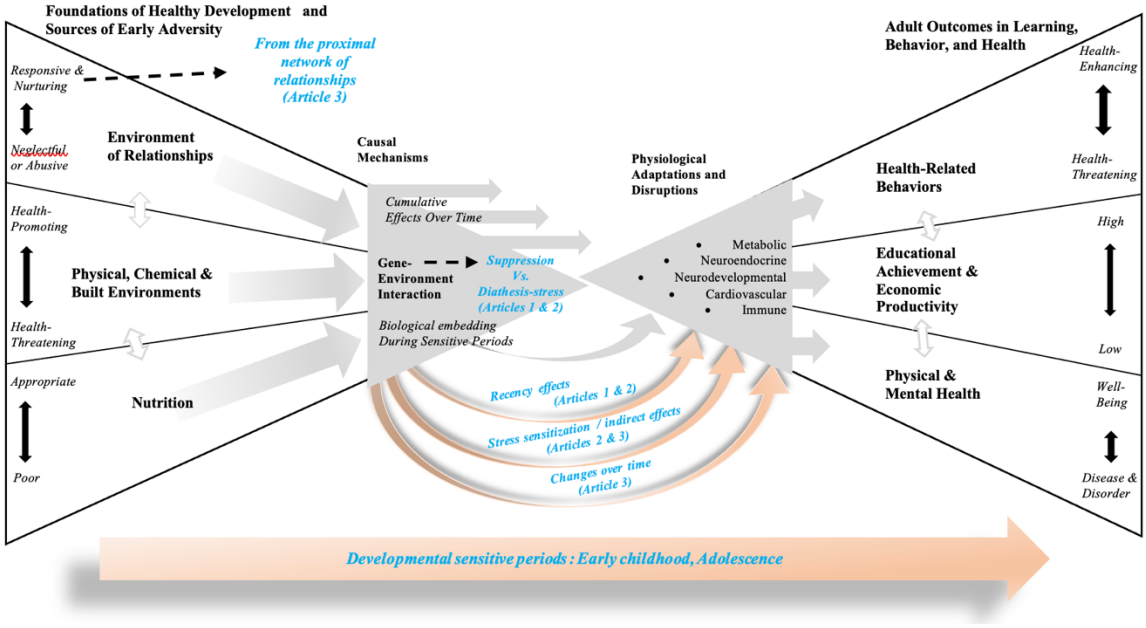
6.5 The Ecobiodevelopmental framework revisited in the context of the thesis results

This thesis is informed by several early-life stress models and hypotheses that are firmly grounded in a developmental psychopathology approach (Toth & Cicchetti, 2013). These models include the Ecobiodevelopmental framework (Shonkoff, 2010; Shonkoff, Garner, et al., 2012), a well-known developmental model explaining the early roots of health inequalities. This model is particularly relevant to our thesis for three reasons. First, the Ecobiodevelopmental framework considers physiological stress systems as a core mechanism underlying the impact of early adversity on disparities in health, education, and behavioural problems in adulthood. Second, compared to other prominent models of stress that consider *either* the timing of onset (e.g., The developmental origins of health and disease concept, Gluckman et al., 2016; The life cycle model, Lupien et al., 2009) *or* the chronicity of adverse experiences (e.g., The allostatic load model; McEwen & Seeman, 1999), this framework argues that both aspects are important to understand the effect of adversity on physiological stress systems activity. Third, this framework emphasizes that the association between adversity and physiological stress systems is affected (i.e., moderated) by individual characteristics as well as the availability of social support. Figure 14 presents an adaptation of the Ecobiodevelopmental framework to which the evidence derived from this dissertation is added, with the goal of reviewing some key aspects of the model and providing ideas about how the model could be refined.

