

Hair Cortisol and Psychopathology
Among Children with a Chronic Physical Illness

by

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This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

Within this thesis contains three manuscripts that have been accepted or submitted to peer-reviewed journals for publication in collaboration with dissertation committee members.

Exceptions to sole authorship are as follows:

Chapter 5: Littler, E., Butt, Z., Gonzalez, A., & Ferro, M. (2025). Association between hair cortisol and psychopathology in children with a chronic physical illness. *Stress and Health*. 41(4), e70087. <https://doi.org/10.1002/smi.70087>

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As lead author of these three manuscripts, I was responsible for developing the objectives and research questions, conducting background research, conducting statistical analyses, interpreting the results, and drafting and submitting manuscripts for publication. My co-authors provided guidance during each step of the research and provided feedback on manuscript drafts.

Abstract

Chronic physical illnesses (CPIs), such as asthma, diabetes, and epilepsy, affect approximately 30-50% of children. Living with and managing a CPI in childhood may be a significant source of chronic stress. As a result, children with a CPI are at a greater risk of developing psychopathology (i.e., multimorbidity). Multimorbidity negatively impacts children's physical and psychosocial health, including child health-related quality of life (HRQoL). Thus, understanding the mechanisms underlying child multimorbidity is a critical public health concern. Chronic stress exposure can lead to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which may be implicated in the development of psychopathology. Over the past two decades, hair cortisol concentration (HCC) has been identified as a viable biomarker for chronic HPA-axis dysregulation in children. However, evidence linking HCC to psychopathology in children is mixed, and very few studies have examined these associations in children with a CPI. Existing studies in children with a CPI are often small, cross-sectional, and illness-specific.

To address these knowledge gaps, this dissertation examined the longitudinal associations between HCC and psychopathology in a large sample of children with diverse CPIs. Specifically, the objectives were to: 1) identify distinct trajectories of HCC among children with a CPI; 2) identify predictors of HCC trajectory group membership; 3) examine associations between HCC trajectories and psychopathology; 4) examine the between- and within-dyad effects of parent distress on child psychopathology; 5) explore child HCC trajectory as a moderator of the associations between parent distress and child psychopathology; 6) examine associations between HCC trajectories and HRQoL; and 7) explore psychopathology as a mediator of the associations between HCC trajectories and HRQoL.

The first study used latent class growth analysis (LCGA) to identify three distinct trajectories of HCC in children with a CPI: Hypersecretion (68%), Hyposecretion (8.6%), and Hyper-to-Hypo (23.4%). Significant predictors of HCC trajectory group membership were child sex, child age, parent age, and time since CPI diagnosis. Linear mixed-effects (LME) models examined associations between HCC trajectories and psychopathology, and found that children in the Hyper-to-Hypo class had fewer internalizing and externalizing psychopathology symptoms compared to the Hypersecretion class. There was no difference in psychopathology symptoms between the Hyposecretion and Hypersecretion classes. These findings suggest that living with a CPI during childhood may be a significant chronic stressor, and HPA-axis dysregulation may be an important mechanism linking childhood CPI to psychopathology.

The second study used LME models to examine the between- and within-dyad effects of parent distress on child psychopathology and explore child HCC trajectory as a moderator of these associations. Higher average parent internalizing symptoms were associated with greater child internalizing and externalizing symptoms. Fluctuations in parent internalizing symptoms only predicted greater child internalizing, not externalizing, symptoms. Higher average levels and fluctuations in parenting stress were associated with greater child externalizing, but not internalizing, symptoms. Child HCC trajectory was identified as a moderating factor, such that the combination of high average parent internalizing symptoms or parenting stress and cortisol hypersecretion predicted greater child internalizing symptoms. These findings suggest that parent and child mental health are strongly linked in families of a child with a CPI, and interventions targeting parent distress may have beneficial downstream effects on child mental health. Moreover, HPA-axis dysregulation in children with a CPI may function as a vulnerability factor that heightens risk for psychopathology when exposed to parent distress.

The third study used latent growth curve models (LGCMs) to examine associations between HCC trajectories and HRQoL over time, and explore psychopathology as a mediator of these associations. Children in the Hyper-to-Hypo class had higher HRQoL in the domains of parents and autonomy, social support and peers, and school environment compared to the Hypersecretion class, and lower psychopathology was identified as a significant mediating mechanism. Children in the Hyposecretion class had higher HRQoL in the physical well-being domain compared to the Hypersecretion class, an effect not mediated by psychopathology. The HCC trajectories were not associated with change in HRQoL over time, but increases in psychopathology were associated with decreases in HRQoL. These findings suggest that HPA-axis dysregulation and psychopathology may be important mechanisms linking childhood CPI to poor HRQoL, and interventions for reducing stress and psychopathology may lead to improvements in HRQoL in this population.

