From Social Cognition Difficulties to Later Emotional and Behavioural Problems: The Roles of Cortisol and Inflammatory Markers

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Declaration

I declare that the thesis has been composed by myself and that the work has not been submitted for any other degree or professional qualification. I confirm that the work submitted is my own, except where work which has formed part of jointly authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

The work presented in Chapter 3 has been published in the journal *Stress & Health* with the title, "Social cognition and cortisol in the general population: A systematic review and meta-analysis", by me, Dongying Ji (author of this thesis and first author of that research article), Professor Eirini Flouri (co-author and first supervisor), and Dr Efstathios Papachristou (co-author and subsidiary supervisor). I carried out the preparation, investigation, validation, and visualisation of the data and the results, wrote up the manuscript draft and led on the editing of the article.

The work presented in Chapter 6 has been published in the *Journal of Attention Disorder* titled, "Childhood trajectories of hyperactivity/inattention symptoms and diurnal cortisol in middle adolescence: Results from a UK birth cohort", by Dongying Ji (student), Professor Eirini Flouri (supervisor), Dr Efstathios Papachristou (supervisor), and Dr Marta Francesconi (supervisor). I carried out the preparation, investigation, validation, and visualisation of the data and the results. I also wrote the manuscript and completed the revision of this article.

The work presented in Chapter 7 has been published in *Brain Behavior and Immunity* as "The role of inflammatory markers and cortisol in the association between early social cognition abilities and later internalising or externalising problems: Evidence from a UK birth cohort", by Dongying Ji (student), Dr Marta Francesconi (supervisor), Professor Eirini Flouri (supervisor), and Dr Efstathios Papachristou (supervisor). I carried out the preparation, investigation, and summarisation of the data and the results, wrote up the manuscript draft and revised the article for publication.

To acknowledge the contributions of co-authors, "we" will be used instead of "I" in Chapters 3, 6 and 7 of this Thesis.

Finally, I declare that this research thesis adheres to the requirements of the ALSPAC study and has included an accurate description of the study numbers, the study details as stated in the manuals and the correct references to the cohort.

Signature:  Date: 23/07/2022

Abstract

Objective: Deficits in social cognition are associated with a variety of emotional and behavioural problems in youth. It has been suggested that stress may be one of the mechanisms underlying these associations. Therefore, the overall aim of this PhD project is to examine the relationships between social cognition abilities, physiological stress, and mental health problems. Specifically, this project aims to evaluate the associations between different domains of social cognition and stress, investigate the link between stress and various emotional and behavioural problems, and explore the role of stress in the longitudinal association between childhood social cognition deficits and mental health problems in late adolescence. The thesis focused on two indicators of physiological stress, hypothalamic-pituitary-adrenal (HPA) axis activities (i.e., diurnal cortisol patterns) and systemic inflammation.

Method: A systematic review and meta-analysis was first conducted to examine the association between social cognition and cortisol in the general population, followed by three empirical studies. The statistical analyses of the empirical studies were based on the secondary data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a UK population-based birth cohort. In the first empirical study, multiple regression models were fitted to investigate the predictive effect of cortisol and inflammation on emotional and behavioural problems at 17 years old, with the adjustment of the mental health problems at 4 years old and covariates. The second study assessed if chronicity and severity of hyperactivity/inattention problems could predict abnormal cortisol profile in adolescence. Growth mixture models were used to identify classes with distinct developmental trajectories of hyperactivity/inattention symptoms from ages 4 to 13 years. In the third study, Bayesian structural equation modelling was used to investigate the mediating effects of cortisol and inflammation on the links between childhood social cognition abilities and emotional or behavioural problems at 17 years.

Results: The meta-analyses showed that emotion control was positively associated with basal cortisol levels, while emotion recognition or theory of mind was not associated with cortisol. The empirical studies found that social communication deficits, but not emotion recognition abilities, were linked with later emotional and

behavioural problems. Flattened diurnal cortisol slope and lower morning cortisol levels were associated with hyperactivity/inattention problems two years later. Adolescents with persistently high levels of hyperactivity/inattention symptoms since childhood showed lower total morning cortisol and a smaller diurnal decline. Lower morning cortisol partially mediated the direct association between social communication deficits at 8 years and hyperactivity/inattention and conduct problems at 17 years, even after adjustments for inflammation and confounders. There was no significant association between systemic inflammation and social cognition difficulties, emotional problems, or behavioural problems.

Conclusion: The findings of this project provided evidence for the hypoactivity of HPA axis among adolescents with chronic hyperactivity/inattention problems since childhood in the general population. Adolescents with childhood social communication deficits were also at risk of blunted HPA axis activity in the morning. However, as the indirect effect of morning cortisol on the association between social cognition and behavioural problems is very small in magnitude, it may not be clinically or practically significant.

Impact Statement

Numerous studies have suggested that children with social, emotional, or behavioural problems are more likely to experience both chronic and acute stressors in their lives, which may further lead to mental health problems in adolescence. However, most of them focused on the impact of stressful life events on the development of mental ill-health, rather than more direct measurements of stress, such as the activities of individuals' physiological stress systems. This PhD project addressed this gap and investigated the roles of the stress hormone cortisol and inflammation in the development of mental health problems, as well as underlying the longitudinal links between social cognition difficulties and mental health problems.

This PhD project contributes to the body of knowledge in several ways. First, it demonstrated the positive association between emotion control ability and basal cortisol levels in the general population through a systematic literature review and meta-analysis. The three empirical studies in this project then added evidence for the association between the lower basal cortisol levels and more behavioural problems, contributing to the understanding of hypocortisolism in the general adolescent population. Specifically, the first study found that lower morning cortisol levels and flatter diurnal cortisol slopes could predict later hyperactivity/inattention symptoms, and lower morning cortisol could also predict later conduct problems in adolescence. The predictive effects survived from the adjustment of behavioural problems in early childhood, inflammation, and confounders. The second empirical study identified three developmental trajectories of hyperactivity/inattention symptoms from early childhood to adolescence. It found that adolescents with persistently high levels of hyperactivity/inattention symptoms since childhood were more likely to exhibit lower morning cortisol and smaller diurnal cortisol decline. This extends our understanding of the longitudinal negative impact of chronic behavioural problems on adolescents' stress systems. Furthermore, the third study added to the literature on social cognition by revealing that adolescents with childhood social communication deficits are more likely to manifest lower basal cortisol, leading to more behavioural symptoms in late adolescence.

This PhD project also offers insight into potential clinical practice and public health policies. Childhood mental health problems and social cognition difficulties

were found to be robustly linked to mental health symptoms in adolescence. This suggested that mental health screening and intervention in the early years are important in identifying and addressing mental health problems as an early stage and potentially reducing the prevalence of mental health problems in adolescence. The findings also suggested that by training educators, parents, and community social workers to promote positive social environments and enhance young people's social skills at an early age, the risk for future emotional and behavioural problems could be reduced.

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List of Terms and Abbreviations

11β-HSD	11β-hydroxysteroid dehydrogenase
ACTH	Adrenocorticotropic Hormone
AIC	Akaike Information Criterion
AUCg	Area Under the Curve with respect to ground
ADHD	Attention-Deficit/Hyperactivity Disorder
ASD	Autistic Spectrum Disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
AVP	Arginine-vasopressin
BIC	Bayesian Information Criterion
BSEM	Bayesian Structural Equation Modelling
BMI	Body Mass Index
CD	Conduct Disorder
CRH	Corticotropin-Releasing Hormone
CAR	Cortisol Awakening Response
CRF	Corticotropin Releasing Factor.
CRP	C-Reactive Protein
DAWBA	Development and Well-being Assessment
DANVA	Diagnostic Analysis of Non-Verbal Accuracy test
EI	Emotional Intelligence
GAS	General Adaptation Syndrome
GAD	Generalised Anxiety Disorder
GR	Glucocorticoid Receptors
GMMs	growth mixture models
HPA	Hypothalamic-Pituitary-Adrenal
IQ	Intelligence Quotient
IFN	Interferon
IL-6	Interleukin 6
IOTF	International Obesity Task Force
IRI	Interpersonal Reactivity Index
MDD	Major Depression Disorder
MCMC	Markov Chain Monte Carlo
MR	Mineralocorticoid Receptors

OPCS	Office of Population Censuses and Surveys
ODD	Oppositional Defiant Disorder
PPP	Posterior Predictive P-Value
PSR	Potential Scale Reduction
SCDC	Social Communication Disorders Checklist
SIP	Social Information Processing theory
SSDV	Social Skills Deficit Vulnerability theory
SDQ	Strengths and Difficulties Questionnaire
SNS	Sympathetic Nervous System
ToM	Theory of Mind
TNF-α	Tumour Necrosis Factor-alpha
Th1	Type 1 T helper
Th2	Type 2 T helper
LRT	Vuong-Lo-Medell-Rubin likelihood ratio test
WASI	Wechsler Abbreviated Scale of Intelligence

Overview

The main aims of this thesis were to investigate the longitudinal associations between social cognition abilities, physiological stress and emotional or behavioural problems in the general child population. This thesis focused on two indicators of physiological stress: aberrant Hypothalamic-Pituitary-Adrenal (HPA) axis activity and systemic inflammation.

This thesis is divided into eight chapters. Chapter 1 provides a conceptualisation of the research question as well as the rationale for this study. Chapter 2 presents a literature review on social cognition, inflammation, HPA axis function and cortisol, emotional and behavioural problems, and their inter-relationships, followed by the main questions and hypotheses of this thesis. Chapter 3 digs into the literature on social cognition and cortisol in more depth by a systematic review and meta-analysis. Chapter 4 describes an overview of the data source and measurement of the main variables in the thesis. Chapter 5 to 7 consist of three empirical studies to address the research questions. Chapter 5 investigates the predictive effect of the inflammation and cortisol parameters on the emotional and behavioural problems in late adolescence, with the adjustment of the mental health problems in childhood. Chapter 6 expands upon the findings of Chapter 5 by looking at the developmental trajectories of behavioural problems, especially hyperactivity/inattention symptoms, in predicting later cortisol parameters. Taking the social cognition abilities into account, Chapter 7 then explores the longitudinal associations of social-cognitive difficulties in childhood with emotional and behavioural problems in adolescence, and whether the associations can be explained by inflammation and/or cortisol parameters. Finally, Chapter 8 discusses the findings of the three studies in light of the research aims and reviewed literature. Chapter 8 also addresses the strengths and limitations of the thesis and its implications for future research and policy.

Chapter 1: Introduction

As reported by Public Health England (2016), about half of people with lifetime mental illness experience symptoms by the age of 14. Longitudinal data from both clinical and community samples have shown that childhood or adolescent-onset of social, emotional, or behavioural problems is associated with increased risks of recurrence of the original problem and development of psychiatric comorbidity in adulthood (Rutter et al., 2006; Jones, 2013). For example, about 40-70% of adolescents with depression experience a recurrence of major depressive disorder in adulthood (Maughan & Collishaw, 2015). Conduct problems or attention-deficit/hyperactivity disorder in childhood and adolescence on the other hand are strongly associated with an elevated risk for antisocial behaviours, poor social functioning, substance abuse, anxiety, and bipolar disorder later in life (Costello et al., 2011; Duffy, 2012; Katusic et al., 2005; Kim-Cohen et al., 2003; Mannuzza et al., 2004). Adults with youth-onset of mental health problems are also more likely to have lower educational attainment and experience financial difficulties compared to those with adult-onset (Kerridge et al., 2020; Zisook et al., 2007). Therefore, it is important to identify risk factors for emotional and behavioural problems in childhood and adolescence.

Social cognitive difficulties have long been established as a factor that precedes the emergence and development of mental health problems. Social cognition refers to a range of dimensions and processes involved in perceiving, understanding, and interpreting oneself and others in social situations (Amodio & Frith, 2006). Numerous theories have been proposed to explain the link between social cognitive difficulties and mental health problems. For instance, Social Information Processing (SIP) theory suggests that individuals with conduct problems tend to have biased mentalisation, encoding and attributing neutral social cues as threats and inappropriately evaluating aggressive behaviours (Dodge & Coie, 1987; Crick & Dodge, 1996). These individuals also show dysregulated emotions to a perceived offence (Crick & Dodge, 1996; Mize & Pettit, 2008). According to the Social Skills Deficit Vulnerability (SSDV) theory (Segrin, 2000; Segrin et al., 2016), on the other hand, social cognitive deficits are related to both quantitative and qualitative aspects of social interactions, shrinking the size of social networks (Bierman & McCauley, 1987), as well as producing more negative interactions and conflicts (Grisset &

Norvell, 1992). Experiences of conflict or rejection in children that are bound up with social cognitive deficits are in turn shown to evoke stress, leading to high vulnerability to mental disorders (Gilmour et al., 2004; Rai et al., 2018). Empirical evidence has convincingly supported both theories, indicating, for example, that adolescents who experience more stressful social interactions and with a biased cognitive style are more likely to have emotional and behavioural problems cross-sectionally and longitudinally (Abramson et al., 1989; Hankin & Abramson, 2001; Abela & Hankin, 2008; Lakdawalla et al., 2007; Lee et al., 2010). However, most of these studies measured stress by checklists of adverse life events or experiences, and none of them examined physiological stress, as evidenced for example by impaired HPA axis functioning and inflammation.

Since the work of Selye in 1936, stress has long been associated with the activation of the HPA axis (Selye, 1936, 1973). A key product of the HPA axis activation, the glucocorticoid hormone cortisol is one of the most frequently studied biomarkers in stress-related psychological research. Cortisol levels are sensitively responsive to both acute and chronic stress. Cortisol is an anti-inflammatory hormone, and reduced cortisol secretion can lead to increased levels of inflammatory markers, such as Interleukin 6 (IL-6) and C-Reactive Protein (CRP) (Hannibal & Bishop, 2014). Increasing evidence demonstrated that repeated, excessive, or prolonged exposure to psychological stressors can lead to dysregulated cortisol activity, resulting in an unmodulated inflammatory response to stressors. Therefore, it is possible that poor social cognition, for example, maladaptive cognitive appraisals regarding social cues, may promote an exaggerated physiological stress response, i.e., prolonged HPA axis activity and widespread inflammation, leaving individuals susceptible to disease and illness (McEwen, 2004; Sapolsky, 2004).

In addition, dysregulated cortisol activity and inflammation are closely related to several mental disorders. Hypercortisolism has been seen in patients with depression disorder (Checkley, 1996; Pariante & Miller, 2001); while HPA hypoactivity has been observed in behavioural disorders (Pauli-Pott et al., 2017; Ouellet-Morin et al., 2011). Both emotional and behavioural problems have been found to correlate with dysregulated immune responses and high levels of inflammatory markers (Slavich & Irwin, 2014; Takahashi et al., 2018). However, HPA axis functioning and inflammation have rarely been examined together,

especially in relation to mental health in the general youth population. Additionally, in the few case-control studies assessing both inflammatory markers and cortisol in clinical samples, only one of the biomarkers showed abnormal levels. For example, in patients with depression disorders, individuals with melancholic depression were found to have higher levels of diurnal cortisol but normal levels of inflammatory markers, while heightened inflammation and normal cortisol levels were found in the individuals with atypical depression (Lamers et al., 2013). Considering these inconsistent and complex findings about the relationship between cortisol, inflammation, and mental health problems, it is important to examine jointly cortisol and inflammation so as to disentangle how physiological stress is associated with the development of mental health problems, especially in the general youth population. Therefore, the primary goal of the current thesis is to investigate the relationship between cortisol, inflammation and emotional or behavioural problems in the general youth population (Chapters 5 and 6). Extending psychoneuroimmunology research in a population-based sample will increase the translational value of clinical findings in the general population and, potentially, support a role for biological screening and preventative interventions for mental health problems at a young age.

As stress-induced HPA axis dysfunction and inflammation have been associated with both social cognitive difficulties (Gonzalez-Liencres et al., 2016; Michel et al., 2012) and mental health problems (Adam et al., 2017; Liukkonen et al., 2011; Odgers et al., 2007), cortisol and inflammatory markers and their joint activity may be critical biological mediators between social cognitive difficulties and mental health problems in childhood and adolescence. To date, no empirical study has tested this mediating path. Thus, the secondary goal of this thesis is to concentrate on social cognitive difficulties, and empirically test the path via physiological stress (HPA axis dysregulation and/or chronic inflammation) to emotional and behavioural problems in a general youth population (Chapter 7).

Chapter summary and next step

This introductory chapter presents a broad background and conceptualisation of the research question. It begins with the rationale for studying mental health in adolescents, followed by a discussion of the link between social cognitive difficulties

and mental health problems and how stress may be the link between the two. Next, there is a brief introduction of physiological stress systems - the HPA axis and immune systems - and an outline of their roles in the development of emotional or behavioural problems. Following this, the main goals of the thesis are reviewed. The next chapter will review the literature on social cognition, inflammation, HPA axis and cortisol, emotional and behavioural problems, and their relations with each other. The main questions and hypotheses of this thesis will be presented at the end of the next chapter.

Chapter 2: Literature Review

2.1 Social cognition and emotional or behavioural problems

2.1.1 Social cognition

Social cognition refers to the cognitive processes that underlie social interactions (Frith, 2008). Despite the undeniable importance of social cognition for successful social communication, little agreement exists as to the exact definition and components of social cognition. In Fiske and Taylor's (2013) textbook on social cognition, 14 domains of social cognition, such as social attention, decision making, social inference, attitudes, stereotyping, and prejudice, were identified. Most social cognition studies concentrate on some of them (Armitage & Conner, 2000; Bora & Pantelis, 2016). There are also review papers sketching a somewhat different structure of social cognition. For example, in the neural bases of social cognitive abilities approach (Ochsner, 2008), there are five core constructs, including acquiring social-affective responses, recognising social-affective stimuli, responding to social-affective stimuli, low- and high-level mental state inference, and context-sensitive regulation. Happé and colleagues (2017) hypothesised a four-level structure of eight key social cognition abilities comprising three domains: empathy, false-belief understanding, and action imitation. Because of the lack of consensus as to what the very construct of social cognition is, a glance at the development of social cognition research can be helpful.

Social cognition research can be traced back to the 1920s when researchers studied social intelligence and interpersonal judgement (Thorndike, 1920; Vernon, 1933). Social cognition research became separate from social intelligence research since the 1960s, when researchers adopted the cognitive information-processing approach from the "cognitive revolution" (Carlston, 2013; Fiske, 2005; Kohlberg, 1969; Sperry, 1993; Walker & Foley, 1973). At first, the topic of social cognition research only focused on egocentrism and role-taking ability (Bowers & London, 1965; Flavell, 1968) or Theory of Mind (ToM) (Bretherton et al., 1981). Then with the integration of pre-existing social psychology areas, such as emotion understanding, empathy, attitudes, stereotyping, attribution, and impression formation, into the information-processing model, the research on social cognition

significantly expanded and became structuralised (Chandler & Greenspan, 1972; Carlston, 2013; Strack & Förster, 2011).

Following the information-processing model, the starting focus was on the attention and perception of informational cues (i.e., facial expression and motion behaviours) that are present in the social environment, followed by distinguishing, recognising, and automatic imitation (i.e., motion mimicry and empathy). Then social information together with prior experience is imbued within mental representations (i.e., schemas, stereotypes, attitudes, scripts, and inference), which are selectively constructed (i.e., social policing) and evaluated (i.e., mental state attribution/ToM). The final process involves the regulation of mental states, emotions, and behaviours for appropriate social interactions (i.e., emotion regulation, reciprocity, impression formation, rumination, and extinction). In turn, social cognition can be roughly divided by function into knowledge-based social cognition (e.g., mental state inference, social policing) and ability-based social cognition (e.g., emotion recognition, ToM). These are not completely independent, and the former can be reflected in the performance of the latter. For instance, children with insufficient emotional situation knowledge may not be able to regulate their emotions well (Garner & Power, 1996). Therefore, the focus of this thesis lies more on ability-based social cognition, and social cognition is defined in this thesis as a wide range of cognitive abilities that facilitate the processes of social interactions.

Findings from neuroscience studies further elucidated the interrelationships among different facets of social cognition, by identifying neural systems related to different social cognitive abilities. Research showed, for example, that patients with frontal damage perform poorly on belief reasoning tasks (Apperly et al., 2004), whereas patients with amygdala damage showed impaired emotion recognition (Adolphs, 2010; Adolphs & Tranel, 2003). Based on comprehensive reviews by Happé and Frith (2014), Happé and colleagues (2017), Kennedy and Adolphs (2012) and Ochsner (2008), there are mainly three neural networks corresponding to key domains/processes of social cognition functions: 1) mirror networks (parietal and prefrontal regions) are related to the identification and automatic mimicry of social cues, such as action discrimination, in-group/out-group distinction, and motion imitation; 2) empathy networks (amygdala, insular and orbitofrontal regions) are related to emotion processing, such as threat detection, emotion recognition, empathy,

and emotion regulation; and 3) mentalising networks (the temporoparietal junction, superior temporal and the media prefrontal cortex) are related to mental states inferencing, such as self-awareness, pragmatic language use, ToM/mental state attribution, and cognitive appraisal. Some of them, particularly higher-order functions, such as emotion recognition, empathy, emotion regulation, rumination, and moral judgement, require and activate more than one network (Happé & Frith, 2014; Happé et al., 2017).

Although motion imitation has also demonstrated benefits for social interaction, this thesis does not focus on this domain. There are two reasons for this. First, such abilities (e.g., gaze following, action discrimination, and automatic mimicry) are relatively lower-order social cognitive abilities, suggesting only very few children would show deficits. What is more, such deficits can improve greatly in the early years. Even studies with children with Autistic Spectrum Disorder (ASD), a severe neurodevelopmental disorder characterised by qualitative impairment in social communication, showed no atypical activation in the mirror network during social processing tasks, but hypoactivation in the mentalising network and hyperactivation in the amygdala (Dichter, 2012; Hirschfeld et al., 2007; Marsh & Hamilton, 2011; Riby et al., 2012). Second, even people who do not show full capacity in motion imitation, such as children with physical disabilities, are socially accepted as long as they show higher social cognition ability (e.g., empathy, social problem-solving and emotion regulation) (Odom et al., 2006). Therefore, this thesis focuses more on middle or higher order social cognitive abilities, such as nonverbal communication (e.g., emotion recognition from the tone of voice) and ToM/empathy.

Nonverbal communication refers to the ability to use nonverbal cues to convey information (e.g., emotion or intention) in social interactions, and includes two parts: recognising the nonverbal cues and appropriately returning them alongside the verbal conversation (Thompson & Campling, 1996). Examples of nonverbal cues include facial expression, eye contact, body language, and tones of voice. Taking recognition of emotion from facial expression as an example, successful recognition needs adequate attention on the face, accurate identification of facial expressions, and proper emotional discrimination/attribution. Therefore, different neural networks are involved, such as the amygdala, the superior temporal gyrus/sulcus, ventro-temporal regions, as well as the bilateral ventromedial prefrontal cortex for visual attention to

the eye regions of faces (Grosbras et al., 2005; Wolf et al., 2014). Although individuals from different cultures may express emotions in distinct ways, evidence shows that the facial expressions for basic emotions, such as happiness, sadness, anger, and fear, are universally common, allowing facial expressions to play a critical role in social communication across cultures (Matsumoto & Willingham, 2009). There are scholars suggesting that nonverbal communication represents almost two-thirds of social interaction (Burgoon et al., 2016). Hence, individuals with poor nonverbal communication skills are likely to have difficulties understanding others' feelings and intentions (Burgoon et al., 2016).

ToM, or mentalising, refers to the understanding and prediction of other people's behaviours based on their mental states, and empathy allows people to feel others' emotional states (Frith & Frith, 2005). There are also scholars defining empathy as a wider category and calling ToM cognitive empathy, in contrast to affective empathy (Marchetti et al., 2020). Both ToM and empathy are high order social cognitive abilities, and they share some neural networks that are responsible for the self-other distinction and mirror mechanism. Concerning their differences, ToM requires mental state inference which is related to the superior temporal and the media prefrontal cortex, while empathy requires involuntary emotional responses which are related to the activation of the amygdala and insular. New-borns show emotional responses to others' distress as early as 18 hours post-birth and children undergo significant development of empathy by middle childhood (McDonald & Messinger, 2011). Core ToM skills, such as the understanding of false beliefs, typically develop by age 4 years (Wimmer & Perner, 1983). More advanced skills, including understanding the influence of emotions on other people's beliefs and embedded mental states ('he thinks she thinks…'), typically develop by age 7 (Perner & Wimmer, 1985). Children who show delays in developing empathy and ToM have an increased risk of being exposed to negative social interactions (i.e., peer rejection, bullying as victims and bully-victims; Miller et al., 2005; Shakoor et al., 2012), interpreting ambiguous situations as threatening, and responding aggressively (Runions & Keating, 2007), and having difficulties in establishing good relationships later in life (Shakoor et al., 2012).

2.1.2 Social cognition and emotional and behavioural problems

Core social cognition processes such as nonverbal communication and ToM/Empathy are key components of social skills and competence (Halberstadt et al., 2001; Trentacosta & Fine, 2010). As just discussed, children who are better able to understand emotional cues in the social environment are more likely to develop superior social skills and form positive interpersonal relationships. Social competence in childhood has consistently been linked to positive developmental outcomes, including peer acceptance, academic achievement, and mental health (Caputi et al., 2012; Cassidy et al., 2003; Ciarrochi et al., 2002; Hartup, 1989; Izard et al., 2001; Thoits, 2011). In contrast, social cognition deficits are often associated with severe communication difficulties, inappropriate social behaviours, and poor social relations (Knox & Douglas, 2009). Other research has shown that children with emotional and behavioural problems frequently have a history of poor ToM (Hughes & Ensor, 2006). Furthermore, social cognition deficits have been found in patients with depression (Ladegaard et al., 2014), conduct disorder (Gilmour et al., 2004), bipolar disorder (Rich et al., 2008), posttraumatic stress disorder (Plana et al., 2014) and schizophrenia (Savla et al., 2012). Prospective longitudinal studies demonstrate that social cognition dysfunction predicts individuals' mental ill-health in the long run (Feng et al., 2009; Hymel et al., 1990; Sullivan et al., 2017), not vice versa (Cole et al., 1996). Interventions targeting social cognition abilities have also been found to reduce emotional and behavioural symptoms (Belvederi Murri et al., 2017; Dadds et al., 2012).

One well-known theory explaining the association between social cognition deficits and emotional or behavioural problems is the SIP theory. As introduced in section 2.1.1, social information processing (SIP) refers to a set of sequential mental processes involved in social interactions. Dodge's famous SIP model suggests six steps in social interactions: 1) encoding of social cues, when individuals observe and process stimuli from the external social environment (e.g., facial expressions and gestures) and internal sensations (e.g., a breath-taking feeling and accelerating heart rate); 2) interpretation and representation of social cues, when individuals make inferences about the causes of the social behaviour and evaluate them in their mind; 3) identification of goals, when individuals identify the desired outcomes of the social interaction; 4) response generation, when individuals think about possible responses based on their experiences or develop new responses; 5) response selection and 6)

behavioural enactment, when the selected response is carried out (Crick & Dodge, 1994). Among these steps, accurate perception, interpretation, and evaluation of social cues are particularly important for competent social performance and building positive relationships with peers. Social knowledge, which is also called relationship schemas or scripts, is assumed to guide these steps of information processing (Baldwin, 1992; Crick & Dodge, 1994).

In developmental psychology, the SIP model has been mostly examined in relation to behavioural problems. For example, children with Attention-Deficit/Hyperactivity Disorder (ADHD) and conduct problems have shown differences in SIP patterns and are especially reactive to provocation from peers compared to other children (Andrade et al., 2012; King et al., 2009; Waschbusch et al. 2002). Specifically, aggressive children are more likely to selectively perceive and recall cues relating to hostility or threat, to use less information before response generation and selection, and to generate incompetent solutions to social interactions (Milich & Dodge, 1984; Mize & Pettit, 2008). They also tend to make more mistakes in recalling the details of social interactions (Mize & Pettit, 2008). In addition, aggressive children are likely to have more instrumental goals and care less about whether others suffer (Boldizar et al., 1989), and hence generate less effective, more physically aggressive responses. Mounting evidence has reported that individuals with conduct disorders or aggressive behaviours are less able to recognise fearful and sad expressions (Marsh & Blair, 2008), which may explain their callous attitude toward the sufferings of others. On top of this, research suggests that aggressive children view aggressive behaviours as being acceptable and some of them feel more confident when they behave aggressively (Bandura et al., 1996; Crick & Dodge, 1996). Nevertheless, individual differences can be seen among proactively aggressive children, aggressive children with callous-unemotional traits and reactively aggressive children (Dodge et al., 1997). For example, hostile attribution bias seems to be more consistent for proactive aggressive children rather than reactively aggressive children, who instead show suppressed attention to social threats (Schippell et al., 2003). Similar to aggressive children, children with ADHD often have biased SIP as well, such as difficulties in encoding social cues, biased interpretations of cues, and more inappropriate social responses compared with children without ADHD (King et al., 2009; Milich & Dodge, 1984; Moore et al., 1992; Murphy et al., 1992; Sibley et al.,

2010). It has been suggested that inattentive children might be less able to perceive relevant social cues, and children with hyperactive traits may spend less time generating possible responses to social situations (Andrade et al., 2012).

Children with emotional problems, such as depression and anxiety, also show distorted SIP patterns (Foland-Ross & Gotlib, 2012). Beck (1976) asserted that depressed children tend to have a "negative cognitive schema", characterised by negative views of themselves and their experiences, as well as low expectations of future outcomes. Depressed children are more likely to recall negative words, exhibit negative attribution styles, engage in prolonged rumination, and be less able to control their own desired outcomes (Kyte & Goodyer, 2008; Park et al., 2004; Weisz et al., 1987). Anxious children are also more likely to have negative cognitions, such as negative attention and interpretation biases. Empirical studies found that children with anxiety disorder tend to encode more negative/threat cues, interpret ambiguous stimuli as threatening, and display an avoidant response to such stimuli (Mansell et al., 1999; Muris et al., 2003; Vasey et al., 1996). There are scholars suggesting that difficulties in mentalising may contribute to a negatively biased evaluation of social cues, which could lead to poor performance in social interactions and even emotional problems (Mathews & MacLeod, 2005; Kyte & Goodyer, 2008).

Social skills deficit vulnerability (SSDV) theory further suggests that children with social cognition deficits are more likely to be exposed to stressors in social interactions, such as peer victimisation and physical conflicts (Segrin, 2000; Segrin et al., 2016), and are less able to secure the social support necessary for dealing with the resulting stress (Knox & Douglas, 2009; Shakoor et al., 2012). Hence, they are more vulnerable to the development of persistent psychological distress and other emotional or behavioural problems. It has been documented in longitudinal research that children who had poor ToM in early childhood are more likely to become victims of bullying in early adolescence (Shakoor et al., 2012), and childhood peer rejection and bullying involvement have been linked to behavioural problems cross-sectionally and longitudinally (Coie, Terry, Lenox, & Lochman, 1995; Hymel et al., 1990; Wolke et al., 2000). In addition, socially isolated adolescents are more likely to join antisocial peer networks, which encourage more antisocial behaviours through peer influence (Dishion, 2000; Dishion & Patterson, 2006). Like the SSDV model, social competence theory posits that the difficulties in expressing oneself and understanding

others can lead to negative feedback from others across different domains of performance, and self-frustration. Then, out of frustration, children become aggressive and disruptive or depressed and withdrawn (Bornstein et al., 2010; Cole, 1991). For instance, Pettersen (1991) found that participants who were poor at recognising emotional facial expressions were also rated by their relatives as showing less socially appropriate behaviours. In all three models discussed social cognition difficulties either produce stress or are the result of stress. SIP models of behavioural problems, for example, propose that the occurrence of negative life events triggers the hostile biased cognitive processes in aggressive children (Gibb & Coles, 2005). Thus, when poor social cognition is considered, stress is directly relevant.

2.2 HPA axis and cortisol response

2.2.1. Stress and the HPA axis

The activation of the HPA axis and the immune system appear to be one of the biological pathways underlying stress-related mental health problems. In 1929, Cannon defined the concept of "fight or flight", which describes the body's physiological response to threat with activation of the Sympathetic Nervous system (SNS) and the HPA axis. This response was recognised as the acute stress response stage of a General Adaptation Syndrome (GAS) postulated by Selye (1936). Selye defined stress as bodily responses to external stimuli (Selye, 1973). GAS is a framework of stress response comprising three stages: 1) acute response stage to release essential hormones in reaction to the threat, 2) resistance stage, when the physiological response is continuously activated under the stimulus of prolonged stressors and 3) exhaustion stage, whereby the stressor persists even longer, resulting in an inability to respond adequately when confronting another stressor (Selye, 1973). The HPA-axis was placed at the centre of the stress process. Therefore, stress has been long associated with an activation of the HPA axis.

When facing acute stressors, the brain signals the activation of SNS via the neurotransmitter epinephrine within seconds of the encounter. The SNS response quickly accelerates the heart rate, widens bronchial passages, and raises blood pressure, but these effects last only minutes. Therefore, physiological markers from SNS are not appropriate indicators for stress due to their short survival time. In

addition to SNS, the HPA axis is activated, which leads to increased secretion of the Corticotropin-Releasing Hormone (CRH), the Adrenocorticotropic Hormone (ACTH), and the glucocorticoid hormone cortisol (see Figure 2-1). HPA axis activation has a similar effect on heart rate and blood pressure. In addition, the end product of HPA axis activation, cortisol, can promote the release of additional energy for hours. Cortisol can also increase glutamate release in the hippocampus, enhancing cognitive ability, needed for functions such as memory consolidation for stressful events (Nagamine et al., 2017; Wolf, 2008).

The actions of cortisol are mainly mediated by two different receptors in the brain: a) Mineralocorticoid Receptors (MR), which are predominantly presented in the limbic system (hippocampus & amygdala) and the prefrontal cortex and bind cortisol with high affinity, and b) Glucocorticoid Receptors (GR), which are co-localised with MR and have approximately one-tenth the affinity of MR (Young et al., 2003). Because of differences in affinity, basal levels of cortisol largely occupy MR, while excessive cortisol secretion, such as that occurring after stress, progressively occupies GR, resulting in a decreased MR/GR ratio (Figure 2-2). Under basal levels of cortisol, negative feedback is mediated mainly through the MR in the hippocampus, whereas under stress and high cortisol concentrations, feedback is mediated by the less sensitive GR in the hippocampus, hypothalamus, and pituitary gland. The balance in these MR- and GR-mediated effects on the stress system is of crucial importance to the set point of the HPA axis activity. Regulation and termination of the stress response in the HPA axis is mainly driven by GR, (Arnett et al., 2016) and GR has also been suggested to regulate the expression of MR. Evidence has consistently demonstrated that GR function is impaired in major depression, resulting in reduced GR-mediated negative feedback on the HPA axis and hence unmodulated high levels of cortisol and decreased MR/GR ratio (Juruena et al., 2004). At the same time, increased expression of MR exerts an inhibition influence on HPA axis activity and is related to reduced anxiety and improved cognition (de Kloet et al., 2016; Otte et al., 2015). Downregulated MR and a low MR/GR ratio are associated with disrupted brain serotonin systems, a range of psychiatric disorders and cognitive impairments (Groch et al., 2013; López et al., 1998; Qi et al., 2013; Villarreal et al., 2002; Watson & Mackin, 2006; Wingenfeld & Wolf, 2015). However, when the hyperactivity of HPA axis persists for years, the number of GR decreases, which was

theorised as a protective adaption to prevent multiple organs from being over-reacted by constantly high levels of cortisol and related hormones, resulting in low levels of cortisol ultimately (Figure 2-2; Fries et al., 2005; Koss & Gunnar, 2018; Oitzl et al., 2010; Watson & Mackin, 2009). Therefore, a change from hypercortisolism to hypocortisolism has been suggested to develop out of chronic stress over a long period (Fries et al., 2005; Heim et al., 2000).

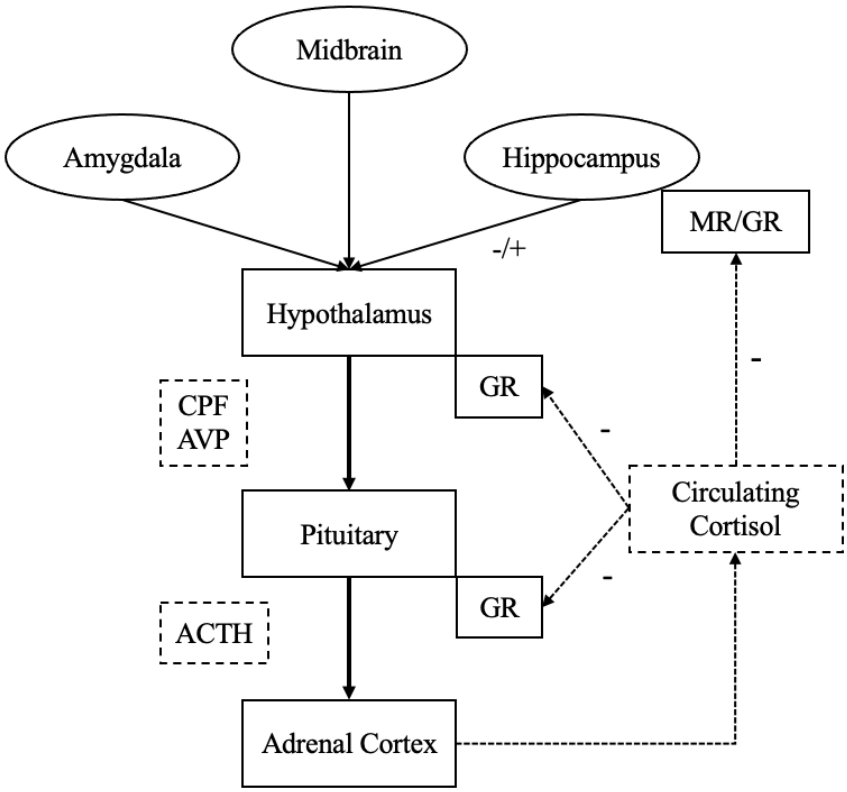

Figure 2-1 Schematic diagram of the HPA axis (from Juruena, 2013 © 2013 Elsevier Inc.). It describes regulation and negative feedback (-) of cortisol via GR and MR. CRF: corticotropin-releasing factor. ACTH: adrenocorticotropic hormone. AVP: Arginine-vasopressin

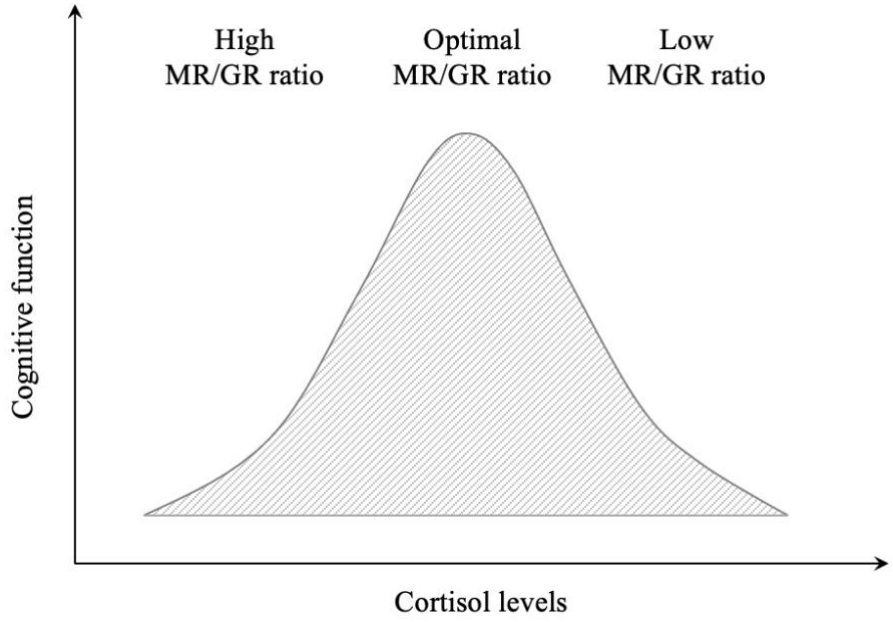

Figure 2-2 The relationships between MR/GR ratio, cortisol, and cognition (from Watson & Mackin, 2009 © 2008 Elsevier Ltd.)

2.2.2 The role of cortisol response

Cortisol levels are sensitively responsive to both acute and chronic stress. A dynamic cortisol response, marked by a rapid rise and decline in cortisol levels following instant stress, is thought to be adaptive and facilitate adequate coping with perceived threats in the environment (Hellhammer et al., 2009). Conversely, an over-reactive stress response (greater cortisol increasing during the stress task) or a diminished recovery (slower decreasing levels of post-stress cortisol) have been taken to be indicative of low-stress resilience (Kudielka et al., 2009). In addition to the acute response to stress, cortisol also follows a typical diurnal circadian rhythm. The natural cortisol diurnal rhythm shows a peak within the first hour after awakening, a rapid decline over the morning hours, and then a slow decline over the rest of the day before reaching a night-time nadir (Pruessner et al., 1997). Cortisol diurnal rhythm can be captured by features such as cortisol awakening response (CAR), diurnal slope, cortisol levels at different time points, average cortisol levels, and estimated daily secretion of cortisol. CAR, the rise of cortisol levels within the first 30 or 45 minutes after awakening, represents body's HPA axis reactivity to natural stimuli, and has been found to be indicative of stress response to laboratory-induced stressors as well

(Chida & Steptoe, 2009). A flat slope, which is characterised by a small diurnal decline over the day, is particularly associated with a variety of psychological and health problems, such as increased body mass index, increased breast cancer mortality, fatigue, and emotional disorders (Milaneschi et al., 2021). Abnormal levels of diurnal cortisol are also related to a range of mental and physical disorders. Elevated diurnal cortisol levels, i.e., hypercortisolism, have been found in patients with depression (see Figure 2-3; Wong et al., 2000) and anxiety disorders (Vreeburg et al., 2010), as discussed earlier, while inadequate production of cortisol, i.e., hypocortisolism, has been found in patients with ADHD (Chang et al., 2021) and conduct disorder (see Figure 2-4; von Polier et al., 2013). As already discussed, both hypercortisolism and hypocortisolism have been linked with chronic stress and hypercortisolism may evolve into hypocortisolism with time. For example, Trickett and colleagues (2010) found that, compared to females without childhood maltreatment experience, cortisol levels of maltreated females showed higher morning cortisol initially in adolescence, but became lower in adulthood. Other studies also documented lower morning cortisol levels and flatter daytime slopes in children who had experienced mild to severe stressors chronically (Adam et al., 2017; Fries et al., 2005). The literature regarding the associations between cortisol and emotional or behavioural problems will be reviewed in more detail in Section 2.4 of this chapter.