According to the Ecobiodevelopmental framework (Shonkoff, 2010; Shonkoff, Garner, et al., 2012), the foundation of healthy and pathological development lies in the interaction between the children's genetic endowment and their early-life environment, which may range from nurturing to abusive. More specifically, this GxE interaction is hypothesized to create biological imprints through epigenetic modifications that are reflected within the developing brain and several other physiological systems implicated in stress management, metabolic and neuroendocrine regulation as well as immunological and cardiovascular functioning. The findings from the first two articles that the genetic-environmental etiology of awakening cortisol and HCC vary along the continuum of early childhood family SES falls in line with this model. Yet, our results also point to the lack of specification in the Ecobiodevelopmental model for explaining interindividual differences in specific phenotypes such as cortisol secretion. This lack of specification concerns 1) the nature of

the gene-environmental interplay expected to take place, 2) the form of adversity likely to be involved in these GxE, 3) which physiological stress systems and indicators are implicated, and 4) for whom (e.g., internal and external protective or vulnerability factors) these GxE interplays are likely to emerge. The extended model—based on our findings as well as those reported by Ouellet-Morin et al. (2008, 2009)—is depicted in Figure 14 (see the blue text inside the left gray triangle).

Figure 14. – Adapted version of the Ecobiodevelopmental framework



Note. Figure reproduced from Building a new biodevelopmental framework to guide the future of early childhood policy by Shonkoff (2010). © 2010, Jack P. Shonkoff.

In regard to the impact of early experiences on physiological stress systems adaptations, the Ecobiodevelopmental framework (Shonkoff, 2010; Shonkoff, Garner, et al., 2012) postulates that, if early experiences are nurturing, stable and predictable, healthy development should ensue. In contrast, when children are exposed to adverse experiences such as family socioeconomic disadvantage during early life *and* protective adult relationships are absent, this may lead to a "toxic stress" response characterized by the overactivation of physiological stress systems, including the HPA axis. Experiences of adversity are expected to trigger stress systems dysregulation through two mechanisms. First, when the "toxic stress" occurs during sensitive periods of development,

stress systems may become calibrated to adapt to an environment perceived as adverse with the expectation that it may remain that way over the life course. This may lead to the permanent dysregulation of these systems (i.e., the biological embedding hypothesis). Second, exposure to chronic adversity over time may also induce the dysregulation of physiological stress systems (i.e., the accumulation hypothesis). Ultimately, the wear and tear of physiological stress systems, either triggered by early adversity or accumulation over time, is hypothesized to confer a greater susceptibility to suffer from a host of health problems in adulthood (Shonkoff, 2010; Shonkoff, Garner, et al., 2012).

The first two articles of this dissertation provided evidence of an association between family SES and HPA axis activity, as measured through (salivary) diurnal and hair cortisol secretion. However, contrary to expectations, we found no empirical support for the biological embedding of early childhood experiences of lower SES on these cortisol indicators. That is, the family socioeconomic context during the first five years of life had no additional relevance for later HPA axis functioning in adolescence beyond the concurrent (or recent) socioeconomic context. This is consistent with prior studies that assessed family SES at different developmental periods and that found no association between early childhood SES and diurnal cortisol in adolescence or adulthood (Desantis et al., 2015; Li et al., 2007; McFarland & Hayward, 2014). Together, these lines of evidence emphasize that the HPA axis might preserve a strong sensitivity to the environment experienced during adolescence and adulthood. This prolonged plasticity to both environmental stability and changes may echo the distinct paths toward maturation in the structures regulating the HPA axis and, thus, favour adaptation to a continuously changing environment (Lupien et al., 2009).

Moreover, the second article's finding that adolescence SES served as an indirect pathway through which early childhood SES was related to HCC suggests that the impact of early experiences on HPA axis activity may not necessarily be direct. Instead, early childhood family SES may set into motion a chain of experiences that may influence youth's stress systems and health. Furthermore, an additional mechanism not considered in this framework—but that is suggested as based on the findings of the third article—is a process consistent with the stress-sensitization hypothesis (Daskalakis et al., 2013; Young et al., 2019, 2020). The third thesis article showed that early childhood SES modulated the association between lower mid-adolescence SES and a trend toward

flatter (salivary) diurnal slope or higher HCC at ages 14 and 19 years, respectively. This could point to a possible recalibration of the HPA axis, where early experiences of socioeconomic deprivation facilitate the expression of an altered pattern of cortisol secretion in youth whose family SES remains lower during mid-adolescence (Daskalakis et al., 2013). In addition, changes related to both upward and downward socioeconomic mobility were also found to be related to HCC in the third article. In sum, our results suggest that early adversity impacts HPA axis activity through different time-related mechanisms, which are likely to vary depending on the HPA axis function that is assessed. Therefore, alongside the cumulative and biological embedding impact of early adversity implied by the Ecobiodevelopmental framework, we have added three other time-related pathways through which early adverse experiences may affect stress systems (see the three orange curve arrows and the straight orange arrow specifying different sensitive periods for adversity in Figure 14).