This dissertation fills critical knowledge gaps and contributes to a greater understanding of the mechanisms underlying child multimorbidity. Taken together, these findings can be summarized into three key themes: (1) living with a CPI during childhood may be a significant chronic stressor, and HPA-axis dysregulation may be an important mechanism linking childhood CPI to negative health outcomes; (2) HPA-axis functioning in children with a CPI is heterogenous, and approaches that identify this heterogeneity may be important for understanding health outcomes and informing intervention strategies; and (3) non-categorical, integrated physical-mental, and family-centered care approaches in pediatric healthcare are needed to improve health outcomes for children with a CPI and their families.

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List of Abbreviations

ACTH	Adrenocorticotrophic Hormone
ADHD	Attention-deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
BD	Between-dyad
BIC	Bayesian Information Criteria
BMI	Body Mass Index
CAR	Cortisol Awakening Response
CD	Conduct Disorder
CES-D	Centre for Epidemiologic Studies Depression Scale
CFI	Comparative Fit Index
CI	Confidence Interval
CPI	Chronic Physical Illness
CRH	Corticotropin-releasing Hormone
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBS	Emotional Behavioural Scales
ELISA	Enzyme-linked Immunosorbent Assay
ELM	Early Life Maltreatment
FIML	Full Information Maximum Likelihood
GAD	Generalized Anxiety Disorder
GAD-7	Generalized Anxiety Disorder-7 Scale
GMM	Growth Mixture Modelling
HCC	Hair Cortisol Concentration
HPA	Hypothalamic Pituitary Adrenal
HRQoL	Health-related Quality of Life
ICD	International Classification of Diseases
LCGA	Latent Class Growth Analysis
LGCM	Latent Growth Curve Model
LC-MS	Liquid Chromatography-mass Spectrometry
LME	Linear Mixed-effects
LMR-LRT	Lo–Mendell–Rubin Likelihood Ratio Test
M	Mean
MAR	Missing at Random
MDE/MDD	Major Depressive Episode/Disorder
MY LIFE	Multimorbidity in Children and Youth Across the Life-course
ODD	Oppositional Defiant Disorder
OR	Odds Ratio
PMD	Perinatal Mental Disorders
PSS	Parental Stress Scale
REML	Restricted Maximum Likelihood
RMSEA	Root Mean Square Error of Approximation
SAD	Separation Anxiety Disorder
SD	Standard Deviation
SP	Social Phobia
SpP	Specific Phobia

SRMR	Standardized Root Mean-square Residual
WD	Within-dyad
WHODAS	World Health Organization Disability Assessment Schedule

Chapter 1 – Introduction

Chronic physical illnesses (CPIs), such as diabetes, asthma, and epilepsy, affect approximately 30-50% of children [1,2]. Children with a CPI often experience considerable stress due to their illness, with most conditions characterized by an acute phase of stress surrounding the initial diagnosis, followed by chronic stress associated with the ongoing treatment and management of the condition [3]. Childhood is a period of enhanced vulnerability to stress, which can lead to a greater susceptibility to the development of psychopathology across the lifespan [4]. As a result, children with a CPI are at a greater risk of developing psychopathology [5,6]. Estimates suggest that approximately 20-50% of children with a CPI will develop psychopathology – a condition known as physical-mental *multimorbidity* [7–9]. Multimorbidity negatively impacts child physical and psychosocial health, including health-related quality of life, suicidality, and substance use [10–12]. Understanding the mechanisms underlying child multimorbidity is a critical public health concern as the number of children diagnosed with a CPI is steadily increasing [2].

Emerging research has focused on the link between physiological stress responses and health outcomes in children exposed to chronic stress [13]. Cortisol is a hormone released by the hypothalamic-pituitary-adrenal (HPA) axis in response to stress [14]. Chronic exposure to stress can lead to HPA-axis dysregulation, which may be implicated in the development of psychopathology [15,16]. Over the last decade, hair cortisol concentration (HCC) has been identified as a viable non-invasive biomarker of chronic HPA-axis dysregulation in children [17,18]. Despite its promising utility in this population, no prior research has examined HCC over time and its longitudinal associations with psychopathology and HRQoL in children with a CPI. This knowledge can support the identification of children with a CPI who exhibit

dysregulated HPA-axis functioning, clarify whether HPA-axis dysregulation may be a key mechanism linking childhood CPI to negative health outcomes, elucidate whether HCC is a valuable biomarker for psychopathology risk, and inform the development of interventions to reduce psychopathology and improve HRQoL in children with a CPI.