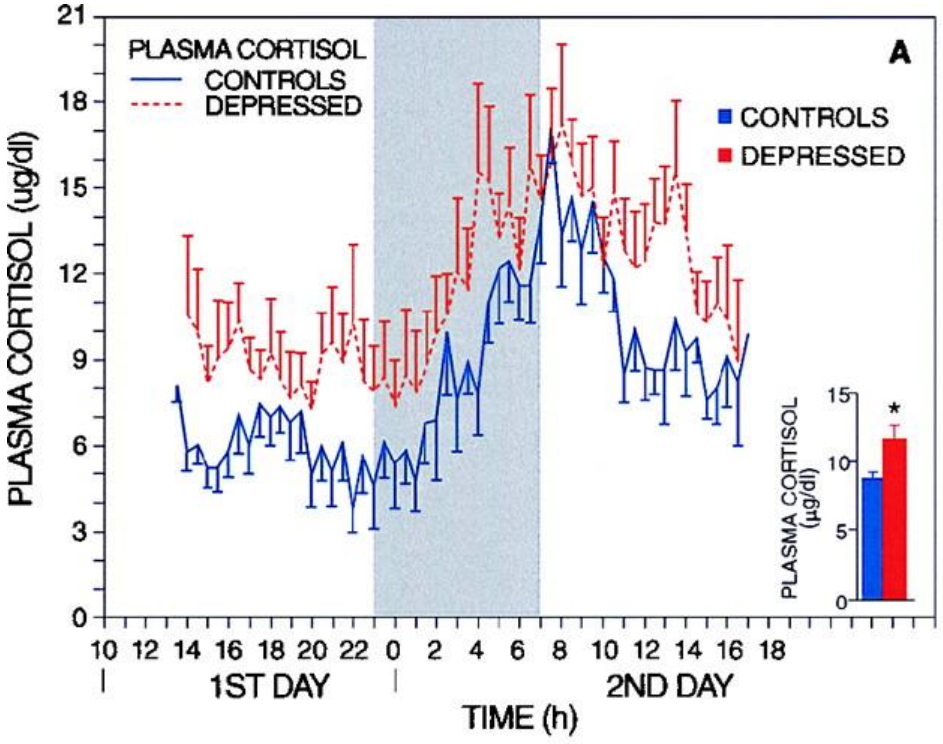

Figure 2-3 Diurnal rhythm of cortisol in health controls and depressed patients (from Wong et al., 2000 © 2000 National Academy of Sciences, USA)

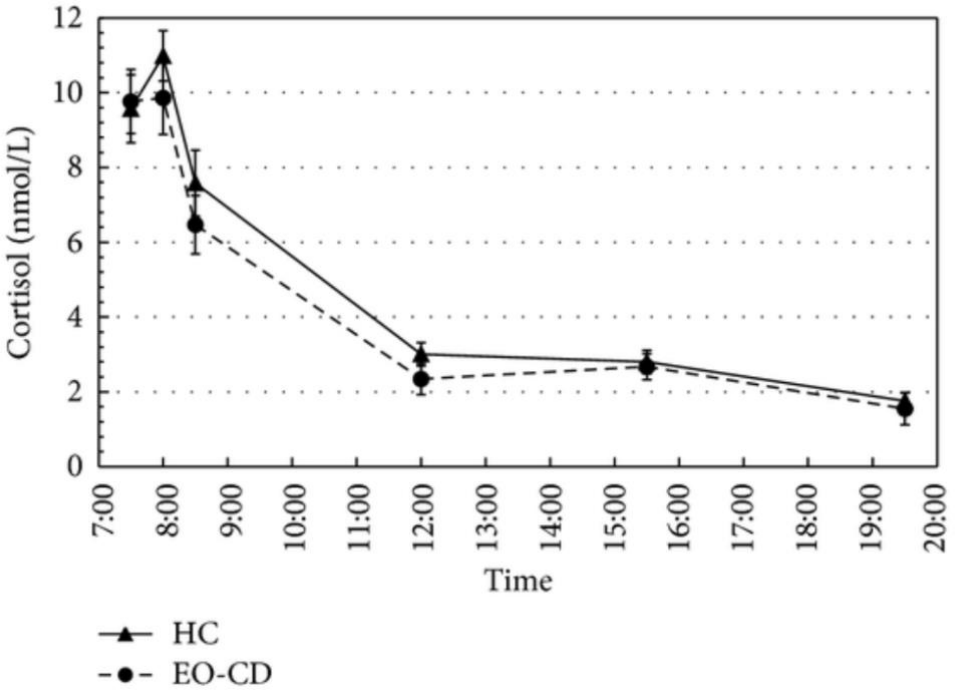

Figure 2-4 Diurnal rhythm of cortisol in health controls and patients with early-onset conduct disorder (from von Polier et al., 2013 © 2013 Georg G. von Polier et al.)

2.3 Inflammation

Inflammation is a generalised response to actual or potential infections and a complex process involving dozens of molecules (Ashley et al., 2012; Lochmiller & Deerenberg, 2000; Parkin & Cohen, 2001). Two inflammatory markers, CRP and IL-6 have been extensively examined in most epidemiological studies on the role of inflammation in emotional and behavioural disorders to date. CRP is an important protein in the immune system which binds to damaged, necrotic, and microbial cells. IL-6 is a pro-inflammatory cytokine and a reliable biomarker of inflammation which is released into circulation when inflammation is triggered. One of the main effects of IL-6 is to arouse the production of CRP, as well as other acute-phase proteins (e.g., fibrinogen, ferritin), in the liver and their release in the bloodstream (Lochmiller & Deerenberg, 2000; Parkin & Cohen, 2001). Consequently, the secretion of CRP is

promoted following elevated IL-6 levels and its level begins to rise 4-6 hours after the start of infection, and peaks 1-2 days later (Schmit & Vincent, 2008). In addition, increased CRP concentrations further activate neutrophils and monocytes, in turn promoting the secretion of IL-6, IL-1b, and Tumour Necrosis Factor-alpha (TNF-α) (Black et al., 2004; Du Clos & Mold, 2004). Both biomarkers are known to play an important role during inflammation as they contribute to somatic maintenance (the organism's investment in the integrity and functionality of the body) (Del Giudice & Gangestad, 2018) and help in wound healing, tissue repair, and clearance of damaged cells (McDade, 2003).

Researchers began to investigate the roles of inflammation in the development of stress-related mental health problems due to its close relationship with the two physiological pathways: the SNS and the HPA axis (Slavich & Irwin, 2014). The SNS allows the release of norepinephrine, which down-regulates the transcription of antiviral type I interferon (IFN) genes in Type 1 T helper (Th1) lymphocytes, as well as stimulates the expression of the genes of IL-1, IL-6 in Type 2 T helper (Th2) cells and TNF-α in macrophages and mast cells (Coico & Sunshinem 2015). At the same time, following activation of the HPA axis, the cortisol exerts anti-inflammatory and immunosuppressive effects by inducing apoptosis of Th1 lymphocytes and neutrophils, and repressing the transcription of pro-inflammatory genes (i.e., negatively regulating mRNA stability of IL-1β, macrophage inflammatory protein-2 and IFN-γ) through signal transduction by GRs (Cruz-Topete & Cidlowski, 2015). The cortisol causes selective suppression of the pro-inflammatory Th1-cellular immunity axis and a shift toward Th2-mediated humoral immunity through which mainly anti-inflammatory cytokines secrete (i.e., IL-10 and IL-4; Elenkov, 2004). Insufficient secretion of cortisol is likely to cause the imbalance of Th1/Th2 with Th1 predominant and chronic inflammation (Elenkov & Chrousos, 2006). However, excessive secretion of cortisol can also result in elevated inflammation as impaired or dysfunctional GRs lead to the inability of cortisol to exert its anti-inflammatory effects on target immune cells - what has been called "glucocorticoid resistance" (McEwen & Seeman, 1999; McEwen, 2005, 2007). Glucocorticoid resistance allows for the increasing levels of inflammatory cytokines to occur with high levels of cortisol (Slavich & Irwin, 2014). It happens both after acute stress and during chronic stress. When the acute stressor diminishes, glucocorticoid resistance allows the body

to elevate systemic inflammation to accelerate wound healing caused by possible injury caused by the acute stressor while cortisol has not retreated to normal levels (Slavich & Irwin, 2014). Under the conditions of frequent or prolonged stressors, hyperactivation of HPA axis leads to glucocorticoid resistance due to impaired GRs function, resulting in heightened inflammation and persistent alterations in neurotransmitter function, thereby potentially increasing the risk of neuropsychiatric dysfunction, such as mood disorders (Cohen et al., 2012; Felger & Lotrich, 2013; Heim et al., 2008; Leonard & Myint, 2009; Slavich et al., 2010). On the other hand, inflammation can also influence the HPA axis activity. The excessive release of inflammatory cytokines such as IL-1, IL-2, IL-6, IL-11, and TNF-α can stimulate HPA axis activations at all levels (CRH, adrenocorticotropic hormone and cortisol; Besedovsky & del Rey, 2000; Chesnokova & Melmed, 2002; Humphreys et al., 2006) to prevent the body from long-lasting systemic inflammation. Some cytokines such as IL-1 and TNF-α are thought to influence the glucocorticoid negative feedback system and cause resistance to cortisol (Beishuizen & Thijs, 2003). Therefore, the HPA axis and immune systems work closely together and interact dynamically as well.

2.4 Cortisol and emotional or behavioural problems

As a key product of the HPA axis activation, cortisol is the most frequently studied biomarker in stress-related psychological research. As already discussed, prolonged, excessive, or insufficient activation of the HPA axis can lead to changes in the brain and result in the development of mental disorders (i.e., major depressive illness and anxiety disorders; McEwen, 2004). Flatter diurnal cortisol slopes have also been proposed as mediators between chronic psychosocial stress and poor mental and health outcomes in extant research (Adam et al., 2017; Davis & Sandman, 2010; Doane et al., 2013).

As outlined above, over-secreted cortisol exerts its effects on mental ill-health by the disrupted expression of genes encoding GR and MR in the brain (Anacker et al., 2013; Baes et al., 2014). In animal experiments, GR gene knockout mice showed increased anxiety behaviours (Boyle et al., 2006). Affinities of GRs were consistently lower in all tissues of chronically stressed fish compared to tissues from controls (Maule & Schreck, 1991). Regarding studies with human subjects, decreased levels of

GR mRNA had been found in the hippocampus of suicide victims with a history of childhood maltreatment, indicating impaired GR function (McGowan et al., 2009). Exposure to accumulating environmental stress in interaction with particular GR gene polymorphisms has been shown to lead to mental disorders (Bet et al., 2009; Curley et al., 2011; Laucht et al., 2013; Tyrka et al., 2012; Turecki & Meaney, 2016), while the genetic variants enhancing MR activity may confer resilience to traumatic stress and subsequent depression (ter Heegde, Rijk, & Vinkers, 2015; Klok et al., 2011). Transgenic mice with MR overexpressing in the forebrain exhibit reduced anxiety (Lai et al., 2007). Post-mortem analysis of brains of patients with major depressive disorder showed a decrease in MR mRNA expression in the hippocampus (Medina et al., 2013). It was suggested that reduced MR activity and emotional problems might be linked via increased negative memory bias and further pessimistic assessment of a stressful situation (Vogel et al., 2014). In addition, the activity of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) is essential for the balance of MRs and GRs expression. 11β-HSD type-2 (11β-HSD2) converts cortisol to the inactivated form, cortisone, to protect MRs from inappropriate occupation by cortisol (Edwards et al., 1988). Decreased 11β-HSD2 activity, which was found in patients with major depression (Poór et al., 2004), has been shown to reduce hippocampal GR expression (Levitt et al., 1996), leading to a reduced cortisol negative feedback and an overactive HPA axis (Cottrell & Seckll, 2009).

Empirical findings on the relationship between cortisol measures (i.e., slope of the peak-to-trough decline, peak cortisol level, baseline/morning cortisol level, evening cortisol levels) and different emotional or behavioural problems are mixed and complex. ADHD symptom severity is mostly associated with reduced baseline cortisol and blunted cortisol stress response in clinical samples (Angeli et al., 2018; Blomqvist et al., 2007; Isaksson et al., 2012; Maldonado et al., 2009; Northover et al., 2016; Pauli-Pott et al., 2017). The relationship between hyperactivity/inattention symptoms and cortisol in community samples is less clear. There is evidence of negative associations (Scerbo & Kolko, 1994; Susman et al., 2007), but a few studies also found positive associations between ADHD symptoms and cortisol (i.e., higher levels of morning cortisol and higher evening cortisol) in population-based samples (Hatzinger et al., 2007; Sondeijker et al., 2007) or comparable cortisol levels in children with and without hyperactivity/inattention symptoms (Freitag et al., 2009;

Klimes-Dougan et al., 2001; Pesonen et al., 2011; Saridjan et al., 2014). For conduct problems, increasing evidence indicates that low daily cortisol levels were associated with persistent and severe conduct problems in childhood or adolescence, especially for conduct problems accompanied by callous-unemotional traits (Loney et al., 2006; Ouellet-Morin et al., 2011; Pajer et al., 2001). In experimental research on cortisol reactivity to social stressors, Northover and colleagues found (2016) that conduct problems are correlated with increased baseline cortisol, while O'Leary and colleagues (2007) found lower baseline levels. Overall, there are few studies on the association between conduct problems and cortisol.

The findings with respect to emotional problems are also inconsistent. For depression, some showed null associations with cortisol measures (Stetler et al., 2004; Strickland et al., 2002), and some suggested that elevated morning cortisol or higher CAR was associated with severe depressive symptoms (Knorr et al., 2010; Owens et al., 2014; Vrshek-Schallhorn et al., 2013; Zorn et al., 2017). It is estimated that 20% to 80% of individuals with Major Depression Disorder (MDD) exhibit some form of HPA hyperactivation (Thase et al., 2002), while literature suggests that the degree of HPA hyperactivity varies considerably between individuals, depending on the intensity, onset, and episode frequency of MDD (Cowen, 2002; Hardeveld et al., 2014; Mangold et al., 2011; Stetler & Miller, 2011). In addition, according to a recent meta-analysis (Zorn et al., 2017), there are also sex-dependent changes in stress reactivity in MDD: women with current MDD exhibited a blunted cortisol stress response, whereas men with current MDD showed an increased cortisol response to psychosocial stress. In individuals with remitted MDD, altered cortisol stress reactivity was less pronounced in women and was absent in men. Moreover, patients with different subtypes of depression may show different HPA axis functions. Compared to individuals with melancholic depression, individuals with atypical depression, for example, have higher comorbidity of anxiety disorders, exhibit more risk of suicidal behaviour, interpersonal sensitivity, affective instability, and report earlier onset of the symptoms (Singh & Williams, 2006). There are studies suggesting that HPA axis hyperactivity (higher saliva cortisol awakening curves) can only be found in patients with melancholic depression, not atypical depression (Juruena et al., 2018; Lamers et al., 2013). Regarding anxiety disorders, there have been links to both lower hourly-assessed night-time plasma cortisol levels, lower morning cortisol and

CAR (Hek et al., 2013; O'Donovan et al., 2010), and higher levels of diurnal salivary cortisol and peak cortisol (Feder et al., 2004; Mantella et al., 2008). Discrepancies in diurnal cortisol patterns in anxiety may underlie variations in severity, type (state or trait, persistent or concurrent) of anxiety, and demographic characteristics (e.g., sex, age) of samples (Greaves-Lord et al., 2007; Kallen et al., 2008). It is also possible that some of the unexpected or null findings may be due to the fact in at least some patients with depression or anxiety hypercortisolism may have been in the process of developing hypocortisolism, as discussed.

2.5 Inflammation and emotional or behavioural problems

A growing number of studies have suggested an aetiological role of inflammation and the HPA axis dysfunction in mental disorders (Liukkonen et al., 2011; Miller & Blackwell, 2006). Prompted initially by the work of Smith (1991) and Maes (1995), research in clinical and general population samples suggests that the concentration of inflammatory markers such as CRP, IL-6 and TNF-α are elevated in patients with depression, suggesting immune dysregulation (Danese & Baldwin, 2017; Howren, Lamkin & Suls, 2009; Liukkonen et al., 2011; Milaneschi et al., 2021; Miller & Blackwell, 2006; Raison et al., 2006). Antidepressants have been shown to decrease inflammation (Leonard, 2001) and the administration of inflammatory cytokines has been shown to induce depressive symptoms in about half of cancer patients (Musselman et al., 2001). Randomised controlled trials found that anti-inflammatory drugs were beneficial for depressed patients who showed evidence of inflammation (Raison et al., 2013; Kappelmann et al., 2018). In a recent systematic review of 30 studies, about a quarter of patients with depression exhibited low-grade inflammation, indicated by CRP > 3mg/L, and 58% of patients showed elevated CRP (> 1mg/L) levels (Osimo et al., 2019). However, Baune and colleagues (2012) suggested that IL-6 might only be a marker of current symptoms of depression because they did not find a predictive effect of IL-6 at baseline on depressive or anxiety symptoms at follow-up. Nevertheless, other studies found that higher IL-6 levels are associated with subsequent persistent depressive symptoms longitudinally in adolescence (Khandaker et al., 2018) and adulthood (Lee, 2020). Furthermore, some studies found that patients with atypical depression, not melancholic depression, exhibit inflammatory metabolic dysregulation (higher levels of CRP, IL-6 and TNF-α)

(Lamers et al., 2013; Rudolf et al., 2014); however, other studies reported higher IL-6 levels in melancholic cases versus healthy controls, but no difference of IL-6 between patients with atypical depression and controls (Dunjic-Kostic et al., 2013).

Whilst perhaps most prominently researched in association with depressive disorders, inflammatory biomarkers have also been explored in a broad range of disorders, though the results are inconsistent. A number of researchers have reported inflammation in patients with Generalised Anxiety Disorder (GAD) compared with controls (Costello et al., 2019; Renna et al., 2018) or associations of inflammation markers with anxiety symptoms in the general population (Khandaker et al., 2016; Pitsavos et al., 2006). However, there are also several studies showing no associations between inflammatory markers and anxiety symptoms or disorders (Milaneschi et al., 2021; Niles et al., 2018). For example, in a large cohort study, only elevated levels of CRP were found to be associated with current anxiety disorder in men, not IL-6 or TNF-α, and no associations were found in women (Vogelzangs et al., 2013).

In addition to emotional problems, a small but growing number of studies examined the link between inflammation and behavioural problems, such as hyperactivity and conduct problems. Studies on patients with ADHD have largely supported the involvement of autoimmune systems in ADHD and demonstrated that patients had increased inflammatory markers such as CRP, IL-6 and IL-10 (Anand et al., 2017; Chang et al., 2020; Darwish et al., 2019; Leffa, Torres, & Rohde, 2018). In community samples, low-grade persistent inflammation is also associated with an increased risk for attention problems two years later in early years children (O'Shea et al., 2014). Nevertheless, there are also studies documenting no difference in IL-1, IL-6, and IL-10 between adolescents with and without ADHD (Chang et al., 2021). With respect to conduct problems, there are only few studies, and those are highly heterogeneous in study designs and samples (Birmaher et al., 1994; Pajer et al., 2002). Moreover, both positive (Pajer et al., 2002; Slopen, et al., 2013) and null findings (Birmaher et al., 1994) have been reported. Notably, Odgers and colleagues (2007) found that adults with life-course-persistent conduct disorder show systemic inflammation, yet adults with adolescence-limited conduct disorder or without conduct disorder do not. More studies on the concurrent and longitudinal associations between inflammation and behavioural problems are needed.

2.6 Social cognition and cortisol or inflammation

As discussed in previous sections, individuals with social cognition difficulties are more likely to face communication problems in social situations. The communication problems may give rise to stress proliferation and lead to more serious stressors such as social rejection and discrimination (Pearlin et al., 1997). Accumulating evidence from both animal and human research has suggested that social stressors, such as being negatively evaluated by others, being rejected from social groups or racial discrimination, are especially potent activators of the stress response compared to non-social stressors (Dickerson et al., 2009; Kemeny, 2009; Kouzakova et al., 2010; Murphy et al., 2013). For example, Sapolsky and colleagues (1997) reported that socially subordinate and isolated wild baboons exhibited higher cortisol secretion. In humans, social stressors with uncontrollable and social-evaluative elements were associated with the greatest cortisol changes and the longest time of recovery (Dickerson & Kemeny, 2004). In a meta-analysis review including 72 articles, Stalder and colleagues (2014) reported that individuals in major stress exposed groups exhibited increased hair cortisol concentrations and that long-term cortisol hypersecretion emerged particularly in the context of ongoing stress. However, they did not find a significant correlation between perceived stress and hair cortisol.

The link between life stress and inflammation has also been widely documented. Adults with childhood trauma or maltreatment history have been found to exhibit increased inflammation and higher rates of depression (Baumeister et al., 2016; Danese et al., 2008; Fagundes & Way, 2014). As already discussed, the association between social stress and inflammation is to a large extent mediated by HPA axis dysregulation and glucocorticoid resistance. It is also possible that physical threats are more likely to occur in situations that involve social threats or rejection, which may trigger inflammatory activity to manage the possibility of injury. In addition, neural sensitivity to social rejection has been found to link with inflammatory responses to acute social stress (Slavich et al., 2010), hence overlapping neural circuitry underlying physical and social pain might also provide an explanation (Eisenberger et al., 2003).

Although much research has suggested that social stressors are potent activators of the HPA axis and inflammatory response, studies linking endocrine-

immune system activities directly with social cognition abilities are sparse and their findings are inconsistent (Heinrichs et al., 2003; Jung et al., 2015; Murphy et al., 2013; Slavich et al., 2010). There are studies reporting that better social cognition is associated with higher levels of cortisol at awakening, greater CAR, and flatter diurnal cortisol slope (Boyer & Nelson, 2015; Otto et al., 2018). A few studies also found a positive correlation between afternoon cortisol levels and higher scores of emotion recognition and ToM in adults, especially in males (Oberle, 2018; Zilioli et al., 2015). However, Ruiz-Robledillo and Moya-Albiol (2014) found that good emotion understanding, and regulation were associated with lower morning cortisol levels and a smaller CAR in caregivers of people with ASD. Similarly, Tout and colleagues (1998) reported that higher social competence scores were related to lower morning cortisol levels in preschool girls during the study period. In addition, a small number of studies indicated a non-significant correlation between various social cognition abilities and fixed-time cortisol levels or diurnal cortisol secretion (Doane et al., 2011; Locke et al., 2009; Smeets et al., 2009; Wilbraham et al., 2018).

Regarding the association between social cognition and inflammation, most existing studies are experimental design, investigating if acute experimental inflammation (triggered by the administration of endotoxin or attenuated vaccine) can lead to negative biases in social cognitive processing (Bollen et al., 2017; Moieni et al., 2015). For example, Moieni and colleagues (2015) found that acute inflammation (induced by endotoxin) led to decreases in emotion recognition and understanding ability. There are also a few observational studies reporting the association between social cognition deficits and neuro-inflammation (elevated TNF-α, IFN-γ, IL-6, and IL-12), but most of them have focused on patients with ASD (Ashwood et al., 2011; Rossignol & Frye, 2012) or schizophrenia (Green et al., 2019; Michel et al., 2012), leaving unanswered the question as to whether the same observations hold for the general population. Thus, more non-clinical-based research examining the role of social cognition deficits in the endocrine-immune system is in order.

2.7 Summary of the existing literature

This chapter critically reviewed the literature on the nature of social cognition by introducing several theoretical models and presenting findings from empirical

research. It seems that most researchers defined social cognition based on the SIP model, referring to the cognitive processes that underlie social interactions, such as perceiving, distinguishing, understanding, and responding to social cues. Others tended to divide social cognition according to the categories of social cues, such as intentions, emotions and behaviours, and the corresponding neural networks: mentalising, empathy and mirroring networks. However, most empirical studies only included limited aspects of social cognition. The number (and type) of aspects highly depend on the purposes, hypotheses, and available datasets of each study.

Then the theories underlying the link between social cognition difficulties and mental health problems were reviewed. For example, under the SSDV model, children with social-cognitive difficulties are more likely to experience both chronic and acute stressors in their lives, and less able to secure the social support necessary for dealing with the resulting stress, leading to a greater vulnerability to developing psychological distress and mental disorders. However, to the best of my knowledge, all studies on this to-date used psychological instruments or survey questions to assess stressors and stress, not biological markers. As cortisol has long been related to the stress response, its absence from the extant research on this is notable. In addition, cortisol-regulated inflammation has been found to play a role in the pathogenesis and expression of a variety of mental disorders, especially emotional problems. Therefore, this thesis focuses on cortisol and inflammation to indicate individuals' stress levels and investigates their roles in the interplay of social-cognitive difficulties and the development of emotional or behavioural problems in children and adolescents.

Next, a brief introduction of cortisol and inflammation was presented, followed by a review of their biological mechanisms and empirical evidence for their associations with emotional or behavioural problems. Most empirical studies focused on either cortisol or inflammation in exploring relationships with emotional or behavioural problems. For instance, adolescents with conduct problems were found to exhibit lower basal cortisol levels (Figueiredo et al., 2020; McBurnett et al., 2000) and higher levels of inflammatory markers (Odgers et al., 2007; O'Shea et al., 2014) than other adolescents, implying the possibility of insufficient anti-inflammatory effects of cortisol due to reduced secretion. However, in patients with depression or anxiety disorders, both cortisol and inflammatory markers were reported at high levels, suggesting the possibility of impaired immune system's sensitivity to cortisol

signals (i.e., glucocorticoid resistance) in these patients (Checkley, 1996; Feder et al., 2004; Mannie et al., 2007; Vreeburg et al., 2010; Osimo et al., 2019; Pariante & Miller, 2001). In addition, there are also studies that found normal levels of cortisol and inflammatory markers in individuals with emotional or behavioural problems (Birmaher et al., 1994; Klimes-Dougan et al., 2001; Milaneschi et al., 2021). Hence, it is possible that some mental health problems may be related to the dysregulation of either the HPA axis or the immune system, rather than being dysregulated simultaneously. For example, some scholars suggested that atypical depression (including symptoms of increased appetite, fatigue, reactive moods, and sensitivity to rejection) was characterised by increased levels of inflammatory markers and normal HPA axis function, while melancholic features of depression (e.g., a loss of appetite and responsiveness to environments) were linked with HPA hyperactivity, but no sign of inflammation (Kaestner et al., 2005; Lamers et al., 2013). To elucidate if HPA axis and inflammation play interactive or independent roles underlying the development of mental health problems, it is necessary to consider both cortisol and inflammatory markers.

In addition, most empirical studies used clinical samples. The number of studies using community samples is relatively small and the results are extremely mixed, especially for the associations between cortisol or inflammation and behavioural problems. Taking the studies on hyperactivity/inattention as an example, some general population studies reported no association of basal cortisol levels with hyperactivity/inattention symptoms (Freitag et al., 2009; Pesonen et al., 2011), some reported negative associations (Scerbo & Kolko, 1994; Susman et al., 2007), and a few reported positive associations (Hatzinger et al., 2007; Sondeijker et al., 2007). Several reasons may account for the mixed findings, including differences in study design (i.e., cross-sectional vs. longitudinal), heterogeneity of cortisol and inflammation measures, and differences in demographic characteristics of the sample, as well in the type, duration of onset and severity of the mental health problems. Therefore, it is important to use a robust study design, relatively large sample size, and accurate biological measures to investigate the association between cortisol or inflammation with emotional or behavioural problems in the general child population.

With regard to the association between social cognition and cortisol and inflammation, results are also far less clear. The literature on social cognition and

inflammation in the general population is extremely limited. Studies on social cognition and cortisol are also scarce and the findings are very mixed. There are several reasons accounting for the mixed results: first, different studies focused on different aspects of social cognition and even for the same aspect they used different measures; second, the measurement of cortisol was not consistent and different cortisol parameters may represent fundamentally different functions; third, age and size of the samples varied greatly. In addition, little research measured the longitudinal association between social cognition and cortisol.

To sum up, due to the limited and mixed evidence, it remains unclear if social cognition difficulties in childhood are longitudinally related to cortisol or inflammatory dysregulation, to what extent cortisol or inflammatory dysregulation plays a role in the pathogenesis and aetiology of subsequent mental health problems in adolescence, how this may differ between different types of symptoms, and how cortisol and inflammation may compound effects given their complex interactions. This thesis goes into more detail on these issues, focusing on the longitudinal influence of difficulties in core aspects of social cognition (emotion recognition and ToM) in childhood, and testing the assumption that cortisol and inflammatory markers play mediating roles in the interplay of social cognition deficits and various emotional and behavioural problems in a general youth population sample. Moreover, it takes the interaction of inflammation and cortisol into consideration. The specific aims and hypotheses are presented in the next section.

2.8 Project aims and hypotheses

In this project I aimed to explore the associations of cortisol and inflammation with emotional (emotion and peer problems) and behavioural (hyperactivity/inattention and conduct problems) problems in a general child population, and to test if inflammation, cortisol, or their interplay, explain all or part of the longitudinal link between poor social cognitive abilities and emotional or behavioural problems. A conceptual model is presented below (Figure 2-5).

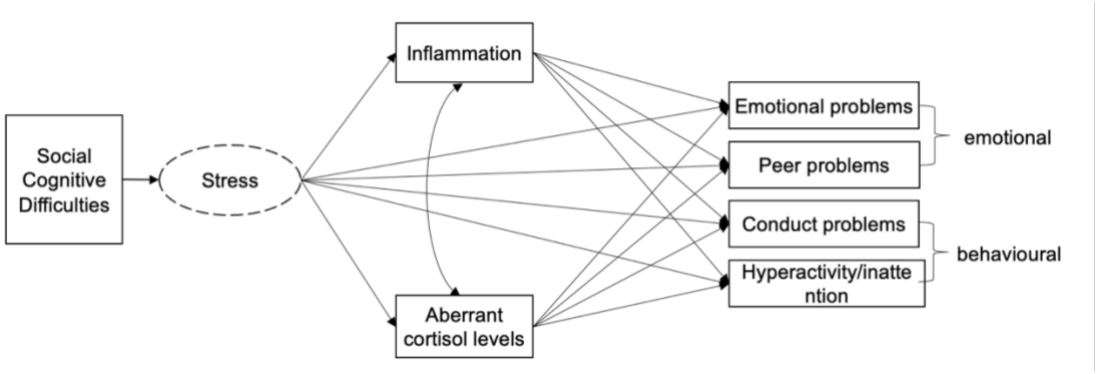

Figure 2-5 Conceptual links between social cognition, cortisol, inflammatory markers, and mental health problems

First, I attempted to systematically identify and evaluate the current literature on social cognition and cortisol due to its complex and mixed results (Chapter 3). Through a systematic review and meta-analysis, I aimed to examine the association between various aspects of social cognition and basal cortisol in the general population. The second aim of that review was to investigate the factors/moderators that may affect the association.

Second, I attempted to investigate the association of inflammation and cortisol with emotional or behavioural problems (Chapter 5). I aimed to test if inflammatory markers, cortisol, or both, can predict later emotional or behavioural problems (age 17 years) with the adjustment of the mental health problems in early years (age 4 years). In line with prior literature, the hypotheses were that 1) emotional problems would be associated with higher basal cortisol levels and flatter diurnal slope, while behavioural problems would be associated with lower basal cortisol levels and flatter diurnal slope; 2) both emotional and behavioural problems would be associated with higher levels of inflammatory markers; and 3) the associations would survive from the adjustment of emotional/behavioural problems in childhood.

Third, I attempted to dig more into the predictive effect of chronic mental health problems for cortisol, especially focusing on hyperactivity/inattention symptoms, given this was a gap in the literature (Chapter 6). The aim of that study was to explore the role of chronicity and severity of hyperactivity/inattention symptoms across childhood on diurnal cortisol levels in adolescence. The hypothesis was that persistently high levels of such symptoms across childhood and adolescence

would predict lower CAR, lower morning cortisol, and lower total daily output as well as flatter diurnal cortisol slope.

Last, I focused on social cognition abilities in childhood and adolescence (Chapter 7). That study aimed to investigate if 1) social cognitive difficulties in childhood could predict emotional or behavioural problems in late adolescence; 2) the inflammatory markers, cortisol measures or both, could explain all or part of the longitudinal relationship between social cognitive difficulties and emotional or behavioural problems. Based on prior literature, the corresponding hypotheses were 1) social cognitive difficulties in childhood would predict emotional or behavioural problems in late adolescence; 2) cortisol and inflammatory markers, would mediate the longitudinal relationship between social cognitive difficulties and behavioural and emotional problems. However, based on the findings from the earlier empirical work in this thesis, I expected that in my sample only cortisol would mediate the longitudinal relationship between social cognitive difficulties and behavioural problems and neither cortisol measures nor inflammatory markers would mediate the relationship between social cognitive difficulties and emotional problems.

2.9 Chapter summary and next step

This chapter reviewed the existing literature on social cognition, inflammation, HPA axis function and cortisol, emotional and behavioural problems, and their associations between each other, focusing on the gaps that this thesis addressed. This chapter also presented the main aims and hypotheses for the studies of this project. Compared with the evidence for the link between social cognition and physiological stress, the evidence for a link between physiological stress and mental health problems is more comprehensive. Indeed, there are already some systematic reviews on the topic (Adam et al., 2017; Chang et al., 2021; Osimo et al., 2019). Therefore, the following chapter will focus on the link between social cognition and cortisol, evaluating the associations between three main aspects of social cognition - emotion recognition, empathy, and emotion regulation, and basal cortisol levels, by conducting a systematic review and meta-analysis. There are very few studies on the association between social cognition and inflammation and so an analogous systematic review on this could not be performed (Higgins et al., 2022).

Chapter 3: Social cognition and cortisol in the general population: A systematic review and meta-analysis

This chapter is based on a published paper as Ji, D., Flouri, E., & Papachristou, E. (2021). Social cognition and cortisol in the general population: A systematic review and meta-analysis. *Stress and Health, 37*(3), 415-430. https://doi.org/10.1002/smi.3013 To acknowledge the contributions of co-authors, "we" will be used instead of "I" in this chapter. Since, as discussed in the previous chapter, the evidence for the association between social cognition and inflammation is insufficient to provide reliable results for a systematic review, this chapters presents a review of the association between social cognition and cortisol.

3.1 Introduction

As reviewed in Chapter 2, findings from studies examining the association between social cognition and basal cortisol in the general population are inconsistent. Some studies found negative correlations between social cognition and cortisol at awakening (Ruiz-Robledillo & Moya-Albiol, 2014), some reported no such association (Katz et al., 2018), while others found that better social cognitive ability is associated with higher levels of cortisol at awakening, greater CAR, and flatter diurnal cortisol slope (Boyer & Nelson, 2015; Otto et al., 2018). Therefore, this chapter uses systematic review and meta-analysis to examine this association. There are multiple factors that may moderate the association between social cognition and cortisol levels. First, social cognition is a multifaceted construct and not all its facets are supported by the same neural networks (Kennedy & Adolphs, 2012). Thus, difficulties in specific social cognition domains could have impacts on cortisol secretion. For example, Bechtoldt and Schneider (2016) found a positive association of poor emotion recognition with cortisol reaction to social stressors, while for emotion management there was no association. Second, the timing of the saliva or blood sample collections may also be a moderator. For example, children with ASD, who generally exhibit social cognition deficits, show higher morning cortisol levels than typically developing children, but similar afternoon cortisol levels (Kidd et al., 2012). Another moderator can be the statistical treatment of cortisol concentration levels. In general population samples, endocrine time series are positively skewed, hence cortisol data should be transformed prior to being analysed using parametric

tests (Miller & Plessow, 2013). However, not all studies have taken this into account. Additional sources of heterogeneity in the findings may include study design (cross-sectional vs. longitudinal), age and sex of the participants, whether the participants had experienced childhood maltreatment, and fasting preceding sample collection (whether the participants were instructed to avoid food and drink intake at least one hour prior to the sample collection in studies analysing blood or saliva). All mentioned factors were considered as potential moderators in this meta-analysis.

An important caveat is that, although social cognition is multifaceted, most studies have focused on emotion recognition, empathy, and emotion control. Therefore, this systematic review and meta-analysis focused on associations between these three core social cognition abilities and basal cortisol levels. Specifically, emotion recognition is defined as the ability to recognise basic emotions in facial expressions. Empathy refers to the ability to understand others' perspectives and mental states (cognitive empathy, also known as mentalizing) and to feel others' emotional states (affective empathy; Birnie et al., 2010). Emotion control concerns the ability to cognitively regulate the intensity, time-course, and valence of emotional experiences. This meta-analysis further investigated if the relationships between social cognition and cortisol are moderated by the following factors: timing of blood or saliva sample collection, treatment of the distribution of cortisol levels, study design (cross-sectional or longitudinal), age, sex, experience of childhood maltreatment, and fasting (whether participants were instructed to avoid food and drink intake at least one hour prior to the sample collection). The type (cognitive or affective) of empathy was also included as a potential moderator because the two components of empathy, though overlapping, engage mostly distinct neural networks (Mehta et al., 2014; Yu & Chou, 2018). For studies that were not amenable to meta-analysis (i.e., if too few), a narrative review of their findings was conducted to synthesize the current state of knowledge.

3.2 Methods

The meta-analytic process was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P; Moher

et al., 2015). The protocol for this review was registered with PROSPERO: International prospective register of systematic reviews CRD42019132363.

3.2.1 Study selection and inclusion criteria

3.2.1.1 Literature search

Terminology was not consistent across studies. For instance, affective Theory of Mind, emotion contagion, emotional mirroring, emotion understanding, and emotional resonance all appear to refer to remarkably similar processes (Happé, et al., 2017). Thus, broad searching terms (e.g., *emot** or *affective*) were used. A systematic database search was conducted on EMBASE, PsycARTICLES, PsychINFO, PubMed, ScienceDirect and Web of Science with the following terms in Title: (*affective* or *affiliation* or *appraisal** or *belief** or *cue(s)* or *communication* or *egocentri** or *empathy* or *emot** or *face** or *facial** or *mirror system* or *mirror neuron* or *mood* or *non-verbal** or *perception** or *reciprocity* or *recognition** or *regulat** or *role-taking* or *social cognition* or *socio-cognitive** or *social-affective** or *social skills* or *social competence* or *stereotyp** or *theory of mind* or *ToM* or *mental** or *expressive suppression* or *attribution bias* or *reciprocity*), combined with the following searching terms in Title, Abstract and Keywords (*hypothalamic-pituitary-adrenocortical* or *HPA* or *cortisol* or *glucocorticoid(s)* or *steroid(s)*), using the Boolean operator "and". The search was restricted to articles written in English. The wildcard asterisk allowed for the inclusion of different word endings. Only papers published in peer-reviewed journals between January 1980 and March 2019 and providing sufficient statistical information to be quantitatively compared to each other were included. The corresponding authors of all relevant studies that did not provide the statistical information needed for analyses were emailed with a request to share it. Of the 45 authors contacted (one had co-authored two articles), nine responded. A summary of the selection and exclusion criteria at each phase of screening is illustrated in the PRISMA flow diagram (Figure 3-1).

3.2.1.2 Exclusion criteria

This meta-analysis focuses on the relationship between core social cognition abilities and naturally occurring cortisol concentration, assayed from either cerebral spinal fluid, urine, blood, saliva, or hair, in general population samples. Studies were excluded based on the following criteria (Figure 3-1): 1) studies on animals; 2) reviews and not original research articles; 3) studies based on small samples (N < 10) or case studies; 4) studies on patients with endocrine disorders and/or receiving hormonal treatment; 5) studies that included samples of patients with diagnosed mental disorders; 6) studies on infants and children younger than 3 years of age; and 7) studies measuring anticipatory cortisol response to acute laboratory-based or real-life stressors.

3.2.1.3 Selected studies

The 24 studies selected for this review used various cortisol measures. Consistent with the findings from a previous meta-analysis of studies on the link between chronic stressors and HPA functions (Miller et al., 2007), most studies (n = 19) assessed cortisol concentrations at certain time points (morning or afternoon cortisol) and were included in the meta-analysis (Table 3-2). As too few studies assessed diurnal cortisol rhythm (CAR, n = 2; diurnal cortisol slope, n = 2; both, n =1), these were synthesized narratively. Only two studies explored the relationships between social cognition and hair cortisol (Kao et al., 2019; Villanueva et al., 2017), and these are also reviewed in the section 3.3.2.

3.2.2 Calculation of effect sizes

Pearson's r correlation coefficient was chosen as an indicator of effect size because it was reported in all 19 studies included in this meta-analysis. Because in some studies the variables we were interested in were reverse coded, we recoded where appropriate so that positive correlations here reflect associations between better social cognition ability and greater cortisol concentration. The guidelines regarding the calculation of effect sizes are outlined in the Table 3-1.