Finally, the Ecobiodevelopmental framework postulates that a "toxic stress" response to experiences of early adversity only happens in the ***absence*** of adult supportive relationships. However, as children grow, they tend to draw support from many people in their lives, including their siblings, their friends, and their romantic partners (Furman & Buhrmester, 1985). The focus on supportive relationships with adults thus fails to consider developmental changes occurring within social support networks. This precludes a full understanding of the protective role of social support for physiological stress systems at different points in the life course. To counter this limitation, we have added the notion that support can come from various agents in an individual's proximal relationship network in Figure 14 (see the top box on the left black triangle).

In short, the Ecobiodevelopmental framework (Shonkoff, 2010; Shonkoff, Garner, et al., 2012) is a well-known theory that offers a parsimonious explanation of how early life adversity may affect physiological stress systems. The scientific appeal of this theory also lies in its putative practical implications for a wide array of developmental outcomes, ranging from physical and mental health to economic productivity. However, many of its proposed hypotheses still await empirical validation or are currently constrained by inconsistent findings—not only those concerning the HPA axis (Dowd et al., 2009; Fogelman & Canli, 2018; Koss & Gunnar, 2018), but also other mechanisms such as epigenetic modifications (Cecil et al., 2020). This shed light on the complexity of the proposed mechanisms, as well as the importance of examining the role of potential

moderators such as genetic factors, social support, and later adverse experiences. Moreover, an analysis of this theory according to our findings revealed that it failed to fully espouse a developmental perspective, which—in its original form—reduces its scientific relevance to longitudinal studies covering different developmental periods.

6.6 Strengths and limitations of the thesis dissertation

Strengths

This thesis presents several strengths with respect to its reliance on an extensive pool of data in regard to both the main variables and potential confounders, as well as the richness of its theoretical and analytical approaches. We will expand on four noteworthy strengths of the articles composing the core of the thesis. First, the twin-based design of this thesis allowed unique insights into the genetic and environmental etiology of distinct cortisol indicators measured during adolescence, as well as the gene-environment processes underlying their associations with family SES (articles 1 and 2). Second, the prospective and repeated collection of SES information allowed testing several time-related hypotheses (e.g., biological embedding, stress sensitization and habituation hypotheses; articles 1 to 3) (Cohen et al., 2010; Daskalakis et al., 2013; Duncan et al., 2017; Miller et al., 2011; Shonkoff, Garner, et al., 2012) that have so far received scant empirical attention. Third, unlike the majority of previous investigations (Malanchini et al., 2020), this study included multiple assessments of cortisol to capture distinct HPA axis parameters and evaluate whether the associations between SES and cortisol vary across different cortisol indicators. The estimation of stable patterns of diurnal cortisol indicators derived from saliva samples measured at four-time points during the day over four collection days—while accounting for a wide array of potential confounders—constitutes another strength of the current study. Fourth, by including two measures of youth's perceived social support from several members of their proximal relationship network, we were able to derive a more stable variable depicting the availability of support during mid-to-late-adolescence. This also allowed testing whether these social resources buffered the effect of lower SES on HPA axis activity, a hypothesis that has rarely been evaluated before (as an exception, see Hooker et al., 2018, 2020). Fifth, the large sample size likely afforded sufficient power to detect small to moderate GxE effects emerging between family SES and hair and diurnal cortisol secretion, in addition to small associations with mid-adolescence SES.