This dissertation examines the complex relationships between HCC and psychopathology in children with a CPI. Specifically, it examines: 1) trajectories of HCC and their associations with psychopathology; 2) the moderating role of HCC on the associations between parent distress and child psychopathology; and 3) the mediating role of psychopathology in the associations between HCC and HRQoL. Chapter 2 provides an overview of the literature pertaining to the scope of this dissertation. Chapter 3 presents the rationale, objectives, and hypotheses for the three studies that make up this dissertation. Chapter 4 summarizes the general methods for each study, including a description of the study sample, study measures, and statistical analyses. Chapters 5, 6, and 7 present the findings of this dissertation in the form of three manuscripts. Finally, Chapter 8 provides an integrated discussion of the overall findings from this dissertation, including opportunities for future research and implications for policy and clinical practice.

Chapter 2 – Background

This chapter begins by reviewing the current literature regarding child psychopathology, childhood CPI, and physical-mental multimorbidity. This is followed by an overview of the physiological HPA-axis stress response, the concept of allostatic load, and the measurement of cortisol in hair. Next, this chapter reviews the current literature regarding associations between HCC and psychopathology in children, including trajectories of HCC over time. The impacts of parent distress on child psychopathology are then discussed, including the potential moderating role of child HCC. Finally, this chapter reviews the current literature regarding associations between HCC and HRQoL in children, and discusses the potential mediating role of child psychopathology.

2.1 Child Psychopathology

In Canada, it is estimated that one in five children and youth aged 4-17 (herein children) meet the criteria for one or more mental disorders [19–22]. Mental disorders diagnosed during childhood can have significant long-term health and economic impacts on children, their families, and society, and are the leading cause of nonfatal disability in children [23–25]. Without effective prevention and treatment, mental disorders can persist into adulthood and have adverse long-term consequences for children and their families [26]. Adults with childhood-onset mental disorders are more likely to experience unemployment, poor quality of life, social and relationship difficulties, and be involved in the criminal justice system [27,28]. A 2026 report estimated the economic cost of mental disorders in Canada at \$180 billion annually, a high cost driven primarily by reactive and downstream spending in sectors never designed to manage them [29]. Without targeted investment in prevention and early intervention, this number is expected to grow considerably by 2050 [29]. Arguably, preventing the development of mental disorders in

childhood should be one of Canada's top healthcare priorities, as roughly 50% of all mental disorders have their initial onset before the age of 18 [24,30,31]. However, to date, child mental health has not received the research and public policy attention that it deserves [32].

2.1.1 Defining and Measuring Child Psychopathology

Mental disorders are characterized by clinically significant disturbances in individual emotions, cognition, or behaviour, and are typically associated with significant distress or disability across several domains (e.g., school, social, etc.) [33]. The most common mental disorders in children include mood disorders such as major depressive episode/disorder (MDE/MDD)¹, anxiety disorders such as generalized anxiety disorder (GAD), separation anxiety disorder (SAD), specific phobia (SpP), and social phobia (SP), and behavioural disorders such as attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) [20]. These disorders can be further classified into internalizing disorders and externalizing disorders based on symptom profiles. Internalizing disorders are characterized by primarily internally-focused symptoms such as anxiety, fear, sadness, and social withdrawal, and include MDE/MDD, GAD, SAD, SpP, and SP [35]. Externalizing disorders are characterized by primarily externally-focused symptoms such as aggression, delinquency, oppositionality, and hyperactivity, and include ADHD, ODD, and CD [35].

Diagnostic interviews and symptom checklists are the most common assessment methods for mental disorders in children [36]. Interviews are designed to classify mental disorders according to criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) [34,37]. Interviews are a categorical

¹ In children, MDE and MDD are often used interchangeably to refer to a depressive disorder where symptoms are present almost every day for a period of at least two weeks [34].

approach to classifying mental disorders and are used to obtain a diagnosis (presence vs. absence of diagnosis) [36,38]. In contrast, checklists are a dimensional approach and are designed to measure the frequency or severity of mental disorder symptoms that exist along an underlying continuum [36]. They can be self-completed by the child or a proxy respondent (e.g., parent or teacher) [36]. Checklist scores can be interpreted according to thresholds to classify the presence/severity of the disorder, but are not designed to obtain a diagnosis [36]. Moving forward, the term *mental disorder* will refer to diagnoses of a mental disorder according to diagnostic criteria (i.e., DSM/ICD), and the term *psychopathology* will refer to both mental disorder diagnoses and symptoms more broadly.

Given the high prevalence of child psychopathology and its substantial impacts on individuals and society at large, research aimed at understanding the determinants of child psychopathology is critical [24,32,39]. A wide body of literature suggests that experiences early in life shape individual neurobiological, behavioural, emotional, and cognitive development, and can contribute to the development of psychopathology [40,41]. Studies in both humans and animals have demonstrated that childhood is a period of enhanced vulnerability to stress, likely due to the rapid and widespread changes occurring in the brain during this time [4]. Specifically, exposure to stressors during childhood (e.g., abuse, neglect, trauma, illness, etc.) can lead to a greater susceptibility to the development of psychopathology throughout the lifespan [41–43]. One childhood stressor that is often overlooked in the literature is childhood chronic physical illness [44,45].