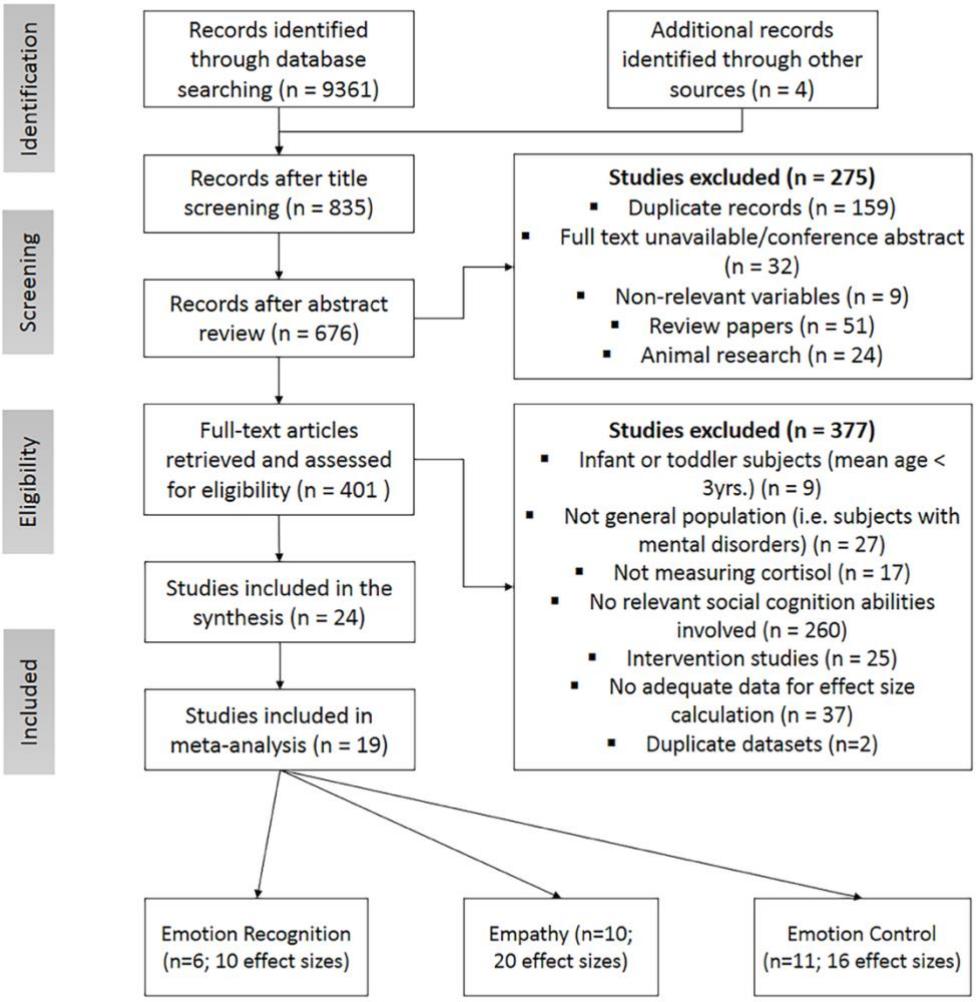

Figure 3-1 PRISMA flow diagram

Table 3-1

Guidelines for the calculation of effect sizes.

Study description	**Decision**
Longitudinal studies in which only cross-sectional baseline data were relevant	Studies were coded as cross-sectional
Experimental studies in which only cross-sectional baseline data were relevant	Studies were coded as cross-sectional

Studies that measured multiple domains of social cognition in the same sample	Effects sizes for each core social cognition domain were extracted as independent effect sizes; effect sizes for each sub-domain of core social cognition were combined as one effect size in the main analysis but treated as independent effect sizes in subgroup analysis
Studies that calculated effect sizes for social cognition subscale scores and overall scale scores	Effect sizes for general social cognition were prioritized
Studies that calculated effect sizes for social cognition subscales	An average effect size was computed to represent the effect size for general social cognition
Studies that reported separate results for different populations (e.g., men vs. women), cortisol measured at different time points.	Effects sizes for each sample were combined as one effect size for each study, but extracted as independent effect sizes in subgroup analysis
Studies that measured cortisol at several time-points in the morning	Effect size for cortisol half an hour post awakening was prioritised

3.2.3 Coding strategy

After full-text review, studies were categorised according to three core social cognition abilities on the basis of the measures used: emotion recognition, empathy (cognitive and affective) and emotion control. Studies were coded for a range of characteristics based on a priori decisions about potential moderators. It was not possible to examine study design and maltreatment history as potential moderators because only one study used longitudinal data (Kliewer et al., 2016) and only one assessed maltreatment history (England-Mason et al., 2017). Of the potential moderators could be examined, two were dummy-coded (whether the cortisol data were transformed to correct skewed distributions, and whether participants were instructed to avoid food and drink intake at least one hour preceding sample collection). Sampling time and sex of the participants were contrast-coded, because none of the three groups (morning, early afternoon, and non-specific time; males, females, and both) could suitably serve as a reference category for the remaining ones. The average age of participants was coded into four categories: children (younger than 10 years), adolescents (from 10 to 18 years), young adults (from 18 to 30 years) and middle-aged and older adults (older than 30 years). If the average

participant age was not reported in the article, the median age was used when available. If that was not available either, the midpoint of the reported age range was used. For empathy specifically, type (cognitive or affective) was also explored as a potential moderator. In the studies we examined, false-belief tasks such as the unexpected-contents task (Perner, Leekam, & Wimmer, 1987) and the switched-location task (Wimmer & Perner, 1983) are widely used to test cognitive empathy. The Interpersonal Reactivity Index (IRI; Davis, 1983) is used to test both cognitive and affective empathy (Table 3-2).

3.2.4 Analytic strategy

Psychometric meta-analysis was employed to estimate pooled effect sizes across studies (Hunter & Schmidt, 2004). This is a random-effects model that accounts for dependence between effect sizes and generates more accurate confidence intervals (CIs) compared to the fixed-model approach (Schmidt, Oh, & Hayes, 2009). Following the suggestions of Schmidt and Hunter (2015), sampling bias was corrected by weighting effects by the size of the samples, and for measurement error (only for studies using scales or questionnaires to measure social cognition; for studies using experimental tasks (e.g., the Reading the Mind in the Eyes Test; Baron-Cohen et al., 2001) to measure it, we respected the values reported) by using the reliability coefficients of the measures. Both mean observed correlations ($\bar{r}$) and mean corrected correlations (ρ) were computed, as well as CIs around the mean corrected correlations. As suggested by Cohen (1988), ρ of less than 0.2 were interpreted as 'small', those larger than 0.37 as 'large', and those in between as 'moderate'. Forest plots were created to illustrate the corrected effect sizes for each study included in the meta-analysis, as well as the pooled effect size, with associated 95% CIs.

After calculating pooled effect sizes, the heterogeneity among individual effect sizes was assessed by means of Cochrane's Q and I^2 statistics. The Cochrane's Q is a measure of the weighted squared deviations of individual effect sizes from the overall mean effect size, indicating the total amount of observed variance (Lipsey & Wilson, 2001). I^2 represents the percentage of observed variation that is attributable to heterogeneity rather than within-study sampling error. I^2 values between 0.3 and 0.6 are considered to represent moderate heterogeneity, and 0.5-0.9 substantial

(O'Connor, Green, & Higgins, 2008). First, we examined whether there was significant heterogeneity between studies measuring each of the three core social cognition domains. Subgroup analysis was then performed to estimate the average effect size within each level of the moderating variable.

To test for publication bias, funnel plots of effect sizes against their standard errors were generated. Asymmetry in funnel plots is indicative of presence of publication bias (Sterne, Egger, & Moher, 2008). Egger's tests were used to formally test for the asymmetry of the funnel plot (Egger et al., 1997). We used the 'psychmeta' (Dahlke & Wiernik, 2018, version 2.2.0) package to conduct the analyses and 'forestplot' package (Gordon, 2016) to create forest plots in R (R core team, 2019, version 3.6.1).

3.3 Results

3.3.1 Quantitative synthesis: meta-analyses

The meta-analysis used 19 studies (Table 3-2) examining social cognition in relation to cortisol concentrations, reporting 46 effect sizes in total. In particular, there were 16 effect sizes (k = 11 studies) for emotion control, 20 (k = 10 studies) for empathy and 10 (k = 6 studies) for emotion recognition (total number of studies is not 27 as it may appear because studies are not mutually exclusive).

Table 3-2

Included studies and descriptive variables

Study	N	Males %	Average (median) age (years)	Collection time of cortisol samples	Fasting instructions	Social cognition domain	Measures
Bechtoldt et al. (2016)	166	100	College students	Afternoon	Yes	Emotion recognition, empathy and emotion control	Emotion recognition, understand and management subscales of MSCEIT V2.0
Brandtstädter et al. (1991)	767	50	45	Morning & afternoon	No	Emotion control	Emotion lability subscale of FPI
England-Mason et al. (2017)	118	0	32	Across the day	Yes	Emotion control	DERS; emotion suppress subscale of ERC

Fox et al. (2010)	104	100	22	Morning	No	Emotion control	Visual Probe tasks
Gonzalez-Liencreset al. (2016)	52	52	24	Afternoon	No	Empathy	Empathic concern and perspective taking subscales of IRI
Kliewer et al. (2016)	229	41	12	Across the day	Yes	Emotion control	ERC
Köther et al. (2018)	14	61	36	Afternoon	Yes	Emotion recognition	The emotion perception and confidence task adapted from RMET
Lane et al. (2013)	102	50	4	Across the day	No	Empathy	False-belief tasks
Locke et al. (2009)	291	51	8	Morning	Yes	Emotion control	Context inappropriate anger
Mikolajczak et al. (2007)	28	50	20	Afternoon	Yes	Emotion control Empathy	Self-control and emotional sensitivity subscales of TEIQ
Miller et al. (2017)	380	50	4	Morning	No	Emotion control	Negative liability subscales of ERC
Oberle (2018)	154	54	11	Afternoon	Yes	Empathy	Perspective taking subscale of IRI
Pascual-Sagastizabal et al. (2019)	159	50	8	Morning	No	Empathy	Empathy quotient-children version
Shields et al. (2016)	36	0	19	Afternoon	No	Emotion control	Emotional Stroop task
Smeets et al. (2009)	64	50	26	Morning	Yes	Emotion recognition and empathy	RMET; MASC
Tomova et al. (2014)	64	50	29	Afternoon	No	Emotion recognition; empathy	RMET; IRI; EC
Van Honk et al. (2000)	20	100	23	Afternoon	No	Emotion control	Emotion Stroop task
Wilbraham et al. (2018)	89	23	19	Afternoon	No	Emotion recognition, empathy and emotion control	Emotion recognition, understand and management subscales of SUEIT
Zilioli et al. (2015)	453	70	29	Afternoon	No	Emotion recognition, empathy	RMET; Empathic concern and perspective taking subscales of IRI

Note. Miller et al. (2017): the sampling time of cortisol was before breakfast, though no more information was provided. Measurements of social cognition: MSCEIT= Mayer–Salovey–Caruso Emotional Intelligence Test (Mayer et al., 2003); ERC = Emotion Regulation Checklist (Shields & Cicchetti, 1997); DERS = Difficulties in Emotion Regulation Scale (Gratz and Roemer, 2004); FPI = Freiburg Personality

Inventory (Fahrenbekc, Hampel, & Selg, 1973); MPQ = Tellegen's Multidimensional Personality Questionnaire (Tellegen, 1982); TEIQ = Trait EI Questionnaire (Petrides and Furnham, 2003); SUEIT = Swinburne University Emotional Intelligence Test (Palmer & Stough, 2001); RMET = Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001); IRI = Interpersonal Reactivity Index (Davis, 1983); EC = Emotion Contagion Scale (Doherty, 1997); MASC = Movie for the Assessment of Social Cognition (Dziobek et al., 2006); Emotion Stroop task in van Honk et al (2000) used pictures of Facial Affect and other comparable specially prepared facial stimuli from Ekman and Friesen's (1976); Visual Probe tasks in Fox et al. (2010) used pictures from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2005); False-belief tasks in Lane et al. (2013) are unexpected-contents task (Perner, Leekam, & Wimmer, 1987) and switched-location task (Wimmer & Perner, 1983).

3.3.1.1 Emotion control

There were 11 studies examining emotion control in relation to cortisol concentration (Bechtoldt & Schneider, 2016; Brandtstädter et al., 1991; England-Mason et al., 2017; Fox, Cahill, & Zougkou, 2010; Kliewer et al., 2016; Locke et al., 2009; Mikolajczak et al., 2007; Miller et al., 2017; Shields et al., 2016; van Honk et al., 2000; Wilbraham, Qualter, & Roy, 2018; Table 3-2). As shown in Figure 3-2, effect sizes for the association between emotion control and cortisol levels ranged from -0.070 to 0.270, with a weighted average effect size of r = 0.083, 95% CI (0.033, 0.132], suggesting that higher emotion control scores are significantly linked to higher cortisol levels. Homogeneity of findings between studies was confirmed, Cochrane Q (10) = 11.134, $p = 0.347$, $I^2 = 10.2\%$. Neither inspection of the funnel plots nor Egger's tests showed any evidence of publication bias [Egger's test: intercept = 0.320; 95% CI (-1.280, 1.920); t (10) = 0.45, $p = 0.662$; Figure 3-3).

Next, we examined the weighted average correlation separately for the different levels of potential moderators (Table 3-3). We observed a significant positive effect size in studies measuring cortisol in the morning (r = 0.085, 95% CI [0.006, 0.164]), but not in studies measuring cortisol at noon or in the afternoon (r = 0.025, 95% CI [-0.041, 0.092]). We also found a significant positive correlation between emotion control and cortisol levels in males (r = 0.086, 95% CI [0.007,

0.164]), but not in females (r = 0.070, 95% CI [-0.068, 0.209]). In terms of the studies using transformed cortisol data [of those that did, Wilbraham et al.'s (2018) used square-root-transformation while the others applied log-transformation], the average effect size was significant (r = 0.086, 95% CI [0.034, 0.137]). The association was not significant in the studies not using data transformation (r = 0.039, 95% CI [-0.451, 0.529]), and heterogeneity was noticeable (Q [4] = 3.817, p > 0.05, I^2 = 47.6%). For studies instructing participants to fast before sample collection, improved emotion control was significantly associated with higher cortisol levels, with trivial heterogeneity (r = 0.119, 95% CI [0.013, 0.224]; Q [4] = 4.896, p > 0.05, I^2 = 18.3%). However, for studies that did not report issuing fasting instructions preceding sample collection, the effect size was not significant (r = 0.061, 95% CI [-0.005, 0.127]). The weighted average correlation between emotion control and cortisol levels was 0.121 (95% CI [0.022, 0.220]) in children, 0.145 (95% CI [-0.753, 1.04]) in adolescents, 0.038 (95% CI [-0.074, 0.150]) in young adults and 0.052 (95% CI [0.003, 0.100]) in older adults. It must be noted however that only one and two studies, respectively, were included in the two subgroups showing significant results (i.e., children and older adults).

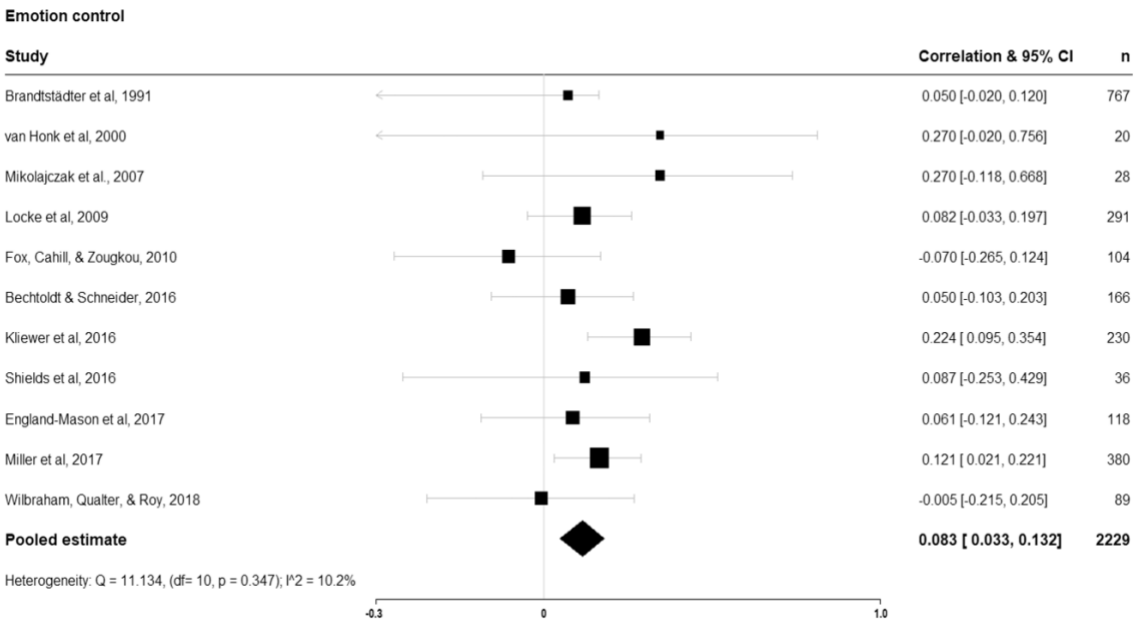

Figure 3-2 Forest plot of studies examining the relationship between emotion control and cortisol levels in general population samples

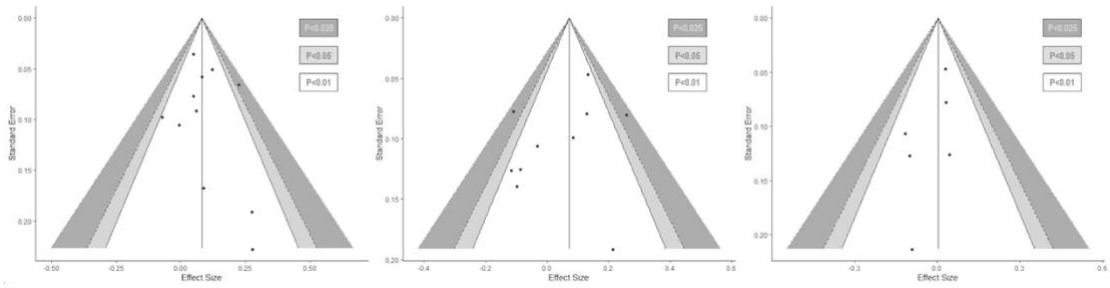

Figure 3-3 Funnel plots of studies for emotion control, empathy, and emotion recognition (respectively, from left to right)

Table 3-3

Meta-Analytic Results for the Relationship between Emotion Control and Cortisol Concentration

Characteristics	**k**	**N**	$\bar{r}$	**P**	**SDρ**	**SEρ**	**95%CI**	**heterogeneity**	
								Q^{α}	I^2(%)
Total set	11	2229	.075	.083*	.074	.023	(.033, .132)	11.13	10.2
Sampling time of cortisol									
Morning	4	1542	.085	.085*	.050	.025	(.006, .164)	2.859	0
(After)noon	6	1106	.023	.025	.063	.026	(-.041, .092)	3.580	0
Non-specific	2	348	.142	.169	.109	.077	(-.813, 1.15)	2.188	54.2
Sex									
Males	7	941	.081	.086*	.085	.032	(.007, .164)	5.766	0
Females	5	819	.061	.070	.111	.050	(-.068, .209)	8.132	50.8
Mixed	2	469	.088	.088	.064	.045	(-.486, .662)	0.965	0
Age									
Children	1	380	.110	.121*	-	.051	(.022, .220)	-	-
Adolescents	2	521	.129	.145	.100	.071	(-.753, 1.04)	2.674	62.6
Young adults	6	443	.033	.038	.107	.044	(-.074, .150)	4.124	0
Middle-aged & older adults	2	885	.050	.052*	.005	.004	(.003, .100)	0.013	0
Cortisol data transformed?									
No	3	152	.035	.039	.197	.114	(-.451, .529)	3.817	47.6
Yes	8	2077	.078	.086*	.062	.022	(.034, .137)	6.621	0
Fasting?									
No	6	1396	.058	.061	.063	.026	(-.005, .127)	4.564	0
Yes	5	833	.104	.119*	.085	.038	(.013, .224)	4.896	18.3

Note. k = number of correlations; n = combined sample size; *r* = mean uncorrected correlation; ρ = estimated true score correlation corrected for measurement error; SD_{ρ}

= observed standard deviation of corrected correlations; SE_ρ = Standard error of corrected correlations; 95%CI = 95% confidence interval for ρ; Q = Q-test statistic for test of heterogeneity in true score correlations. * ρ = significant effect sizes.

3.3.1.2 Empathy

Ten studies were found examining empathy in relation to cortisol concentration (Bechtoldt & Schneider, 2016; Gonzalez-Liencres, Breidenstein, Wolf, & Brüne, 2016; Lane et al., 2013; Mikolajczak et al., 2007; Oberle, 2018; Pascual-Sagastizabal et al., 2019; Smeets, Dziobek, & Wolf, 2009; Tomova, von Dawans, Heinrichs, Silani, & Lamm, 2014; Wilbraham et al., 2018; Zilioli, Ponzi, & Henry, 2015, Table 2). As shown in Figure 3-4, effect sizes for the association between empathy and cortisol levels ranged from -0.116 to 0.257, with a weighted average effect size of r = 0.072, 95% CI (-0.020, 0.165). The CI suggests that empathy scores are not significantly associated with cortisol levels, although substantial heterogeneity was detected (Cochrane Q [9] = 19.870, p = 0.019; I2 = 54.7%). However, the pooled effect sizes for all subgroups were not statistically significant (Table 3-4). Neither visual inspection of the funnel plots nor Egger's test showed any evidence of publication bias (intercept = -1.591; 95% CI [-4.362, 1.181], t [9] = -1.32, p = 0.222; Figure 3).

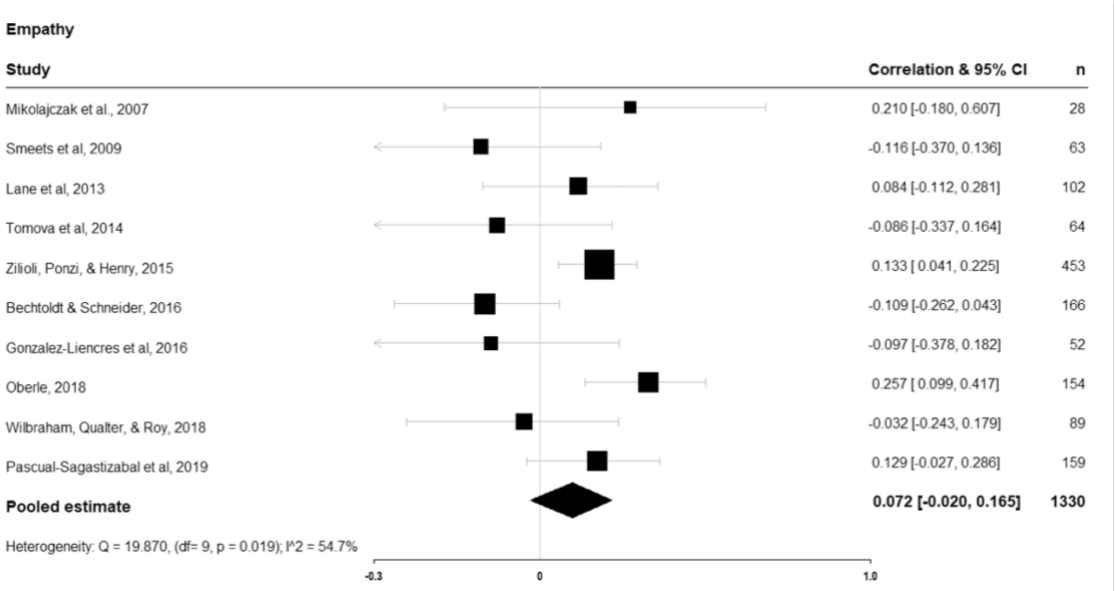

Figure 3-4 Forest plot of studies examining the relationship between empathy and cortisol levels in general population samples

Table 3-4

Meta-Analytic Results for the Relationships of Empathy and Cortisol Concentration

Characteristics	K	n	$\bar{r}$	ρ	SDρ	SEρ	95%CI
Total set	10	1330	.062	.072	.129	.041	(-.020, .165)
Sampling time of cortisol							
Morning	2	222	.055	.060	.157	.111	(-1.35, 1.47)
(After)noon	7	1006	.061	.074	.141	.053	(-.056, .204)
Non-specific	1	102	.084	.084	-	.099	(-.109, .278)
Sex							
Males	8	730	.067	.057	.140	.050	(-.060, .174)
Females	6	357	-.004	.006	.133	.054	(-.134, .146)
Mixed	2	243	.136	.152	.198	.140	(-1.63, 1.93)
Age							
Children	1	102	.084	.084	-	.099	(-.109, .278)
Adolescents	2	313	.178	.193	.091	.064	(-.625, 1.01)
Young adults	7	915	.020	.030	.126	.048	(-.087, .146)
Cortisol data transformed?							
No	5	309	-.012	-.011	.124	.056	(-.165, .143)
Yes	5	1021	.084	.098	.128	.057	(-.061, .256)
Fasting?							
No	6	919	.069	.083	.090	.037	(-.012, .177)
Yes	4	411	.047	.049	.208	.104	(-.283, .381)
Subtype of empathy							
Cognitive	3	229	-.013	.026	.089	.051	(-.194, .247)
Affective	6	569	-.012	-.013	.124	.051	(-.143, .117)
Both	3	659	.121	.144	.108	.062	(-.124, .412)

Note. k = number of correlations; n = combined sample size; *r* = mean uncorrected correlation; ρ = estimated true score correlation corrected for measurement error; SD_ρ = observed standard deviation of corrected correlations; SE_ρ = Standard error of corrected correlations; 95%CI = 95% confidence interval for ρ; Q = Q-test statistic for test of heterogeneity in true score correlations.

3.3.1.3 Emotion recognition

Six studies were found examining emotion recognition in relation to cortisol concentrations] (Bechtoldt & Schneider, 2016; Köther, Lincoin, & Moritz, 2018; Smeets et al., 2009; Tomova et al., 2014; Wilbraham et al., 2018; Zilioli, Ponzi, &

Henry, 2015, Table 2). As shown in Figure 3-5, effect sizes for the association between emotion recognition and cortisol levels ranged from -0.115 to 0.045. The weighted average effect size was not significant, r = 0.004, 95% CI (-0.061, 0.068). There was negligible heterogeneity, Q (5) = 2.673, p = 0.750, I^2 = 0%, indicating that effect sizes were consistent between studies, and subgroup analyses revealed no significant result for any of the subgroups (Table 3-5). Neither visual inspection of the funnel plots nor Egger's test showed any evidence of publication bias (intercept = -0.936; 95% CI [-2.522, 0.649]; t [5] = -1.64, p = 0.177; Figure 3-5).

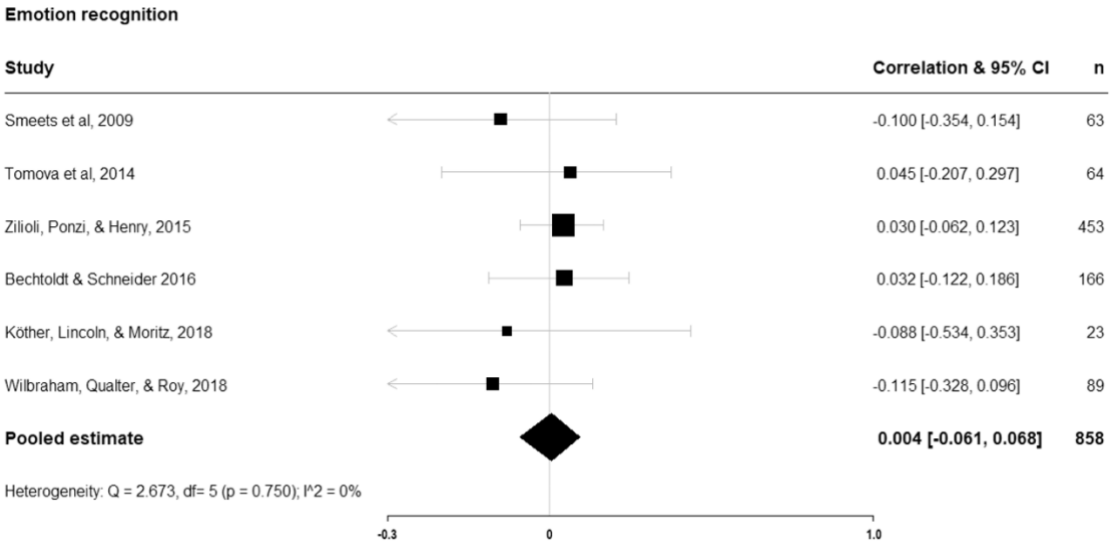

Figure 3-5 Forest plot of studies examining the relationship between emotion recognition and cortisol levels in general population samples

Table 3-5

Meta-Analytic Results for the Relationships of Emotion Recognition and Cortisol Concentration

Characteristics	k	n	$\bar{r}$	ρ	SDρ	SEρ	95%CI
Total set	6	858	.004	.004	.062	.025	(-.061, .068)
Sampling time of cortisol							
Morning	1	63	-.100	-.100	-	.126	(-.347, .146)
(After)noon	5	795	.012	.012	.055	.025	(-.057, .081)
Sex							
Males	5	559	.021	.021	.059	.026	(-.052, .094)

Females	4	210	.008	.008	.022	.022	(-.062, .077)
Mixed	1	89	-.116	-.116	-	.105	(-.322, .091)
Cortisol data transformed?							
No	3	150	-.035	-.037	.086	.050	(-.252, .178)
Yes	3	708	.012	.012	.060	.034	(-.135, .160)
Fasting?							
No	2	517	.032	.032	.007	.005	(-.029, .094)
Yes	4	341	-.039	-.039	.081	.040	(-.167, .089)

Note. k = number of correlations; n = combined sample size; *r* = mean uncorrected correlation; ρ = estimated true score correlation corrected for measurement error; SD_ρ = observed standard deviation of corrected correlations; SE_ρ = Standard error of corrected correlations; 95%CI = 95% confidence interval for ρ; Q = Q-test statistic for test of heterogeneity in true score correlations.

3.3.2 Narrative synthesis

3.3.2.1 Studies on diurnal cortisol rhythm

Five studies examined the relationships between social cognition and diurnal cortisol rhythm (CAR or diurnal cortisol slope) in the general population (Table 3-6). Four of them focused on emotion control (Katz et al., 2018; Locke et al., 2009; Miller et al., 2017; Otto, Sin, & Almeida, 2018), and one on empathy (Johnson et al., 2014). The results of these studies were inconsistent. Two studies found no association between emotion control and CAR (Miller et al., 2017) or diurnal cortisol slope (Katz et al., 2018). In the two studies with significant findings, poor emotion control was linked to lower CAR (Otto, Sin & Almeida, 2018) and a flatter diurnal slope (Locke et al, 2009). However, Otto, Sin and Almeida (2018) reported a notable, albeit non-significant, link between poor emotion control and steeper diurnal slope. The study on empathy suggested that greater CAR was related to affective empathy but not cognitive empathy (Johnson et al., 2014).

Table 3-6

Summary of Studies on Social Cognition and Diurnal Cortisol Rhythm

Study	Study design	Sample	Saliva cortisol sampling	Cortisol measure	Social cognition	Main findings

					domain (measures)	
Johnson et al., 2014	Cross-sectional	57 adults (Mage = 19, 56% males)	At awakening and 30 min after awakening for one day.	CAR	Empathy (IRI)	Better affective empathy was associated with greater CAR. Cognitive empathy was not associated with CAR.
Katz et al., 2018	Longitudinal	29 adults (Mage = 45, 17.2% males)	At awakening, 30 min after awakening, before lunch, and at bedtime for one day at each of three waves (in the October of year 1 and the March and October of year 2)	Morning cortisol; CAR	Emotion control (ERQ)	Emotional control was not associated with cortisol at awakening or CAR over the year.
Locke et al., 2009	Cross-sectional	292 children (M age = 8.3 years, 48% boys)	Within half an hour after awakening, at 4 p.m., and at bedtime for three days.	Morning cortisol; diurnal cortisol slope	Emotion control (Context inappropriate anger)	Poorer emotion control was associated with a lower morning cortisol and flatter diurnal cortisol slope. Sex-specific analysis showed this association was only significant in boys.
Miller et al., 2017	Cross-sectional	380 children (M age = 4.2, 50% boys)	At 1.5 hours after awakening, before lunch and in the afternoon for three days.	Morning cortisol; diurnal cortisol slope	Emotion control (ERC)	Emotional control was not associated with diurnal cortisol slope.
Otto, Sin, & Almeida, 2018	Cross-sectional	46 adults (Mage = 54, 50% males),	At awakening, 30 min after awakening, before lunch, and at bedtime for four days.	CAR; diurnal cortisol slope ; AUC	Emotion control (ERQ)	Better emotion control was associated with greater CAR and marginally flatter diurnal cortisol slope (p=.08) but was not associated with AUC.

Note: AUC = area under the curve, total daily cortisol; IRI = Interpersonal Reactivity Index (Davis & Franzoi, 1991); ERQ = Emotion Regulation Questionnaire (Gross & John, 2003); ERC = Emotion Regulation Checklist (Shields & Cicchetti, 1997)

Heterogeneity in study design, developmental stage of the sample and treatment of confounding was considerable across the reviewed studies, which may

partly explain the inconsistent findings. For example, one study controlled for a variety of demographic variables that might influence diurnal cortisol, such as age, sex, race, smoking, illness, BMI, and steroidal medication use (i.e., Otto, Sin & Almeida, 2018), while another only considered one or a few of them (i.e., Johnson et al., 2014). The association between emotion control and flattened diurnal slope was marginally positive in adults (Otto, Sin & Almeida, 2018), but was significantly negative in children (Locke et al, 2009). In addition, moderator effects were inconsistently tested. For example, Locke et al. (2009) found moderation by sex, such that boys with poorer emotion control exhibited flatter diurnal slope. Moderation by sex was not tested however in the other study exploring the link between diurnal slope and emotion control (i.e., Otto, Sin & Almeida, 2018).

3.3.2.2 Studies on hair cortisol

There were two studies testing the relationship between social cognition and hair cortisol concentrations. Villanueva, Montoya-Castilla, and Prado-Gascó (2017) examined how biological stress was related to trait emotional intelligence (EI), using a sample of 170 adolescents (12 - 14 years old; 88 girls). The sample was mainly from upper-middle class families and 30% of mothers had a university degree. The well-validated Trait Emotional Meta-Mood Scale (Fernández-Berrocal et al., 2004; Salovey et al., 1995) was used in this study, including three elements of EI, emotional attention, emotional clarity (affective empathy) and emotional repair (emotion control). The collection of samples of hair cortisol followed standard procedure and method. Unadjusted correlation analyses showed that hair cortisol concentration was not associated with either component of social cognition ($r = 0.00$ for affective empathy and $r = 0.02$ for emotion control). Neither of these variables was significant in predicting cortisol with the adjustment of age, sex, and hedonic balance ($\beta = -.06$, $p > .05$ for affective empathy and $\beta = .06$, $p > .05$ for emotion control).

The second study (Kao et al., 2019) explored if emotion regulation could moderate the association between parent and child hair cortisol concentrations in a sample of 3.5-year-olds ($n = 86$, 44 girls). Most of the parents who participated in the study were mothers (90.7%). Emotion regulation/control was measured by the parent-reported Emotion Regulation Checklist (Shields & Cicchetti, 1997), a widely used

questionnaire to assess emotion control. In correlation analysis, children's emotion regulation was not correlated with hair cortisol concentration (r = 0.10, p = 0.36). The moderation model showed a main effect of emotion regulation on child HCC (b = 1.53, p = 0.03), and a significant parent hair cortisol × emotion regulation interaction (b = -0.77, p = 0.02), revealing a conditional effect of parent hair cortisol on child hair cortisol. However, in this model, no other confounder was controlled other than emotional reactivity.

3.4 Discussion

This is the first comprehensive systematic review and meta-analysis of studies examining the associations between core social cognition abilities and cortisol in the general population. The included studies focused on three core social cognition abilities: emotion recognition, empathy, and emotion control. The associations between cortisol concentrations and empathy or emotion recognition were not significant. Emotion control was positively associated with basal cortisol, and results were largely homogeneous. Effect sizes were, in general, small in magnitude, which is line with the magnitude of the associations between psychosocial factors and cortisol in naturalistic settings reported elsewhere (Chida & Steptoe, 2009). The findings of the very few studies on the relationship between social cognition and diurnal cortisol rhythm were inconsistent and there was substantial heterogeneity across the studies that produced them.

One possible explanation for the positive correlation between emotion control and cortisol concentrations is that emotion regulation, including suppression and inhibition of emotional expression (i.e., "emotion control"), is cognitively effortful and therefore physically taxing (Otto et al., 2018; Richards & Gross, 1999). Experimental research has demonstrated a link between voluntary emotion suppression and heightened physiological responses, such as increased cardiovascular or sympathetic nervous system activity (Egloff et al., 2006; Gross & Levenson, 1993), and greater adrenocorticotropic hormone and cortisol reaction to laboratory-induced stressors (Al'Absi et al., 1997; Denson, Creswell, Terides, & Blundell, 2014; Denson, Spanovic, & Miller, 2009; Lam et al., 2009). By contrast, emotion recognition and

empathy are more automatic and less effortful cognitive processes (Happé & Frith, 2014).

Thus, the findings did not support our expectation that better social cognition would be negatively associated with cortisol concentrations. This expectation was partly built on results from studies on people with schizophrenia and ASD who exhibit atypical social cognition and cortisol profiles. Another explanation for the positive correlation with emotion control is therefore that the relationship between social cognition and cortisol may be different in people with serious social cognition deficits compared to the general population. Social cognition may function as a "key resource" for clinical groups having difficulties with social interactions, by reducing social stress. For the general population, however, where social skills would not be severely impaired, emotion control, may come at a cost and add physical stress on the body (Richards & Gross, 1999). Of course, as the relationship between cortisol levels and emotion control was cross-sectional, an alternative hypothesis could be that higher levels of cortisol result in better social cognition (Putman & Roelofs, 2011). A recent review suggests that stress-related changes in the HPA-axis may lead to self-regulation difficulties through persistent immune system dysregulation (Shields, Moons, & Slavich, 2017). However, one placebo-controlled, double-blind study did not find evidence that cortisol administration can enhance the three aspects of social cognition examined here in healthy individuals (Duesenberg et al., 2016; Ma et al., 2017), indicating that it is more plausible that better emotion control may raise cortisol levels than vice versa.

3.4.1 Moderators in the meta-analysis

The moderation (subgroup) analyses for the association between cortisol concentration and each of emotion control, empathy and emotion recognition yielded inconsistent findings. Significant findings were observed only for the association between cortisol and emotion control. First, there was a significant positive effect size in studies sampling cortisol in the morning, but not in studies sampling cortisol in the (after)noon or when the timing of the sample collection was not specified, which indicates that people with poor emotion control have lower cortisol levels in the morning. To the extent that poor emotion control may generate psychosocial stressors

and be a source of chronic stress, this may be explained by the hypocortisolism observed under chronic stress (Gunnar & Vazquez, 2001; Heim et al., 2000), when individuals can transition from hypercortisolism to hypocortisolism (Koss & Gunnar, 2018). Indeed, several studies have documented flatter daytime slopes in children who had experienced mild to severe stressors because of lower morning cortisol levels, which can be a result of chronic stress (Fries et al., 2005). Relatedly, Trickett et al., (2010) found that cortisol levels of maltreated females were initially higher than those of non-maltreated females but became lower in adulthood. To react to instant stressors, the HPA axis adapts as a protective response by elevated production of cortisol and other related hormones (i.e., adrenocorticotropic hormone). However, in the long run the receptors of these hormones may be downregulated as a response to elevated levels of them, resulting in lower cortisol production (Fries et al., 2005). Poor emotion control may generate psychosocial stressors and be a source of chronic stress (or indeed poor emotion control may be the result of exposure to chronic stressors), further leading to hypocortisolism. However, because of lack of longitudinal data, this hypothesis could not be tested here.

The finding of a significant positive association between emotion control and cortisol levels in males was unexpected. It is not clear why emotion control was not related to cortisol levels in females or in mixed-sex groups. We speculate that biological explanations about sex differences are plausible but also that gender roles and gender socialization may make emotion control more effortful in males (Barnett & Hyde, 2001; Mccann, Stewin, & Short, 1991). We also observed a significant positive effect size in studies transforming their cortisol data. Wilbraham et al. (2018) used square-root-transformation, Pascual-Sagastizabal et al. (2019) used Blom transformation while others applied log-transformation. Because most of studies used log-transformation, we cannot compare between ways of transforming the data. In agreement with Miller and Plessow's (2013) suggestion, we encourage the use of transformed data and advise care with the selection of the transformation method.

There was also a significant positive effect size in studies reporting fasting instructions preceding the sample collection. Consumption of food can cause variability in salivary cortisol levels as it can alter the oral environment and affect the quality of salivary samples (Hanrahan, McCarthy, Kleiber, Lutgendorf, & Tsalikian, 2006). Some drinks and foods may affect salivary pH, leading to false high or low

levels (Schwartz, Granger, Susman, Gunnar, & Laird, 1998). In addition, a variety of foods and drinks contain caffeine which may increase HPA axis activity (Ping et al., 2012). Thus, we suggest that in the future researchers ask participants to avoid food and drink intake at least one hour prior to the collection of salivary cortisol samples.