Limitations

Over and beyond the limitations already addressed in each of the articles of this thesis, several general shortcomings inherent to this thesis warrant further attention. First, the latent genetic and environmental estimates uncovered for cortisol do not identify the specific genes and environments that contribute to the broad sources of genetic, shared, and unique environmental influences to variation in cortisol secretion (Brendgen et al., 2012; Klahr & Burt, 2014; Moffitt, 2005). Moreover, these genetic and environmental estimates are inferred from the variation of cortisol within the population under study and therefore cannot be generalized to specific individuals (Moffitt, 2005; Price & Jaffee, 2008). Future candidate genes and GWAS studies will offer a more comprehensive understanding of the contribution of specific genes to these cortisol indicators, as well as the interplay of these genes with empirically-supported environmental risk and protective factors. Second, the inability to properly account for potential *r*GE between SES and the diurnal cortisol indicators may have introduced bias to the estimation of GxE parameters (Brendgen et al., 2012; Price & Jaffee, 2008). Third, the SES assessments included in the present study possess several limitations. Indeed, the mid-adolescence SES composite score was based only on the assessment of family income and of parental education evaluated at age 14. In contrast, the early childhood SES composite score included four assessments of family income and three evaluations of parental education measured during the first 5 years of life, and thus represented a more reliable assessment of twins' family income. In addition, we did not assess the twins' family socioeconomic context at age 19 concurrent with the HCC measure. Consequently, it remains unknown whether the association reported between mid-adolescence SES and HCC will stay unchanged if this factor is considered. Indeed, it is possible that this association is spurious and is instead due to a potentially unmeasured correlation between SES at ages 14 and 19 years. Furthermore, we only measured family income and education. However, as acknowledged by previous investigations, several other dimensions of SES more readily experienced by children (i.e., household chaos, food insecurity; Tarullo et al., 2020) and/or experienced within the broader social context (e.g., neighbourhood and school SES; Malanchini et al., 2020; Ouellet-Morin et al., 2021) may also affect cortisol secretion. Relatedly, we did not examine whether specific dimensions of SES are more strongly associated with cortisol secretion. Although there is some evidence that the strength of this association might vary according to the nature of the SES indicator assessed (Dowd et al., 2009; Malanchini et al., 2020; Merz et al., 2019; Schloß et al., 2019; Tarullo et al., 2020), other results are inconclusive (Anand et al., 2020; Bryson et al., 2019; Ouellet-Morin, Cantave, Lupien,

et al., 2021; Simmons et al., 2018; Wagner et al., 2019). Future studies investigating this hypothesis are warranted. Fourth, although our SES measurements were continuous in nature, theoretical arguments to explain the SES-cortisol association are rooted in a perspective of presence and/or absence of adversity (or stress). While this is one of the prevailing hypotheses to explain SES disparities in health and development (Amso & Lynn, 2017; Duncan et al., 2017; Kim et al., 2018; Lupien et al., 2001), several researchers have also argued that SES is not equivalent to adversity as the impact of SES on development spans the entire poverty-to-wealth continuum (Amso & Lynn, 2017). It is further theorized that stress is unlikely to be a driving mechanism of SES effects along the entire spectrum. Instead, these researchers have postulated that the wealth advantages in terms of the enrichment opportunities available in higher SES households (e.g., education quality, language complexity, travel experiences) enable higher SES children to develop out of the typical range and this constitutes the mechanism underlying SES inequalities in development (Amso & Lynn, 2017). A formal test of these competing hypotheses in relation to the SES-cortisol association, however, awaits. Fifth, we only measured the level of twins' perceived social support within their proximal social network. However, social relationships may sometimes be both supportive and stressful and the level of stress experienced within a relationship may undermine the buffering impact of the perceived social support available within that same relationship (Belle, 1983; Raikes & Thompson, 2005). Future studies that include both positive (support) and negative (stress) features of participants' social relationships will contribute to a fuller understanding of the protective role of social support on HPA axis activity in the context of socioeconomic disadvantage.

6.7 Directions for future studies

While the findings of this thesis have extended prior knowledge of the genetic-environmental etiology of diurnal and hair cortisol secretion, as well as its moderation by family SES and social support, they also raise several interesting avenues for future research. Some of these research questions will be presented here.

6.7.1 The importance of considering the moderating role of age

As stated before, evidence to date shows inconsistent associations between family SES and diurnal and hair cortisol indicators that may be explained by a host of factors (Bryson et al., 2021; Dowd et al., 2009; Gray et al., 2018; Koss & Gunnar, 2018). As important developmental changes in