2.2 Childhood Chronic Physical Illness

Current research suggests that approximately 30-50% of children globally are affected by a chronic physical illness (CPI) [1,2,46]. Childhood CPIs are defined as physical conditions

expected to last 12 months or longer, resulting in functional limitations, dependencies, or additional healthcare use [47]. This encompasses a broad range of highly prevalent conditions such as type 1 diabetes, asthma, epilepsy, juvenile arthritis, and cerebral palsy. Chronic illnesses are often primary sources of stress for children, who have to navigate the prolonged and repeated demands of living with a CPI [3]. Most chronic illnesses are characterized by an acute phase of stress associated with the lead-up to the initial diagnosis, followed by prolonged chronic stress associated with ongoing treatment and management of the condition [3]. Specifically, diagnostic procedures, painful symptoms, invasive and unpleasant treatments, physical constraints, and family conflicts may be significant sources of chronic stress for children with a CPI. Children with a CPI also face considerable psychosocial and emotional burdens due to their health challenges, leading to feelings of distress, worry, hopelessness, uncertainty, and loneliness [48]. Overall, the stressors faced by children with a CPI are multifaceted and are often unanticipated, uncontrollable, and functionally impairing [3].

2.2.1 Child Physical-Mental Multimorbidity

Chronic exposure to stress can impair child health and well-being, leading to an increased risk of developing psychopathology [4]. It is well established that children with a CPI are at a greater risk of developing psychopathology compared to their healthy peers [5,6,49]. The prevalence of child physical-mental multimorbidity – the co-occurrence of a physical illness and mental disorder – is high, affecting approximately 20-30% of children with a CPI [1,49,50]. In clinical samples, this estimate is higher, suggesting that approximately 40-50% of children with a CPI develop a mental disorder [7,8]. Multimorbidity negatively impacts child physical and psychosocial health. Compared to children living with a physical illness or mental disorder only, children with multimorbidity experience greater physical and mental symptom severity [51],

poorer quality of life [7,11], reduced self-esteem [52], increased suicidality [10,53], and greater substance use [12]. These negative effects also extend to the parents and families of children with multimorbidity, who often experience greater psychological distress, parenting stress, and reduced family functioning [52,54–56].

Understanding predictors of psychopathology in children with a CPI is a critical public health concern and has significant implications for the Canadian healthcare system. Over the past few decades, the number of children diagnosed with a CPI has been steadily increasing [2]. As a result, children with a CPI represent a substantial and growing population of children at high risk of developing psychopathology. Additionally, advances in medicine have decreased mortality rates from common childhood chronic illnesses, so many children with a CPI continue to experience long-term consequences to their physical and mental health as they age [7,57]. Healthcare spending in Ontario is also highly concentrated among a small proportion of children [58,59]. Among children aged <18 years, the top 5% of cost users are responsible for 60% of total healthcare expenditures in Ontario, and mental disorders are one of the most common diagnoses in this high-cost group [59]. Despite robust evidence that children with a CPI are at a greater risk of psychopathology, and the negative impacts of multimorbidity on children, their families, and society, few studies have examined the mechanisms involved in this relationship [60].

2.3 Stress Physiology: The Hypothalamic-Pituitary-Adrenal (HPA) Axis

Recent research efforts have focused on the link between physiological stress responses and the development of psychopathology in children exposed to chronic stressors [13]. The hypothalamic-pituitary-adrenal (HPA) axis is the primary system that controls the body's physiological response to stress, and extensive research has highlighted the HPA-axis as a key

mechanism through which childhood stress “gets under the skin” to impact physical and mental health throughout the lifespan [14,61]. In response to stress, neurons in the paraventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone (CRH), which travels to the anterior pituitary gland to stimulate the secretion of adrenocorticotrophic hormone (ACTH) [62]. Subsequently, ACTH travels through the bloodstream to the adrenal cortex, where it stimulates the release of the glucocorticoid cortisol (often referred to as the *stress hormone*) [62]. The release of cortisol is the best characterized biomarker of the HPA-axis stress response, and plays a key role in preparing the body to react to stress by increasing access to energy stores, maintaining blood pressure, decreasing inflammation, and enhancing cognitive function [62,63].

The HPA-axis is regulated by a negative feedback system, by which acutely elevated cortisol levels suppress the release of CRH and ACTH, which inhibits the release of cortisol, allowing cortisol to return to baseline levels [14]. However, under conditions of prolonged or intense stress, ongoing input can override the negative feedback system and continue cortisol secretion [62]. While this response is adaptive acutely, chronic exposure to stressors, and thus chronic activation of the HPA-axis, can lead to dysregulation [14]. Research shows that children exposed to unpredictable, intense, and chronic stressors are more likely to show alterations in HPA-axis activity and cortisol levels, which can manifest as either heightened (i.e., hypersecretion) or blunted (i.e., hyposecretion) activity [14,64,65]. Over time, HPA-axis dysregulation can have damaging effects on the body and brain, and may be implicated in the development of psychopathology [15,63].