Unfortunately, there was not enough evidence to examine moderation by age. The only study on children showed a positive link between emotion control and cortisol (Miller et al., 2017). It is possible that the immaturity of the HPA axis in children and adolescents results in greater cortisol secretion and longer recovery time from exposure to stressors. Studies with animals have shown similar findings; pre-pubertal rats have a more prolonged, stress-induced corticosterone response compared to adult rats (Holder & Blaustein, 2014; Romeo, Lee, & McEwen, 2004). A previous study on young adolescents' diurnal cortisol profiles in relation to their social competence also showed that poorer emotion control was linked to lower cortisol concentration at awakening and a more blunted diurnal slope (Jiang et al., 2018). Yet in this meta-analysis the studies on adolescents did not yield a significant effect size. Only a small number of studies on children or adolescents were included in this meta-analysis, however, and therefore our null findings may be due to lack of power. The middle aged and older-adult group (two studies) showed significant pooled effect sizes although each study reported non-significant findings. We suggest that age differences are worth exploring systematically in future studies linking social cognition to stress.

3.4.2 Future directions

The current review contributes to the existing literature on social cognition and cortisol concentrations by suggesting that one particular aspect of social cognition, emotion control, is positively associated with cortisol concentrations in the general population. However, the causal direction of the link is unknown. There are theories suggesting effects in both directions. For example, social stress may reduce attention to social cues, and may therefore worsen social cognition (Nolte et al., 2013). At the same time, poor social cognition may not arouse enough cognitive and physical response to cope with stress (Otto et al., 2018). Longitudinally designed studies tracking both social cognition and HPA activity over time are in order. The

very few longitudinal studies conducted to date report mixed findings. One study indicated that increased social competence at age 7 and age 12 was associated with higher cortisol at awakening at age 15 (Boyer & Nelson, 2015). A more recent study on emotion regulation on adults suggested that emotional suppression was not significantly associated with changes in cortisol secretion over a year (Katz et al., 2018).

Furthermore, despite rhythm parameters of salivary cortisol being most robustly linked to stress and health problems (Adam et al., 2017; Adam & Kumari, 2009), only about a third of our studies had measured either CAR or diurnal cortisol slope. Most of the studies we identified (and indeed all of the ones we included in the meta-analysis) had only measured cortisol concentration at a time of day. Whilst cortisol concentration is useful in exploring between-group differences, it is difficult to interpret its meaning without a co-measure of diurnal rhythm. As discussed above, both hypocortisolism and hypercortisolism have been related to chronic stress, and therefore the amount of cortisol at a fixed time, especially without detailed life history information, can only crudely approximate stress in the general population. Therefore, more research on the relationship between social cognition and all three key cortisol rhythm parameters (CAR, diurnal slope, and area under the curve) is required.

In addition, the effects of cortisol in this meta-analysis were considered in isolation, whereas typically cortisol exerts its effects alongside reactivity in catecholamines, the sympathetic nervous system and the immune system (Hall, Podawiltz, Mummert, Jones, & Mummert, 2012). Hence, other biological processes or hormones may influence the relationship between social cognition abilities and cortisol. For example, there is increasing support for the involvement of testosterone in the relationship between social cognition and cortisol in older adolescents or adults. Bechtoldt and Schneider (2016) for instance found moderating effects of testosterone on the interplay between emotion recognition and stress reactivity on young adults. In their study, better recognition of negative emotions predicted higher cortisol response to social-evaluation stressors at high concentrations of basal testosterone. However, this dual-hormone hypothesis to emotion recognition, or indeed social cognition in general, has not been tested in naturalistic settings. Testosterone and cortisol are also inter-related. Testosterone is the product of the hypothalamic-pituitary gonadal axis,

which is co-regulated with the HPA axis. Testosterone can inhibit the release of cortisol, while cortisol can inhibit the secretion of testosterone (Viau, 2002).

Finally, the correlation between social cognition and cortisol levels may turn to negative in a long-term highly stressful environment, when social cognition might function as "key resource" to coping with stress. Ruiz-Robledillo and Moya-Albiol (2013) showed that better emotion control was related to a lower morning cortisol profile in caregivers of children with ASD. Extreme adversity can have a similar long-term effect. For example, childhood maltreatment can cause long-term stress and has been demonstrated to contribute to chronic hypocortisolism in adults (Kuras et al., 2017). It can also be related to social cognition deficits. Koizumi and Takagishi (2014) studied 129 children and adolescents (age 6 to 19 years) and found that those with a maltreatment history showed worse emotion recognition, especially for positive emotions, compared with those without a maltreatment history. However, because our review only included studies in the general population, we could not explore the effect of adversity on the relationship between social cognition abilities and cortisol or HPA function. Future research should attempt to examine how early adversity or major life stressors might affect this relationship.

3.4.3 Limitations

This meta-analysis has several limitations too. First, the studies showed substantial heterogeneity. Social cognition is a multifaceted construct but, in this review, we could only explore three of its aspects, and they were not measured with the same instruments. For instance, four of the included studies used the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001) to measure emotion recognition, while others used emotional intelligence scales (e.g., Mayer-Salovey-Caruso Emotional Intelligence Test; Mayer, Salovey, Caruso, & Sitarenios, 2003). This could be a potential source of the heterogeneity observed. Second, we only had 19 studies with a total of 46 effect sizes, with even fewer effect sizes when subgroup analysis was conducted. Therefore, lack of power to detect small effects is likely. Third, since we had to rely on secondary data, the exact sampling time of cortisol in the morning could not be obtained for every study included in our review. The range of time of collection spanned from 8:30 AM to 12 PM, a time window too wide to capture the

same point in the circadian rhythm of cortisol for everyone in every study. Fourth, this meta-analysis could not assess potential differences pertaining to the type of sample collected, for example, urine, blood, and hair, due to insufficient numbers of studies available. Fifth, variables that may be relevant to the relationship between cortisol levels and social cognition, such as childhood maltreatment, mental illness history and genetic vulnerability, were not available. Sixth, we did not do a systematic quality assessment of the included studies before conducting the meta-analysis, to carefully account for any methodological factors that could potentially affect the reliability of the results. Although there is no standard approach to the evaluation, there are some checklists and assessment tools, such as the Cochrane Risk of Bias (Corbett et al., 2014) and MINORS criteria (Slim et al., 2013). They cover key aspects that could affect the reliability of results such as clarity of aims, study design, sample size (or participation rate for longitudinal studies), selection bias, measurement bias, and the handling of missing data. In case of no or insufficient information, it is recommended to contact the authors for additional information or clarification.

3.5 Chapter summary and next step

This chapter systematically reviewed the current literature on the association between cortisol concentrations and three core aspects of social cognition (emotion recognition, empathy, and emotion regulation) in the general population. The meta-analysis found that better emotion control was associated with higher cortisol concentrations. Subgroup analysis further showed that this association was significant for morning cortisol, in males, when fasting instructions preceding cortisol sampling were issued, and when the cortisol data were transformed in the analysis to deal with the skewness of the data distribution. No association was found between emotion recognition or empathy and cortisol levels. There was not enough evidence supporting the link between social cognition and measures of diurnal cortisol rhythm. Considering the great heterogeneity among reviewed studies, more validation work with greater standardization of methodological procedures is required. Next chapter will introduce the source of data and analytic sample in this PhD project, describing how cortisol data were derived and how social cognition, inflammation, emotional and behavioural problems, and key covariates were measured.

Chapter 4: Data

4.1 The ALSPAC study

The Avon Longitudinal Study of Children and Parents (ALSPAC) is an ongoing transgenerational longitudinal cohort study (Boyd et al., 2013) that enrolled 14,541 pregnant women with expected delivery dates between 1 April 1991 and 31 December 1992 (Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool http://www.bristol.ac.uk/alspac/researchers/our-data/). It has been estimated that 85-90% of the eligible population participated in the study. Additional children were recruited using the original enrolment definition from the participating children's age seven years onwards, increasing the number to 15,454 pregnancies, resulting in 15,589 foetuses to date. Of these, 14,901 were alive at one year of age. All the children were invited to attend annual assessments from age seven years onwards (Fraser et al., 2013). At age 15 years, 10,472 cohort children remained productive (O'Donnell et al., 2013). Ethical approval for all measures was gained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees (NHS Haydock REC: 10/H1010/70). All participants provided written informed consent and there was no financial compensation (details at www.alspac.bris.ac.uk).

The ALSPAC was designed to understand how genetic, biological, and environmental factors influence health and development in parents and children. Hence the information collected in ALSPAC is diverse and detailed, including phenotypic, genetic, and biological sampling across different time points, as well as social and behavioural characteristics influencing the well-being of children and parents (Golding et al., 2001). Various approaches were used for the data collection, such as in-depth interviews, questionnaires, hands-on assessments and examinations, biological samples (e.g., saliva and blood samples), environmental measures (e.g., noise and levels of air pollutants), and the linkage of medical and educational records.

Regarding the representativeness of the ALSPAC cohort, there were some socio-demographic differences between ALSPAC maternal sample in the 1991 census and the mothers with infants < 1 year of age in the Avon population as well as the general British population (Fraser et al., 2013). Specifically, compared to those in the general Avon and British populations, ALSPAC mothers were slightly more likely to

live in owner-occupied accommodation and overcrowded conditions, have access to a car, be White in ethnicity, be married, and with better socioeconomic status. ALSPAC team suggested that although the limitation of representativeness to the target population might bias the estimates of prevalence but would not necessarily influence association or causal effect estimates (Lawlor et al., 2019). In addition, they found growth standards (e.g., weights and lengths) of the ALSPAC cohort children are very similar to national standards at birth, age 1 year and 2 years. Data from ALSPAC were used for the analyses that are described in Chapters 5-7.

4.2 Analytic sample

As inflammation and cortisol are main variables of interest in this project, the analytic sample is restricted to ALSPAC cohort children who had valid data on inflammation or cortisol. Inflammation and cortisol data were collected at different time points in ALSPAC and only about 500 cohort children provided both. More than 5,000 children had valid data on inflammation and less than 1000 children provided valid data on cortisol (details introduced below). As we need to include both inflammation and cortisol in one statistical model rather than doing separate analyses, including in the analytic sample those children with data on inflammation but not with data on cortisol would make the missing rate of cortisol variables over 90%, producing extremely unreliable results. Therefore, the cohort children with valid data on cortisol were chosen to be the analytic sample.

At age 15 years, 5,501 of the ALSPAC cohort children attended a clinical assessment. Of those, 3,020 were invited at random to participate in the cortisol data collection and 1,845 agreed. For 968 participants who provided at least one valid saliva sample for the cortisol analysis, we applied the following exclusion criteria: 1) second born in case of a twin birth (n = 8); 2) gestation at birth <= 32 weeks (n = 0); 3) birth weight <= 1500g (n = 0); 4) exposure to steroid medication when cortisol was measured (n = 3); 5) had an infection when inflammation was measured (n = 85). Of the 864 participants who survived this exclusion process, 729 individuals had valid data on the dependent variables, emotional and behavioural problems on 17 years old, which comprised the analytic sample of the study in Chapter 5.

In the study that is presented in Chapter 6, the above exclusion criteria were also applied, except for criterion 5) the 85 participants who had an infection when inflammation was measured were not excluded because inflammation was not included in the study. Therefore, 939 individuals were included in this study.

In the study that is described in Chapter 7, in addition to the criteria that were used in Chapter 5, 16 participants whose Wechsler Intelligence Quotient (IQ) < 70 (two standard deviations below the mean; Wechsler et al., 1992) at age 15 years were further excluded, because the main variable in that study - social cognition ability, is closely related to individuals' IQ. Following the exclusion process, only those who had data on the dependent variables of this study (emotional and behavioural problems on 17 years old) were included in the analyses, resulting in a total sample of 714.

The detailed flow charts of analytic sample selection processes for three studies are presented in the corresponding Chapters.

4.3 Main Measures

4.3.1 Cortisol sampling

At age 15 years, adolescents were invited for a clinical visit. At the visit, a random subsample of adolescents was approached about the cortisol sub-study. Those agreeing to take part in the sub-study were given full instructions and provided with a saliva sampling pack. Each pack contained detailed written sampling instructions, 12 salivate collection devices (Sarstedt, Germany), a sample collection sheet, and a prepaid envelope in which to return the samples to the laboratory. For each participant, four measurements were taken daily over three consecutive school days: wake-up, 30 min post-wake-up, mid-afternoon, and before bedtime. Participants were shown how to collect saliva and were instructed to avoid eating or brushing their teeth before the collection of each sample, to record collection times, and to place samples in their freezers until they returned the samples to the laboratory. Samples were mailed back and stored at -20°C until they were assayed. Cortisol samples, expressed as nmol/L, were assayed using a commercially available enzyme immunoassay (Salimetrics, UK). Inter-assay and intra-assay coefficients of variation were 7.9% and 8.9% respectively (O'Donnell et al., 2013).

In addition to mean cortisol levels at the four time points, five between-person measures of cortisol were further derived: 1) total morning cortisol output, estimated as the sum of the two morning samples; 2) Cortisol Awakening Response (CAR), calculated by subtracting the wake-up cortisol from the post-awakening cortisol; 3) diurnal cortisol decline, taken as the difference between mean morning and bedtime cortisol levels; 4) diurnal cortisol slope, calculated using diurnal cortisol decline divided by time in hours; 5) total daily cortisol output, derived from the Area Under the Curve with respect to ground (AUCg) of four time points based on the trapezoid formula (Pruessner et al., 2003). To accurately calculate these cortisol measures, cortisol data were first cleaned by replacing the sample as missing if 1) values were undetectable; 2) values larger than 82 nmol/l; 3) values larger than 4 standard deviations above the sample mean for that time point; 4) for CAR, the first sample was taken after 10.00 h, or the second sample was provided less than 20 or more than 60 min after the first; 5) for mean cortisol level, the second time point was after 11.00 h; 6) for mean cortisol level, the third time point was before 15.00 h or after 18.00 h; 7) for mean cortisol level, the fourth time point was before 19.00 h. Each cortisol measure was calculated as a mean of the available samples over the study period. Following previous practice (Carnegie et al., 2014), we replaced absent or negative CAR as missing, in case this was the result of sampling error or non-adherence (Kudielka et al., 2003). Only the study in Chapter 6 included all the cortisol variables (i.e., mean cortisol levels at four time points and five derived cortisol measures) as cortisol was the outcome in that study. In Chapters 5 and 7 where cortisol was the potential mediator, I only used four important cortisol measures to capture individuals' diurnal cortisol rhythm: total morning cortisol output, CAR, diurnal cortisol slope, and AUCg.

4.3.2 Inflammation

In ALSPAC, inflammation in childhood was measured with Interleukin-6 (IL-6) at age 9 years and C-reactive protein (CRP) at age 9 and 16 years. Blood samples were collected from participants who gave consent for venepuncture during the clinical assessments at ages 9 and 16 years. A note was made for any infections, and treatments or medications being used at the time. Consent was collected in accordance with the Human Tissue Act (2004), including the mother's or father's informed

written consent, the children's willingness, and the option to stop during the procedure.

At 9 years, blood samples were collected from non-fasting participants. Samples were immediately centrifuged frozen and stored at -80 °C in 1 ml aliquots. IL-6 and CRP levels were assayed in 2008 after a median storage period of 7.5 years. There was no evidence of freeze-thaw cycles during storage. At 16 years, blood samples were collected from fasting participants, when they fasted overnight or at least for 6 h before attending the clinic. Samples were also immediately spun, frozen, and stored at -80 °C. They were analysed within 3-9 months of blood sampling with no freeze-thaw cycles in between.

Serum high sensitivity IL-6 levels (pg/mL) at 9 years were measured by enzyme-linked immunosorbent assay (ELISA; R&D Systems, Abingdon, UK). The minimum detection limit was 0.007 pg/mL. Serum high sensitivity CRP levels (mg/L) at 9 and 16 years were measured by automated particle-enhanced immunoturbidimetric assay (Roche, UK, Welwyn Garden City, UK). The minimum detection limit was 0.03 mg/L. Inter-assay and intra-assay coefficients of variation for IL-6 and CRP were < 5% (see more details from Chu et al., 2019). Both CRP and IL-6 were log-transformed to correct the skewness in all analyses.

4.3.3 Social Cognition

4.3.3.1 Social communication ability

Social communication ability was assessed using the parent-rated Social Communication Disorders Checklist (SCDC) at ages 8, 11, and 14 years. SCDC is a brief and sensitive screening tool for autistic traits in large community samples (Skuse et al., 2005). There are 12 items in the SCDC measuring social reciprocity, non-verbal skills, pragmatic language usage, and behavioural characteristics in the past 6 months, ranging from 0 ("not true") to 2 ("very or often true") for each item. Example items include "Does not realise if s/he offends people with her/his behaviour", "Does not pick up on body language", and "Cannot follow a command unless it is carefully worded". Some of the items in this checklist cover aspects of empathy and emotional control (e.g., "not aware of other people's feelings" and "difficult to reason with when upset", respectively), but the SCDC was not designed specifically for empathy or

emotional control. Higher scores indicate more difficulties in social communication. The SCDC has been demonstrated to have high internal consistency, test-retest reliability, and heritability in both sexes (Skuse et al., 2005). For participants with less than 50% missing data on the SCDC, total scores were calculated using prorating (if more than six items had missing data then the total score was set to missing; Otherwise, the total score was scaled by a factor of 12 / (12 - the number of missing items) and rounded to the nearest integer). To account for the positive skewness of total scores, SCDC scores were also dichotomised using a cut-off of ≥ 9, which has been found to yield sound diagnostic accuracy for autism in the ALSPAC sample (Barona et al., 2015; Kothari et al., 2013; Skuse et al., 2009).

4.3.3.2 Emotion recognition from facial expressions

Emotion recognition from facial expressions was assessed with the Diagnostic Analysis of Non-Verbal Accuracy (DANVA) test during an annual assessment clinic held when the children were approximately 8 years (Nowicki & Duke, 1994). The DANVA test was designed to identify children who may have difficulties in processing nonverbal information about emotions, specifically for emotion recognition. It consists of seven subsets to assess four types of nonverbal receiving abilities (facial expressions, postures, gestures, and tones of voice) and three types of nonverbal sending abilities (facial expressions, gestures, and tones of voice) in children aged 6 to 10 years. In ALSPAC, only the receptive subtest for facial expressions was used. This subset consists of 24 colour photos of both boys and girls at school age, with each face showing one of four emotions: fear, happiness, sadness, or anger. Each photo was presented for 2 seconds, and the child was asked to choose which emotion was displayed. Pictures were classified as high (easy to identify) or low (harder to identify) intensity. The measure is scored by simply adding up the number of errors/misattributions for each emotion. The number of errors made for each emotion with high- and low-intensity stimuli can also be used. DANVA scores were also positively skewed, therefore, cut-offs for each of the variables (based on the upper 20th percentile) were derived in collaboration with the author who developed the DANVA test (Stephen Nowicki) for ALSPAC and were based upon the distribution of results in the entire sample. These specific cut-offs have been previously used in studies using ALSPAC (Barona et al., 2015; Kothari et al., 2013;

Thompson et al., 2011). For all emotions, participants who made at least 7 errors were coded as 1 (versus 0 "total errors < 7"), indicating deficits in emotion recognition from facial expressions. The DANVA has been shown to have good internal consistency, test-retest reliability, and convergent and construct validity (Nowicki & Duke, 1994; Kidd & Castano, 2013).

4.3.3.3 ToM/Emotion recognition from movements

Emotion recognition from movements was assessed using the computer-based Emotional Triangles test at 14 years. The test result was also indicative of individuals' ToM/cognitive empathy ability (Warrier & Baron-Cohen, 2018). Participants were asked to attribute emotion to a nonhuman animate entity which consists of a black outline triangle and a circle. The movements of the triangle were designed to represent a particular emotion: happy, sad, angry, and scared. For example, "angry" was depicted by the triangle repeatedly 'jabbing' at the circle (For more details on the task, see Boraston et al., 2007). For each of the four emotion trials, there were two positive questions, where the mental state of the triangle matched the mental state described in the question (e.g., "is the triangle happy?" for a happy animation), and two negative questions, where the mental state of the triangle did not match the mental state described in the question (e.g., "is the triangle sad?" for a happy animation). Hence, there were four questions that were scored for each emotion and 16 in total. Each question was scored from 0 ("the triangle did not possess the mental state") to 5 ("the triangle definitely possessed the mental state"). The total score was calculated by adding the scores of all the positive questions and subtracting the score of the negative items. High scores represent better ability in recognising and inferring particular emotions (i.e., better emotion recognition and empathy). Following previous studies using this test (Holland et al., 2020; Warrier & Baron-Cohen, 2018), to avoid negative scores, we added 40 to the total score, giving the score a range from 0 - 80.

4.3.4 Emotional and behavioural problems

Emotional and behavioural problems were assessed in ALSPAC using the mother-rated Strengths and Difficulties Questionnaire (SDQ) at ages at ages 4, 7, 8, 9,

11, 13, and 17 years (Goodman, 1997; Goodman et al., 2010). The SDQ is widely used to screen for mental health problems in children and adolescents and has shown good validity and reliability in different population samples (Goodman & Scott, 1999; Goodman, 2001; Shojaei et al., 2009). It consists of 20 "difficulties" items related to behaviours in the past 6 months, which form four subscales: emotion difficulties, conduct problems, hyperactivity/inattention, and peer problems. The subscale of emotion difficulties includes items related to children's anxiety (e.g., "worry a lot") and depressive symptoms (e.g., "unhappy, downhearted"). The conduct problems subscale includes items relate to the children's disruptive behaviours, such as "often has temper tantrums" and "often lies or cheats". The hyperactivity/inattention subscale includes three items assessing hyperactive-impulsive behaviours (i.e., "restless, overactive. cannot stay still for long", "constantly fidgeting or squirming", "thinks things out before acting") and two questions measuring symptoms of inattention (i.e., "easily distracted, concentration wanders", "sees tasks through to the end. good attention span"). Peer problems subscale includes items such as "picked on or bullied by other children" and "rather solitary, tends to play alone". In line with the recommended practice for community samples (Goodman et al. 2010), the emotional problems scale comprises the 10 items from the emotion and peer problems subscales, and the behavioural problems scale comprises the 10 items from the hyperactivity/inattention and conduct problems subscales. Scores on the emotional and behavioural problems scales range from 0 to 20 with higher scores indicating more serious problems.

4.3.5 Confounders

A range of variables were considered as potential confounders for cortisol, inflammation, social cognition, and emotional or behavioural problems. The main ones can be divided into three main categories: 1) demographic confounders, 2) health and lifestyle characteristics, and 3) other confounders. Additional covariates for the specific study will be introduced in the corresponding chapter.

4.3.5.1 Demographic confounders

Sex: Previous research has demonstrated sex differences in the prevalence of emotional or behavioural problems in children and adolescents; for example, females are more likely to have adolescent-onset depression and anxiety (Zahn-Waxler et al., 2008). There are also studies reporting sex differences in social cognition (Thompson & Voyer, 2014), as females perform better in affect recognition tasks compared to males (Hall & Matsumoto, 2004). In terms of inflammation, there was evidence suggesting that the association between stress and systemic inflammation is stronger in females than that in males (Dolsen et al., 2019). Similarly, females' HPA axis also shows more rapid reaction and produces a greater output of cortisol in responding to stress (Goel et al., 2014). Therefore, sex was included as a cofounder in all analyses. In ALSPAC, it was a binary male/female measure recorded at birth.

Ethnicity: Ethnicity is also known to be associated with children's emotional and behavioural problems; for instance, research has reported that Asians and Blacks have a lower lifetime risk for mood disorders than Whites (Alvarez et al., 2019). Regarding social cognition, facial cues indicating a person's ethnicity have been found to influence people's emotion recognition ability (Craig et al., 2017). In addition, the ethnic minority is also associated with increased psychosocial stress, elevated levels of CRP and flatter diurnal cortisol slopes (DeSantis et al., 2007; Richman, 2018). Similar to sex, ethnicity was also recorded at birth and coded as a dichotomous (White vs. non-White).

Socioeconomic status: Socioeconomic status (SES) is associated with inflammation, cortisol, and mental health, as lower socioeconomic status in childhood is associated with maladaptive social functioning, higher risk of mental disorders and health problems such as systemic inflammation and HPA axis dysfunction (Bradley & Corwyn, 2002; Marsman et al., 2012; Richman, 2018; Russell et al., 2016). It has been suggested that it might be advantageous to use a composite SES variable rather than several indicators separately (Moreno-Maldonado et al., 2018). As SES is a multi-dimensional construct related to social stratification, a composite SES variable may capture a more comprehensive representation, taking into account the various aspects of SES that may be relevant to the study. This allows a more straightforward data analysis and interpretation (Lindberg et al., 2022). In addition, a composite SES variable can capture the synergies between different aspects (Moreno-Maldonado et

al., 2018). The SES variable in this thesis was derived from a principal components analysis of the following variables:

1) Maternal social class: A categorical measure of maternal social class was recorded at 32 weeks of pregnancy using the 1991 Office of Population Censuses and Surveys (OPCS) classification with six categories: a) Professional; b) Managerial and technical; c) Skilled (non-manual); d) Skilled (manual); e) Party-skilled; and f) Unskilled.

2) Maternal educational status: A measure of maternal educational status was recorded at 32 weeks of pregnancy. It was categorised into the following categories: a) below O level (examination taken and passed at 16 years); b) O level only; c) A level only (examination taken and passed at 18 years); and d) University degree or more.

3) Financial difficulties: The financial difficulties measure was constructed of a series of questions in ALSPAC. The participated mother was asked to rate on a scale from zero to three how difficult it is currently to afford food, clothes, heating, housing, and other things considered essential for the baby, ranging from 0 to 20 for each time point, with higher scores indicating more difficulty. It was measured repeated at children's 8, 21, and 33 months. Mean score of the three time points was calculated for the final financial difficulties score.

A higher SES composite score indicates lower socioeconomic status.

4.3.5.2 Health and lifestyle characteristics

Overweight: Similar to other cofounders, being overweight has also been found to be associated with children's emotional and behavioural problems, social cognition, inflammation and HPA axis activity (Luppino et al., 2010; Percinel et al., 2018; Visser et al., 2001; Yu et al., 2020). Body Mass Index (BMI) was measured using information from the clinic assessments at age 9 years and 15 years and was calculated as weight (in kg) divided by height (in m) squared rounded to 1 decimal place. Because BMI at 15 years (when cortisol was measured) is significantly correlated with BMI at 9 years (when inflammation was measured) (Pearson's r = 0.81, $p < .001$), and BMI at 15 years old had more valid data (missingness 0.4%) than BMI at 9 years old (missingness 3.4%), I used BMI at 15 years old to represent

general body fatness in later analyses. Being overweight was determined using the International Obesity Task Force (IOTF; Cole et al., 2000) age- and sex-specific cut-offs for BMI (males: 23.29 kg/m^2; females: 23.94 kg/m^2 at age 15 years). The reason for using a binary overweight variable rather than a continuous BMI score is that the association between BMI and physical and mental health outcomes tends to be non-linear, meaning that associations with health may not be constant across the entire range of BMI values. Various studies have found spline regression models produce a better fit (Apple et al., 2018; Kwasny et al., 2018).

Physical activities: Doing vigorous physical activities has long been linked with mental health (Pengpid & Peltzer, 2020) and HPA axis activities (Anderson & Wideman, 2017). In all analyses related to cortisol and emotional or behavioural problems, we controlled for the frequency of doing vigorous activities, such as running, playing football and swimming. It was scored on a 3-point scale of 1 = "less than once a week", 2 = "1-3 times a week" and 3 = "more than three times a week".

Substance use: Previous studies have documented that substance use is associated with a range of mental health problems (Chang et al., 2005; Homman et al., 2019), blunted HPA axis activities (Eiden et al., 2020; Ruttle et al., 2015) and systemic inflammation (Arnson et al., 2010; Imhof et al., 2001). Therefore, I included variables "daily smokers" and "alcohol users" as covariates in all regression analyses. They were binary coded (Yes vs. No) to control for those who usually smoke at least one cigarette per day, and those who reported drinking on more than two days a week over last six months.

4.3.5.3 Other confounders

Stressful life events: The experience of stressful life events in childhood has been widely associated with adverse health outcomes, such as the development of mental disorders (Assari & Lankarani, 2016; Croft et al., 2019), poor social cognition abilities (Kliewer et al., 2009; Vrijsen et al., 2018), decreased HPA axis activities (Elzinga et al., 2008), and systemic inflammation (Danese et al., 2009; Nettle et al., 2017). In ALSPAC, the participated mothers were asked to complete a stressful events checklist at children's ages 8 months, 21 months, 33 months, 47 months, 61 months, 73 months, 110 months, and 134 months. The checklist includes 43

dichotomous items, such as “you attempted suicide”, “you became homeless”, “you and your husband/partner separated”, “you lost your job”, and “a friend or relative died” (Barnett, Hanna, & Parker, 1983). For each item, a score of 0 was assigned if the event did not occur and a score of 1 if it did. Stressful life events score in this thesis was calculated as the sum of total scores at the eight time points.

Total IQ: Previous research has found that each standard deviation unit increase of IQ in children was associated with reduced risk of psychiatric comorbidity and persistence of depression in adulthood (Koenen et al., 2009). Hence in studies in Chapters 5 and 6, children’s IQ score was included as a continuous covariate in regression models predicting emotional or behavioural problems. The exact age (in month) of children was also controlled for in these studies as IQ is closely related to children’s age. In Chapter 7, we removed participants with low IQ score (< 70) for all analyses involving social cognitive variables. This is because children with low intellectual functioning tend to show poor social cognitive performance (Buitelaar et al., 1999; Ross et al., 1990) and social cognition tasks are not sensitive enough to assess their social cognitive abilities (Farrant et al., 2005). ALSPAC used the Wechsler Abbreviated Scale of Intelligence (WASI) to assess the cohort children’s intelligence at age 15 years (Wecshler, 1999). WASI is a measure of general cognitive ability comprising four subscales, two verbal and two non-verbal. The two verbal subtests include 1) vocabulary and 2) similarities, and the two performance subtests are 1) block design and 2) matrix reasoning. The WASI provides standard scores (M = 100, SD = 15) on verbal IQ, nonverbal IQ, and full-scale IQ.

The distribution of the covariates mentioned above is displayed in Table 4-1. The statistics in this table is based on the whole ALSPAC sample. The comparison between the analytic sample for each study and the ALSPAC sample will be presented in later chapters.

Table 4-1

Distribution of the covariates in the ALSPAC sample

Categorical variables	N	Percentage	Min	Max

Sex (male)	7315	51.79%	0	1
Ethnicity (white)	10869	94.82%	0	1
Overweight	965	20.59%	0	1
Daily smoker	377	8.40%	0	1
Alcohol > 2 days/week	216	5.42%	0	1

Continuous variables	Mean	Standard Deviation	Range	Median
Socioeconomic status	0.02	1.27	(-2.46, 4.29)	-0.06
Vigorous physical activity	2.31	0.66	(1, 3)	2
Stressful life events	35.33	17.99	(0, 125)	33
IQ	91.65	12.99	(55, 137)	91

4.4 Strengths and weaknesses of the ALSPAC study

ALSPAC study has some compelling strengths. For example, as mentioned at the beginning of this chapter, it is based on the general population with a large sample size, which means that the statistical power can be sufficient to detect effects and the findings are easier to be generalised to the wider public and support policymaking. It also covers a wide range of genetic, biological, environmental, social, and psychological factors, as well as the possibility of the linkage to other medical, criminal, and educational records (Fraser et al., 2013). Cortisol and inflammation are two main variables in this thesis. However, most large-scale longitudinal data failed to collect blood and saliva samples for the measurements of cortisol and inflammatory markers. The availability of these variables in ALSPAC study makes it possible to investigate the longitudinal roles of cortisol and inflammation in the development of mental health problems. In addition, ALSPAC team used mixed approaches to collect data, including questionnaires completed by the caregivers and children from age 5 onwards, in person interviews with caregivers and children, tasks and tests completed by the children, and clinic visits for physical measurements and biological samples (Niarchou, Zammit, & Lewis, 2015). For example, to assess the social cognition abilities of children, ALSPAC used not only parent-rated SCDC questionaries, but also the DANVA and computer-based Emotional Triangles tests, which allowed a more comprehensive assessment of social cognition. Finally, thanks to the ongoing support and commitment from the study families, the time resolution of data is high (approximately every year), and most variables were repeatedly measured, which

allows for the exploration of the change or trajectory of interested factors (Boyd et al., 2013).

ALSPAC study has several limitations too. First, as mentioned in section 4.1, compared with the whole eligible Avon population and national population, the sample has an over-representation of White and advantaged families, under-representing non-White ethnic groups and families in low socioeconomic status (Fraser et al., 2013). However, as studies in this thesis concern the longitudinal associations between variables rather than the prevalence of certain variables, the compromised representativeness should not influence the results significantly. Second, although it covers a variety of biological measures, the collection of cortisol data was limited to a 6.7% subsample. Collecting repeated saliva samples from young people is difficult and thus the cortisol data that are qualified for analyses are even more limited. Nevertheless, compared to most longitudinal studies on cortisol (Miller et al., 2018; Van Bokhoven et al., 2005; Valentino et al., 2021; Yu et al., 2018), around 800 participants in this thesis can still be considered a relatively large sample. Third, the measures for the inflammation were not consistent for different sweeps. At age 9 years, both IL-6 and CRP were measured, while at age 16 years, IL-6 was not measured. Previous findings indicated that, compared with other inflammatory markers, IL-6 might be more consistently related to daily cortisol profiles such as smaller CAR and flatter diurnal decline (DeSantis et al., 2012). Hence, an additional measure of IL-6 at the age 16 sweep would be useful for more robust analyses. Fourth, as an observational study, ALSPAC does not have the benefit of random treatment assignment (Nørgaard, Ehrenstein, & Vandenbroucke, 2017). Our finding may reflect residual confounding by factors that was not measured by the ALSPAC, despite our best attempts to adjust for potential confounders. Fifth, some main variables in this project (e.g., social communication, emotional and behavioural problems) were ascertained by parental completion of the questionnaires. This may result in reporting bias, especially for the those measured in children's adolescence years.

4.5 Chapter summary and next step

This Chapter introduced the data source for the empirical studies in Chapter 5, 6 and 7, the ALSPAC study, A prospective birth cohort based in Avon, England. This Chapter also outlined the procedure of analytic sample selection and how other main variables were measured or derived. This thesis is particularly interested in cortisol, inflammation, social cognition, and emotional and behavioural problems in childhood to late adolescence. The strengths and weaknesses of the ALSPAC data were also presented at the end of this chapter. In the following chapter, I will explore the predictive effect of cortisol or inflammation on the emotional and behavioural problems.

Chapter 5: The associations of cortisol measures and inflammatory markers with emotional and behavioural problems

5.1 Introduction

Much attention has been paid to the risk factors for mental health problems in adolescence, and psychosocial stress appears to be one of the strongest predictors (Cohen, 2000; Esch et al., 2002; Gershon et al., 2013). The association between the exposure to specific domains of stress (e.g., academic performance, social stressors, or adverse life events) and negative mental health outcomes has been well established (Giota & Gustafsson, 2017; Hazel et al., 2008; Moore et al., 2017; Östberg et al., 2015). As described in Chapter 2, at the biological level, stress is closely related to the activity of the HPA axis and can impact the body's ability to regulate the immune system (i.e., the body's inflammatory responses) (Miller & Blackwell, 2006; Ruttle et al., 2011; Slavich & Irwin, 2014). Specifically, when facing threatening situations, the HPA axis is activated, upregulating the secretion of cortisol to prepare an individual for a "fight-or-flight" response. Cortisol exerts a strong anti-inflammatory effect which allows the body to react to the acute threat without being hampered by sickness behaviours, such as lethargy and reduced social exploration (Slavich & Irwin, 2014). Yet repetitive or prolonged exposure to stressors can lead to a dysregulation of both systems (Miller et al., 2002; Miller et al., 2008). Therefore, dysregulated HPA axis activity and immune processes may be related to the development of various emotional and behavioural disorders.

Chapter 2 has reviewed numerous empirical studies that show links for cortisol levels and inflammation with different emotional and behavioural problems (Liukkonen et al., 2011; Miller & Blackwell, 2006). For example, it has been reported that about half of the patients with depression or anxiety disorders display basal hypercortisolism, glucocorticoid resistance and elevated levels of inflammatory markers (Checkley, 1996; Feder et al., 2004; Mannie et al., 2007; Vreeburg et al., 2010; Osimo et al., 2019; Pariante & Miller, 2001). Longitudinal studies have also shown that increased cortisol levels at night (Hsiao et al., 2013) and higher levels of inflammatory markers in childhood (Flouri et al., 2020) are associated with worsening depressive symptoms over time. As opposed to the hypercortisolism found in

individuals with depression, adolescents with behavioural problems exhibit hypocortisolism, including low morning cortisol levels, a flatter diurnal rhythm, and low hair cortisol concentration (Figueiredo et al., 2020; Pauli-Pott et al., 2019). There is also evidence that increased levels of inflammatory markers are related to hyperactivity/inattention and conduct disorder both concurrently and longitudinally, supporting the possibility that low levels of basal cortisol lead to the inadequate regulation of inflammation (Chang et al., 2020; Odgers et al., 2007; O'Shea et al., 2014; Pajer et al., 2001). However, many studies show no significant associations between dysregulated HPA axis activity or immune processes with mental health problems (Parsons, Roberts, & Mills, 2021; Pesonen et al., 2011; Vedhara et al., 2003). In addition, most studies to date have measured either cortisol or inflammation, but not both jointly. The few exceptions were cross-sectional case-control studies conducted in clinical samples (Chang et al., 2020; Kaestner et al., 2005; Lamers et al., 2013). For example, Kaestner et al. (2005) and Lamers et al. (2013) found hyperactivity of the HPA axis and normal levels of inflammatory makers in patients with melancholic depression but normal HPA axis activity and higher levels of inflammatory markers in patients with non-melancholic depression. Chang et al. (2020) reported that, compared with the typical developing youth, young people with ADHD have lower bedtime salivary cortisol and higher level of inflammatory markers. The synergistic longitudinal effects of HPA-axis and inflammation on the development of mental health problems in the general adolescent population remained unclear.

Therefore, this study aimed to examine if diurnal cortisol, inflammation, or both can predict emotional and behavioural problems in late adolescence (age 17 years). It was expected that cortisol or inflammatory markers would be associated with later emotional and behavioural problems while controlling for one another. Specifically, cortisol measures would be positively associated with emotional problems but negatively associated with behavioural problems. Inflammatory markers would be positively associated with both emotional and behavioural problems in adolescence. It was also expected that the associations would remain significant after adjustments for the emotional or behavioural problems in early childhood (age 4 years) and confounders.

5.2 Method

5.2.1 Participants

In this study, data from the ALSPAC were used. As discussed in Chapter 4, ALSPAC is an ongoing transgenerational longitudinal cohort study (Boyd et al., 2013) that enrolled 14,541 pregnant women with expected delivery dates between 1 April 1991 and 31 December 1992. 5,501 of the ALSPAC cohort children were recruited for a clinical assessment at age 15 years when they were invited for the cortisol data collection. As presented in Figure 5-1, 968 participants consented to participate and provided at least one valid saliva sample. For this study, the following exclusion criteria were applied: 1) second born in case of a twin birth; 2) gestation at birth <= 32 weeks; 3) birth weight <= 1500 g; 4) exposure to steroid medication when cortisol was measured; and 5) had an infection when IL-6 was measured. 864 participants survived this exclusion process. Of those, 729 had valid data of emotional or behavioural problems at 17 years old, comprising the analytic sample of this study.

5.2.2 Measures

5.2.2.1 Cortisol

Information on the cortisol sampling, data cleaning and variable deriving processes have been previously described in Chapter 4. In this study, I focused on four derived cortisol measures: 1) total morning cortisol, the sum of the two morning samples; 2) diurnal cortisol slope calculated using the difference between mean morning and bedtime cortisol levels divided by time in hours; 3) CAR, the difference between the post-awakening cortisol and wake-up cortisol; 4) AUCg, the estimate of total daily cortisol output. To correct for skewed distributions, the values of these cortisol measures were log-transformed.

5.2.2.2 Inflammation

In this study, inflammation in childhood was indicated by IL-6 at age 9 years and CRP at age 16 years. Levels of IL-6 (pg/mL) was measured by enzyme-linked immunosorbent assay (R&D Systems) and high-sensitivity CRP (mg/L) was measured by automated particle-enhanced immunoturbidimetric assay (Roche, UK,

Welwyn Garden City, UK). All inter-assay coefficients of variation were less than 5% (Chu et al., 2019). Similar to the procedure followed for the cortisol measures, IL-6 and CRP were log-transformed to correct the skewness of the distributions for the analyses.