basal cortisol have been reported before (Gunnar et al., 2009; Shirtcliff et al., 2012), one factor that has received little research attention but that may underlie these mixed findings concerns age-related differences in previous study samples (Ursache et al., 2015). Consistent with this hypothesis is a study showing higher levels of morning cortisol among low SES children aged between 6 and 10 years compared to their high-SES counterparts (Lupien et al., 2001), whereas no significant SES differences in cortisol were documented for youth aged between 12 and 16 years. Relatedly, a more recent study yielded evidence of a stronger association between neighbourhood poverty and diurnal cortisol among the younger children of their sample (i.e., less than 12 years of age) compared to the wider age sample (i.e., 8-to-14 years old; Malanchini et al., 2020). Nevertheless, this association was not significantly modulated by participants' age in that study. In another study, however, evidence of a moderating role of age was found, with lower SES related to *higher* mean cortisol secretion among younger children (aged 6-to-11 years) but to *lower* mean cortisol among older children (12 years old; Ursache et al., 2015). Collectively, these studies provide circumstantial evidence that the strength and/or direction of the SES-cortisol association may not be the same in childhood and adolescence, a hypothesis that could not be tested in this thesis considering our focus on adolescence cortisol. Additional studies examining this issue are thus needed to provide a more detailed understanding of this association.

6.7.2 A more in-depth understanding of the impact of cumulative and specific measures of adversity

In the past, researchers have used a variety of ways to conceptualize SES, with some measuring discrete individual-level SES dimensions (most commonly family income and education), while others have used composite scores of multiple SES measures (Dowd et al., 2009; Farah, 2017; Pluck et al., 2021). The same can be found in the wider literature on early life adversity, where two prominent conceptual models exist: the *cumulative* approach, which amounts to aggregating participants' total exposure to stress, and the *specific* approach, which involves measuring the impact of distinct features of adverse experiences (e.g., threat or deprivation) (McLaughlin et al., 2014; Smith, 2020). Despite the fact that different types of socioeconomic adverse experiences typically co-occur (Smith, 2020), there has been a call in recent years to investigate their unique impacts on HPA axis activity, as this may offer greater insights into the mechanisms linking early adversity to psychopathologies (Chen & Paterson, 2006; Dowd et al., 2009; Masten et al., 2021;

McLaughlin et al., 2014; Smith, 2020). However, relatively few investigations have formally tested this hypothesis, particularly in regard to diurnal cortisol secretion. Nevertheless, a handful of studies have pointed to a significant association of parental education—and, to a lesser extent, family income—with children HCC (Malanchini et al., 2020; Merz et al., 2019; Schloß et al., 2019; Tarullo et al., 2020; Ursache et al., 2017; Vaghri et al., 2013; Vliegenthart et al., 2016). Furthermore, previous studies have reported associations of family income and parental education with diurnal cortisol indicators (Chen & Paterson, 2006; Ford et al., 2021; Saridjan et al., 2010; Zalewski et al., 2012). Other SES factors beyond family income and parental education (e.g., including household chaos, food insecurity as well as neighbourhood SES) have also been uniquely associated with diurnal and hair cortisol indicators (Chen & Paterson, 2006; Malanchini et al., 2020; Roubinov et al., 2018; Tarullo et al., 2020). Taken together, these studies make a compelling case for extending the examination of the SES-cortisol association to specific dimensions of SES, from the family to the neighbourhood contexts.

6.7.3 The importance of considering the role of multisystem protective factors

Although it is well recognized that lower SES experiences do not always lead to the dysregulation of the HPA axis (Shonkoff, 2010; Shonkoff, Garner, et al., 2012), relatively few studies have examined potential protective factors that may underlie this association. Emerging studies have highlighted the protective nature of warm, nurturing and supportive relationships between children and their parents in the recalibration of the HPA axis toward a more normative pattern of functioning following exposure to adversity (Colich et al., 2021; Gunnar, 2017). However, protective factors within other ecological contexts have yet to be addressed (Gunnar, 2017; Masten et al., 2021). As child development is impacted by individual and environmental influences emanating from embedded and interrelated ecological systems working in synergy, positive experiences extending to the peer, school and neighbourhood contexts may also promote resilient functioning in lower SES youth (Bronfenbrenner et al., 1986; Masten et al., 2021; Sameroff, 2010; Yule et al., 2019). Additional studies investigating the modulating role of multisystem protective factors—particularly during sensitive periods of development—are needed for a more comprehensive understanding of HPA axis functioning in lower SES youth.