2.3.1 Theoretical Framework: Allostatic Load Model

A potential mechanism underlying the association between chronic stress and psychopathology is modelled in McEwen and Stellar’s theory of Allostatic Load [15]. The

release of cortisol in response to stressors is essential for the body to adequately prepare and adapt to stress [66]. This process – that is, the body’s ability to maintain stability when faced with a stressor through adaptive physiological responses – has been termed “allostasis” [67]. While the allostatic process is adaptive acutely, chronic exposure to stressors, and thus chronic activation of these bodily systems, leads to *wear and tear* on the body and brain [15]. Over weeks, months, or years, the increased exposure to cortisol and *wear and tear* can predispose an individual to disease – this state has been termed “allostatic load” [15]. Thus, cortisol is thought to be one of the primary biological mechanisms by which chronic stressors exert their negative effects on the body and brain [15].

The Allostatic Load model suggests that individual differences in the way the body reacts to stressors are the main determinant of whether an individual is resilient against or vulnerable to developing diseases [15]. The activation of the HPA-axis is shaped by individual differences at the biological (i.e., genetics, development), behavioural (i.e., coping and health habits), and historical (i.e., trauma and stressful life experiences) levels [68]. As discussed above, in a normal physiological stress response, the HPA-axis responds to stress by initiating the release of cortisol, sustaining it until the stress ceases, and then shuts it off. Four situations are associated with allostatic load, which reflect overactivation and/or dysregulation of the HPA-axis [68]. First, repeated or prolonged exposure to multiple stressors can lead to chronically elevated concentrations of cortisol over time [68,69]. Second, repeated exposure to the same stressor can result in a failure to habituate or adapt. Specifically, the failure of the body to dampen or eliminate the HPA-axis response to the same stressor can also lead to elevated cortisol levels over time. A third and related type involves the failure of the HPA-axis stress response to shut off after a stressor has ended due to impaired negative feedback, again leading to elevated

cortisol levels over time. Finally, the fourth type involves an inadequate HPA-axis stress response leading to a hypoactive state and low cortisol levels. Specifically, the HPA-axis stress response may become blunted over time through the potent negative feedback system as a protective mechanism to avoid overexposure to cortisol [14]. This may explain why some individuals exposed to chronic stressors initially exhibit elevated cortisol but then subsequently have lower levels and blunted HPA-axis reactivity [13,70,71]. Overall, chronic exposure to stress during childhood can result in increased allostatic load and may contribute to increased susceptibility to psychopathology [66].

2.3.2 Stress Physiology and Child Psychopathology

To date, the majority of studies have investigated associations between HPA-axis dysregulation and psychopathology in children by measuring cortisol in urine, blood, or saliva [13]. In children, cortisol is most commonly measured in saliva due to its nonpainful sampling and ease of storage [17]. Salivary cortisol can be used to measure cortisol reactivity in response to acute stressors as well as non-stressed basal (diurnal) cortisol [13]. Measures of salivary cortisol reactivity in response to an acute stressor reflect the ability of the HPA-axis to respond and rapidly recover from an acute stressor. Alternatively, measures of basal salivary cortisol reflect the general functioning of the HPA-axis throughout the day.

A wide body of literature has demonstrated a link between HPA-axis dysregulation and psychopathology in children [13,70,72–76]. Some previous research also suggests that the pattern of HPA-axis dysregulation underlying specific mental disorders may differ [13,14,70]. Specifically, higher basal cortisol levels and higher cortisol reactivity have been correlated with the presence of internalizing symptoms/disorders (e.g., depression and anxiety) in children [74,76,77]. In contrast, lower basal cortisol levels and lower cortisol reactivity have been

correlated with the presence of externalizing symptoms/disorders (e.g., ADHD and conduct disorder) [70,72,73]. Although the exact mechanisms underlying the association between lower cortisol and externalizing symptoms remain unclear, several theories have been postulated. Children characterized by blunted HPA-axis reactivity may be predisposed to engage in externalizing behaviours (e.g., aggression, fighting, impulsivity) to increase reactivity [70]. Additionally, children who exhibit externalizing behaviours may be repeatedly exposed to stressful situations and may habituate to these situations over time, eventually leading to a blunted HPA-axis stress response [70,71]

Taken together, the existing evidence suggests that both elevated and blunted cortisol levels/reactivity in children are likely to be deleterious. However, far less work has explored the relationship between cortisol and psychopathology in children with a CPI. Childhood CPIs may be significant sources of chronic stress for children, and as a result, children with a CPI are at a greater risk of developing psychopathology [3,5,6]. This is consistent with the consequences of allostatic load stemming from the physical and psychological *wear and tear* associated with the repeated demands of living with and managing a CPI. Exploring the relationship between allostatic load biomarkers, such as cortisol, and psychopathology in this population can help to clarify whether HPA-axis dysregulation may be an underlying mechanism contributing to multimorbidity, and could support the early detection of children with a CPI at high risk for negative health outcomes.