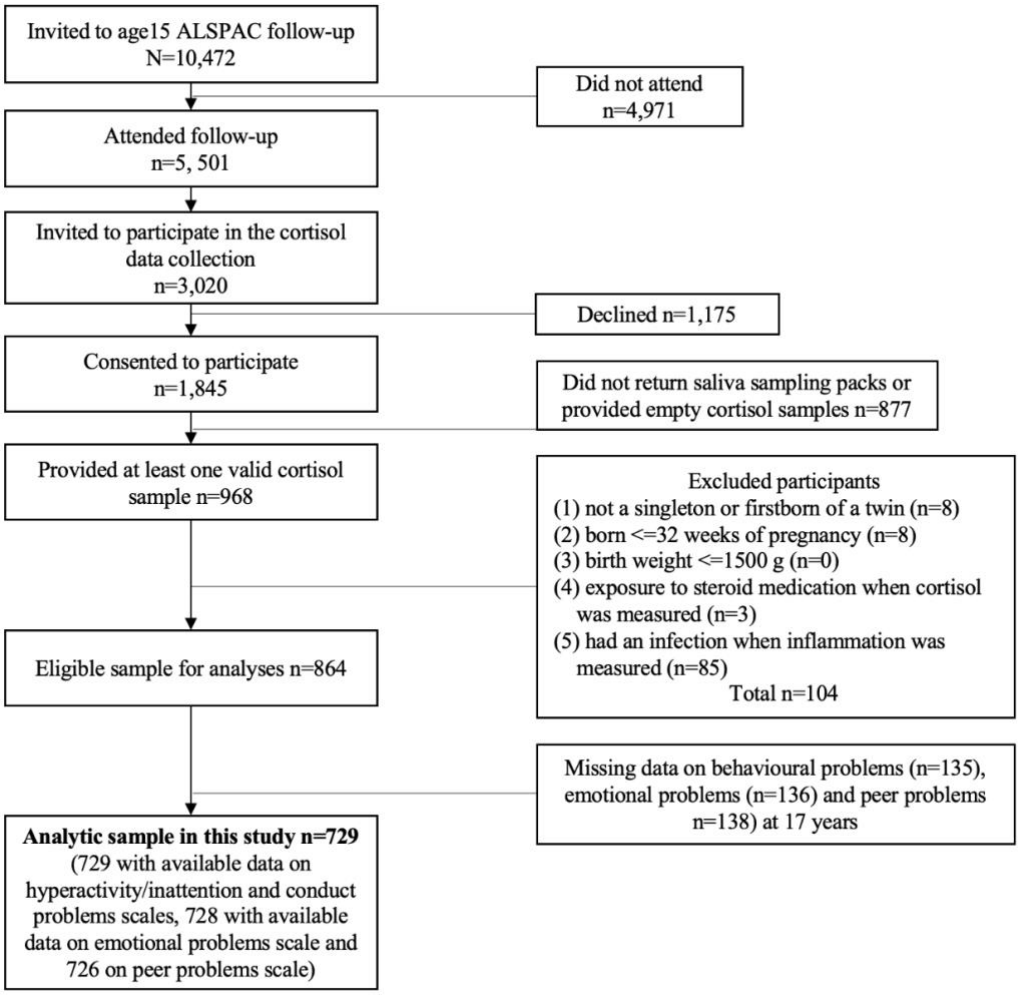

Figure 5-1 Analytic sample selection process

5.2.2.3 Emotional and behavioural problems

Emotional symptoms, conduct problems, hyperactivity/inattention, and peer problems were measured with subscales of the mother rated SDQ at ages 4 and 17 years (Goodman et al., 2010). As described in the previous chapter, the SDQ is a widely used questionnaire to assess mental health problems in general child and adolescent populations. It has sound psychometric properties (Goodman & Scott, 1999; Goodman, 2001; Shojaei et al., 2009).

5.2.2.4 Covariates

In this study, a series of covariates that are known to be associated with cortisol, inflammation, and emotional and behavioural problems were controlled for. These included sex (Dolsen et al., 2019; Goel et al., 2011; Hermens et al., 2005), ethnicity (Bax et al., 2019; DeSantis et al., 2007; Richman, 2018), socioeconomic status (Marsman et al., 2012; Richman, 2018; Russell et al., 2016), stressful life events (Elzinga et al., 2008; Nettle et al., 2017; Vrijsen et al., 2018), overweight (Luppino et al., 2010; Visser et al., 2001; Yu et al., 2020), exact age (Kudielka & Kirschbaum, 2003), vigorous physical activity (Anderson & Wideman, 2017), daily smoking (Eiden et al., 2020), and alcohol use (Ruttle et al., 2015). Details on these covariates and how they were measured can be found in Chapter 4. Contraceptive and psychotropic medication use is known to related to one's HPA axis function and activity (Kirschbaum, Pirke, & Hellhammer, 1995; O'Donnell et al., 2013); hence as a potential covariate, we included medication use, reported during the clinic visit at 15 years old. As cognitive function has been linked to both basal responsive cortisol levels (Lupien et al., 2001) and emotional and behavioural problems (Polderman et al., 2009), IQ at age 15 years was also included as a covariate. In addition, diurnal cortisol rhythm is influenced by wake-up time (Dahlgren et al., 2009; Stalder et al., 2009). Therefore, we calculated the mean wake-up time during the cortisol data collection period (3 days) and considered it as an additional covariate.

5.2.3 Analytic strategy

Data were cleaned and analysed in Stata 16 (StataCorp. 2019). First, descriptive statistics were obtained and pairwise correlation coefficients between the study's main variables were calculated. Thereafter, sets of multiple regression models were fitted in Mplus 8.1 (Muthén & Muthén, 1998-2017) to investigate the predictive effect of cortisol and inflammation for the four types of mental health problems (hyperactivity/inattention, conduct problems, emotion problems and peer problems) at age 17 years, with adjustments made for the equivalent type of mental health problem at 4 years. Separate sets of models were run for the four cortisol measures: diurnal cortisol slope, total morning cortisol, CAR, and AUCg. For each cortisol measure, unadjusted regression models were initially run (i.e., only cortisol and emotional or

behavioural problems at age 4 as predictors), followed by models adjusted for confounders (sex, ethnicity, overweight, socioeconomic status, age, smoking, alcohol use, medication use, vigorous physical activity, wake-up time, IQ, and stressful life events). Next, inflammatory markers were added to the adjusted models to examine its predictive effect for emotional or behavioural problems at 17 years old, and whether the effects of cortisol and inflammation would survive after adjustments for one another. As a sensitivity analysis, we then removed the covariates that were not statistically associated with the mental health problems and reran the models (for hyperactivity/inattention, sex, smoking, socioeconomic status, stressful life events and IQ were adjusted; for conduct problems, smoking, vigorous physical activity, stressful life events and IQ were adjusted; for emotional problems, sex and stressful life events were adjusted; for peer problems, sex and vigorous physical activity were adjusted). Full information maximum likelihood was used to account for missing data in the scores of emotional and behavioural problems at age four years, inflammation and cortisol measures, and the covariates. A robust maximum likelihood estimator was used to account for skewed data distributions in the variables.

There were two reasons for fitting cortisol as a main predictor and adding inflammation at a later step: first, as the analytic sample was based on the cohort children with valid cortisol data, missingness for inflammation was high; second, the correlation analysis showed that inflammatory markers were not correlated with any mental health problems. Hence, it was not necessary to run separate regression models to test the predictive effect of inflammation on later mental health problem.

5.3 Results

5.3.1 Descriptive statistics and correlation analyses

Comparison of the descriptive information between the analytic and the non-analytic samples demonstrated some sample selection bias (Table 5-1). On average, children in the analytic sample had a less deprived socioeconomic background and higher IQ, had experienced more stressful events, were more likely to be female and White, scored lower on the emotional and behavioural problems considered and had lower average levels of inflammation. The descriptive statistics and correlation coefficients for main variables in this study are shown in Table 5-2. In the analytic

sample of 729 participants, everyone had valid data on hyperactivity/inattention and conduct problems at age 17 years, 728 had complete data on emotional problems and 726 had complete data on peer problems. A total of 61 (8.37%) participants had missing data on emotional and behavioural problems at age 4 years. The amount of missing data for most variables in the analytic sample was low, ranging from 0% to 6% (3.98% for total morning cortisol, 5.35% for IQ, 4.53% for vigorous activity, 3.70% for wake-up time, 5.62% for ethnicity, 0.41% for overweight, 2.33% for medication use and 0% for age and sex). The remaining variables had over 10% missing values (12.21% for diurnal cortisol slope, 17.97% for CAR, 13.17% for AUCg, 29.77% for IL-6, 17.15% for socioeconomic status, 12.21% for stressful life events, 13.17% for daily smoking, and 15.64% for alcohol use). Of the 729 participants, 43.90% were female, 97.09% were White, 19.28% were overweight at 15 years, 15.73% were using steroid medication when cortisol was measured, 6.64% were daily smokers and 3.90% consumed alcohol on more than two days a week.

The correlation coefficients suggested that mental health problems in childhood and adolescence are closely associated. Specifically, hyperactivity/inattention at 4 years was significantly and positively correlated with hyperactivity/inattention at 17 years, and so were conduct problems, emotion problems and peer problems. Diurnal cortisol slope and total morning cortisol were negatively associated with hyperactivity/inattention at 17 years old. Total morning cortisol was also negatively associated with conduct problems at 17 years old. There were no associations of the cortisol measures with emotional or behavioural problems measured at 4 years. The four cortisol measures were positively associated with each other and negatively associated with vigorous activity. Sex may play a role in the negative association between diurnal cortisol levels and vigorous activity as boys are more likely to engage in vigorous physical activities and tend to have lower morning cortisol levels, smaller CAR, flatter diurnal slopes, and smaller AUCg. The two inflammatory markers (IL-6 and CRP) were also positively correlated. No significant associations between emotional or behavioural problems and IL-6 or CRP were observed. Greater CAR was associated with higher levels of IL-6, but not CRP. Both inflammatory markers (IL-6 and CRP) were positively related to being overweight, suggesting that overweight children might be more likely to have low-grade inflammation.

Table 5-1

Sample characteristics in the analytic sample and non-analytic sample

	Analytic sample (N=729)	**Non-analytic sample (N=14716)**		
Categorical variables	N (%)	N (%)	χ^2	P-value
Sex (male)	320 (43.90%)	7315 (51.79%)	17.28	**0.000**
Ethnicity (white)	668 (97.09%)	10869 (94.82%)	6.96	**0.008**
Overweight	140 (19.28%)	965 (20.59%)	0.66	0.415
Medication use	112 (15.73%)	760 (16.47%)	0.25	0.620
Daily smoker	42 (6.64%)	377 (8.40%)	2.29	0.130
Alcohol > 2 days/week	24 (3.90%)	216 (5.42%)	2.49	0.114
Continuous variables	Mean (SD)	Mean (SD)	t	P-value
Age (months) [a]	184.2 (2.26)	185.9 (4.43)	10.37	**0.000**
Socioeconomic status	-0.30 (1.20)	0.02 (1.27)	6.02	**0.000**
Vigorous physical activity	2.33 (0.61)	2.31 (0.66)	-0.69	0.490
Stressful life events	37.22 (17.30)	35.33 (17.99)	-2.56	**0.011**
Inflammation [b]				
IL-6 at 9 years	-0.29 (0.86)	-0.20 (0.79)	2.34	**0.019**
CRP at 16 years	-0.83 (0.99)	-0.71 (1.05)	2.53	**0.012**
IQ	93.91 (13.00)	91.65 (12.99)	-4.25	**0.000**
Emotional and behavioural problems				
Hyperactivity at 17 years	2.32 (2.01)	2.58 (2.13)	3.07	**0.002**
Conduct problems at 17	0.87 (1.20)	1.05 (1.38)	3.34	**0.001**
Emotional problems at 17	1.29 (1.66)	1.53 (1.88)	3.15	**0.002**
Peer problems at 17	1.07 (1.40)	1.12 (1.52)	0.93	0.354
Hyperactivity at 4 years	3.80 (2.30)	3.98 (2.33)	1.94	**0.053**
Conduct problems at 4	1.77 (1.28)	1.98 (1.43)	3.62	**0.000**
Emotional problems at 4	1.33 (1.39)	1.46 (1.53)	2.16	**0.031**
Peer problems at 4	1.40 (1.39)	1.55 (1.51)	2.39	**0.017**

Note. SD: standard deviations. IL-6: interleukin 6. CRP: C-reactive protein. [a] Exact month age when cortisol was measured. [b] Inflammatory markers are log-transformed. Bold: $p < .05$.

5.3.2 Multiple regression models

The unstandardised coefficients of the regression models are summarised in Table 5-3. As expected, hyperactivity/inattention symptoms at 4 years were significant predictors of the hyperactivity/inattention scores at age 17 years, in both unadjusted and adjusted models. This was also true for the conduct problems, emotion problems and peer problems. Diurnal cortisol slope was negatively associated with hyperactivity/inattention at age 17 (b = -0.40, p = 0.01) while adjusting for hyperactivity/inattention symptoms at 4 years. The effect remained significant after controlling for confounders (b = -0.35, p = 0.02) and IL-6 (b = -0.35, p = 0.02) or CRP (b = -0.35, p = 0.02). Specifically, the results suggested that more blunted (i.e., flatter) cortisol slopes predicted higher hyperactivity/inattention behaviours. Hyperactivity/inattention symptoms at age 17 were also be predicted by lower total morning cortisol levels at age 15 (b = -0.47, p = 0.00), even after adjustments for confounders (b = -0.40, p = 0.01). Lower levels of total morning cortisol also predicted higher scores in conduct problems in both the unadjusted (b = -0.25, p = 0.01) and adjusted models (b = -0.25, p = 0.01). These associations survived adjustments for IL-6 (for hyperactivity/inattention b = -0.39, p = 0.01; for conduct problems b = -0.25, p = 0.01) and CRP (for hyperactivity/inattention b = -0.37, p = 0.03; for conduct problems b = -0.26, p = 0.01). CAR and AUCg did not predict hyperactivity/inattention or conduct problems. For the sensitivity analysis, removing the covariates that were not associated with the outcome did not change the model results (Model D). Full results of the adjusted models for conduct problems and hyperactivity/inattention are presented in Tables 5-4 and 5-5, respectively.

As sex was a significant predictor in all models of hyperactivity/inattention, we explored if the associations of basal cortisol with hyperactivity/inattention varied by sex. The results showed that none of the interaction terms between sex and cortisol measures was significant, indicating that the associations of basal cortisol with hyperactivity/inattention did not differ by sex. Full results are presented in Table 5-6.

Emotional problems and peer problems were not associated with any of the cortisol or inflammation measures. Considering that emotional problems were measured by the SDQ, which is a general screening instrument, we further tested the

predictive effect of cortisol and inflammation on depressive symptoms measured by the short Moods and Feeling Questionnaire (Angold et al., 1995) at age 17.5 years for a robustness check. As shown in Table 5-7, neither cortisol nor inflammation measures were linked with depressive symptoms after adjustment for confounders. These findings provide support the notion that early flattened diurnal cortisol rhythms predict an increase in later behaviour problems (hyperactivity/inattention and conduct problems), but not emotional behaviours (emotion problems and peer problems). The effect for conduct problems was specific to morning levels rather than diurnal slope.

5.3.3 Power analysis

Post-hoc power analysis was conducted using the "pwr" package in R (Champely et al., 2017; R Core Team, 2022). The analytic sample offered enough power for small effect sizes (f^{2}[1] = 0.02) to be detected at a .05 level of significance (94% power for the unadjusted models; 80-88% for adjusted models depending on analytic sample size and number of confounding variables entered in each model). This means that if a small effect had existed, we would have had the adequate power to detect it. Therefore, for the non-significant effect that we observed for emotional problems, even if the effect existed, it would be too small to be meaningful.

5.3.4 Correction for multiple testing

To control for the effects of multiple testing, we applied a Bonferroni correction to our analyses. This resulted in a corrected alpha level of 0.000568 for our main analyses (i.e., $p < 0.000568$ was considered statistically significant). The results showed that the associations of mental health problems at 4 years and 17 years survived the correction of multiple testing. However, none of the associations between cortisol measures and behavioural problems at 17 years remained significant after this correction.

[1] Guidelines for interpretation of f^2 indicate that 0.02 is a small effect, 0.15 is a medium effect, and 0.35 is a large effect (Cohen 1992)

Table 5-2

Descriptive statistics and bivariate correlation matrix for all variables of this study

	M(SD)/ proportion	Miss. (%)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Continuous Var.	M (S.D.)																										
1. HY at 4 years	3.80 (2.30)	8.37	-																								
2. CP at 4 years	1.77 (1.28)	8.37	**.42***	-																							
3. EP at 4 years	1.33 (1.39)	8.37	**.16***	**.24***	-																						
4. PP at 4 years	1.40 (1.39)	8.37	**.15***	**.14***	**.21***	-																					
5. HY at 17 years	2.32 (2.01)	0	**.34***	**.24***	**.11***	**.14***	-																				
6. CP at 17 years	.87 (1.20)	0	**.16***	**.21***	.07	.06	**.45***	-																			
7. EP at 17 years	1.29 (1.66)	0.00	**.10***	**.13***	**.22***	**.12***	**.28***	**.24***	-																		
8. PP at 17 years	1.07 (1.40)	0.00	.04	**.11***	**.14***	**.26***	**.16***	**.13***	**.31***	-																	
9. DCS at 15 years	-.64 (.51)	12.21	-.04	.00	-.02	-.06	**-.11***	-.05	-.01	-.02	-																
10. TMC at 15 years	2.85 (.45)	3.98	-.05	-.02	-.02	-.06	**-.12***	**-.10***	.01	-.04	**.85***	-															
11. CAR at 15 years	1.41 (.89)	17.97	-.06	.01	.01	-.06	-.02	-.02	.02	-.08	**.46***	**.54***	-														
12. AUCg at 15 years	4.27 (.42)	13.17	-.03	-.02	-.04	-.08	-.05	-.05	.03	-.05	**.67***	**.82***	**.60***	-													
13. IL-6 at 9 years	-.29 (.86)	29.77	.00	.01	.06	.01	-.02	-.01	-.04	.02	-.01	.05	.10	.07	-												
14. CRP at 16 years	-.83 (.99)	25.79	.04	.04	.00	.02	-.01	.06	-.01	-.00	-.03	-.01	-.04	.01	.12	-											
15. Age in months	184.19 (2.26)	0	.04	-.03	.05	-.03	-.04	.03	-.01	-.00	.03	.01	.02	.03	-.02	.04	-										
16. SES	-0.30 (1.20)	17.15	**.12***	.06	.07	**.09**	**.10**	.08	.02	-.02	.05	.01	.03	.05	.06	.05	.03	-									
17. SLE	37.22 (17.30)	12.21	.08	**.13***	**.12***	-.01	**.15***	**.13***	**.17***	.04	-.04	.01	.06	.02	.05	.05	**.03**	.02	-								
18. IQ	93.91 (13.00)	5.35	**-.13***	-.06	-.05	.04	**-.20***	**-.12***	-.06	.02	-.02	.03	.02	-.00	-.05	-.05	.02	**-.32***	.02	-							
19. Vigorous activity	2.33 (.61)	4.53	.00	-.01	.02	-.00	.01	-.08	**-.07**	**-.12***	**-.10***	**-.08**	**-.13***	**-.10**	-.07	.05	-.04	-.03	.01	.01	-						
20. Wake-up time	7.05 (.44)	3.70	.06	**.12***	**.08**	-.05	.07	.05	.02	.00	**.09**	.05	.03	-.04	-.05	-.04	.07	.05	-.04	**-.10**	.01	-					

Dichotomous Var.	Proportions																									
21. Sex (male)	43.90%	0	.07	.04	.01	**.08**	**.10***	.01	**-.19***	**-.12***	**-.21***	**-.28***	**-.29***	**-.26***	**-.16***	.03	-.01	-.02	-.07	.03	**.22***	-.00	-			
22. Ethnicity (White)	97.09%	5.62	-.02	.02	-.07	.04	-.06	.01	-.01	.01	-.01	-.04	.07	.01	-.00	.08	-.07	-.02	-.01	.07	-.02	-.02	-.03	-		
23. Overweight	19.28%	0.41	**.12***	.06	-.04	.05	.04	.05	-.03	.01	-.07	-.06	-.03	-.04	**.21***	**.30***	-.00	**.11***	**.12***	-.07	-.05	-.05	-.02	.01	-	
24. Medication use	15.73%	2.33	-.03	-.00	-.01	.00	.02	.03	.06	-.00	-.05	.01	-.04	-.04	.02	**.10**	-.02	.03	**.09**	.07	-.03	-.05	-.04	.05	.07	-
25. Daily smoker	6.64%	13.17	-.01	-.01	-.07	-.03	**.11***	**.17***	.02	-.05	-.02	-.01	.07	-.00	.07	.01	-.01	.08	**.10**	**-.13***	**-.08**	**.10**	-.05	-.01	-.06	.04	-
26. Alcohol user	3.90%	15.64	.02	-.01	-.06	-.03	.03	.03	-.01	-.03	-.04	-.05	-.00	.00	.08	.02	-.02	-.01	-.01	-.01	.06	.05	.06	-.03	**.10**	.01	**.19***

Note. Pearson's correlation coefficients were used to test the pairwise associations between variables; The cortisol measures and inflammatory markers are log-transformed; Means, Standard Deviation (SD) for continuous variables and proportions for dichotomous variables; Miss. (%): missingness; HY: hyperactivity/inattention; CP: conduct problems; EP: emotion problems; PP: peer problems; DCS: diurnal cortisol slope; TMC: total morning cortisol; SES: Socioeconomic status; SLE: Stressful life events; Alcohol user: Alcohol >2 days/week; Bold: $p < .05$, *$p < .01$

Table 5-3

Unstandardised regression coefficients of unadjusted and adjusted multiple regression models testing the predictive effects of cortisol measures for later emotional and behavioural problems

	Unadjusted Model		**Model A[a]**		**Model B[b]**		**Model C[c]**		**Model D[d]**	
	Coef. (SE)	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***
Diurnal cortisol slope										
Hyperactivity/inattention at age 17										
Diurnal cortisol slope	**-0.40 (0.16)**	**0.01**	**-0.34 (0.15)**	**0.03**	**-0.34 (0.15)**	**0.03**	**-0.34 (0.15)**	**0.03**	**-0.34 (0.15)**	**0.03**
Hyperactivity/inattention at age 4	**0.29 (0.04)**	**0.00**	**0.26 (0.04)**	**0.00**	**0.26 (0.04)**	**0.00**	**0.26 (0.04)**	**0.00**	**0.26 (0.04)**	**0.00**

IL-6					-0.07 (0.09)	0.41		0.167		
CRP						0.409	-0.12 (0.08)	0.17		
Conduct problems at age 17										
Diurnal cortisol slope	-0.12 (0.08)	0.15	-0.12 (0.08)	0.15	-0.12 (0.08)	0.14	-0.12 (0.08)	0.15	-0.13 (0.08)	0.11
Conduct problems at age 4	**0.20 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.19 (0.03)**	**0.00**
IL-6					-0.06 (0.07)	0.39				
CRP							0.02 (0.05)	0.77		
Emotional problems at age 17										
Diurnal cortisol slope	-0.01 (0.11)	0.94	-0.14 (0.10)	0.20	-0.14 (0.11)	0.20	-0.14 (0.11)	0.20	-0.13 (0.11)	0.23
Emotional problems at age 4	**0.26 (0.06)**	**0.00**	**0.24 (0.06)**	**0.00**	**0.25 (0.06)**	**0.00**	**0.24 (0.06)**	**0.00**	**0.24 (0.06)**	**0.00**
IL-6					-0.15 (0.08)	0.08				
CRP							-0.01 (0.08)	0.90		
Peer problems at age 17										
Diurnal cortisol slope	-0.02 (0.11)	0.88	0.02 (0.11)	0.87	0.02 (0.11)	0.86	0.02 (0.11)	0.88	0.01 (0.11)	0.90
Peer problems at age 4	**0.27 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**
IL-6					0.06 (0.07)	0.38				
CRP							0.01 (0.06)	0.88		
Total morning cortisol										
Hyperactivity/inattention at age 17										
Total morning cortisol	**-0.47 (0.15)**	**0.00**	**-0.40 (0.15)**	**0.01**	**-0.39 (0.15)**	**0.01**	**-0.39 (0.15)**	**0.01**	**-0.37 (0.15)**	**0.01**
Hyperactivity/inattention at age 4	**0.29 (0.04)**	**0.00**	**0.26 (0.03)**	**0.00**	**0.26 (0.03)**	**0.00**	**0.26 (0.04)**	**0.00**	**0.26 (0.03)**	**0.00**

IL-6					-0.07 (0.09)	0.46				
CRP							-0.12 (0.08)	0.17		
Conduct problems at age 17										
Total morning cortisol	**-0.25 (0.09)**	**0.01**	**-0.25 (0.09)**	**0.01**	**-0.25 (0.09)**	**0.01**	**-0.26 (0.10)**	**0.01**	**-0.26 (0.09)**	**0.00**
Conduct problems at age 4	**0.20 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.03)**	**0.00**
IL-6					-0.05 (0.07)	0.44				
CRP							0.02 (0.05)	0.73		
Emotional problems at age 17										
Total morning cortisol	0.04 (0.12)	0.72	-0.17 (0.12)	0.16	-0.16 (0.13)	0.20	-0.17 (0.12)	0.16	-0.16 (0.12)	0.18
Emotional problems at age 4	**0.26 (0.06)**	**0.00**	**0.24 (0.06)**	**0.00**	**0.24 (0.06)**	**0.00**	**0.24 (0.06)**	**0.00**	**0.24 (0.06)**	**0.00**
IL-6					-0.14 (0.08)	0.08				
CRP							-0.01 (0.08)	0.92		
Peer problems at age 17										
Total morning cortisol	-0.07 (0.11)	0.53	0.00 (0.11)	1.00	-0.00 (0.11)	0.97	-0.00 (0.11)	0.99	0.01 (0.11)	0.92
Peer problems at age 4	**0.27 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**
IL-6					0.06 (0.07)	0.37				
CRP							0.01 (0.06)	0.88		
CAR										
Hyperactivity/inattention at age 17										
CAR	0.01 (0.10)	0.91	0.06 (0.09)	0.52	0.07 (0.10)	0.49	0.06 (0.09)	0.54	0.05 (0.09)	0.58
Hyperactivity/inattention at age 4	**0.30 (0.04)**	**0.00**	**0.27 (0.04)**	**0.00**	**0.27 (0.04)**	**0.00**	**0.27 (0.04)**	**0.00**	**0.27 (0.03)**	**0.00**

IL-6					-0.08 (0.09)	0.40				
CRP							-0.12 (0.08)	0.16		
Conduct problems at age 17										
CAR	-0.03 (0.05)	0.86	-0.05 (0.05)	0.39	-0.04 (0.05)	0.46	-0.05 (0.05)	0.39	-0.06 (0.05)	0.23
Conduct problems at age 4	**0.20 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.19 (0.03)**	**0.00**
IL-6					-0.06 (0.07)	0.41				
CRP							0.01 (0.05)	0.80		
Emotional problems at age 17										
CAR	0.03 (0.08)	0.67	-0.07 (0.08)	0.40	-0.06 (0.08)	0.48	-0.07 (0.08)	0.39	-0.08 (0.08)	0.32
Emotional problems at age 4	**0.26 (0.06)**	**0.00**	**0.24 (0.05)**	**0.00**	**0.25 (0.06)**	**0.00**	**0.24 (0.05)**	**0.00**	**0.24 (0.06)**	**0.00**
IL-6					-0.14 (0.08)	0.09				
CRP							-0.01 (0.08)	0.87		
Peer problems at age 17										
CAR	-0.09 (0.07)	0.16	-0.06 (0.07)	0.40	-0.06 (0.07)	0.38	-0.06 (0.07)	0.40	-0.07 (0.07)	0.34
Peer problems at age 4	**0.27 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**
IL-6					0.07 (0.07)	0.31				
CRP							0.01 (0.06)	0.90		
AUCg										
Hyperactivity/inattention at age 17										
AUCg	-0.18 (0.19)	0.33	-0.09 (0.19)	0.63	-0.08 (0.19)	0.66	-0.08 (0.19)	0.66	-0.10 (0.19)	0.59
Hyperactivity/inattention at age 4	**0.30 (0.04)**	**0.00**	**0.26 (0.04)**	**0.00**	**0.26 (0.04)**	**0.00**	**0.26 (0.04)**	**0.00**	**0.26 (0.03)**	**0.00**

IL-6					-0.07 (0.09)	0.42				
CRP							-0.12 (0.08)	0.16		
Conduct problems at age 17										
AUCg	-0.11 (0.12)	0.34	-0.14 (0.12)	0.25	-0.14 (0.12)	0.27	-0.14 (0.12)	0.25	-0.14 (0.12)	0.22
Conduct problems at age 4	**0.20 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**
IL-6					-0.06 (0.07)	0.42				
CRP							0.02 (0.05)	0.76		
Emotional problems at age 17										
AUCg	0.16 (0.16)	0.30	-0.05 (0.15)	0.77	-0.03 (0.15)	0.86	-0.044 (0.15)	0.77	-0.04 (0.15)	0.78
Emotional problems at age 4	**0.26 (0.06)**	**0.00**	**0.24 (0.06)**	**0.00**	**0.25 (0.06)**	**0.00**	**0.24 (0.06)**	**0.00**	**0.24 (0.06)**	**0.00**
IL-6					-0.15 (0.08)	0.07				
CRP							-0.01 (0.08)	0.91		
Peer problems at age 17										
AUCg	-0.07 (0.13)	0.60	-0.01 (0.14)	0.93	-0.02 (0.14)	0.89	-0.02 (0.14)	0.91	-0.02 (0.14)	0.88
Peer problems at age 4	**0.27 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**	**0.26 (0.05)**	**0.00**
IL-6					0.06 (0.07)	0.37				
CRP							0.01 (0.06)	0.87		

Note. Cortisol measures (Diurnal cortisol slope, total morning cortisol, CAR and AUCg) were measured at 15 years. IL-6 was measured at 9 years. CRP was measured at 16 years. Bold: $p < .05$

[a]Adjusted for sex, ethnicity, overweight, socioeconomic status, age, smoking, alcohol use, medication use, vigorous physical activity, wake-up time, IQ, and stressful life events

[b]Model A + additional adjustment for inflammation (IL-6).

[c]Model A + additional adjustment for inflammation (CRP).

[d]Adjusted for covariates that were significantly associated with outcome variables. For *Hyperactivity/inattention*, sex, smoking, socioeconomic status, stressful life events and IQ were adjusted. For *Conduct problems*, smoking, vigorous physical activity, stressful life events and IQ were adjusted. For *Emotional problems*, sex and stressful life events were adjusted. For *Peer problems*, sex and vigorous physical activity were adjusted.

Complete results of the Model Bs predicting *Hyperactivity/inattention* and *Conduct problems* are presented in table 5-3 and table 5-4 respectively.

Table 5-4

Unstandardised regression coefficients of multiple regression models testing the predictive effects of cortisol measures hyperactivity/inattention at 17 years while adjusting for covariates, IL-6, and hyperactivity/inattention at 4 years (N=729)

	Model B - DCS		**Model B - TMC**		**Model B - CAR**		**Model B - AUCg**	
	Coef. (SE)	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***
Cortisol measures								
Diurnal cortisol slope	**-0.34 (0.15)**	**0.03**						
Total morning cortisol			**-0.39 (0.15)**	**0.01**				
CAR					0.07 (0.10)	0.49		
AUCg							-0.08 (0.19)	0.66
Hyperactivity at age 4	**0.26 (0.04)**	**0.00**	**0.26 (0.03)**	**0.00**	**0.27 (0.04)**	**0.00**	**0.26 (0.04)**	**0.00**

IL-6	-0.07 (0.09)	0.41	-0.07 (0.09)	0.46	-0.08 (0.09)	0.39	-0.07 (0.09)	0.42
Sex (male)	**0.31 (0.15)**	**0.03**	**0.29 (0.15)**	**0.05**	**0.41 (0.15)**	**0.01**	**0.36 (0.15)**	**0.02**
Overweight	-0.07 (0.19)	0.73	-0.07 (0.19)	0.72	-0.03 (0.19)	0.89	-0.04 (0.19)	0.84
Ethnicity	-0.54 (0.38)	0.15	-0.57 (0.39)	0.14	-0.56 (0.40)	0.16	-0.52 (0.49)	0.18
Socioeconomic status	0.02 (0.07)	0.76	0.02 (0.07)	0.78	0.02 (0.07)	0.83	0.02 (0.07)	0.80
Age	-0.05 (0.03)	0.11	-0.05 (0.03)	0.10	-0.05 (0.03)	0.09	-0.05 (0.03)	0.10
Waking time	0.21 (0.16)	0.20	0.20 (0.16)	0.22	0.17 (0.16)	0.29	0.17 (0.16)	0.29
Vigorous activity	-0.05 (0.12)	0.67	-0.04 (0.12)	0.75	-0.02 (0.12)	0.85	-0.03 (0.12)	0.78
Stressful life Events	**0.02 (0.00)**	**0.00**	**0.02 (0.00)**	**0.00**	**0.02 (0.00)**	**0.00**	**0.02 (0.00)**	**0.00**
IQ	**-0.02 (0.01)**	**0.00**	**-0.02 (0.01)**	**0.00**	**-0.02 (0.01)**	**0.00**	**-0.02 (0.01)**	**0.00**
Medication use	0.17 (0.21)	0.41	0.19 (0.21)	0.36	0.20 (0.21)	0.35	0.18 (0.21)	0.39
Daily smoker	0.56 (0.35)	0.11	0.56 (0.35)	0.11	0.57 (0.35)	0.11	0.58 (0.35)	0.10
Alcohol use	0.10 (0.48)	0.84	0.09 (0.48)	0.85	0.10 (0.47)	0.82	0.12 (0.48)	0.81
Intercept	10.01 (5.59)	0.07	**11.64 (5.60)**	**0.04**	10.63 (5.62)	0.06	10.94 (5.72)	0.06

Note. Bold: $p < .05$

Table 5-5

Unstandardised regression coefficients of multiple regression models testing the predictive effects of cortisol measures conduct problems at 17 years while adjusting for covariates, IL-6, and conduct problems at 4 years. (N=729)

	Model B - DCS		**Model B - TMC**		**Model B - CAR**		**Model B - AUCg**	

	Coef. (SE)	*p*	Coef. (SE)	*p*	Coef. (SE)	*p*	Coef. (SE)	*p*
Cortisol measures								
Diurnal cortisol slope	-0.13 (0.08)	0.14						
Total morning cortisol			**-0.25 (0.09)**	**0.01**				
CAR					-0.04 (0.05)	0.46		
AUCg							-0.14 (0.12)	0.27
Conduct problems at age 4 years	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**	**0.18 (0.04)**	**0.00**
IL-6	-0.06 (0.07)	0.39	-0.05 (0.07)	0.44	-0.06 (0.07)	0.41	-0.06 (0.07)	0.42
Sex (male)	0.05 (0.09)	0.56	0.02 (0.09)	0.85	0.06 (0.09)	0.53	0.05 (0.09)	0.60
Overweight	0.09 (0.12)	0.43	0.08 (0.12)	0.48	0.10 (0.12)	0.39	0.10 (0.12)	0.43
Ethnicity (non-White)	0.13 (0.23)	0.58	0.10 (0.23)	0.67	0.14 (0.23)	0.53	0.14 (0.23)	0.55
Socioeconomic status	0.03 (0.04)	0.55	0.03 (0.04)	0.55	0.03 (0.04)	0.55	0.03 (0.04)	0.52
Age	0.02 (0.02)	0.27	0.02 (0.02)	0.28	0.02 (0.02)	0.28	0.02 (0.02)	0.26
Waking time	0.03 (0.12)	0.79	0.03 (0.12)	0.79	0.02 (0.12)	0.85	0.01 (0.12)	0.90
Vigorous activity	**-0.14 (0.07)**	**0.04**	**-0.14 (0.07)**	**0.04**	**-0.14 (0.07)**	**0.04**	**-0.14 (0.07)**	**0.04**
Stressful life Events	0.01 (0.00)	0.05	**0.01 (0.00)**	**0.05**	**0.01 (0.00)**	**0.05**	**0.01 (0.00)**	**0.05**
IQ	**-0.01 (0.00)**	**0.03**	**-0.01 (0.00)**	**0.03**	**-0.01 (0.00)**	**0.03**	**-0.01 (0.00)**	**0.03**
Medication use	0.05 (0.13)	0.71	0.06 (0.13)	0.66	0.05 (0.13)	0.72	0.05 (0.13)	0.72
Daily smoker	**0.69 (0.24)**	**0.00**	**0.69 (0.24)**	**0.01**	**0.72 (0.24)**	**0.00**	**0.70 (0.24)**	**0.00**
Alcohol use	0.05 (0.23)	0.82	0.05 (0.22)	0.82	0.06 (0.22)	0.80	0.07 (0.23)	0.77

Intercept	-2.69 (3.33)	0.42	-1.78 (3.25)	0.58	-2.43 (3.31)	0.46	-1.95 (3.27)	0.55

Note. Bold: $p < .05$

Table 5-6 *Results of regression models examining the moderating effects of sex on the association between cortisol measures and hyperactivity/inattention at 17 years*

	Model D - DCS		**Model D - TMC**		**Model D - CAR**		**Model D - AUCg**	
	Coef. (SE)	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***
Cortisol measures								
Diurnal cortisol slope	-0.35 (0.22)	0.10						
Total morning cortisol			-0.23 (0.21)	0.28				
CAR					0.13 (0.12)	0.26		
AUCg							-0.03 (0.23)	0.89
Hyperactivity at age 4	**0.26 (0.03)**	**0.00**	**0.26 (0.03)**	**0.00**	**0.27 (0.03)**	**0.00**	**0.26 (0.03)**	**0.00**
Sex (male)	0.35 (0.24)	0.15	1.09 (0.86)	0.20	**0.65 (0.28)**	**0.02**	1.30 (1.72)	0.45
Cortisol * Sex	0.04 (0.30)	0.89	-0.28 (0.29)	0.35	-0.17 (0.18)	0.35	-0.22 (0.40)	0.59
Socioeconomic status	0.02 (0.07)	0.75	0.02 (0.07)	0.82	0.01 (0.07)	0.87	0.02 (0.07)	0.82
Stressful life events	**0.02 (0.00)**	**0.00**	**0.02 (0.00)**	**0.00**	**0.02 (0.00)**	**0.00**	**0.02 (0.00)**	**0.00**
IQ	**-0.02 (0.01)**	**0.00**	**-0.02 (0.01)**	**0.00**	**-0.02 (0.01)**	**0.00**	**-0.02 (0.01)**	**0.00**
Daily smoker	**0.65 (0.33)**	**0.05**	**0.66 (0.33)**	**0.05**	**0.66 (0.33)**	**0.05**	**0.67 (0.33)**	**0.04**

Intercept	**2.55 (0.68)**	**0.00**	**3.36 (0.90)**	**0.00**	**2.48 (0.69)**	**0.00**	**2.85 (1.18)**	**0.02**

Note. Bold: $p < .05$

Table 5-7 *Results of regression models on associations between cortisol measures and depressive symptoms at 17.5 years (n=619)*

	DCS		**TMC**		**CAR**		**AUCg**	
	Coef. (SE)	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***
Cortisol measures								
Diurnal cortisol slope	-0.26 (0.40)	0.51						
Total morning cortisol			-0.70 (0.47)	0.14				
CAR					-0.33 (0.24)	0.17		
AUCg							-0.57 (0.54)	0.29
Depression at age 9	**0.26 (0.07)**	**0.00**	**0.26 (0.07)**	**0.00**	**0.27 (0.07)**	**0.00**	**0.26 (0.07)**	**0.00**
Sex (male)	**-1.83 (0.40)**	**0.00**	**-1.94 (0.42)**	**0.00**	**-1.92 (0.39)**	**0.00**	**-1.89 (0.41)**	**0.00**
Ethnicity (White)	**3.34 (1.16)**	**0.00**	**3.28 (1.16)**	**0.01**	**3.47 (1.16)**	**0.00**	**3.37 (1.15)**	**0.00**
Vigorous activity	-0.15 (0.33)	0.65	-0.15 (0.33)	0.64	-0.17 (0.33)	0.61	-0.16 (0.33)	0.65
Stressful life events	**0.04 (0.01)**	**0.00**	**0.04 (0.01)**	**0.00**	**0.04 (0.01)**	**0.00**	**0.04 (0.01)**	**0.00**
Daily smoker	**2.05 (0.83)**	**0.01**	**2.04 (0.83)**	**0.01**	**2.14 (0.84)**	**0.01**	**2.06 (0.83)**	**0.01**
IL-6	0.48 (0.28)	0.09	0.50 (0.28)	0.08	0.51 (0.28)	0.07	0.50 (0.28)	0.08
Intercept	**3.78 (0.93)**	**0.00**	**6.01 (1.57)**	**0.00**	**4.48 (0.97)**	**0.00**	**6.46 (2.45)**	**0.01**

Note. Bold: $p < .05$. Depressive symptoms at ages 9 and 17.5 were measured by short Moods and Feeling questionnaires (Angold et al., 1995).

5.4 Summary

This study investigated the associations of inflammation and diurnal cortisol levels with the emotional and behavioural problems in adolescence. First, correlation coefficients between main variables were calculated. Hyperactivity/inattention and conduct problems in late adolescence were correlated with cortisol measures, but not inflammatory markers. Early mental health symptoms were not found to be correlated with any inflammatory markers or cortisol measures. Next, several sets of multiple regression models were run to test the predictive effects of cortisol measures and inflammation markers on later emotional and behavioural problems while adjusting for each other. Contrary to the hypotheses, no evidence was found for the role of inflammation or other cortisol measures (i.e., CAR and AUCg) in explaining the development of emotional or behavioural problems. Yet, lower morning cortisol and flatter diurnal cortisol slope were found to be associated with higher levels of hyperactivity/inattention symptoms two years later, which was consistent with previous evidence (Blomqvist et al., 2007; Ibrahim et al., 2016; Salis et al., 2016). These associations survived from further adjustments for the hyperactivity/inattention problems in early childhood and covariates. It is likely that the significant association found for flatter cortisol slope was driven by the lower morning cortisol levels as they were strongly correlated. Similarly, lower morning cortisol was predictive of future conduct problems after adjustments for conduct problems in early childhood, inflammation, and covariates. These results were in line with previous evidence on cortisol profiles in adolescents with ADHD (Angeli et al., 2018; Isaksson et al., 2012) and conduct problems/disorders (Pajer et al., 2001; Salis et al., 2016; Shoal et al., 2003). They suggest that hypocortisolism might be indicative of adolescents' later behavioural problems. However, it should be noted that after multiple testing correction, the associations between cortisol measures and hyperactivity/inattention and conduct problems became nonsignificant.