6.8 Practical implications

Our findings have several implications. Firstly, the observation of a strong environmental influence on diurnal and hair cortisol indicators in the first and second thesis articles is consistent with the notion that the HPA axis remains sensitive to environmental inputs during adolescence (Koss & Gunnar, 2018). This may be informative to future intervention efforts aiming to recalibrate HPA axis activity following experiences of adversity, as it suggests that adolescence might be an opportune time to intervene. Our findings nonetheless suggest that the putative effectiveness of these psychosocial interventions on awakening cortisol and HCC may vary according to family SES background as well as participants' genetic endowment. Secondly, the findings of the third thesis article revealed that living in a higher SES family environment during the first five years of life may protect against the impact of downward socioeconomic mobility on youth's HPA axis activity. Nevertheless, the sensitization and indirect impact of early childhood SES on the association between adolescence SES and HCC (articles 2 and 3) also highlight the potentially enduring impact of early socioeconomic adversity on chronic HPA axis activity. Collectively, these findings underscore the importance of intervening as early as possible to intercept the crystallization of socioeconomic deprivation experiences in adolescence and their later impact on physiological stress systems. Considering the widespread impact of family SES on youth's HPA axis activity, investing in programs that help alleviate the negative impact of lower SES or promote resilience in lower SES youth should constitute a priority.

6.9 Conclusion

This doctoral thesis aimed to a) assess the gene-environment processes underlying the association of family SES with adolescence diurnal and hair cortisol secretion and b) test the role of timing, stability and change within family SES as well as social support in these associations. This dissertation provided first-time evidence that the genetic etiology of youth's awakening cortisol and HCC are contingent on family SES. Furthermore, this thesis documented concurrent associations of family SES with diurnal and hair cortisol indicators and highlighted the role of time-related mechanisms and, to a lesser extent, social support in these associations. Collectively, our findings underscore the importance of espousing a developmental approach sensitive to the timing, persistence and changes of experiences when investigating the association between adversity and HPA axis activity. Moreover, they advocate for the use of genetically informative

studies to investigate the early origins of SES disparities in health, as this may bring forth unprecedented and essential insights into the role of environmental experiences for the functioning of physiological stress systems.

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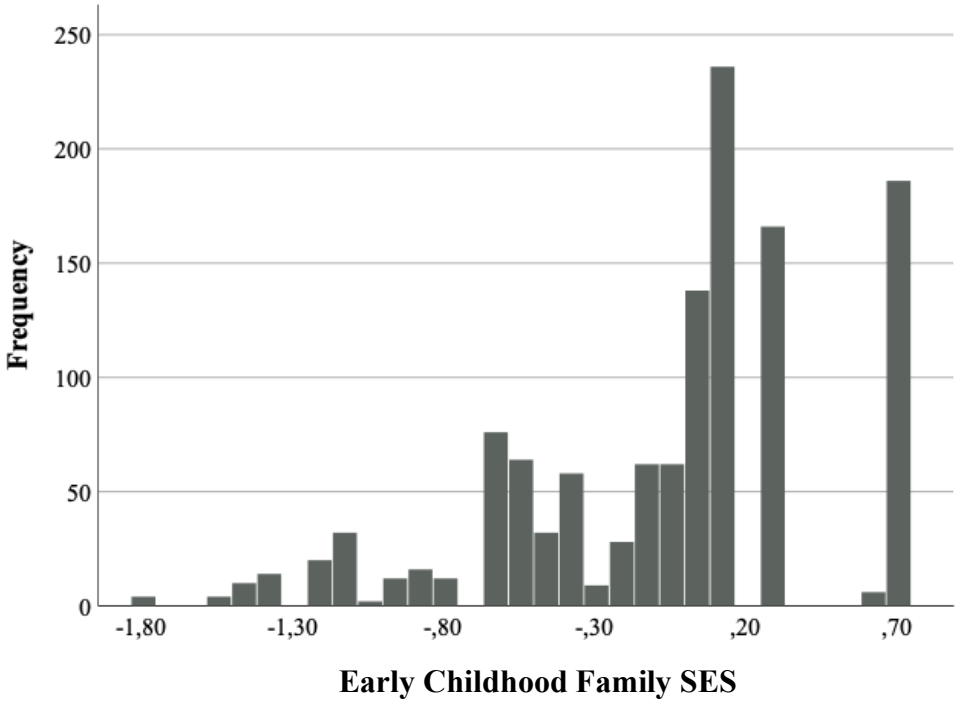
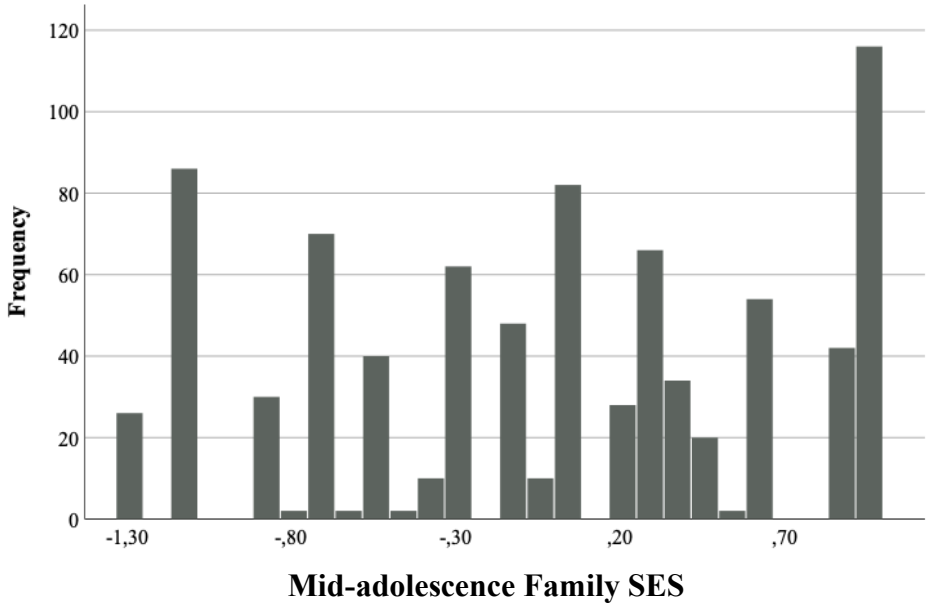
Appendices