2.4 Hair Cortisol

While traditional measures of cortisol (i.e., urine, blood, saliva) are useful for capturing acute cortisol levels/reactivity, often the core question in populations exposed to chronic stress is whether the HPA-axis has become *chronically* dysregulated. These measures only provide a

short-term measure of cortisol secretion (i.e., minutes to hours), and thus are not well-suited for examining the impacts of chronic HPA-axis dysregulation on health outcomes [78]. They are highly dependent on daily fluctuations and can be influenced by a range of situational factors (i.e., food intake, exercise) [79]. Following a circadian rhythm, cortisol peaks in the morning (referred to as the cortisol awakening response), followed by a gradual decline throughout the day, and is at its lowest in the evening [80]. Thus, a single basal salivary cortisol measurement cannot provide an assessment of long-term cortisol secretion [81]. The assessment of long-term cortisol secretion requires repeated measurements of salivary cortisol throughout the day over several days or weeks to approximate average levels, which may be costly and burdensome [17].

Over the last two decades, hair cortisol concentration (HCC) has emerged as a novel technique to measure long-term cortisol secretion in children [17,18]. Hair sampling is non-invasive, and hair concentration of cortisol averages daily circulating levels of cortisol over an extended period (i.e., months) [82]. Cortisol may be incorporated into hair via passive diffusion from blood, sweat, and/or sebum into the hair follicles during the growth phase [81,82]. Hair typically grows at a rate of 1 cm per month, with the proximal 1 cm segment to the scalp reflecting average daily cortisol secretion in the preceding month [78,83–85]. Typically, 3 cm samples are used to measure average cortisol levels in the preceding 3 months, but HCC can be reliably measured in up to 5-6 cm of hair [80]. Thus, HCC is a potentially valuable biomarker of chronic HPA-axis dysregulation and may be an indicator of chronic stress [18]. Researchers have also historically relied on self-report tools to measure chronic stress in children, which are limited by their subjective nature and potential for recall bias [86]. Children often struggle to adequately self-report their stress levels, making hair analysis an ideal method for objectively measuring chronic stress in young populations [17].

2.4.1 Chronic Stress and Hair Cortisol

Previous cross-sectional research has found both higher and lower HCC levels in children exposed to chronic stressors, such as maltreatment, traumatic life events, and violence [87–95]. Although being diagnosed with a childhood CPI is considered a significant chronic stressor [3], few studies have examined HCC in children with a CPI. Prior studies comparing HCC levels between children with a CPI and healthy controls have yielded mixed results, reporting higher [96–98], lower [99], and null findings [100]. Additionally, there is a lack of literature examining how exposure to chronic stressors, such as childhood CPI, influences change in HCC over time in children. One study found greater increases in HCC from mid-childhood to early adolescence in children with a chronic illness compared to healthy controls [96]. However, the number of children with a chronic illness included in this study was small ($n = 19$) and was primarily made up of children with autism and ADHD [96]. While the goal of this dissertation is not to compare HCC between children with a CPI and healthy controls, examining changes in HCC over time in children with a CPI is promising for evaluating the long-term impacts of chronic illness on HPA-axis functioning.

2.4.2 Hair Cortisol and Child Psychopathology

Given its promising utility for measuring chronic stress in young populations, HCC has been increasingly explored as a potential early biomarker for psychopathology in children. However, the relationship between HCC and psychopathology in children remains unclear, specifically regarding the direction of the association. Studies comparing children with and without diagnosed mental disorders have found evidence of higher [101], lower [102] and comparable [103,104] HCC levels in children with mental disorders. Cross-sectional studies examining associations between HCC and internalizing or externalizing symptoms in children

have found evidence of positive [95,105–107], negative [94,108,109], and no associations [89,110–118]. In addition, findings from some studies suggest that the association between HCC and psychopathology in children may be disorder/symptom specific [94,119], sex-dependent [120–122], age-dependent [94,119], non-linear [123], and depend on sample type (i.e., stressed vs. non-stressed children) [94,124] or the nature and severity of stress exposure [94]. The heterogeneity in findings to date highlights the need for future research in this area.