5.5 Chapter summary and next step

In this chapter, a series of longitudinal regression models were run to explore temporal associations of cortisol measures and inflammatory markers with future emotional and behavioural problems. The results revealed a robust predictive effect of

cortisol measures for behaviour problems, but not emotional problems, in late adolescence. Yet, emotional and behavioural problems in early childhood were not associated with diurnal cortisol levels or inflammation. The latter finding was rather unexpected given the empirical evidence available suggesting that early mental health problems often continue through childhood and adolescence and can induce chronic stress (Bosquet & Egeland, 2006; Champion et al., 1995; Frick & Dantagnan, 2005; Rudolph et al., 2009). Therefore, the next chapter will attempt to dig deeper into possible effects of childhood mental health problems on stress systems in adolescence. However, because the association between the trajectories of emotional and behavioural symptoms and inflammatory markers has been studied using the ALSPAC sample in a previous study (Flouri, Lewis, & Francesconi, 2020), the next chapter will focus on the diurnal cortisol activity. In addition, as the developmental courses of mental health problems are needed to be identified first (before investigating how they may be associated with cortisol), including all four kinds of mental health problems in one study would be excessive. Since lower morning cortisol and flatter diurnal cortisol slope were found to be associated with higher levels of hyperactivity/inattention symptoms in adolescence in this chapter, evidence for a link between early hyperactivity/inattention symptoms and blunted diurnal cortisol (if found) might suggest a mechanism underlying the continuity of hyperactivity/inattention from childhood to adolescence. Therefore, in the next chapter, I chose to explore the relationship between the hyperactivity/inattention trajectories throughout childhood and the diurnal cortisol pattern in adolescence.

Chapter 6: Childhood Trajectories of Hyperactivity/ Inattention Symptoms and Diurnal Cortisol in Middle Adolescence

This chapter is based on a published paper as Ji, D., Flouri, E., Papachristou, E., & Francesconi, M. (2021). Childhood Trajectories of Hyperactivity/Inattention Symptoms and Diurnal Cortisol in Middle Adolescence: Results from a UK Birth Cohort. *Journal of Attention Disorders, 26*(6), 809-821. https://doi.org/10.1177/10870547211036755 To acknowledge the contributions of co-authors, "we" will be used instead of "I" in this chapter.

6.1 Introduction

Hyperactivity/inattention symptoms are common among children and adolescents (Smalley et al., 2007; Smidts & Oosterlaan, 2007; Warner-Rogers et al., 2000), with prevalence rates ranging between 7% and 16% in the general population (Faraone et al., 2003), and have been shown to be associated with future adverse outcomes, such as depression (Humphreys et al., 2013), nicotine dependence (Pingault et al., 2013), and suicidal behaviours (Galéra et al., 2008). Empirical research on clinical samples of children with ADHD suggests that one potential reason underlying symptom onset might be an impaired HPA axis (Angeli et al., 2018; Blomqvist et al., 2007; Isaksson et al., 2012). However, as reviewed in Chapter 2, findings of studies on the relation between hyperactivity/inattention symptoms and HPA dysfunction in community samples are mixed (Hatzinger et al., 2007; Pesonen et al., 2011; Sondeijker et al., 2007). Except for the evidence of the association between HPA axis hypoactivity and hyperactivity/inattention found in two studies (Scerbo & Kolko, 1994; Susman et al., 2007), most research in community samples has reported normal activity of the HPA axis (i.e., a normal diurnal cortisol rhythm) in children with hyperactivity/inattention symptoms (Klimes-Dougan et al., 2001; Pesonen et al., 2011; Saridjan et al., 2014). A few studies even found evidence of hypercortisolism in children with hyperactivity/inattention symptoms (Hatzinger et al., 2007; Sondeijker et al., 2007). In Chapter 5 we found that hyperactivity/inattention symptoms at the age 4 years were not associated with morning cortisol levels or diurnal cortisol slope in adolescence, whereas the cortisol measures significantly predicted hyperactivity/inattention problems two years later.

Two reasons may contribute to the inconsistency in findings from community samples. First, most studies using community samples used linear regression models which assume that the relationship between hyperactivity/inattention symptoms and HPA axis function is linear. However, HPA axis hypoactivity might be associated only with severe symptoms, i.e., when symptom severity surpasses a certain threshold. Second, most studies using community samples are cross-sectional or use variables measured at two fixed time points (e.g., behavioural problems at around 8 years and morning cortisol levels at 11 years in Ruttle et al., 2011), and are, thus, unable to investigate potential effects of chronic hyperactivity/inattention symptoms on HPA axis function. Though symptoms of hyperactivity and inattention tend to decline over time, a significant number of children follow persistently high or increasing symptom trajectories (Arnold et al., 2014; Jester et al., 2008; Malone et al., 2010). Previous research suggests that compared to children with decreasing numbers of hyperactivity/inattention symptoms over time, those with symptoms that persist through to adolescence are more likely to exhibit a blunted cortisol response to stressors (Campbell, 1994; King et al., 1998). It is, therefore, possible that only persistently high levels of hyperactivity may be related to impaired HPA axis activity.

The aim of the present study was to explore for the first time the role of chronicity and severity of hyperactivity/inattention symptoms across childhood in HPA axis function in adolescence using data from ALSPAC. Growth mixture models were used to identify classes with distinct developmental trajectories of hyperactivity/inattention symptoms and the HPA axis function was captured by diurnal cortisol output. It was hypothesised that persistently high levels of these symptoms across childhood and adolescence would be associated with hypoactivity of the HPA axis (hypocortisolism, i.e., lower CAR, lower cortisol levels throughout the day, and lower total daily output as well as flatter diurnal cortisol slope).

6.2 Method

Participants and variables from the Avon Longitudinal Study of Parents and Children have previously been described in detail in Chapter 4; a summary of these methods is included below.

6.2.1 Participants

At age 15, 5,501 of the ALSPAC cohort children were recruited for a clinical assessment. Of those, 3,020 were invited at random to participate in the cortisol data collection and 1,845 agreed. For 968 participants who provided at least one valid saliva sample, we applied the following exclusion criteria: 1) second born in case of a twin birth; 2) gestation at birth <= 32 weeks; 3) birth weight <= 1500 g; and 4) current exposure to steroid medication. We further excluded 10 participants due to the lack of hyperactivity/inattention data, resulting in a total sample of 939 individuals in this study (see the details in Figure 6-1).

6.2.2 Measures

6.2.2.1 Cortisol

Information on the cortisol sampling, data cleaning and variable deriving processes have been previously described in Chapter 4. In this study, we used mean cortisol levels at four time points and derived five cortisol measures to capture diurnal cortisol pattern: diurnal cortisol decline, diurnal cortisol slope, total morning cortisol, CAR and AUCg. The data cleaning process for these cortisol measures were described in Chapter 3 and are summarised in Figure 6-1.

6.2.2.2 Hyperactivity/inattention symptoms

Hyperactivity/inattention symptoms were measured with the hyperactivity/inattention symptoms subscale of the mother rated SDQ (Goodman 1997) at ages 4, 7, 8, 9, 11, and 13 years. The SDQ is a behavioural screening questionnaire with sound psychometric properties (Goodman et al., 2010). The subscale assesses hyperactivity/inattention using five items, scored 0 to 2 (“not true”, “somewhat true”, and “certainly true”). Questions include three items assessing hyperactive-impulsive behaviours (“Restless, overactive. Cannot stay still for long”, “Constantly fidgeting or squirming”, “Thinks things out before acting”) and two questions measuring symptoms of inattention (“Easily distracted, concentration wanders”, “Sees tasks through to the end. Good attention span”). Symptom scores

showed moderate temporal stability across the years in our analytic sample (0.44 < Spearman's Rho < 0.73; Table 6-1).

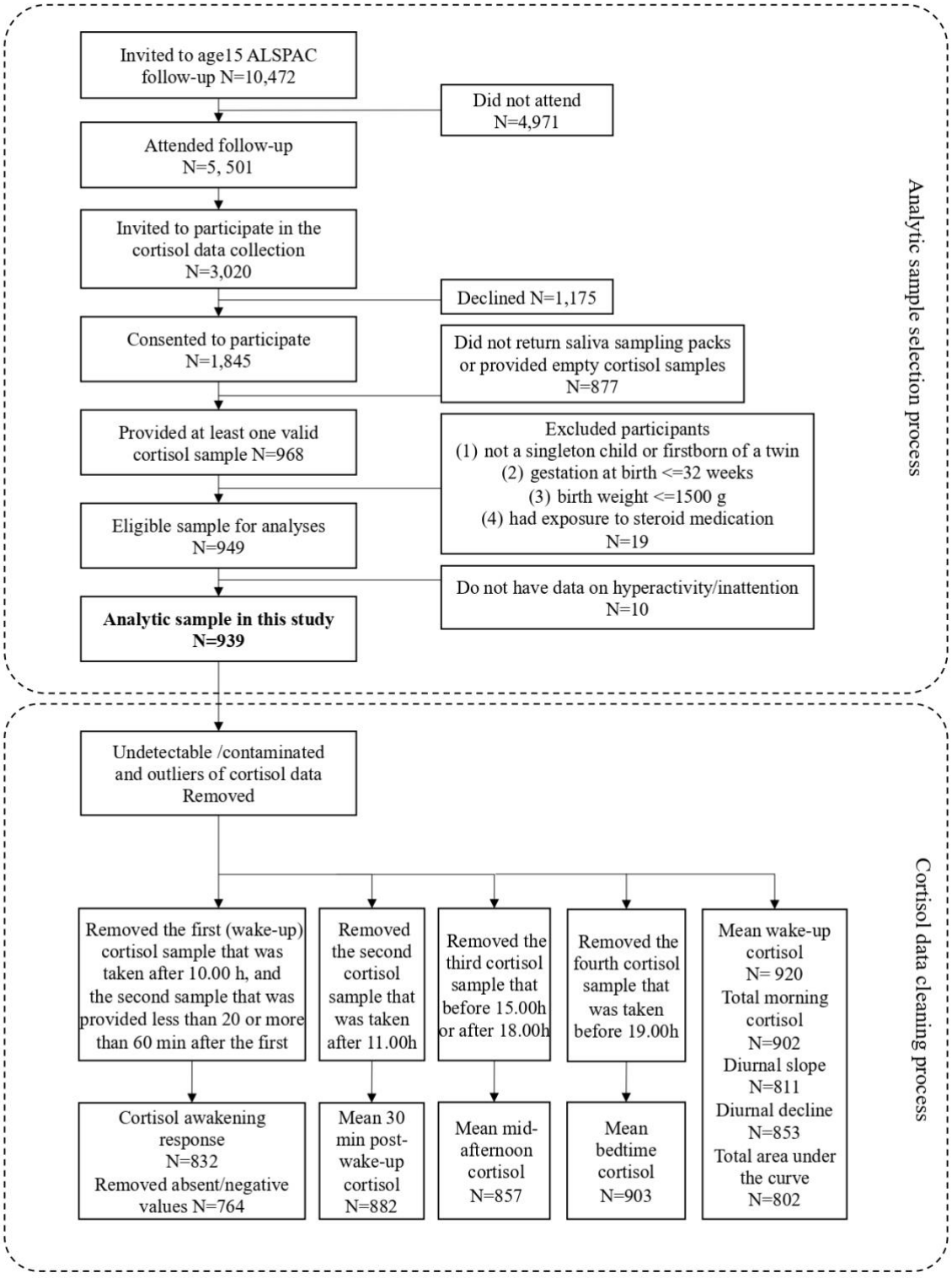

Figure 6-1 Analytic sample selection process

Table 6-1

Spearman's correlation coefficients of hyperactivity/inattention symptoms across assessments

Age (year)	4	7	8	9	11
4	1				
7	0.5617*	1			
8	0.5271*	0.7049*	1		
9	0.4995*	0.7019*	0.7323*	1	
11	0.4374*	0.6289*	0.6374*	0.7106*	1
13	0.4501*	0.5871*	0.5941*	0.6745*	0.7455*

Note. *$p < .01$

6.2.2.3 Covariates

In this study, several covariates that are known to be associated with children's hyperactivity/inattention symptoms and HPA axis activity were controlled for. These included sex (Goel et al., 2011; Hermens et al., 2005), ethnicity (Bax et al., 2019; DeSantis et al., 2007), socioeconomic status (Marsman et al., 2012; Russell et al., 2016) and stressful life events (Elzinga et al., 2008; Vrijsen et al., 2018). Additional covariates measured at participants' age 15 years included age in months (Kudielka & Kirschbaum, 2003), wake-up time (the mean values of repetitive records during the cortisol sampling period) (Dahlgren et al., 2009; Stalder et al., 2009), overweight ("yes", "no"); (Yu et al., 2020), vigorous physical activity (Anderson & Wideman, 2017), daily smoker (Eiden et al., 2020), contraceptive and psychotropic medication use (Kirschbaum, Pirke, & Hellhammer, 1995; O'Donnell et al., 2013), and alcohol use (Ruttle et al., 2015). As cognitive function has been linked to both basal responsive cortisol levels (Lupien et al., 2001) and inattention/hyperactivity symptoms (Polderman et al., 2009), IQ at age 15 years was also considered as a covariate. Details on these covariates and how they were measured can be found in Chapter 4.

In sensitivity analyses, we further adjusted for diagnoses of ADHD, Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD) by age 15, using the parent version of the Development and Well-being Assessment (DAWBA, Goodman et al, 2000). In analyses involving CAR only, we additionally controlled for wake-up cortisol levels, as it is frequently reported that high levels of salivary cortisol at wake-up are associated with an attenuated CAR (Adam et al., 2006).

6.2.3 Statistical Analysis

The values of cortisol measures were log-transformed in all analyses to correct for skewed distributions. The analytic approach was as follows. First, growth mixture models (GMMs) were fitted to identify classes of participants with distinct developmental trajectories of hyperactivity/inattention symptoms from ages 4 to 13 years. A Robust maximum likelihood estimator was used to account for skewed data distributions in hyperactivity/inattention scores and the covariates. Full information maximum likelihood was used to account for missing data in hyperactivity/inattention scores and covariates. The optimal number of classes was determined using the following fit indices (Jung & Wickrama, 2008): (a) The Bayesian information criterion (BIC), the sample size adjusted BIC (SSA-BIC) and the Akaike information criterion (AIC). Lower values in all three indices indicate better fit; (b) the Vuong-Lo-Medell-Rubin likelihood ratio test (LRT), which compares a model with K classes to a model with (K-1) classes. Significant p-values (< .05) indicate significantly better model fit compared to the more parsimonious model; and (c) the entropy of the model, which evaluates the accuracy of model classification, with values closer to 1 indicating less uncertainty in class allocation. Upon selection of the best-fitting solution, participants were assigned to the class for which they had the highest posterior probability of belonging. We tested for differences in sociodemographic characteristics and cortisol measures between classes using analyses of variance and chi-square tests. Next, we computed the average predicted levels (marginal means) of cortisol based on a linear regression model with an interaction term between sampling time and class membership. By doing so we were able to graphically illustrate the diurnal cortisol profiles of adolescents across classes and to compare predicted mean cortisol levels across classes at the four time points.

In the second part of the analysis, two multiple linear regression models were fitted to investigate the predictive effect of class membership for CAR, total morning cortisol, diurnal cortisol decline/slope, and AUCg. For each cortisol measure, unadjusted regression models were initially run, followed by models adjusted for confounders (sex, ethnicity, overweight, socioeconomic status, age, smoking, alcohol use, medication use, vigorous physical activity, wake-up time, IQ, stressful life events, and behavioural disorders) and models adjusted for only the confounders that were statistically associated with the cortisol measures (sex and vigorous physical activity). We weighted all regression models using the conditional probabilities of individuals' group membership, thereby giving more weight to participants with higher certainty of class assignment. Analyses were conducted in Mplus 8.1 (Muthén & Muthén, 1998-2017) and Stata 16 (StataCorp, 2019).

6.3 Results

The comparison between the analytic sample and the rest of ALSPAC sample is presented in Table 6-2. The results showed that compared with the non-analytic sample, our analytic sample was more likely to be White and female and have more stressful life events in childhood. They also tend to be younger, have higher socio-economic status, higher IQ, and lower levels of hyperactivity/inattention problems.

6.3.1 Identification of Developmental Trajectories of Hyperactivity/Inattention Symptoms

GMM was conducted for 939 children with available data in at least one of the assessments for hyperactivity/inattention symptoms at ages 4, 7, 8, 9, 11, and 13 years. Starting with a one-class model, stepwise addition of classes resulted in lower BIC, SSA-BIC, and AIC values, suggesting a better model fit to the data for higher-class solutions (Table 6-3). However, the 4- and 5-class solutions had non-significant LRT p-values while changes in BIC values became negligible compared to the 3-class model. Moreover, the 3-class solution had the highest entropy value of the five competing models, indicating the least ambiguity in class assignment. The 3-class solution was therefore selected for further testing. Based on the developmental patterns of hyperactivity/inattention problems from 4 to 13 years observed in the

classes we termed them as follows. (a) “Low and decreasing” (71.0% of the sample). Children in this class showed decreasing number of symptoms with a low score at baseline (intercept = 3.04, $p < .01$; slope = -0.18, $p < .01$). (b) “Intermediate” (24.5% of the sample). Children in this class had a moderate and stable number of symptoms throughout the study period (intercept = 4.81, $p < .01$; slope = -0.04, $p = .20$). (c) “High” (4.5%). Children in this class were characterised by high levels of symptoms throughout the study period (intercept = 7.17, $p < .01$; slope = 0.10, $p = .12$). The trajectories of symptoms characterising each of the three classes are illustrated in Figure 6-2.

Table 6-2

Sample characteristics in the analytic and non-analytic samples

	Analytic sample (N=939)	**Non-analytic sample (N=14506)**		
Categorical variables	N (%)	N (%)	χ^2	P-value
Sex (male)	422 (44.94%)	7213 (51.84%)	16.74	**0.000**
Ethnicity (white)	848 (96.36%)	10689 (94.84%)	3.93	**0.047**
Overweight	183 (19.55%)	922 (20.60%)	0.52	0.470
Medication use	140 (15.22%)	732 (16.61%)	1.09	0.299
Daily smoker	57 (7.45%)	362 (8.31%)	0.63	0.426
Alcohol > 2 days/week	31 (3.92%)	209 (5.49%)	3.24	0.072
Behavioural disorder				
Continuous variables	Mean (SD)	Mean (SD)	t	P-value
Age (months) [a]	184.3 (2.32)	186.0 (4.49)	10.92	**0.000**
Socioeconomic status	-0.22 (1.19)	0.02 (1.27)	5.06	**0.000**
Vigorous physical activity	2.32 (0.62)	2.31 (0.66)	-0.56	0.575
Stressful life events	37.45 (17.40)	35.26 (17.99)	-3.27	**0.001**
IQ	93,32 (13.01)	91.67 (12.99)	-3.43	**0.001**
Hyperactivity at 4 years	3.94 (2.35)	3.97 (2.33)	0.39	0.696
Hyperactivity at 7 years	3.21 (2.36)	3.41 (2.37)	2.27	**0.023**
Hyperactivity at 8 years	3.12 (2.33)	3.37 (2.48)	2.74	**0.006**
Hyperactivity at 9 years	2.69 (2.15)	2.99 (2.27)	3.72	**0.000**
Hyperactivity at 11 years	2.52 (2.13)	2.82 (2.25)	3.62	**0.000**
Hyperactivity at 13 years	2.61 (2.11)	2.96 (2.24)	4.31	**0.000**

Note. SD: standard deviations. [a] Exact month age at which cortisol was measured. Bold: $p < .05$.

Table 6-3

Fit indices of 1- to 5-class solutions of growth mixture models examining the developmental trajectories of hyperactivity/inattention from ages 4 to 13 years.

	1 class (C1)	2 classes (C2)	3 classes (C3)	4 classes (C4)	5 classes (C5)
BIC	19809.195	19688.248	19652.523	19652.137	19650.631
AIC	19755.902	19620.421	19570.161	19555.241	19539.201
SSA-BIC	19774.259	19643.785	19598.532	19588.618	19577.585
Entropy	–	0.811	0.811	0.737	0.734
Vuong-Lo-Medell-Rubin adj. LRT (*p*-value)	–	.000	.000	.504	.072
Estimated group sizes (%)					
C1	100	15.6	71.0	13.4	3.9
C2	–	84.4	24.5	18.2	4.0
C3	–	–	4.5	5.1	55.8
C4	–	–	–	63.3	18.9
C5	–	–	–	–	17.5

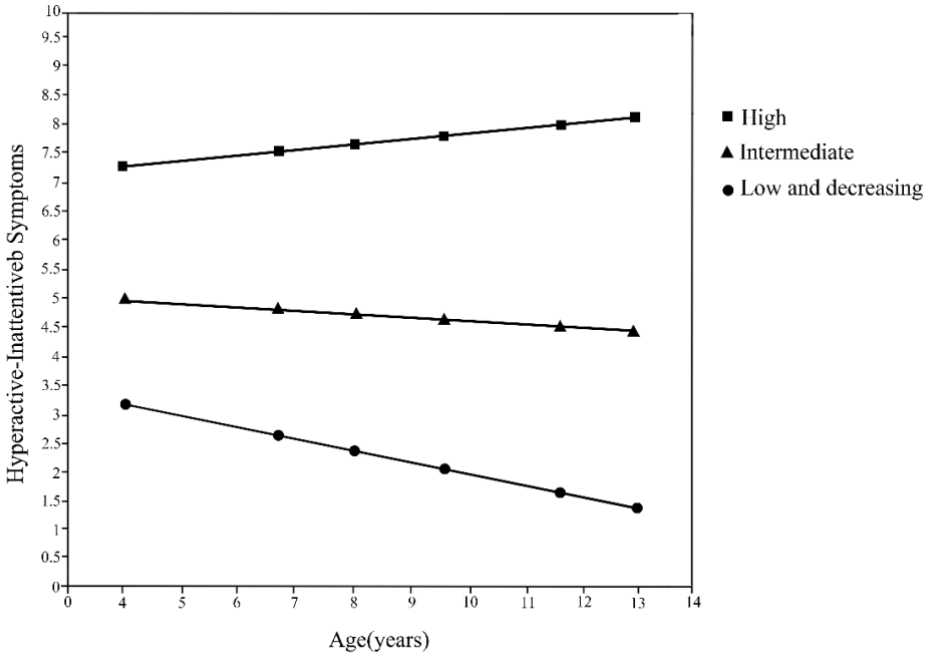

Figure 6-2 3-class solution of the GMM showing the developmental trajectories of hyperactivity/inattention symptoms from ages 4 to 13 years

Table 6-4 summarises the characteristics of participants and all cortisol measures by class membership. Compared to the "low and decreasing" class, participants assigned to the "intermediate" class were more likely to be male ($p < .01$), regular smokers ($p = .02$), at socioeconomic disadvantage, and have lower IQ and more adverse life events in childhood (all $p < .01$). Participants allocated in the "high" group were also more likely to be male ($p < .01$), have lower average IQ ($p < .01$) and higher rates of behavioural disorders (i.e., ODD, CD or ADHD; $p < .01$), compared to the "low and decreasing" class. There were no significant differences in age, ethnicity, obesity rates or any of the other lifestyle factors considered (i.e., vigorous physical activity and alcohol use) at age 15 years between classes. The four daily samples displayed the typical diurnal cortisol rhythm, i.e., the cortisol level was highest at 30 minutes post-wake-up, and declined over the day. The estimated marginal means of the "high" group was 0.334 log(nmol/L) lower compared to the "low and decreasing" group ($p = .02$) at wake-up, whereas cortisol levels at the remaining three time points did not differ between classes (Table 6-5). Figure 6-3 illustrates the predicted diurnal cortisol rhythm for the three classes.

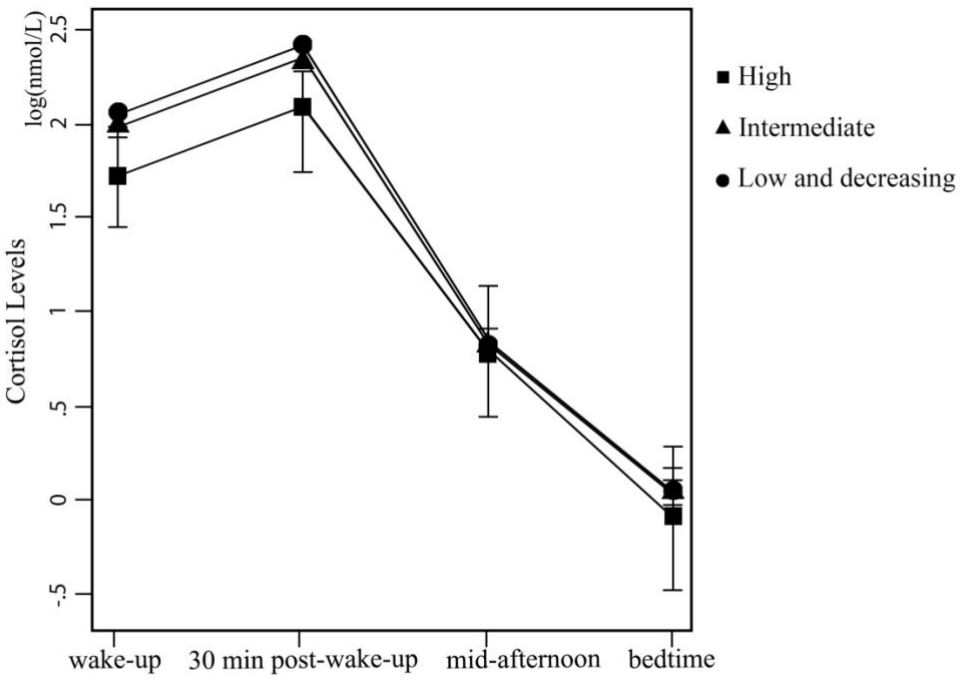

Figure 6-3 Predicted diurnal cortisol rhythm across classes (95% CI)

Table 6-4

Characteristics of participants by class membership of hyperactivity/inattention symptom trajectories.

	Low and decreasing (C1)		Intermediate (C2)		High (C3)				Significant pairwise
	N	**Mean (S.D.)**	**N**	**Mean (S.D.)**	**N**	**Mean (S.D.)**	**F**	***p***	**comparison**
Cortisol at wake-up	665	1.95 (0.49)	218	1.88 (0. 84)	37	1.63 (0.89)	7.6	**0.00**	**C3<C1; C3<C2**
Cortisol at 30 min post-wake-up	644	2.34 (0.51)	206	2.27 (0.52)	32	2.01 (1.05)	6.3	**0.00**	**C3<C1; C3<C2**
Mid-afternoon cortisol	627	0.69 (0.72)	199	0.68 (0.56)	31	0.66 (1.03)	0.0	0.96	-
Bedtime cortisol	653	-0.16 (0.90)	212	-0.15 (0.88)	38	-0.26 (1.21)	0.3	0.77	-
CAR	565	1.43 (0.88)	171	1.39 (0.94)	28	1.43 (1.18)	0.1	0.90	-
Total morning cortisol	654	2.88 (0.41)	212	2.81 (0.41)	36	2.53 (0.87)	11.9	**0.00**	**C3<C1; C3<C2**
Diurnal cortisol slope	595	-0.60 (0.46)	186	-0.70 (0.59)	30	-0.75 (0.50)	4.2	**0.02**	**C2<C1**
Diurnal cortisol decline	620	2.06 (0.47)	200	1.91 (0.70)	33	1.80 (0.53)	8.8	**0.00**	**C2<C1; C3<C1**
AUCg	591	4.29 (0.42)	181	4.22 (0.43)	30	4.22 (0.47)	2.1	0.12	-

Age	676	184.34 (2.33)	223	184.28 (2.19)	40	184.38 (2.75)	0.1	0.93	-
Socioeconomic status	564	-0.09 (1.25)	177	0.22 (1.34)	31	0.42 (1.27)	5.9	**0.00**	**C2>C1**
Stressful life events	581	36.03 (16.79)	191	41.13 (18.83)	28	41.79 (15.67)	7.2	**0.00**	**C2>C1**
IQ	639	94.72 (12.82)	211	89.85 (12.60)	38	88.89 (14.18)	13.8	**0.00**	**C2>C1; C3>C1**
Vigorous activity	644	2.32 (0.61)	212	2.32 (0.65)	37	2.35 (0.68)	0.1	0.96	-
Waking time	652	7.05 (0.47)	210	7.11 (0.48)	34	7.21 (0.49)	3.0	0.05	-
	N	**Proportion**	**N**	**Proportion**	**N**	**Proportion**	χ^2	***p***	
Sex (male)	274	40.5%	120	53.8%	28	70.0%	22.6	**0.00**	**C2>C1; C3>C1**
Ethnicity (white)	23	3.6%	6	2.9%	3	8.1%	2.5	0.29	-
Overweight	125	18.5%	51	23.1%	7	17.5%	2.3	0.32	-
Medication use	99	14.9%	36	16.7%	5	13.2%	0.5	0.76	-
Daily smoker	35	6.6%	19	11.3%	3	10.7%	5.5	0.07	**C2>C1**
Alcohol >2 days/week	23	4.0%	6	3.2%	2	5.9%	0.6	0.75	-
Behavioural disorders	7	1.0%	6	2.7%	8	20%	62.3	**0.00**	**C3>C1; C3>C2**

Note. SES: Socioeconomic status; SLE: Stressful life events. The cortisol measures are log-transformed. Bonferroni correction was used to adjust p-values of pairwise comparisons. Bold values denote statistical significance at the $p < 0.05$ level.

Table 6-5

Predicted mean differences of cortisol levels across classes at four time points (weighted by the conditional probabilities of individuals' group membership).

	dy/dx	**Delta-method S.E.**	**t**	***p***	**[95% CI]**
Low and decreasing (base outcome)					
Intermediate					
Wake-up	-0.055	0.038	-1.45	0.148	[-0.130, 0.020]
30 min post-wake-up	-0.072	0.042	-1.70	0.089	[-0.155, 0.011]
Mid-afternoon	-0.009	0.050	-0.17	0.865	[-0.107, 0.090]
Bedtime	0.012	0.072	0.17	0.864	[-0.128, 0.153]
High					
Wake-up	**-0.334**	**0.148**	**-2.26**	**0.024**	**[-0.624, -0.044]**
30 min post-wake-up	-0.343	0.187	-1.83	0.067	[-0.711, 0.025]
Mid-afternoon	-0.059	0.189	-0.31	0.754	[-0.429, 0.311]

Bedtime	-0.142	0.205	-0.69	0.490	[-0.544, 0.261]

Note. dy/dx refers to the changes in predicted mean cortisol levels using the "low and decreasing" class as the reference.

6.3.2 Predictive Value of Class Membership

The main results of linear regression models for the cortisol parameters are summarised in Table 6-6. Full results of the adjusted model (Model C) are presented in Table 6-7. Compared to the "low and decreasing" class, total morning cortisol was found to be significantly lower among the adolescents in the "high" group in the unadjusted model (b = -0.37, p = .01) but also after adjusting for covariates (Model B: b = −0.31, p = .03; and Model C: b = -0.32, p = .03). Compared to the "low and decreasing" class, the diurnal cortisol decline was shown to be significantly larger among adolescents in the "high" (Model C: b = -0.21, p = .03) and "intermediate" classes (Model C: b = -0.11, p = .03) after adjustments for confounding. For both low morning cortisol and diurnal cortisol decline, the differences between adolescents in the "low and decreasing" class and those in the "high" class remained significant after adjustment for sex and vigorous physical activity, which were significantly associated cortisol measures (For total morning cortisol, Model A: b = -0.31, p = .03; for diurnal cortisol decline: Model A: b = -0.20, p = .03). There was no difference in the diurnal cortisol slope between adolescents in the "high" or "low and decreasing" classes. The diurnal cortisol slope of adolescents in the "intermediate" class was significantly flatter than that in the "low and decreasing" class in the unadjusted model (b = -0.10, p = .04), but this finding did not survive adjustments for confounding. There was no evidence for an association of CAR or AUCg with class membership.

As sex was a significant predictor in all fully adjusted models, we explored if the associations of class membership with cortisol measures varied by sex. Of all interaction terms examined, only the interaction between sex and "intermediate" class was a significant predictor of AUCg, indicating that males in the intermediate group had more total daily output of cortisol than females in this group. The results of the remaining regression analyses examining the effects of the interaction terms between sex and class membership on all cortisol measures are presented in Table 6-8.

6.3.3 Power analysis

Post-hoc power analysis for the effect of class membership on cortisol measures was conducted using the "pwr" package in R (Champely et al., 2017; R Core Team, 2022). The analytic sample offered enough power for small effect sizes ($f^2 = 0.02$) to be detected at a .05 level of significance (95-97% power for the unadjusted models; 90-94% for adjusted models depending on analytic sample size). I.e., if a small effect had existed, we would have had the adequate power to detect it. Therefore, for the non-significant effect that we observed for CAR and AUCg, even if the effect existed, it would be too small to be meaningful.

6.3.4 Correction for multiple testing

To control for the effects of multiple testing, the Bonferroni correction was applied to the multiple regression analyses. This resulted in a corrected alpha level of 0.00208 for the regression models (i.e., $p < 0.00208$ was considered statistically significant). The corrected results indicated that there was no longer a difference in diurnal cortisol levels among trajectory groups.

Table 6-6

Unadjusted and Adjusted Coefficients (S.E.) of Regression Models Examining the Association of Class Membership with Cortisol Measures.

	Unadjusted model		Model A[a]		Model B[b]		Model C[c]	
	Coef. (*SE*)	*p*	Coef. (*SE*)	*p*	Coef. (*SE*)	*p*	Coef. (*SE*)	*p*
Total morning (*n* = 902)								
Low and decreasing (ref)								
Intermediate	–0.05 (0.03)	.10	–0.03 (0.03)	.43	–0.02 (0.03)	.45	–0.03 (0.03)	.43
High	**–0.37 (0.15)**	**.01**	**–0.31 (0.14)**	**.03**	**–0.31 (0.14)**	**.03**	**–0.32 (0.15)**	**.03**
Diurnal decline (n = 853)								
Low and decreasing (ref)								
Intermediate	**–0.15 (0.05)**	**.01**	**–0.12 (0.05)**	**.02**	**–0.11 (0.05)**	**.03**	**–0.11 (0.05)**	**.03**
High	**–0.26 (0.09)**	**.00**	**–0.20 (0.09)**	**.03**	**–0.19 (0.09)**	**.04**	**–0.21 (0.09)**	**.03**
Diurnal slope (*n* = 811)								
Low and decreasing (ref)								

Intermediate	**–0.10 (0.05)**	**.04**	–0.06 (0.05)	.17	–0.07 (0.05)	.16	–0.07 (0.05)	.16
High	–0.15 (0.08)	.07	–0.10 (0.09)	.26	–0.10 (0.09)	.27	–0.11 (0.09)	.24
CAR (*n* = 764)								
Low and decreasing (ref)								
Intermediate	–0.04 (0.08)	.59	-0.02 (0.05)	.67	0.03 (0.08)	.72	–0.04 (0.06)	.49
High	0.00 (0.23)	1.00	0.06 (0.04)	.11	0.08 (0.22)	.71	0.07 (0.05)	.16
AUCg (*n* = 802)								
Low and decreasing (ref)								
Intermediate	–0.07 (0.04)	.07	–0.03 (0.04)	.41	–0.03 (0.04)	.48	–0.02 (0.04)	.54
High	–0.09 (0.09)	.35	–0.03 (0.09)	.75	–0.02 (0.09)	.83	0.01 (0.08)	.94

Note. Bold: $p < 0.05$.

[a] Adjusted for sex and vigorous physical activity, which were associated with cortisol measures.

[b] Model A+ additional adjustment for ethnicity, overweight, socioeconomic status, age, smoking, alcohol use, medication use, wake-up time, IQ, and stressful life events.

[c] Model B+ additional adjustment for behavioural disorder diagnoses at 15 years old. Full results of the Model Cs are presented in Table 6-6.

Table 6-7

Adjusted Coefficients (SE) of regression models examining the association of class membership with cortisol measures (full results of Model C)

	TMC (n=902)		**DCD (n=853)**		**DCS (n=811)**		**CAR (n=764)**		**AUCg (n=804)**	
	Coef. (SE)	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***	**Coef. (SE))**	***p***
Low and decreasing (ref)										
Intermediate	-0.03 (0.03)	0.43	**-0.11 (0.05)**	**0.03**	-0.07 (0.05)	0.16	-0.04 (0.06)	0.49	-0.02 (0.04)	0.54
High	**-0.32 (0.15)**	**0.03**	**-0.21 (0.09)**	**0.03**	-0.11 (0.09)	0.24	0.07 (0.05)	0.16	0.01 (0.08)	0.94
Sex (male)	**-0.22 (0.03)**	**0.00**	**-0.22 (0.04)**	**0.00**	**-0.22 (0.04)**	**0.00**	**0.12 (0.05)**	**0.01**	**-0.23 (0.03)**	**0.00**
Ethnicity	-0.09 (0.06)	0.13	-0.08 (0.06)	0.20	-0.09 (0.06)	0.14	0.09 (0.13)	0.47	-0.04 (0.07)	0.61
Overweight	-0.04 (0.04)	0.28	-0.04 (0.05)	0.47	-0.07 (0.05)	0.15	-0.03 (0.03)	0.38	-0.04 (0.04)	0.26
Socioeconomic status	-0.00 (0.01)	0.79	-0.00 (0.02)	0.93	0.01 (0.02)	0.62	0.01 (0.01)	0.46	0.01 (0.01)	0.69
Age	0.00 (0.01)	0.91	0.01 (0.01)	0.39	0.01 (0.01)	0.20	-0.00 (0.01)	0.58	0.01 (0.01)	0.36
Waking time	0.01 (0.03)	0.87	0.03 (0.04)	0.46	0.07 (0.04)	0.05	0.05 (0.03)	0.16	**-0.07 (0.03)**	**0.03**
Vigorous activity	-0.03 (0.02)	0.30	-0.05 (0.04)	0.14	**-0.07 (0.03)**	**0.01**	0.85 (0.04)	0.00	-0.04 (0.03)	0.10
Stressful life events	0.00 (0.00)	0.73	-0.00 (0.00)	0.44	-0.00 (0.00)	0.35	0.00 (0.00)	0.13	-0.00 (0.00)	0.71
IQ	0.00 (0.00)	0.90	0.00 (0.00)	0.80	0.00 (0.00)	0.45	-0.00 (0.00)	0.29	-0.00 (0.00)	0.56
Medication use	-0.02 (0.04)	0.51	-0.06 (0.05)	0.30	-0.08 (0.06)	0.15	-0.01 (0.04)	0.77	-0.03 (0.05)	0.52

Daily smoker	0.01 (0.06)	0.85	-0.04 (0.08)	0.60	-0.03 (0.07)	0.62	-0.01 (0.05)	0.82	0.00 (0.07)	0.92
Alcohol use	-0.01 (0.08)	0.91	0.00 (0.10)	1.00	0.01 (0.09)	0.91	-0.04 (0.05)	0.47	0.06 (0.06)	0.29
Behavioural disorders	0.07 (0.10)	0.52	0.08 (0.11)	0.46	0.04 (0.10)	0.70	1.13 (0.24)	0.00	-0.14 (0.13)	0.27
Wake-up cortisol							0.03 (0.05)	0.61		
Intercept	2.87 (1.07)	0.01	0.98 (1.31)	0.46	-2.22 (1.23)	0.07	1.62 (1.30)	0.21	4.12 (1.10)	0.00

Note. Bold: $p < .05$.

Table 6-8

Regression models examining the moderating effects of sex on association between class membership and cortisol measures

	TMC (n=902)		**DCD (n=853)**		**DCS (n=811)**		**CAR (n=764)**		**AUCg (n=802)**	
	Coef. (SE)	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***	**Coef. (SE)**	***p***	**Coef. (SE))**	***p***
Low and decreasing (ref)										
Intermediate	-0.08 (0.04)	0.08	-0.10 (0.06)	0.07	-0.09 (0.06)	0.14	-0.06 (0.05)	0.19	-0.10 (0.06)	0.09
High	-0.13 (0.10)	0.18	-0.31 (0.19)	0.09	-0.31 (0.19)	0.10	0.03 (0.04)	0.40	-0.15 (0.17)	0.38
Sex (male)	**-0.24 (0.03)**	**0.00**	**-0.22 (0.04)**	**0.00**	**-0.24 (0.04)**	**0.00**	**-0.04 (0.18)**	**0.82**	**-0.27 (0.03)**	**0.00**
Intermediate× male	0.10 (0.06)	0.12	-0.01 (0.10)	0.94	0.05 (0.09)	0.62	0.08 (0.12)	0.49	**0.15 (0.07)**	**0.04**
High × male	-0.25 (0.22)	0.26	0.15 (0.21)	0.47	0.30 (0.21)	0.15	0.05 (0.07)	0.43	0.24 (0.20)	0.22
Ethnicity	-0.10 (0.06)	0.07	-0.07 (0.07)	0.32	-0.07 (0.07)	0.31	0.10 (0.13)	0.41	-0.02 (0.07)	0.82
Overweight	-0.04 (0.04)	0.27	-0.04 (0.05)	0.46	-0.07 (0.05)	0.14	-0.03 (0.03)	0.30	-0.04 (0.04)	0.24
Socioeconomic status	-0.00 (0.01)	0.77	-0.00 (0.02)	0.95	0.01 (0.02)	0.57	0.01 (0.01)	0.39	0.01 (0.01)	0.66
Age	0.00 (0.01)	0.92	0.01 (0.01)	0.39	0.01 (0.01)	0.21	-0.00 (0.01)	0.66	0.01 (0.01)	0.36
Waking time	0.01 (0.03)	0.87	0.03 (0.04)	0.44	**0.07 (0.04)**	**0.05**	0.04 (0.03)	0.17	**-0.07 (0.03)**	**0.03**
Vigorous activity	-0.03 (0.03)	0.26	-0.05 (0.04)	0.17	**-0.07 (0.03)**	**0.02**	**0.85 (0.04)**	**0.00**	-0.04 (0.03)	0.11
Stressful life Events	0.00 (0.00)	0.72	-0.00 (0.00)	0.43	-0.00 (0.00)	0.32	0.00 (0.00)	0.08	0.00 (0.00)	0.71
IQ	0.00 (0.00)	0.94	0.00 (0.00)	0.79	-0.00 (0.00)	0.48	-0.00 (0.00)	0.26	-0.00 (0.00)	0.55
Medication use	-0.03 (0.04)	0.52	-0.05 (0.05)	0.31	-0.08 (0.06)	0.16	-0.03 (0.04)	0.52	-0.02 (0.04)	0.58
Daily smoker	0.01 (0.06)	0.84	-0.04 (0.07)	0.58	-0.03 (0.06)	0.60	-0.01 (0.04)	0.79	-0.01 (0.07)	0.87
Alcohol use	-0.01 (0.08)	0.95	-0.00 (0.10)	0.97	0.01 (0.09)	0.90	-0.04 (0.05)	0.47	0.07 (0.06)	0.23
Behavioural disorders	0.05 (0.10)	0.61	0.09 (0.11)	0.40	0.06 (0.10)	0.55	**1.10 (0.24)**	**0.00**	-0.13 (0.12)	0.28
Wake-up cortisol							0.01 (0.05)	0.91		
Intercept	**2.90 (1.09)**	**0.01**	0.97 (1.31)	0.46	-2.21 (1.22)	0.07	1.58 (1.28)	0.22	**4.14 (1.09)**	**0.00**

Note. Bold: $p < .05$.