Supplementary Figure 1. Distribution of family socioeconomic status during early childhood



Supplementary Figure 2. Distribution of family socioeconomic status during mid-adolescence



Supplementary Table 1 - Univariate models factors for the CAR, awakening cortisol levels and cortisol diurnal change

	A	C or D	E	A^2	C^2 or D^2	E^2	RMSEA	AIC	BIC	-2ll(np)	$\Delta\chi^2$	Δdf	*P*
CAR													
ADE	**.48**	**.86**	**1.07**	**11%**	**35%**	**54%**	**0.10**	**1455.10**	**1469.68**	**-723.10(4)**	**.97**	**2**	**.61**
	[.00;1.1]	**[.00;1.1]**	**[.94;.82]**										
AE	.96	—	1.09	44%	—	56%	0.09	1454.56	1464.82	-724.28(3)	1.53	3	.67
	[.71;1.2]		[.96;1.2]										
DE	—	.28	-.27	—	54%	46%	0.09	1454.05	1464.31	-724.02(3)	1.02	3	.79
		[.24;.33]	[-.30;-.24]										
E	—	—	1	—	—	100%	0.18	1477.59	1484.43	-736.79(2)	26.56	4	.00
			[.90;1.06]										
Awakening cortisol													
ACE	**.55**	**.33**	**.701**	**34%**	**12%**	**54%**	**.07**	**1183.59**	**1197.32**	**-587.79(4)**	**3**	**2**	**.22**
	[.00;.72]	**[.00;.64]**	**[.62;.78]**										
AE	.65	—	.69	40%	—	60%	.06	1181.91	1192.21	-587.95(3)	3.32	3	.34

	[.53;.75]		[.61;.77]										
CE	—	.59	.74	—	39%	61%	.08	1183.85	1194.15	-588.92(3)	5.26	3	.15
		[.48;.69]	[.67;.81]										
E	—	—	1	—	—	100%	0.21	1217.462	1224.33	-606.731(2)	40.87	4	.00
			[.89;1.01]										
Diurnal change													
ACE	**.22**	**.18**	**-.27**	**32%**	**20%**	**48%**	**.07**	**403.9**	**417.74**	**-197.95(4)**	**3.62**	**2**	**.16**
	[.00;.31]	**[.00;.27]**	**[-.30;-.24]**										
AE	.29	—	.27	54%	—	46%	.07	403.21	413.59	-198.61(3)	4.94	3	.18
	[.24;.33]		[.24;.30]										
CE	—	.83	1.19	—	32.5%	67.5%	.08	404.51	414.89	-199.256(2)	6.24	3	.10
		[.58;1.03]	[1.07;1.32]										
E	—	—	1	—	—	100%	.24	452.46	459.38	-224.23(2)	56.18	4	.00
			[.36;.42]										

Note. The selected models are in bold.