To date, very few studies have examined associations between HCC and psychopathology in children with a chronic illness. Gorter et al. (2022) found a negative association between HCC and depressive symptoms in adolescents and young adults (aged 16–30) with cerebral palsy, but no association between HCC and anxiety symptoms [125]. Buse et al. (2022), however, found no associations between HCC and emotional or conduct problems in children (aged 3–16 years) with a chronic tic disorder [126]. It is presently unclear whether high or low HCC levels are associated with the development of psychopathology in children with a CPI. Further, chronically high or low HCC levels may be more important in relation to psychopathology outcomes than one-time measurements of HCC. Thus, longitudinal research is needed to clarify this relationship before HCC can reliably be used to identify children with a CPI at high-risk of developing psychopathology.

Longitudinal studies of HCC in children are scarce, and I am only aware of a handful of studies that have utilized repeated measures of both HCC and psychopathology to examine associations over time. Hagan et al. (2021) examined HCC over one year in low-income children (aged 2–6 years) and found that while baseline HCC was not associated with baseline levels or changes in behavioural problems, decreases in HCC were associated with increases in behavioural problems [127]. Similarly, Walther et al. (2025) found a negative association

between HCC and depressive symptoms in a sample of children and adolescents (aged 8-17 years) with MDD over 36 months [102]. However, Barron-Linnankoski et al. (2024) examined HCC over seven months in children (aged 6-12 years) with diagnosed psychiatric disorders, and found that changes in HCC levels were not associated with changes in internalizing or externalizing symptoms [128]. I am only aware of one study that has examined the longitudinal relationship between HCC and psychopathology in children with a physical illness [129]. Kornelsen et al. (2019) examined HCC in children (aged 6-16 years) with a CPI, and found that while HCC and externalizing symptoms were consistently positively associated over six months, HCC and internalizing symptoms were only positively associated at baseline. This previous work was also limited to exploring this association over a short follow-up period (i.e., 6 months) and with a relatively small sample ($n = 42$) [129]. Longitudinal studies that repeatedly measure HCC and psychopathology in children with a CPI are needed to better understand the role of HPA-axis dysregulation in the development of psychopathology in this population, and to elucidate whether HCC is a valuable biomarker for psychopathology risk.

2.4.3 Trajectories of Child Hair Cortisol

Most longitudinal research exploring HCC in children utilizes variable-centred modelling approaches to examine predictors of change in HCC, or to examine associations between HCC and psychopathology. Variable-centred approaches assume *population homogeneity*, or that all children come from a single population and follow roughly the same pattern of change in HCC over time [130,131]. Specifically, variable-centred models estimate a single average growth trajectory, where covariates can only predict deviation from the average pattern of change [130,131]. Thus, variable-centred approaches overlook the possibility that there may exist subgroups of children in the population whose HCC trajectories are significantly different from

the average pattern [131]. Because dysregulated HPA-axis functioning among children likely involves not only varying cortisol levels (high vs. low), but also different patterns of change in cortisol over time, it is difficult to identify these distinct trajectories using variable-centred approaches [68,132]. In contrast, person-centred modelling approaches assume *population heterogeneity*, and aim to identify distinct growth trajectories that exist within a population [133]. These approaches allow researchers to identify and describe distinct subgroups of children in a population who share similar HCC trajectories over time [131]. Moreover, if these distinct subgroups do exist, they may be uniquely associated with health outcomes and can aid in the identification of children at high risk of developing psychopathology. For example, a group of children with persistently elevated HCC over several years may be especially likely to exhibit greater psychopathology symptoms. The heterogeneity in HPA-axis functioning observed in children, particularly in children exposed to chronic stress, emphasizes the need for person-centred approaches that focus on intra-individual patterns of change in HCC over time.

Despite the variability in HPA-axis functioning observed among children, little research has examined HCC variability in children using person-centred approaches. I am only aware of three previous studies that have explored trajectories of HCC in children using person-centred modelling approaches, and only two have explored associations between HCC trajectories and psychopathology [134–136]. Downes et al. (2024) measured HCC in children at birth, 1, 3, and 5 years, but did not classify children into distinct HCC trajectories (i.e., a 1-class solution was the superior model). Dajani et al. (2018) identified three HCC trajectories in war-affected adolescents (12-18 years) over one year: hypersecretion (9.6%), medium secretion (87.5%), and hyposecretion (2.9%). Girls were more likely to belong to the hypersecretion trajectory compared to the medium secretion trajectory group; however, a subsequent study found no

association between these trajectories and mental health symptoms [137]. Rovnaghi et al. (2021) measured HCC in children at 1, 2, and 3 years and identified four HCC trajectories: declining (26%), high increasing (6.4%), high declining (24.5%), and sustained high (42.6%). They argue that the declining trajectory may represent adaptive HPA-axis functioning, whereas the other trajectories may represent allostatic load with dysregulated HPA-axis functioning [136]. Compared to all other trajectory groups, mothers of children in the declining trajectory group were more likely to be married, white, older, and have a higher household income. Additionally, children in the declining trajectory group had lower internalizing and externalizing behaviours compared to all other trajectory groups [136]. To date, no study has identified trajectories of HCC and examined associations between HCC trajectories and psychopathology in children with a CPI. This knowledge can support the identification of children with a CPI who exhibit dysregulated HPA-axis functioning, and clarify whether HPA-axis dysregulation is associated with the development of psychopathology in this population.