6.4 Summary

This is the largest prospective study available to investigate the association between the course of hyperactivity/inattention symptoms since preschool years and up until adolescence with HPA axis function in adolescence. In line with previous research (Sasser et al., 2016), three distinct classes (low and decreasing, intermediate, high) were identified. Next, the associations between class membership and diurnal cortisol output were tested. The results partially support the hypothesis that chronically high levels of hyperactivity/inattention symptoms relate to hypoactivity of the HPA axis. The results showed that children with high, but not intermediate, levels of symptoms during childhood were characterised by a lower total morning cortisol level by mid-adolescence compared to those with low levels of symptoms, even after controlling for confounders. The findings suggest that hypocortisolism may be a characteristic of adolescents with a history of chronic hyperactivity/inattention. Previous literature suggests that a low, flat diurnal rhythm can be considered as a marker of allostatic load, indicating chronic mild (e.g., following exposure to adverse life events) or high stress (e.g., post-traumatic stress or burnout) (Anda et al., 2006; Milller et al., 2017). Therefore, the results may indicate that children with hyperactivity/inattention symptoms are more likely to be exposed to chronic stressors (i.e., tend to seek risks and/or experience more adverse events/accidents), leading to allostatic overload and hypoactivity of the HPA axis longitudinally. However, because the difference of total morning cortisol between adolescents with high and those with low levels of hyperactivity/inattention symptoms was small in magnitude, it may not bring great practical benefits. It should also be noted that the difference did not survive correction for multiple testing. This means that the significant difference might be a false-positive finding. Therefore, it needs to be interpreted with caution and no practical or clinical implications of this finding are recommended for now.

In addition, the results of multiple regression analyses revealed smaller diurnal cortisol declines in the classes of adolescents with high and intermediate levels of hyperactivity/inattention symptoms after adjustment for cofounders. It is likely, however, that this finding was driven by the lower morning cortisol levels observed, since there were no differences in afternoon or evening cortisol levels between classes. Moreover, this study found no evidence for an association between the different trajectories of hyperactivity/inattention and diurnal cortisol slope. Compared with the diurnal cortisol decline, diurnal cortisol slope is a more robust measure of

basal cortisol activity since it is adjusted for differences in total awake time (Adam & Kumari, 2009). The association between diurnal cortisol slope and hyperactivity/inattention symptoms did not survive adjustments for sex. This indicates that flatter diurnal cortisol slopes in the high and intermediate hyperactivity/inattention groups may be partly due to the higher proportion of males in those groups, given the known sex differences in the prevalence rates of hyperactivity/inattention symptoms (the symptoms are less common in females; Loyer Carbonneau et al., 2021) and in diurnal cortisol profiles in the general population (higher cortisol levels and/or a steeper decline in females; Hollanders et al., 2017). In addition, we did not find the moderating effect of sex on the association between hyperactivity/inattention and diurnal slope, suggesting that this association does not differ between sexes. Taken together, these results suggest that even if there is a true difference in diurnal cortisol change between adolescents with hyperactivity/inattention symptoms and their typically developing peers, it is very small and markedly attenuated by confounders.

Finally, there was no robust link between any of the atypical developmental trajectories of hyperactivity/inattention symptoms and CAR or AUCg at 15 years old; thus, no evidence in support of the hypothesis was found that adolescents with persistently high levels of symptoms are characterised by smaller CAR and daily cortisol output (Angeli et al., 2018). The null finding regarding CAR indicates that chronic hyperactivity/inattention symptoms do not impair one's ability to react to a natural stimulus (i.e., awakening). Since the power analysis showed that the study has the power to detect small effect sizes, the non-significant results should not be attributed to Type II error.

6.5 Chapter summary and next step

In this chapter, growth mixture models were fitted to capture the longitudinal unfolding of hyperactivity/inattention symptoms from ages 4 to 13 years. This study also assessed associations between class memberships and basal cortisol profiles at age 15 years. The results show that, as expected, adolescents with persistently high levels of hyperactivity/inattention symptoms across childhood and adolescence show lower total morning cortisol and a smaller diurnal decline in mid-adolescence, even

after adjustments for confounding. The following chapter will explore how early social cognition, is related to emotional and behavioural problems in later adolescence and if cortisol and/or inflammation can mediate this longitudinal relationship.

Chapter 7: The role of inflammatory markers and cortisol in the association between early social cognition abilities and later emotional or behavioural problems

This chapter is based on a published paper as Ji, D., Francesconi, M., & Papachristou, E. (2022). The role of inflammatory markers and cortisol in the association between early social cognition abilities and later internalising or externalising problems: Evidence from a UK birth cohort. *Brain, Behavior, and Immunity, 105*, 225-236. https://doi.org/10.1016/j.bbi.2022.07.002 To acknowledge the contributions of co-authors, "we" will be used instead of "I" in this chapter.

7.1 Introduction

In Chapter 6 we found that chronically high levels of hyperactivity/inattention symptoms are associated with lower morning cortisol levels. Given that children with hyperactivity/inattention tend to take more risks and experience more adverse events (Brown et al., 2017), a possible explanation for this finding is that the hypoactivity of the HPA axis observed results from repetitive exposure to stressors associated with sustained behavioural problems. As reviewed in Chapter 2, children with social cognition difficulties, such as poor emotion perception and understanding, are also more likely to experience both chronic and acute stressors in their lives, such as peer victimisation, social rejection, and physical conflict, in line with the social skills deficit vulnerability (SSDV) theory (Segrin, 2000; Segrin et al., 2016). They are also less able to secure the social support necessary for dealing with such stressors (Knox & Douglas, 2009; Shakoor et al., 2012). Stress, in turn, is a robust predictor of adverse mental health outcomes (Cohen, 2000; Esch et al., 2002; Gershon et al., 2013). It is, therefore, possible that stress, (i.e., HPA axis dysregulation), mediates the pathway linking social cognition difficulties with mental health problems. In addition, it is known that cortisol, the core product of HPA axis, exerts a strong anti-inflammatory effect. Dysregulated cortisol secretion can provoke abnormal inflammatory signalling (Miller et al., 2014). Hence, children with social cognitive difficulties and abnormal cortisol levels may also exhibit heightened inflammation, which was found to be associated with the development of various mental disorders (Osimo et al., 2019; Parsons et al., 2021). Nevertheless, the potential association

between social cognition difficulties and inflammation may not be entirely via cortisol. As suggested by Danese and Baldwin (2017), behavioural factors, such as disrupted eating and sleeping patterns, substance and alcohol abuse, and self-harm can also induce heightened inflammation levels. Individuals with early stress are more likely to have those behaviours (Danese & Baldwin, 2017), thereby increasing the risk for elevated inflammation and mental health problems. However, the potential mediating effect of inflammation, either indirectly via cortisol or not, on the association between early social cognition difficulties and later mental health problems has yet been tested. Neither was the mediating effect of abnormal diurnal cortisol on this association.

This study sought to examine for the first time whether HPA axis dysregulation, inflammatory process, or both, can mediate the association between social cognition difficulties with emotional and behavioural symptoms. The purpose of this study was twofold; 1) to investigate if social cognitive difficulties in childhood can predict emotional or behavioural problems in late adolescence; 2) to assess if inflammatory markers or cortisol measures can -at least partially, explain the longitudinal association between social cognitive difficulties with emotional and behavioural problems. Based on the literature described in Chapter 2, it is hypothesised that social cognitive difficulties in childhood could predict both emotional and behavioural problems in late adolescence. Regarding the second aim, based on the findings presented in Chapter 5 and Chapter 6, it is expected that cortisol measures will mediate the longitudinal association between social cognitive difficulties and behavioural, but not emotional, problems. In contrast, inflammatory markers were not expected to show significant mediating effects for this relationship.

7.2 Method

Participants and variables from the ALSPAC have previously been described in detail in Chapter 4; a summary of these methods is presented below.

7.2.1 Participants

At age 15 years, 5,501 of the ALSPAC cohort children were recruited for a clinical assessment. Figure 7-1 illustrates the sample selection process for this study. For 968 participants who provided at least one valid saliva sample, the following

exclusion criteria were applied: 1) second born in case of a twin birth; 2) gestation at birth <=32 weeks; 3) birth weight <=1500g; 4) exposure to steroid medication when cortisol was measured; 5) infection when IL-6 when inflammation was measured; and 6) IQ < 70 (two standard deviations below the mean). IQ was assessed using the Wechsler abbreviated scale of intelligence at age 15 (Wechsler, 1999). Of 864 participants who survived the exclusion process, 714 had data on hyperactivity/inattention and conduct problems at 17 years old, 713 had data on emotional problems and 711 had data on peer problems, which comprised the analytic sample (see Figure 7-1 for details).

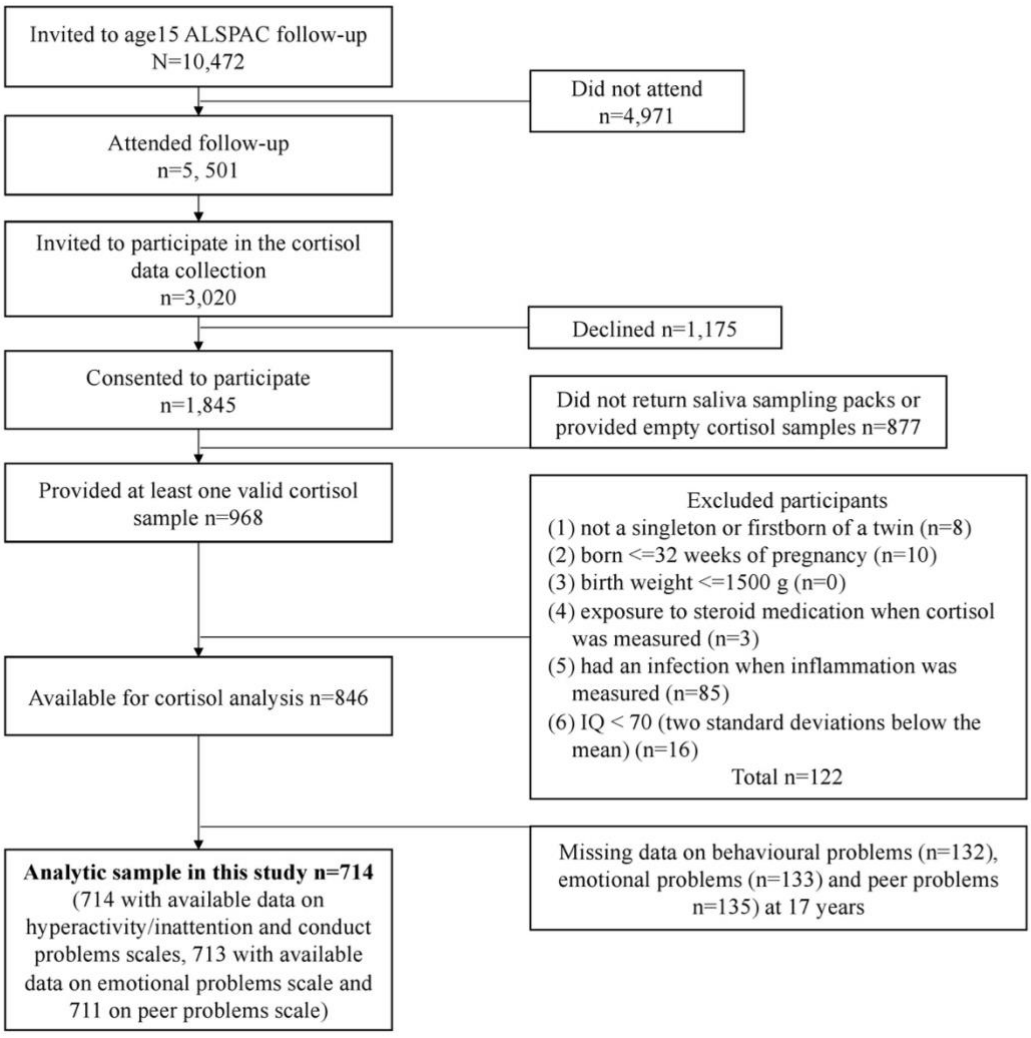

Figure 7-1 Analytic sample selection process

7.2.2 Measures

7.2.2.1 Cortisol

This study used four cortisol measures to capture diurnal cortisol pattern, including total morning cortisol, CAR, diurnal cortisol slope and AUCg. To correct for skewed distributions, all cortisol measures were log-transformed for the analyses. Details about the collection of the saliva samples and the variable deriving processes are described in Chapter 4.

7.2.2.2 Inflammation

Inflammation was measured with IL-6 at age 9 and CRP at ages 9 and 16 years. Both CRP and IL-6 were log-transformed to correct the skewness of the distribution for the analyses. Details about the collection of the blood samples are described in Chapter 4.

7.2.2.3 Social cognition

Three social cognition variables were included in this study. Details about the measures can be found in chapter 4, section 4.3.3.

Social communication ability was assessed using the parent rated Social Communication Disorders Checklist (SCDC) at ages 8, 11, and 14 years. The SCDC comprises 12 items measuring social reciprocity and verbal/nonverbal characteristics in the past 6 months, with answers ranging from 0 (“not true”) to 2 (“very or often true”). Higher scores indicate more difficulties in social communication. To account for the positive skewness of total scores, SCDC scores were dichotomised in this study using a validated cut-off of ≥ 9 (Barona et al., 2015; Kothari et al., 2015; Skuse et al., 2009).

Emotion recognition from facial expressions was assessed with the Diagnostic Analysis of Non-Verbal Accuracy (DANVA) at age 8 years (Nowicki & Duke, 1994). The faces subtest of the DANVA consists of 24 colour photos of both boys and girls at school age, with each face showing one of four emotions: fear, happiness, sadness, or anger. The measure is scored by adding up the number of errors/misattributions for each emotion. DANVA scores were positively skewed; therefore, cut-offs for each of the variables were derived by ALSPAC in collaboration with Stephen Nowicki, the

creator of the task. For all emotions, participants who made at least 7 errors were coded as 1 (versus 0 “total errors < 7”), indicating difficulties in emotion recognition from facial expressions.

Emotion recognition from movements/Theory of mind was assessed using the computer-based Emotional Triangles test at 14 years. Participants were asked to attribute emotion to a nonhuman animate entity which consists of a black outline triangle and a circle. For each of the four emotion (i.e., happy, sad, angry, and scared) trials, there were two positive questions and two negative questions. The total score was calculated by adding the scores of all the positive questions and subtracting the score of the negative items. High scores represent better ability in identifying particular emotions. Following previous studies using this test (Holland et al., 2020; Warrier & Baron-Cohen, 2018), to avoid negative scores, we added 40 to the total score, giving the score a range from 0-80.

7.2.2.4 Emotional and behavioural problems

Emotional and behavioural problems were assessed using the SDQ at 17 years (Goodman et al., 2010). The SDQ includes four sub-scales: emotion problems, conduct problems, hyperactivity/inattention, and peer problems. Higher scores indicate more serious problems. The SDQ is widely used to screen for mental health problems in children and adolescents in the general population and has shown good validity and reliability in various samples (Goodman & Scott, 1999; Goodman, 2001; Shojaei et al., 2009).

7.2.2.5 Covariates

The potential covariates of the study consisted of several variables which are known to be associated with children’s emotional and behavioural problems, social cognition, inflammation and HPA axis activity. These included sex (Dolsen et al., 2019; Goel et al., 2011; Hermens et al., 2005; Thompson & Voyer, 2014), ethnicity (Bax et al., 2019; Craig et al., 2017; DeSantis et al., 2007; Richman, 2018), being overweight at age 15 years (Luppino et al., 2010; Percinel et al., 2018; Visser et al., 2001; Yu et al., 2020), socioeconomic status (Marsman et al., 2012; Richman, 2018; Russell et al., 2016), stressful life events before age 11 years (Elzinga et al., 2008;

Kliewer et al., 2009; Nettle et al., 2017; Vrijsen et al., 2018), vigorous physical activity at age 15 years (Pengpid & Peltzer, 2020; Anderson & Wideman, 2017), and unhealthy behaviours at age 15 years (i.e., smoking and alcohol use; Chang et al., 2005; Eiden et al., 2020; Homman et al., 2019; Ruttle et al., 2015). More information on these covariates and how they were derived can be found in Chapter 4, section 4.3.5.

7.2.3 Analytic strategy

Analyses were performed in *Stata 16* (StataCorp, 2019) and Mplus 8.1 (Muthén & Muthén, 1998-2017). First, demographic characteristics, social cognition measures, inflammatory markers and emotional and behavioural problems were compared between the analytic and non-analytic samples (ALSPAC members who were excluded from the analyses; Figure 7-1) to assess sample bias. Next, Pearson's correlation coefficients between social cognition abilities, cortisol measures, inflammatory markers, and emotional and behavioural problems were calculated in the analytic sample.

If cortisol and inflammation were correlated with both social cognition abilities and emotional and behavioural problems, Bayesian structural equation modelling (BSEM) was performed to test their mediating effects in the association between social cognition and SDQ scores. Mediation models allow the exploration of the underlying mechanisms linking the predictor variables and outcomes (Baron & Kenny, 1986). In a mediation model, it is hypothesised that the effect of a predictor variable(s) upon an outcome operates, either fully or in part, through a mediator variable (MacKinnon, 2008). If the direct link between the predictor and outcome is no longer significant when a mediator is introduced, this is referred to as a full mediation; if the direct link is still present but reduced, it is a partial mediation. We chose a Bayesian estimator for the mediation analyses as it does not assume a normal distribution of estimates (Muthén, 2010). This is particularly relevant for indirect effects which are commonly skewed (Yuan & MacKinnon, 2009). In addition, BSEM has been shown to produce more accurate estimates than frequentist approaches using the maximum likelihood estimation method with bootstrapping (Kuss et al., 2005; Wang & Preacher, 2015). For the Bayesian mediation model, a Markov Chain Monte

Carlo (MCMC) algorithm was used for the estimation of direct and indirect effects (Yuan & Mackinnon, 2009). We used a Bayesian estimator with non-informative priors (default normal distribution with a mean hyperparameter of zero and a variance of 10^{10}; Muthén & Muthén, 1998–2017). Model convergence was assessed by the potential scale reduction (PSR) factor and the convergence criterion was set at 1.001. To meet the PSR convergence criterion the number of iterations was set to 6,000 for unadjusted models, and 10,000 for the fully adjusted models. Model fit was assessed by the posterior predictive p-value (PPP) which is based on chi-square difference tests for structural equation models (Muthén & Asparouhov, 2012). PPP values above 0.05 represent an acceptable model fit, and values close to 0.50 indicate a good fit (Muthén & Asparouhov, 2012). BSEM uses 95% credible interval (CI) to indicate the range of posterior probability distribution which the true parameter has a 95% chance of falling in. Full information maximum likelihood method was used to account for missing data in social cognition scores, inflammation or cortisol measures, and covariates. For each mediation model, unadjusted models were initially fitted, followed by models with adjustments for potential covariates (sex, exact age when social communication was assessed, ethnicity, overweight, socioeconomic status, wake-up time, vigorous physical activity, smoking, alcohol use, medication use, stressful life events, and cortisol or inflammation when not included in the model as mediators). Then, as a sensitivity analysis, we removed the covariates that were not significantly associated with the mental health problems in our sample and refit the models. Specifically, covariates that were associated with hyperactivity/inattention include sex, socioeconomic status, stressful life events, smoking, and exact age when social communication was assessed. And the model for conduct problems was controlled for vigorous physical activity, stressful life events, and smoking.

7.3 Results

7.3.1 Descriptive statistics

The analytic sample comprised 714 ALSPAC members with valid data on hyperactivity/inattention (n = 714), conduct problems (n = 714), emotion problems (N = 713), or peer problems (n = 711) at age 17 years. Of those, 56.44% (n = 403) were female, 97.03% (n = 653) were white, 18.71% (n = 133) were overweight at 15 years,

15.78% (n = 110) were taking steroid medication when cortisol was measured, 6.59% (n = 41) were daily smokers and 3.98% (n = 24) were consuming alcohol more than two days a week at age 15. Comparison of the descriptive information between the analytic and the non-analytic samples demonstrated some sample selection bias (Table 7-1). On average, children in the analytic sample had a less deprived socioeconomic background, had experienced more stressful events, were more likely to be female and White, scored lower in the emotional and behavioural problems considered and had lower average levels of inflammation. They also showed better emotion recognition from movements and social communication abilities.

Table 7-1

Sample characteristics in the analytic and non-analytic samples

	Analytic sample (N=714)	**Non-analytic sample (N=14931)**		
Categorical variables	N (%)	N (%)	χ^2	P-value
Sex (male)	311 (43.56%)	7380 (51.52%)	17.25	**0.000**
Ethnicity (white)	653 (97.03%)	10871 (94.66%)	6.42	**0.011**
Overweight	133 (18.71%)	971 (20.67%)	1.47	0.225
Medication use	110 (15.78)	762 (16.46)	0.20	0.651
Daily smoker	41 (6.59%)	378 (8.40%)	2.38	0.123
Alcohol > 2 days/week	24 (3.98%)	216 (5.41%)	2.16	0.141
Continuous variables	Mean (SD)	Mean (SD)	t	P-value
Age (months) [a]	91.63 (1.35)	91.91 (1.72)	4.07	**0.000**
Socioeconomic status	-0.32 (1.20)	0.02 (1.27)	6.38	**0.000**
Vigorous physical activity	2.33 (0.61)	2.31 (0.66)	-0.86	0.388
Stressful life events	37.42 (17.35)	35.32 (17.98)	-2.81	**0.005**
Inflammation [b]				
IL-6 at 9 years	-0.29 (0.87)	-0.19 (0.81)	2.64	**0.008**
CRP at 9 years	-1.47 (1.11)	-1.33 (1.16)	2.61	**0.009**
CRP at 16 years	-0.84 (0.98)	-0.71 (1.05)	2.63	**0.009**
Social cognition				
SCDC at 8 years	0.06 (0.23)	0.09 (0.27)	2.22	**0.026**

SCDC at 11 years	0.03 (0.17)	0.07 (0.26)	4.20	**0.000**
SCDC at 14 years	0.05 (0.21)	0.07 (0.26)	2.64	**0.008**
DANVA at 8 years	1.84 (0.37)	1.82 (0.38)	-0.81	0.421
Triangle test at 14 years	57.81 (7.10)	56.62 (7.61)	-3.90	**0.000**
Emotional and behavioural problems at 17 years				
Hyperactivity	2.31 (2.01)	2.58 (2.13)	3.25	**0.001**
Conduct problems	0.86 (1.19)	1.05 (1.38)	3.48	**0.001**
Emotion problems	1.28 (1.63)	1.53 (1.88)	3.38	**0.001**
Peer problems	1.06 (1.39)	1.12 (1.52)	1.11	0.267

Note. SD : standard deviations. IL-6 : interleukin 6. CRP: C-reactive protein. SCDC: Social and Communication Disorders Checklist (Skuse et al., 2005). DANVA: Diagnostic Analysis of Non-Verbal Accuracy (Nowicki & Duke, 1994). [a] Exact month age at which social communication difficulties was first assessed in ALSPAC. [b] Inflammatory markers are log-transformed. Bold: $p < .05$.

7.3.2 Correlation analyses

Pairwise associations between social cognition measures, cortisol measures, inflammatory markers, and emotional and behavioural problems were tested using Pearson's correlations. The results are summarised in Table 7-2. Social communication difficulties (SCDC at 8, 11 and 14 years) were not correlated with emotion recognition ability from facial expression (DANVA) at 8 years or motions (Triangles) at 14 years, suggesting that these capture substantively distinct cognitive domains. Social communication difficulties at 8, 11 and 14 years were significantly associated with more hyperactivity/inattention (all $p < .01$) and conduct problems at 17 years (all $p < .01$). There were also significant positive associations between social communication difficulties at 11 and 14 years with emotional problems (both $p < .01$) at age 17, while social communication difficulties at 14 were additionally positively related to peer problems ($p < .01$). Emotion recognition abilities were not associated with emotional and behavioural problems. The four cortisol measures were positively associated with each other (all $p < .01$). Of the four cortisol measures, total morning cortisol and CAR were positively associated with CRP at age 9 years (both $p < .01$), but not with IL-6 at age 9 or CRP at age 16. Regarding the associations between cortisol measures and the outcomes, diurnal cortisol slope and total morning cortisol

were negatively associated with hyperactivity/inattention at age 17 years (all $p < .01$) while total morning cortisol was also negatively correlated with conduct problems at 17 years ($p < .01$). There was no significant association between any of the cortisol measures with emotional problems. No significant associations of emotional and behavioural problems with inflammation emerged either. Finally, regarding the relationship between social cognition and cortisol, only social communication at 8 was correlated with total morning cortisol ($p < .01$).

Table 7-2

Bivariate correlations between main variables of this study

Main Variables	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Social cognition															
1. SCDC at 8															
2. SCDC at 11	**0.37***														
3. SCDC at 14	**0.20***	**0.40***													
4. DANVA at 8	-0.01	-0.03	-0.03												
5. Triangles at 14	**0.09**	0.07	0.04	**0.11***											
Cortisol measures[a]															
6. DCS at 15	-0.01	-0.06	-0.03	-0.02	-0.02										
7. TMC at 15	**-0.11***	-0.06	-0.07	0.05	-0.05	**0.84***									
8. CAR at 15	-0.07	0.04	-0.02	**0.10***	-0.02	**0.45***	**0.54***								
9. AUCg at15	0.00	-0.01	-0.05	0.04	0.02	**0.67***	**0.82***	**0.61***							
Inflammatory markers[a]															
10. IL-6 at 9	-0.02	-0.03	-0.04	0.02	0.00	0.00	0.06	0.09	0.09						
11. CRP at 9	0.01	-0.02	0.03	0.04	0.01	0.06	**0.14***	**0.11**	0.09	**0.47***					
12. CRP at 16	0.08	0.01	0.06	0.02	0.06	-0.04	-0.02	-0.04	-0.00	**0.12**	**0.39***				
Emotional and behavioural problems[b]															
13.Hyperactivity	**0.24***	**0.21***	**0.23***	-0.08	-0.02	**-0.12***	**-0.13***	-0.01	-0.06	-0.02	-0.00	-0.02			
14. CP	**0.21***	**0.19***	**0.24***	-0.07	0.01	-0.06	**-0.10***	-0.00	-0.04	-0.00	-0.00	0.05	**0.45***		
15. EP	0.06	**0.14***	**0.11***	-0.00	-0.03	-0.02	-0.01	0.03	0.02	-0.05	-0.03	-0.00	**0.27***	**0.25***	
16. Peer problem	0.06	0.07	**0.12***	**-0.08**	0.00	-0.03	-0.05	-0.08	-0.06	0.02	-0.01	0.00	**0.16***	**0.14***	**0.30***

Note. SCDC: Social and Communication Disorders Checklist (Skuse et al., 2005). DANVA: Diagnostic Analysis of Non-Verbal Accuracy (Nowicki & Duke, 1994). DCS: diurnal cortisol slope. TMC: total morning cortisol. CAR: cortisol awakening response. AUCg: area under curve with respect to ground. IL-6: interleukin 6. CRP: C-reactive protein. EP: Emotion problem. CP: Conduct problem. [a] Cortisol measures and inflammatory markers are log-transformed. [b] emotional and behavioural problems were measured at 17 years old. Bold $< .05$; *$p < .01$.

7.3.3 Mediation models

Of all the associations tested between the inflammatory markers and cortisol measures with the outcomes and exposures, only total morning cortisol was related to at least one of the social cognition measures (social communication deficits at 8 years) and two of the outcomes (hyperactivity/inattention and conduct problem at 17 years). Therefore, our mediation analysis tested whether total morning cortisol can mediate the link between 1) social communication at 8 and hyperactivity/inattention at 17; 2) social communication at 8 and conduct problems at 17.

Table 7-3 and Table 7-4 summarise the results of the mediation models before and after adjustments for confounding. Figure 2 illustrates the results of the two fully adjusted mediation models and presents the standardised coefficients (β) for the direct and indirect effects. Both unadjusted and fully adjusted models for hyperactivity/inattention (unadjusted model: PPP = 0.54; adjusted model: PPP = 0.43) and conduct problems (unadjusted model: PPP = 0.54; adjusted model: PPP = 0.43) showed satisfactory model fit. For hyperactivity/inattention, a significant direct path from social communication difficulties at 8 years was found (unadjusted model: b = 2.03, 95% CI [1.38, 2.69], $p < .001$). Social communication difficulties also significantly predicted lower levels of total morning cortisol at 15 years (unadjusted model: b = -0.21, 95% CI [-0.36, -0.05], $p = .008$), indicating that childhood social communication difficulties were related to hypoactivity of the HPA axis in adolescence. Lower total morning cortisol further predicted later hyperactivity/inattention at 17 years (unadjusted model: b = -0.48, 95% CI [-0.81, -0.16], $p = .004$). The links between social communication difficulties and hyperactivity/inattention (fully adjusted model: b = 1.80, 95% CI [1.13, 2.47], $p < .001$), social communication difficulties and morning cortisol (fully adjusted model: b = -0.18, 95% CI [-0.33, -0.02], $p = .024$), and morning cortisol and hyperactivity/inattention adjusted model (b = -0.41, 95% CI [-0.76, 0.07], $p = .016$) survived adjustment for covariates. A significant indirect path from social communication difficulties to hyperactivity/inattention was found via total morning cortisol (indirect effect = 0.10, 95% CI [0.02, 0.22], $p = .014$) and the path remained significant after the adjustment for inflammation and other covariates (indirect effect = 0.07, 95% CI [0.00, 0.18], $p = .042$). Similarly, there was evidence for a direct association between social communication difficulties at 8 and conduct problems at

17 years (unadjusted model: b = 1.06, 95% CI [0.66, 1.44], $p < .001$), and for a significant indirect effect through lower total morning cortisol at 15 years (unadjusted model: indirect effect = 0.04, 95% CI [0.00, 0.11], $p = .046$). The direct effect (fully adjusted model: b = 0.90, 95% CI [0.51, 1.30], $p < .001$) and indirect effects (fully adjusted model: indirect effect = 0.04, 95% CI [0.00, 0.11], $p = .040$) also survived adjustments for all covariates including inflammation. For both behavioural problems, the indirect effects remained significant with the adjustment of only covariates that were statistically associated with the outcome (for hyperactivity/inattention: indirect effect = 0.07, 95% CI [0.00, 0.18], $p = .042$; for conduct problems: indirect effect = 0.05, 95% CI [0.00, 0.12], $p = .032$; Table 7-4),

In addition, we tested if the indirect effects of social cognition on behavioural problems through total morning cortisol levels were different by sex. For hyperactivity/inattention, moderated mediation analyses showed that the path from social communication difficulties to morning cortisol was not moderated by sex (adjusted model: moderation effect = 0.19, 95% CI [-0.02, 0.52], $p = .080$), neither was the path from morning cortisol levels to conduct problems (adjusted model, interaction term: b = -0.07, 95% CI [-0.78, 0.62], $p = .842$). For conduct problems, moderated mediation analyses showed that the path from social communication difficulties to morning cortisol was moderated by sex (adjusted model: moderation effect = 0.15, 95% CI [0.02, 0.34], $p = .024$), while the path from morning cortisol levels to conduct problems was not (adjusted model, interaction term: b = -0.01, 95% CI [0.07, 0.06], $p = .800$). Grouping analyses showed that the indirect path from social communication difficulties to conduct problems via lower morning cortisol was significant for males (adjusted model: indirect effect = 0.04, 95% CI [0.00, 0.11], $p = .040$), but not for females (adjusted model: indirect effect = -0.00, 95% CI [-0.06, 0.04], $p = .828$).

7.3.4 Power analysis

To assess the statistical power of the mediation path, a post-hoc power analysis was conducted using the "pwr" package in R (Champely et al., 2017; R Core Team, 2022). The results indicated that the analytic sample provided the study with sufficient power to detect medium effect sizes for the indirect effect at the .05 level of

significance (f^2 = 0.15) in both unadjusted models (Power $_{\text{path A x path B}}$ = 99%) and adjusted models (models in Table 7-5, Power $_{\text{path A x path B}}$ = 99%). The study also had enough power to detect a small sizes for the indirect effects (f^2 = 0.02) in unadjusted models (Power $_{\text{path A x path B}}$ = 0.90), but a slightly larger sample size would be required to achieve a power of 0.80 for the detection of small effect sizes for the indirect effect in the adjusted models (models in Table 7-5, Power $_{\text{path A x path B}}$ = 65% for Hyperactivity/inattention, Power $_{\text{path A x path B}}$ = 74% for Conduct problems). Emotional and peer problems were not correlated with cortisol measures or inflammatory markers, and hence they were not included in further analysis. Therefore, statistical power for emotional and peer problems was calculated based on the correlation analyses. Results showed that the study had a large enough sample to detect a medium association[2] (r = 0.3, power = 100%) between emotional or peer problems and cortisol or inflammation, but not enough to detect a small association (r = 0.1, power ranged from 61% to 75%). As the absolute values of correlation coefficients between emotional problems and cortisol measures and inflammatory markers were smaller than 0.08, to detect such small effects between those variables, a sample size >1224 participants would have been required to achieve 80% power at the .05 level of significance.

7.3.5 Correction for multiple testing

To control for the effects of multiple testing, the Bonferroni correction was applied to the mediation models. This resulted in a corrected alpha level of 0.00416 for the regression models (i.e., $p < 0.00416$ was considered statistically significant). The results showed that the association between social communication at age 8 and behavioural problems at age 17 survived the correction of multiple testing, but the association between social communication and morning cortisol levels did not. The negative association between morning cortisol level and later hyperactivity/inattention symptoms remained significant in the unadjusted, but not the adjusted model. The indirect paths from social communication difficulties to hyperactivity/inattention and conduct problems via total morning cortisol turned to non-significant after the multiplicity correction. For moderated mediation analysis, the moderating effect of

[2] According to Cohen's (1988) interpretation of effect size, a correlation coefficient of 0.10 is thought to be a small association, 0.30 is a moderate association, and 0.50 is a large association.

sex on the path from social communication difficulties to morning cortisol in the model for conduct problems lost its significance too.

Table 7-3

Unstandardised regression coefficients of unadjusted and adjusted (including IL-6 at 9 years and covariates) mediation models testing the association between social communication difficulties and hyperactivity/inattention and conduct problems via total morning cortisol (N=714).

	Unadjusted models				Adjusted models			
	b	**SD_P**	**95% CI**	**P-value**	**b**	**SD_P**	**95% CI**	**P-value**
SCD → TMC → HI								
Direct effects								
SCD → TMC	-0.21	0.08	[-0.36, -0.05]	**0.008**	-0.18	0.08	[-0.33, -0.02]	**0.024**
SCD → HI	2.03	0.34	[1.38, 2.69]	**0.000**	1.80	0.34	[1.13, 2.47]	**0.000**
TMC→ HI	-0.48	0.17	[-0.81, -0.16]	**0.004**	-0.41	0.18	[-0.76, -0.07]	**0.016**
Indirect effect	0.10	0.05	[0.02, 0.22]	**0.014**	0.07	0.05	[0.00, 0.18]	**0.042**
Total effect	2.13	0.34	[1.48, 2.79]	**0.000**	1.87	0.34	[1.20, 2.53]	**0.000**
SCD → TMC → CP								
Direct effects								
SCD → TMC	-0.21	0.08	[-0.37, -0.06]	**0.008**	-0.18	0.08	[-0.34, -0.03]	**0.020**
SCD → CP	1.06	0.20	[0.66, 1.44]	**0.000**	0.90	0.20	[0.51, 1.30]	**0.000**
TMC→ CP	-0.21	0.10	[-0.40, -0.01]	**0.040**	-0.24	0.11	[-0.44, -0.04]	**0.020**
Indirect effect	0.04	0.03	[0.00, 0.11]	**0.046**	0.04	0.03	[0.00, 0.11]	**0.040**
Total effect	1.10	0.20	[0.70, 1.49]	**0.000**	0.95	0.20	[0.55, 1.35]	**0.000**

Note: b: unstandardised coefficient. SD_P: standard deviations of the posterior distribution. 95% CI: 95% credible interval. SCD: social communication difficulties. TMC: total morning cortisol. HI: hyperactivity/inattention. CP: conduct problems. Bold: $p < .05$. The covariates in the adjusted models include inflammation (IL-6) at 9 years old, sex, exact age when social communication was assessed, ethnicity, overweight, socioeconomic status, wake-up time, vigorous physical activity, smoking, alcohol use, medication use and stressful life events. Mediation models adjusting for inflammation (CRP) at 9 years and all other covariates were presented in the Table 7-4 and revealed the same findings.

Table 7-4

Unstandardised and standardised regression coefficients of adjusted (including CRP at 9 years and covariates) mediation models testing the association between social communication difficulties and hyperactivity/inattention and conduct problems via total morning cortisol (N=714)

	b	SD_P	95% CI	P-value	β	SD_P	95% CI	P-value
SCD → TMC → HI								
Direct effects								
SCD → TMC	-0.17	0.08	[-0.33, -0.02]	**0.024**	-0.09	0.04	[-0.17, -0.01]	**0.019**
SCD → HI	1.81	0.34	[1.14, 2.47]	**0.000**	0.21	0.04	[0.13, 0.28]	**0.000**
TMC → HI	-0.40	0.17	[-0.75, -0.06]	**0.004**	-0.09	0.04	[-0.17, -0.01]	**0.004**
Indirect effect	0.06	0.05	[0.00, 0.18]	**0.044**	0.01	0.01	[0.00, 0.20]	**0.044**
Total effect	1.88	0.34	[1.21, 2.54]	**0.000**	0.24	0.04	[0.14, 0.29]	**0.000**
SCD → TMC → CP								
Direct effects								
SCD → TMC	-0.18	0.08	[-0.34, -0.03]	**0.018**	-0.09	0.04	[-0.17, -0.02]	**0.018**
SCD → CP	0.91	0.20	[0.51, 1.31]	**0.000**	0.17	0.04	[0.10, 0.25]	**0.000**
TMC → CP	-0.23	0.11	[-0.43, -0.02]	**0.028**	-0.09	0.04	[-0.16, -0.01]	**0.028**
Indirect effect	0.04	0.03	[0.00, 0.11]	**0.046**	0.01	0.01	[0.00, 0.02]	**0.046**
Total effect	0.95	0.20	[0.55, 1.35]	**0.000**	0.18	0.04	[0.11, 0.26]	**0.000**

Note: b: unstandardized coefficient. β: standardized coefficient. SDP: standard deviations of the posterior distribution. 95% CI: 95% credible interval. SCD: social communication difficulties. TMC: total morning cortisol. HI: hyperactivity/inattention. CP: conduct problems. Bold: $p < .05$. The models are controlled for inflammation (CRP) at 9 years old, sex, exact age when social communication was assessed, ethnicity, overweight, socioeconomic status, wake-up time, vigorous physical activity, smoking, alcohol use, medication use and stressful life events.

Table 7-5

Unstandardised and standardised regression coefficients of adjusted (only covariates that are associated with outcome variables) mediation models testing the association between social communication difficulties and hyperactivity/inattention and conduct problems via total morning cortisol (N=714)

	b	SD_P	95% CI	P-value	β	SD_P	95% CI	P-value
SCD → TMC → HI								

Direct effects								
SCD → TMC	-0.18	0.08	[-0.34, -0.03]	**0.018**	-0.09	0.04	[-0.17, -0.02]	**0.018**
SCD → HI	1.78	0.34	[1.11, 2.44]	**0.000**	0.20	0.04	[0.13, 0.28]	**0.000**
TMC → HI	-0.39	0.17	[-0.73, -0.05]	**0.024**	-0.09	0.04	[-0.16, -0.01]	**0.024**
Indirect effect	0.07	0.05	[0.00, 0.18]	**0.042**	0.01	0.01	[0.00, 0.20]	**0.042**
Total effect	1.85	0.34	[1.18, 2.52]	**0.000**	0.21	0.04	[0.14, 0.28]	**0.000**
SCD → TMC → CP								
Direct effects								
SCD → TMC	-0.22	0.08	[-0.38, -0.06]	**0.008**	-0.11	0.04	[-0.19, -0.03]	**0.008**
SCD → CP	0.95	0.20	[0.56, 1.36]	**0.000**	0.18	0.04	[0.11, 0.26]	**0.000**
TMC → CP	-0.23	0.10	[-0.42, -0.03]	**0.024**	-0.09	0.04	[-0.16, -0.01]	**0.024**
Indirect effect	0.05	0.03	[0.00, 0.12]	**0.032**	0.01	0.01	[0.00, 0.02]	**0.032**
Total effect	1.00	0.20	[0.61, 1.40]	**0.000**	0.19	0.04	[0.12, 0.27]	**0.000**

Note: b: unstandardized coefficient. β: standardized coefficient. SDP: standard deviations of the posterior distribution. 95% CI: 95% credible interval. SCD: social communication difficulties. TMC: total morning cortisol. HI: hyperactivity/inattention. CP: conduct problems. Bold: $p < .05$. The model for hyperactivity/inattention is controlled for sex, socioeconomic status, stressful life events, smoking, and exact age when social communication was assessed. The model for conduct problems is controlled for vigorous physical activity, stressful life events and smoking.