Ethical approval

From: **Karine Sénécal** karine.senecal.1@umontreal.ca
Subject: Approbation éthique _ Projet CERSC-2022-040-D
Date: May 30, 2022 at 1:56 PM
To: Yamiley Christina Cantave yamiley.christina.cantave@umontreal.ca
Cc: Isabelle Ouellet-Morin isabelle.ouellet-morin@umontreal.ca, brendgen.mara@uqam.ca

30 mai 2022

Projet CERSC-2022-040-D
Chercheure-étudiante : Yamiley Christina Cantave, étudiante au doctorat, FAS – École de criminologie
Directrices de recherche : Isabelle Ouellet-Morin, professeure associée, FAS – École de criminologie et Mara Rosemarie, professeure titulaire, FAS – Département de psychologie

OBJET : **Approbation éthique**
Projet : CERSC-2022-040-D
Titre : The social regulation and genetic and environmental underpinnings of cortisol: A longitudinal genetically-informed study

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Bonjour,

Le Comité d'éthique de la recherche – société et culture (CERSC) de l'Université de Montréal a évalué les documents que vous avez transmis lors de votre demande. La participation au projet de recherche, selon toute vraisemblance, ne comportant qu'un risque minimal, il a été déterminé que l'évaluation éthique pouvait être déléguée à des membres du CERSC, le tout en conformité aux politiques et aux procédures applicables.

Suite à cette évaluation, il me fait plaisir de vous confirmer que le CER-SC considère que **le projet de recherche susmentionné répond aux normes en vigueur au chapitre de l'éthique de la recherche** et est en conséquence approuvé tel quel.

Cette approbation éthique est valide pour **un an**, à compter du 30 mai 2022 jusqu'au 30 mai 2023.

Je vous prie toutefois de considérer les remarques suivantes :

Le CERSC demeure responsable de l'acceptabilité éthique des activités de recherche menées sous son autorité. Une fois l'approbation éthique initiale obtenue, une évaluation éthique minimalement annuelle est requise. L'évaluation éthique continue sera effectuée par le CERSC à partir des notifications qui lui seront transmises par l'équipe de recherche pendant le déroulement de la recherche. À cette fin, le CERSC fixe les mesures suivantes de suivi éthique continu de votre projet de recherche :

- La soumission d'un r**apport d'étape annuel,** à soumettre un mois avant

l'échéance de la date d'approbation afin de renouveler l'approbation éthique.

- La soumission de toute **modification au projet de recherche qui touche les participants**; une modification ne peut être mise en œuvre sans l'approbation du CERSC.
- La soumission dans les meilleurs délais d'un rapport **de tout accident ou de tout incident** lié à la réalisation du projet de recherche.
- La soumission d'un rapport sur toute **déviation au protocole** de recherche susceptible d'augmenter le niveau de risque ou susceptibles d'influer sur le bien-être du participant ou son consentement.
- La notification de toute **cessation prématurée, interruption temporaire ou suspension**, qu'elle soit temporaire ou permanente.
- La soumission d'un **rapport de fin de projet.**

Ces notifications doivent être transmises au CERSC en complétant le questionnaire de suivi disponible sur la page web du CERSC à la section « Modifications envisagées à un projet de recherche » et en le retournant par courriel à suivi-ethique@umontreal.ca avec la mention « Suivi éthique – [no d'approbation éthique] – date de complétion » dans le champ « Objet ».

Tout défaut de respecter une de ces mesures de suivi éthique pourrait résulter en une suspension ou une révocation de l'approbation.

Le CERSC de l'Université de Montréal est désigné par le ministre de la Santé et des Services Sociaux aux fins de l'application de l'article 21 du Code civil du Québec. Il exerce ses activités en conformité avec la *Politique sur la recherche avec des êtres humains* (60.1) de l'Université de Montréal ainsi que l'Énoncé de politique des trois conseils (EPTC). Il suit également les normes et règlements applicables au Québec et au Canada.

La présente lettre d'approbation éthique est la décision officielle du CERSC.

Cordialement,

Pour le CERSC

Karine Sénécal,
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