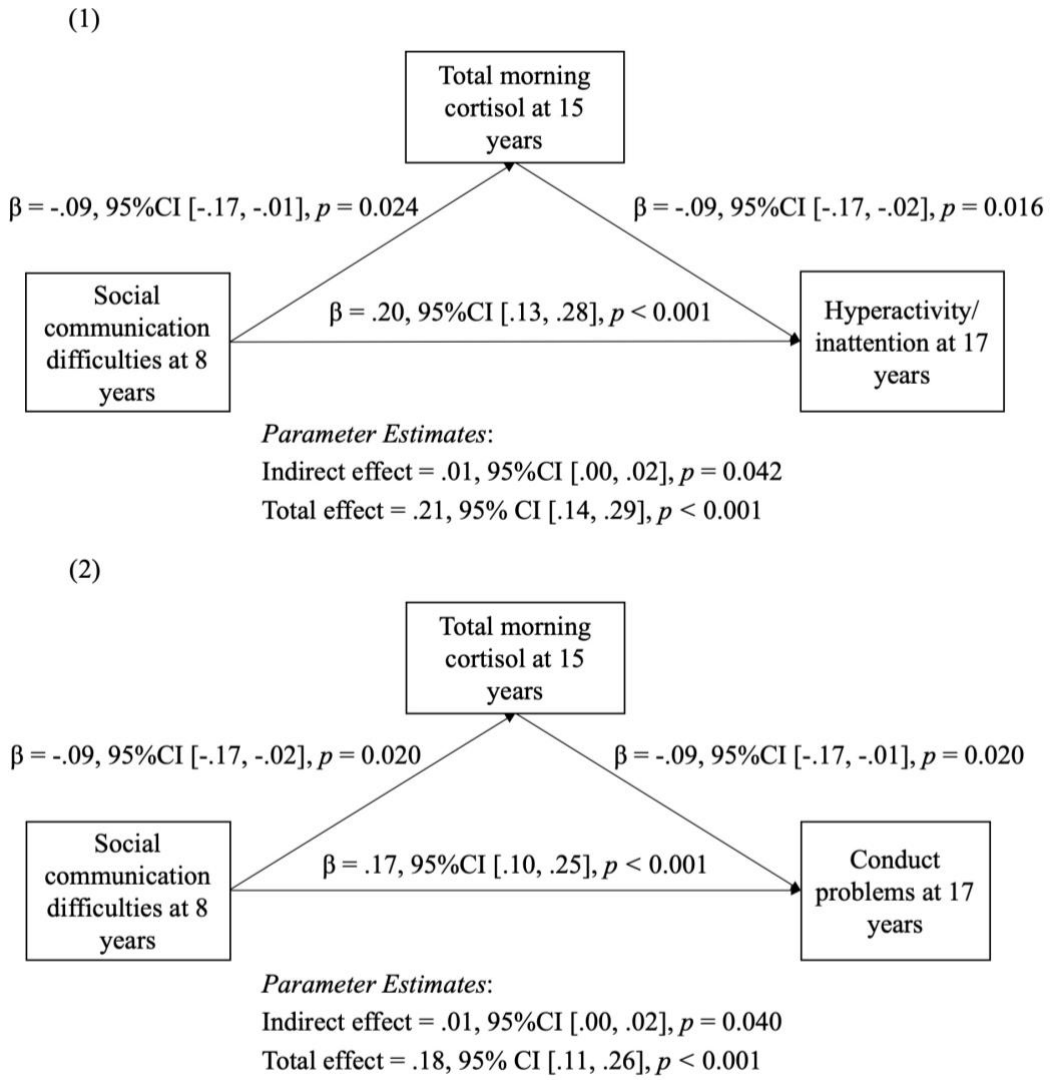

Figure 7-2 Summary of fully adjusted mediation models with standardised coefficients for hyperactivity/inattention and conduct problems via total morning cortisol (N=714)

7.4 Summary

In this Chapter, we first explored the correlations between social cognitive abilities, cortisol measures, inflammatory markers, and mental health outcomes. Next, we investigated the role of inflammation and basal cortisol in the longitudinal associations between social cognition in childhood and early adolescence and emotional and behavioural problems in late adolescence. Consistent with previous evidence (Lancelot & Nowicki, 1997; Yaghoub Zadeh et al., 2007), we found that social communication difficulties were longitudinally related to both emotional and

behavioural problems, giving support to the first hypothesis. The second hypothesis was also confirmed. The results of the structural equation models showed that cortisol measures, including flattened diurnal slope and low morning cortisol levels, were associated with behavioural, but not emotional problems. Moreover, children with social communication difficulties at 8 years were found to be more likely to have lower morning cortisol levels at 15 years, while low morning cortisol emerged as a significant partial mediator for the relationship between social communication difficulties at 8 and behavioural problems at 17. Although the effects were small in magnitude, they were robust to adjustments for confounding. These findings expand the available literature by suggesting that hypoactivity of the HPA axis can, at least partially, explain the longitudinal relation between childhood social communication difficulties and behavioural problems in late adolescence. However, due to the small magnitude of the effect, the findings are limited in informing practice or policy decisions. Social communication difficulties measured at later years (i.e., 11 or 14 years), as well as difficulties in emotion recognition from facial expressions or animated motions, were not associated with any of the diurnal cortisol measures. In addition, there was no evidence for an association between social cognition variables and inflammatory markers (CRP and IL-6), and, as expected, these markers were not linked with later emotional or behavioural problems either. In addition, it is important to note that the indirect effect of lower morning cortisol on the association between social cognition and behavioural problems in the adjusted models became nonsignificant after correction for multiple testing. This suggests that the partial mediation effect might be a false positive conclusion.

7.5 Chapter summary and next step

This chapter investigated one of the main questions of the thesis, namely the associations of social cognition abilities at ages 8, 11, and 14 years with emotional and behavioural problems at age 17 years and the potential mediating effects of cortisol measures at age 15 years and inflammatory markers at ages 9 and 16 years. Mediation analyses revealed that lower morning cortisol partially mediates the association between social communication difficulties with behavioural problems, even after adjustment for confounding. In contrast, inflammation did not appear to mediate the association. This finding indicates that social communication difficulties may affect

long-term behavioural problems through hypoactivity of the HPA axis. The next chapter will discuss the results and key findings of the studies presented in Chapters 3, 5, 6 and 7 in more detail. In addition, the strengths and limitations of those studies, future research directions and potential policy implications will also be discussed.

Chapter 8: Discussion

8.1 Thesis aims and hypotheses

This thesis explored the associations of cortisol and inflammation with emotional (emotion and peer problems) and behavioural (hyperactivity/inattention and conduct problems) problems in a general child population, and attempted to disentangle if inflammation, cortisol, or the two jointly, explain all or part of the longitudinal link between poor social cognitive abilities and emotional or behavioural problems. First, I evaluated the current literature on social cognition and cortisol using a meta-analytic approach. Second, I examined whether diurnal cortisol and inflammation are associated with emotional and behavioural problems in late adolescence (age 17 years). I also tested if abnormal basal cortisol is related to persistent hyperactivity/inattention symptoms from childhood to adolescence. Finally, I investigated if cortisol or inflammation mediated the association between childhood social cognitive abilities and later emotional and behavioural problems. To meet those aims, I used a range of different statistical methods, including a systematic review of the prior literature, multiple regression analyses, growth mixture modelling, and Bayesian structural equation modelling. All analyses were run on data from a UK general population birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC).

8.2 Summary and discussion of key findings

8.2.1 The association between social cognition and cortisol

Following an extensive literature review on the associations between cortisol, inflammation, social cognition, and emotional and behavioural problems presented in Chapter 2, a systematic review was conducted to systematically examine all available articles on the association between social cognition and cortisol. This systematic review and meta-analysis summarised existing evidence on the relationship between social cognition and cortisol in the general population. Literature was searched in six databases: EMBASE, PsycARTICLES, PsychINFO, PubMed, ScienceDirect and Web of Science. Of the 401 studies identified, 19 studies reporting a total of 46 effect sizes (Pearson's correlation coefficients) were included in the meta-analysis, supplemented by a narrative review. The systematic review focused on three core

social cognition domains: emotion recognition, empathy, and emotion control. For each of them, a separate meta-analysis was conducted. Potential sources of variability, including age and sex of participants, timing of blood or salivary cortisol sample collection, transformation of the distribution of cortisol data, and fasting prior to the sample collection, were evaluated in subgroup analyses. The meta-analyses found that better emotion control was positively associated with cortisol concentrations. Subgroup analysis showed that this association was significant in males, for morning cortisol, when the cortisol data were transformed to correct for skewed distributions, and when participants were instructed to avoid food and drink intake for at least one hour before sample collection. However, no significant results were found for emotion recognition or empathy for any of the subgroups examined.

The association between social cognition and cortisol was also explored in Chapter 7. Using Bayesian structural equation modelling, we found that children with social communication difficulties at 8 years were more likely to have lower morning cortisol levels at age 15 years. Social communication was measured in ALSPAC with the parent-rated Social Communication Disorders Checklist, a general instrument covering most domains of social cognition, such as reciprocity social interaction skills, verbal and nonverbal communication and behavioural control. The positive and significant link between social communication deficits and low morning cortisol levels found is in line with, and expands, the results of the systematic review in Chapter 3. However, the results of positive associations found in two Chapters should be interpreted differently. The pooled effect of the meta-analysis was based on available cross-sectional studies on emotion control ability (measured with continuous variables to assess how individuals are good at emotion control), while the study presented in Chapter 7 established a significant prospective association between social communication deficits (measured by a binary variable using a cut-off to separate children who had social communication difficulties from others) in childhood with morning cortisol levels in adolescence. As discussed in Chapter 2, the HPA axis is activated under acute stress and upregulates the secretion of cortisol. In the case of chronic stress, however, the activity of the HPA axis may change from hypercortisolism to hypocortisolism. Hence, the cross-sectional association found in Chapter 3 indicated that the HPA axis may be more sensitive to daily stress for individuals with better emotion control ability, suggesting that emotion control, may

come at a cost and add physical stress on the body (Richards & Gross, 1999). The longitudinal association found in Chapter 7, however, reflects that poor social communication ability in childhood may be related to long-term stress and lead to an impaired and downregulated HPA axis in adolescence.

In contrast, social communication measured at ages 11 or 14 years was not associated with cortisol measures. There are two possible explanations. First, children exhibiting social communication difficulties from a younger age (i.e., eight years) might suffer from prolonged exposure to social stressors. Mounting evidence suggests a link between a low, flat diurnal cortisol rhythm and chronic stress (Anda et al., 2006; Trickett et al., 2010). Therefore, compared to social communication difficulties presenting in adolescence, social communication difficulties with earlier onset might be more likely to be associated with hypoactivity of the HPA axis. Second, only very few children in the sample showed social communication difficulties at ages 11 (2.82%) and 14 years (4.69%), hence this analysis could be underpowered and thus, unable to detect a small effect.

In contrast to the significant association found between social communication at age 8 and cortisol at age 15, emotion recognition difficulties were not associated with morning cortisol levels. This is in line with the results of the meta-analysis in Chapter 3 which suggested that emotion regulation, but not emotion recognition, is related to higher cortisol levels. These findings demonstrate that different social cognition domains do not necessarily overlap and are characterised by different underlying biological mechanisms. It is also possible that emotion recognition and theory of mind may be more automatic and less effortful than other social cognitive processes (e.g., social reciprocity and attribution of nonverbal cues), therefore less likely to induce dysregulation of HPA axis (Happé & Frith, 2014). In addition, compared to children with poor general social communication ability, children with difficulties in emotion recognition may be high-functioning socially if they have intact higher-level social cognition abilities (e.g., emotion regulation and social reciprocity). Thus, they may experience fewer social stressors and therefore may be less likely to show dysregulated HPA axis activity. However, this could not be tested in this study. Further investigation is needed to disentangle the relationship between the various social cognition abilities and stress.

8.2.2 Cortisol and emotional or behavioural problems

Chapter 5 explored for the first time the predictive effect of inflammation and diurnal cortisol levels for emotional and behavioural problems in adolescence (age 17 years) while adjusting for earlier mental health symptoms. The results of multiple regression models showed that adolescents with lower total morning cortisol levels and flatter cortisol slopes were at risk for higher levels of hyperactivity/inattention symptoms two years later, after adjustments for behavioural symptoms in early childhood, inflammation, and confounding. Lower morning cortisol was also associated with later conduct problems after adjustment for early conduct problems, inflammation, and covariates. These findings suggest a tentatively casual association between the hypoactivity of the HPA axis and later behavioural problems, as early behavioural problems were adjusted for in all models. One explanation for this association is that children with underregulated HPA axis may tend to seek more stimulation to raise their arousal levels, thereby engaging in more disruptive or aggressive behaviours (Kruesi et al., 1989). This finding is also in line with existing evidence on cortisol profiles in children or adolescents with hyperactivity/inattention symptoms (Angeli et al., 2018; Ibrahim et al., 2016; Isaksson et al., 2012) and conduct problems/disorder (Pajer et al., 2001; Salis et al., 2016; Schloß et al., 2018; Shoal et al., 2003). For example, Schloß and colleagues (2018) found that low hair cortisol concentrations are associated with an increase of ADHD symptoms between ages 4 and 5 years. Salis and colleagues (2016) found that flattened cortisol rhythms could predict a greater increase of conduct and aggressive behaviours over three years in young school-age children. Our results expand these findings by indicating that morning cortisol may also be regarded as a biomarker of risk for later hyperactivity/inattention and conduct problems in the general adolescent population.

In Chapter 5, I did not find evidence for an association of hyperactivity/inattention or conduct problems at age 4 years with cortisol measures at age 15 years. As described in Chapter 2 and above, hypocortisolism in the general child population can be considered a marker of allostatic load. A low, flat diurnal rhythm is indicative of chronic mild (e.g., following exposure to adverse life events) or high (e.g., post-traumatic stress or burnout) stress (Anda et al., 2006; Millller et al., 2017). Behavioural problems measured at a single time point (4 years) can be transient and do not always relate to later behavioural problems at age 15; those

children whose symptoms improved during the period may not be exposed to chronic stress, resulting in the normal cortisol rhythm observed at age 15.

Chapter 6, therefore, investigated the role of chronicity and severity of hyperactivity/inattention symptoms across childhood in HPA axis function in adolescence. In that study, growth mixture models were fitted to identify classes of children with distinct developmental trajectories of hyperactivity/inattention symptoms from ages 4 to 13 years. HPA axis function was measured by diurnal cortisol output at age 15 years. In line with previous research (Sasser et al., 2016), three distinct hyperactivity/inattention trajectory classes (low and decreasing, intermediate, high) were identified. Results of multiple regression analyses showed that compared to adolescents in the low trajectory class, those with persistently high levels of inattention/hyperactivity symptoms showed lower morning cortisol levels, even after adjustments for confounders. This finding is consistent with previous evidence of attenuated morning cortisol profiles in adolescents diagnosed with ADHD (Angeli et al., 2018; Fortier et al., 2013; Ibrahim et al., 2016; Imeraj et al., 2012; Isaksson et al., 2012). Given that hypoactivity of the HPA axis is related to chronic stress, this finding indicated that compared to their typically developing peers, children with hyperactivity/inattention may experience more adverse events or accidents, as they tend to take more risks and seek novelty, resulting in higher exposure to chronic stressors (Brown et al., 2017).

There was also evidence for smaller diurnal cortisol declines in the classes of adolescents with high and intermediate levels of hyperactivity/inattention symptoms after adjustment for cofounders. It is likely that this decline was driven by the lower morning cortisol levels seen in these two groups as there were no differences in afternoon or evening cortisol levels between classes. However, I found no evidence for an association between the different trajectories of hyperactivity/inattention and diurnal cortisol slope which is a more robust measure of basal cortisol activity since it is adjusted for differences in the total awake time (Adam & Kumari, 2009). In fact, the association between diurnal cortisol slope and symptoms disappeared when sex was controlled for. Hyperactivity/inattention symptoms are more common in males than females, and there are pronounced sex differences in diurnal cortisol profiles in the general population too (Barkley, 2003). Hence, this finding might be an artefact of the higher proportion of males in the high and intermediate symptom groups.

Nonetheless, there was no moderating effect of sex on the association between hyperactivity/inattention and diurnal slope. Taken together, these results suggest that even if there is a true difference in diurnal cortisol change between adolescents with hyperactivity/inattention symptoms and their typically developing peers, it is very small and markedly attenuated by confounders.

Regarding the remaining cortisol measures, i.e., CAR and AUCg, these were not associated with behavioural problems at ages 4 years or 17 years. CAR and AUCg did not differ between the three classes of hyperactivity/inattention symptoms either; thus, there was no evidence in support to the hypothesis that adolescents with persistently high levels of symptoms are characterised by smaller CAR or total daily cortisol output (Angeli et al., 2018). CAR measures a response to awakening rather than the circadian increase in HPA axis activity during the early morning hours (Fink, 2012). It does not represent total daily cortisol exposure or diurnal cortisol rhythm and captures a different aspect of HPA axis function (Golden et al., 2013). Hence, these findings suggest that chronic behavioural problems may not impair one's ability to react to a natural stimulus (i.e., awakening).

Regarding emotional problems, contrary to previous evidence of flattened diurnal cortisol slopes in patients with affective disorders (Doane et al., 2013; Mantella et al., 2008; Paslakis et al., 2011), in this thesis I did not find an association between emotional problems at age 4 or 17 years and any of the cortisol measures considered. This finding indicates that childhood emotional problems are not related to abnormal HPA axis function in adolescence, and that cortisol is not a predictor of later emotional problems in the general population. As the power analysis suggested that the study's sample size was adequate to allow detection of small to medium effect sizes (f^2 = 0.02 in Chapter 5 and r = 0.3 in Chapter 7), the null findings are likely to reflect true absence of meaningful associations, rather than a lack of power. However, if the sample size had been larger (i.e., more than 1224 as suggested in Section 7.3.4), the study would have been to detect correlation coefficients r as small as 0.1. In addition, this non-significant finding could be related to the measure of emotional problems used in this study. The emotion problems subscale of the SDQ is quite broad and measures depressive and anxiety symptoms. It is possible that only certain types of emotion problems are related to basal cortisol. For example, Lamers and colleagues (2013) found higher levels of diurnal cortisol in individuals with

melancholic depression, but not atypical depression. Additionally, it is likely that parent-reported emotional problems in adolescence could be biased, leading to greater measurement error. Hence, for a robustness check, analyses in Chapter 5 were replicated with a more specific self-reported measure of depressive symptoms, the short Moods and Feelings Questionnaire. However, the association between cortisol and depressive symptoms were still not significant, indicating that diurnal cortisol is very unlikely to be linked with future emotional problems in the general adolescent population.

8.2.3 Cortisol and inflammation

The four cortisol measures were strongly associated with each other, with Pearson's correlation coefficients ranging from 0.45 to 0.85. IL-6 and CRP at 9 years and CRP at 16 years were also positively correlated with each other, but moderately, with Pearson's correlation coefficients ranging from 0.12 to 0.47. Of the four cortisol measures, in Chapter 5 I found only CAR to be positively correlated with IL-6 at age 9 years, but not CRP at age 9. In the study presented in Chapter 7, both total morning cortisol and CAR were positively associated with CRP at age 9, but not with IL-6 at age 9 or CRP at age 16. Since all the correlation coefficients were positive, it indicates that children with higher levels of inflammatory markers have a higher possibility to exhibit hyperactivity of the HPA axis, such as higher morning cortisol levels and greater cortisol awakening response in adolescence. This positive association is in line with the longitudinal link between dysregulated diurnal cortisol pattern (i.e., all days elevated, flattened, or a combination of elevated and flattened) and heightened inflammation found in older general population samples (Piazza et al., 2018). However, because the coefficients for the correlation between CAR or total morning cortisol and IL-6 or CRP in this thesis were very small in magnitude, around 0.10, and the significance was not consistent (p-values became non-significant with only small changes in analytic sample definition criteria, for example from 729 children in Chapter 5 to 714 in Chapter 7 depending on data missingness rates), this thesis did not find a robust longitudinal link between cortisol and inflammatory markers in the general population.

8.2.4 Inflammation, social cognition, and emotional or behavioural problems

In this thesis, I did not find evidence for an association between inflammatory markers with any of the social cognition variables, or the emotional and behavioural problems considered. Specifically, the study in Chapter 5 showed that there was no correlation between CRP or IL-6 and emotional or behavioural problems in early childhood. Those inflammatory markers could not predict emotional or behavioural problems in late adolescence either. The study in Chapter 7 further found that social communication difficulties and emotional recognition abilities in childhood and early adolescence were not linked with inflammation in adolescence. One possible reason for the null findings could be that the longitudinal associations between biological and psychological factors tend to be weaker, hence, more difficult to be detected in small population-based samples compared to larger cohorts or clinical and high-risk samples. For example, significant associations between inflammation and psychosocial outcomes have been reported in clinical populations (e.g., patients with ADHD in Chang et al., 2020 and Leffa et al., 2018; more studies were reviewed in Chapter 2) and larger community samples (e.g., n = 4,583 in Flouri et al., 2019; n = 13,775 in Niles et al., 2018). The analytic samples in Chapter 5 and Chapter 7 included around 500 participants with valid data for inflammatory markers, and it is likely that there was not enough statistical power to detect a very small effect. However, power analyses suggested that the studies' analytic samples were adequate to allow 80% power for detecting effect sizes (correlation coefficients r) larger than 0.11. Therefore, if an association between inflammatory markers and mental health had existed, the correlation coefficients would be very small, if not negligible. Future studies could replicate the analyses with a larger sample size to check the exact magnitude of the association between inflammatory markers and social cognition or mental health outcomes in the general population. Second, only two inflammatory markers are available in ALSPAC. It is possible that other inflammatory markers may show a stronger association with social cognition and mental well-being, such as interferon-γ and TNF-α (Costello et al., 2019). In addition, levels of IL-6 and CRP at age 9 years were measured from non-fasting samples which may increase measurement error caused by diurnal variation in the levels of cytokines. Therefore, future studies should use larger samples and fasting blood samples, and consider

additional pro and anti-inflammatory markers for a more accurate and comprehensive understanding of the immune changes linking social abilities and mental wellbeing.

8.2.5 Social cognition, cortisol, and behavioural problems

Section 8.2.1 discussed the findings of the association between social cognition and cortisol, and Section 8.2.2 focused on the findings related to the link between cortisol and emotional or behavioural problems. In this section, I will integrate the two parts together and discuss the mediating role of cortisol in the link between social cognition deficits and mental health problems, which was investigated in the study presented in Chapter 7. The results showed that the predictive effects of childhood social communication difficulties on conduct problems and hyperactivity/inattention symptoms in adolescence were partially mediated by lower morning cortisol levels, even after adjusting for inflammation and confounders. This finding demonstrates the role of HPA hypoactivity in the pathophysiology of behavioural problems in adolescents with early social communication difficulties.

As mentioned in Chapter 2, dysregulation of the HPA axis has been implicated as one physiological pathway that mediates the effects of chronic stress on physical and mental health problems (McEwen, 2004; Raison & Miller, 2003). Prolonged or repeated stress over years has been found to conduce blunted HPA axis activity among children, particularly when exposure occurs at a young age (Anda et al., 2006; Trickett et al., 2010). It is suggested that the HPA axis arousal response is suppressed to adapt to the repeated exposure to stressors by increasing feedback sensitivity or receptor down-regulation to prevent chronic behavioural and endocrine overactivity (Lovell, Moss, & Wetherell, 2011; Susman, 2006; Miller et al., 2007). Downregulated HPA axis is further associated with behavioural problems, as the results of this thesis and other available literature (McBurnett et al., 2000; Shirtcliff et al., 2005). Accordingly, increasing number of studies evinced that the individuals with repeated adversities in early life (e.g., prenatal substance exposure, marital conflicts, and early life stress) showed blunted reactivity of the HPA axis to stress, which was in turn related to their later externalising symptoms or maladjustment (Conradt et al., 2014; Davies et al., 2007). Similar to the effect of early life adversities, social communication difficulties can also induce chronic stress. As discussed in Chapter 2,

children with social communication difficulties are more likely to experience more social exclusions, become victims of bullying, and have lower self-esteem compared to children with better social communication ability (Caqueo-Urízar et al., 2022; Shakoor et al., 2012). Hence, they may also be vulnerable to dysregulation of HPA axis and the consequent development of behavioural problems. The results of Chapter 7 supported these insights by providing empirical evidence for the mediating role of hypocortisolism in the relationship between childhood social communication difficulties and behavioural problems in late adolescence.

In addition, the moderating effect of sex on the mediation models was tested. Different results were found for hyperactivity/inattention and conduct problems. For the association between social communication difficulties and hyperactivity/inattention, the indirect effects of morning cortisol levels did not differ by sex, while for conduct problems, the path from social communication difficulties to morning cortisol was moderated by sex and the path from morning cortisol levels to conduct problems was not. Specifically, the mediating effect of lower morning cortisol was only significant in adolescent boys, not in girls, indicating that the HPA axis may be more vulnerable to social stress in boys. This may be related to the findings of greater acute cortisol responses to psychological stressors in males, as revealed by prior experimental studies (Kudielka & Kirschbaum, 2005; Uhart et al., 2006). Repeated stressors and greater cortisol response to every single stressor may be more likely to lead to dysregulation of the HPA axis in the long term. However, the moderating effect of sex on the association between social cognition and cortisol only existed in the models for conduct problems, not the models for hyperactivity/inattention, although the sample and the theoretical logic behind the path were the same for both. The conflicting results may be related to different confounders that were included in the two models and the possibility of type I (p-value of the interaction term in the model for conduct problems did not survive the multiplicity correction) or type II errors (the statistical power of the model for the hyperactivity/inattention may be not enough because more confounders included and lower degrees of freedom). Therefore, the results of the moderated mediation models should be interpreted with caution and future replication is needed.

8.2.6 Reflection on the results after correction for multiple testing

An issue with multiple testing occurs when a dataset is subjected to statistical testing a set of hypotheses simultaneously, which increases the probability of false-positive finding (Ranganathan et al., 2016). Multiple testing correction is commonly used to control for the family-wise error rate or the false discovery rate. The widely used Bonferroni correction was applied to the analyses in this thesis. The longitudinal links between mental health problems in early childhood and adolescence and between early social cognition and later mental health were still significant after multiplicity correction, but all the significant associations between cortisol measures and psychological variables became non-significant. The Bonferroni correction is criticised as being too conservative and leading to a higher rate of false negative (Benjamini & Hochberg, 1995). There are several alternative approaches which are less stringent, such as the Holm-Bonferroni method (Holm, 1979) and the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995). However, none of the associations between cortisol measures and psychological variables survived these two multiplicity correction approaches either. This means that there was no credible evidence for the associations of cortisol measures with social communication and behavioural problems in the general population, or that the associations are too weak (effect sizes are too small) to be statistically significant after controlling for the effects of multiple testing. Additionally, there was no robust difference of total morning cortisol between adolescents with persistently high levels of hyperactivity/inattention symptoms and those with low and decreasing levels of symptoms. Two explanations might be related to very small effect sizes found for the associations between cortisol measures and mental health: 1. The links between biological measures and psychological variables are weak (Chida & Steptoe, 2009); 2. The association between cortisol and mental health problems or social cognition may not be linear. That is, the association between cortisol and mental health problems might be stronger if cortisol levels/activities passed a “normal” range. Increasing the sample size can increase the power of detecting very small effects. However, some scholars suggested that corrections for multiple testing may not be needed if only a few planned tests were made: the focus are a few theoretically sensible hypotheses rather than every possible test (Rothman, 1990; Saville, 1990). In this case, all tests should be reported, and it should be stated clearly that no mathematical correction was made for multiple testing. Readers should interpret the results carefully, with the potential risk of multiple testing in mind.

8.3 Implications of main thesis findings

From a research perspective, this thesis contributes to the body of knowledge in the fields of biological psychology and psychoneuroendocrinology, and helps to identify some future directions and research priorities. The systematic review presented in Chapter 3 found great heterogeneity in the methodologies and results in studies on the association between social cognition and basal cortisol concentration. Few studies used a longitudinal design or considered adjustment for confounders. Some studies only reported a broad range of sample collection time for cortisol, which makes the results difficult to interpret. This suggests that greater standardisation of methodological procedures is warranted for future research. The three empirical studies presented in Chapters 5-7 added new evidence for an association between HPA axis hypoactivity and behavioural problems in the general adolescent population. The hypocortisolism found in adolescents with hyperactivity/inattention symptoms or conduct problems may partly explain their increased risk for inflammation, autoimmune diseases, and atopic illnesses (Buske-Kirschbaum et al., 1997; Heim et al., 2000), and generally poor health in adulthood (Agnew-Blais et al., 2018; Bevilacqua et al., 2018; Brook et al., 2013). Future research can further explore this topic by testing the role of HPA axis on longitudinal health outcomes among the youth population with chronic behavioural problems. Chapter 7 further supported the stress strand of theories (e.g., SSDV and social competence theory, described in Section 2.1.2) by demonstrating that adolescents with childhood social communication deficits are more likely to manifest lower basal cortisol which, in turn, can lead to more behavioural symptoms in late adolescence. As this is a partial mediation effect, additional mechanisms, such as stress perception and negative cognitive appraisal, linking social communication difficulties with behaviour problems, could be explored in future research. A more comprehensive understanding of how social cognitive difficulties can bring about mental health problems is important to identify points for intervention in early stages of behaviour problem emergence. Last but not least, as none of the findings on cortisol measures remained significant after multiple testing correction, all the evidence mentioned above can be non-reliable. Replications with larger sample sizes are needed.

From a practical perspective, childhood mental health problems and social cognition difficulties were found to be robustly linked to the mental health symptoms in adolescence. This suggested that mental health screening and intervention in the early years are important in reducing the prevalence of mental health problems in adolescence. The findings also suggested that by training educators, parents, and community social workers to promote positive social environments and enhance young people's social skills at an early age, the risk for future emotional and behavioural problems could be reduced. Regarding the findings related to cortisol measures, it could be inferred that decreased morning cortisol levels might be a potential indicator for childhood social communication difficulties and chronic hyperactivity/inattention problems, and blunted cortisol activities might also aid in the identification of adolescents at risk for behavioural problems. However, the small effect sizes mean that the practical benefit of these findings can be very limited and may lack of real-world importance. On top of that, the findings did not survive correction for multiple testing, and therefore they were not recommended to be applied in educational practice or inform policy until further testing.

As the current PhD project did not find evidence for an association between inflammation and social cognition or emotional and behavioural problems, inflammatory markers are not suggested to be considered as indicators for mental health problems in the general child population. Nonetheless, studies using larger samples (e.g., Colasanto et al., 2020; Flouri et al., 2020) have demonstrated that inflammation may be related to emotional problems in community youth. It appears that additional empirical studies are required to establish the role of inflammation in the pathogenesis of problem behaviours.

8.4 Thesis strengths

This thesis has several strengths.

First, this thesis includes a comprehensive synthesis of studies and theories on the biological mechanisms underlying the longitudinal link between social cognition abilities and mental wellbeing. The systematic review presented in Chapter 2 examined for the first time the associations between three core social cognition abilities with basal cortisol using meta-analytic techniques, and showed that better emotion control is associated with increased cortisol concentrations. The empirical

studies presented in Chapters 6-7 were the first to examine the endocrine function of adolescents with chronic hyperactivity/inattention problems and the roles of immune and endocrine systems in the longitudinal association between childhood social cognition and mental health in late adolescence. These studies added more evidence to the body of work that has identified hypocortisolism as a key feature of adolescents with behavioural problems and/or poor social communication abilities, and expanded the evidence by using a longitudinal approach and a general population sample. By doing so, it shed light on the long-term effect of childhood social cognition deficits and chronic behavioural problems on adolescents' physiological health.

Second, in this thesis, a large longitudinal population sample of children was utilised, the Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC provides rich information on multiple biological, psychosocial, social, and other developmental factors for a range of psychological, social and health outcomes in children (Boyd et al., 2013). This allowed us to control for a wealth of confounders in all analyses, such as demographic characteristics, measures of lifestyle and psychosocial risk, and others, thus making the analyses and results more robust. In addition, due to the comprehensive biological data collection in ALSPAC, I was able to include both inflammation and cortisol measures in the same models to adjust for one another; to date, this had only been done in smaller clinical samples (Miller et al., 2014; O'Donovan et al., 2010). Therefore, this thesis includes the first and largest longitudinal studies exploring the roles of both inflammation and cortisol in explaining the association between early social-cognitive abilities with emotional and behavioural problems in adolescence. Furthermore, ALSPAC has maintained consistency in measurements of variables across age groups. This allowed me to capture developmental profiles of hyperactivity/inattention symptom since preschool, and to investigate the HPA axis function in adolescents with different developmental profiles.

Third, advanced and appropriate statistical techniques were used in the thesis, allowing for robust estimation of statistical models. Structural Equation Modelling (SEM) is a powerful alternative to multiple regression, path analysis, and factor analysis, allowing the development of complex path models with direct and indirect effects. It also allows for making causal inferences for the mechanisms under study (Markus, 2010). I used Bayesian estimation methods for the mediation models, which

provided even more robust estimates for mediation effects as they do not rely on assumptions of normality for indirect effects (Muthén, 2010). In addition, to identify the discrete trajectories of hyperactivity/inattention symptoms in Chapter 6, I used growth mixture modelling (GMM), which combines latent growth curve modelling (LGCM) and finite mixture modelling approaches. Compared to other commonly used classification models, such as latent class growth analysis (LCGA), GMM allows within-class variation of growth parameters (intercept and slope), thus providing a more accurate classification by imposing fewer constraints on the model parameters being estimated (Jung & Wickrama, 2008).

8.5 Limitations and future work

Despite its strengths, this thesis also has several limitations.

The limitations of the systematic review on social cognition and cortisol have been discussed in depth in Chapter 3. It should be highlighted here that the meta-analysis results need to be interpreted with those caveats in mind, particularly the substantial methodological heterogeneity of the included studies and the lack of a careful quality assessment prior to the meta-analysis. It should also be noted that despite rhythm parameters of basal cortisol being most robustly linked to stress and health problems, only five studies measured the link between social cognition and cortisol rhythm parameters such as CAR or diurnal cortisol slope, which means that more studies with reliable measures of cortisol are warranted. In addition, as there are too few studies focussing on the relationship between inflammation and social cognition, these were not included in this systematic review. However, it would be useful to have inflammation considered together with cortisol measures. Therefore, more research on this topic is also needed.

The following section will focus on the limitations of the three empirical studies and the thesis as a whole.

8.5.1 External validity of study samples

First, as discussed in Chapter 4, although ALSPAC includes a large and socioeconomically diverse sample, it does not vary widely across other demographic

characteristics, such as ethnicity. Non-White participants comprise only around 3% of the analytic samples in the empirical studies presented here. Thus, the number of non-White participants was not sufficient to allow for statistically robust comparisons across ethnic backgrounds. Moreover, sample bias analysis showed that participants in the analytic sample of this thesis were significantly more advantaged in terms of socioeconomic characteristics and scored lower in the emotional and behavioural problems considered, compared to ALSPAC families that were not included in the study, primarily because of differential attrition and non-response bias. Considering that the socioeconomic background of ALSPAC families was already better than that in the general Avon and British populations (described in Chapter 4), the analytic sample of this thesis is not entirely representative of the national population. Therefore, the external validity of the study may be somewhat compromised.

8.5.2 Validity of measures

As this thesis was conducted entirely using secondary data, it was limited to the variables that were available in ALSPAC. First, the brief questionnaire and the two computer-based tests that were used to assess social cognition may not provide a clear picture of a child's social cognition ability. The SCDC is a screening instrument for general social communication ability which does not distinguish between different aspects of social cognition. As it was mainly designed to discriminate clinically diagnosed children with ASD from non-clinical samples, it is appropriate for targeting children with severe social cognition deficits but cannot differentiate higher levels of social communication ability due to positive skewness in the whole child population. Future studies should be cautious of this potential floor effect when using SCDC as a measure of social cognition in general population samples. Regarding the two computer-based tests, DANVA tests children's nonverbal communication skills and focuses on emotional facial expressions, without considering body language such as postures and gestures. The emotional triangles test measures adolescents' theory of mind, focusing on emotional states attribution but not cognitive perspective-taking. Future studies may consider using other social cognition tests to determine if the associations between social cognition and physiological stress that we found can be replicated for other sub-domains of social cognition.

Second, the assessment of the HPA axis function was limited to basal salivary cortisol. Other hormones released by the HPA axis, such as CRH and ACTH, and HPA-related genetic polymorphisms, were not directly assessed in ALSPAC. Cortisol levels may be similar in individuals with different levels of glucocorticoid sensitivity, cortisol-evoked genomic activity, and GR expression, which are also related to physical and mental health problems (Saxbe, 2008). Nevertheless, as the final product of the HPA axis, cortisol is sensitive to all the upstream hormones, and has a direct impact on GR availability and expression.

Third, social communication and emotional and behavioural symptoms were reported by mothers, which may raise concerns about a possible reporting bias. However, many scholars consider caregiver-reported SDQ to be a reliable proxy (Stokes et al., 2014), even for older adolescents (Vugteveen et al., 2021; van Roy et al., 2008; van Widenfelt et al., 2003). Nevertheless, future studies may consider using multi-informant SDQ in the screening and assessment of children's mental health problems as parent-rated and self-reported SDQ yield different factorial structures and show only modest agreement (Goodman, 2001; van Roy et al., 2008).

Fourth, there might be some concerns related to the selection and generation of the confounder SES. Analyses in this thesis used a composite SES variable as a confounder, which was calculated using information of financial difficulties, maternal social class and maternal education backgrounds. Despite the merits of this approach discussed in Chapter 4, a composite SES variable may mask variations in SES within a group (Saisana et al., 2005). In addition, sometimes certain individual SES indicators may be more appropriate to use, especially if they are very closely associated with the outcome in question. It has also been argued that a composite SES variable may be subject to measurement bias, which can occur if an indicator that makes up the composite variable was not well measured.

8.5.3 Data and model design

The time points when cortisol and inflammatory markers were measured in ALSPAC were also limited, resulting in compromises in model design and hypothesis testing. First, inflammatory markers and cortisol were not measured at the same time, so we were not able to examine the concurrent effects of inflammation and cortisol.

ALSPAC collected saliva samples for cortisol when cohort children were 15 years and measured inflammatory markers at children's ages 9 and 16 years. Although the levels of inflammatory markers at different time points are correlated (Nash et al., 2013), the levels of IL-6 at age 9 or CRP at ages 9 and 16 do not coincide and cannot be considered as being perfectly aligned with cortisol measurements which were available at age 15 years. Hence, the mutual adjustments for inflammation and cortisol in some of the models were not ideal. Future research should replicate the studies presented as part of this thesis by including inflammation and cortisol measures taken at the same time to examine their concurrent and/or joint effects on the outcomes of interest.

Second, as cortisol was not measured in childhood, we could not adjust for early HPA axis function when exploring the mediating effect of cortisol in the association between social cognition and mental health problems. Therefore, we cannot disentangle the temporal relationship between HPA axis dysregulation and social communication difficulties. If social cognition variables were available in adolescence too, and biological markers were also measured in childhood and later adolescence, more complex hypotheses examining the directionality of the associations between those measures could be tested using more sophisticated statistical models, such as cross-lagged panel models. Such analyses would allow making tentative causal inferences regarding the complex interplay between social cognition, stress, and mental health problems.

Third, the absence of longitudinal data on cortisol did not allow us to test the link between hyperactivity/inattention and *long-term* HPA axis habituation which may be particularly relevant in the general population. HPA axis response to acute stress is related to steeper CAR and steeper diurnal cortisol decline (Chen et al., 2017) while chronic stress is related to glucocorticoid resistance (Rohleder, 2012). Hence, future studies could track within-individual longitudinal changes in HPA axis in response to stress in children and adolescents with high levels of hyperactivity/inattention symptoms, a group widely considered at risk for increased exposure to stressors. This group could initially show adaptive responses to stress which might then become maladaptive as stress becomes chronic.

8.6 Concluding remarks

This PhD has provided evidence on the longitudinal associations between childhood social communication difficulties and emotional and behavioural problems in adolescence. Emotion recognition ability was not found to be associated with later emotional or behavioural problems. Lower morning cortisol partially mediated the associations between social cognition difficulties and behavioural problems, even after adjustment for inflammation and other confounders. Lower morning cortisol was also found in adolescents with persistently high levels of hyperactivity/inattention symptoms since early childhood, which is in line with findings in studies on children with ADHD. These findings suggest that hypocortisolism in children with social cognition deficits may be indicative of future behavioural problems, and that basal cortisol may be used as a biomarker of chronic hyperactivity/inattention problems in community samples of youth. However, it should be noted that the effect sizes for all the significant findings are very small in magnitude and did not survive correction for multiple testing. Therefore, replication in the future is needed to test the validity of the findings. Although inflammatory markers were related to cortisol levels, inflammation was not found to be associated with social cognition or emotional and behavioural problems in the general population sample used in this thesis.

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