2.5 Parent Distress and Child Psychopathology

The health of a child with a chronic illness is influenced not only by the characteristics and stressful experiences related to their condition, but also by the medical, psychosocial, and environmental support they receive from those around them [138]. Parents and primary caregivers play a significant role in managing the medical and psychosocial impacts of their child's CPI [138]. In addition to the typical everyday demands of parenting, parents of a child with a CPI often perform additional tasks such as managing and attending medical appointments, monitoring and administering treatments, and performing illness-related caretaking responsibilities [138,139]. Parents of a child with a CPI may also experience significant psychological distress stemming from uncertainty around the course of their child's illness,

illness-related financial burdens, the loss of leisure and family time, and worries about meeting future caregiving demands [138]. As a result, parents of children with a chronic illness often report greater depression and anxiety symptoms and higher levels of parenting stress compared to parents of healthy children [140–143]. Moving forward, the term *parent distress* is used as an umbrella term referring to symptoms of depression and anxiety, as well as parenting stress.

Exposure to parent distress may place children at greater risk of developing psychopathology. It is well documented that children of parents with a depressive or anxiety disorder are at a greater risk of developing a mental disorder [144,145]. Similarly, meta-analyses have shown strong positive associations between parent depressive and anxiety symptoms and psychopathology symptoms in offspring [146,147]. Parenting stress, defined as the psychological distress experienced by caregivers related to their parenting role, has also shown strong positive associations with child psychopathology symptoms [148]. The association between parent distress and child psychopathology may involve several mechanisms and likely involves a complex intersection of genetic vulnerability and environmental influences [149]. In addition to transmitting risk genetically [149,150], parent distress has been linked to negative parenting practices, reduced parental support, poorer parent-child relationships, and exposure to stressful life events [151], which may condition risk for psychopathology symptoms in children [149,152].

Although this area remains relatively underexplored, previous studies have shown that greater parental depressive and anxiety symptoms and higher levels of parenting stress are associated with greater psychopathology symptoms in children with a CPI [141,153,154]. In fact, children with a CPI may be particularly vulnerable to the impacts of parent distress due to the compounding burden of managing illness-related and environmental stressors [155,156]. Ferro et

al. (2015) found that the positive association between maternal and child depressive symptoms was stronger for children with a CPI compared to healthy children, suggesting that the risk of transmission in this population may be higher. Families of a child with a CPI are also more likely to exhibit less positive parent-child relationships, lower parental responsiveness, and higher levels of neglectful parenting compared to families with healthy children [157]. Lim et al. (2011) found that maternal depressive symptoms were associated with negative maternal parenting practices, which in turn were associated with greater internalizing symptoms in children with asthma [156]. Chronic psychological distress among parents of children with a CPI may also interfere with the management of their child's illness, which can negatively affect child health and psychological well-being [54,156]. Despite preliminary evidence linking parent distress to greater psychopathology in children with a CPI, no prior study had examined these relationships longitudinally.

2.5.1 Disaggregating Between-dyad Effects from Within-dyad Effects

While prior longitudinal research had largely examined between-dyad pathways linking parent distress to child psychopathology, developmental theories also highlight the importance of examining changes that occur within-dyads, and these sources of variation are often confounded in longitudinal studies [158]. Specifically, research has consistently shown that children of parents who display higher levels of psychological distress on average relative to other parents exhibit greater psychopathology [145,147]. This is an example of a between-dyad effect because child psychopathology symptoms are being compared between individuals. At the same time, another reasonable hypothesis might be that children exhibit greater psychopathology at times when their parent is experiencing higher levels of psychological distress relative to their own average levels [159]. This is an example of a within-dyad effect because child psychopathology

symptoms are being compared within individuals. Specifically, disaggregating between- vs. within-dyad effects provides an understanding of not only the average (i.e., stable) relationship between parent distress and child psychopathology, but also the dynamic and changing nature of the relationship over time [160]. In other words, between-dyad and within-dyad effects can be conceptualized as “trait” versus “state” relationships, respectively [160]. Longitudinal data provide an advantage over cross-sectional data as they allow researchers to distinguish between effects that are attributable to between-dyad and within-dyad processes [160].

Previous studies have shown support for both between-dyad and within-dyad pathways from parent depressive and anxiety symptoms to child internalizing and externalizing psychopathology [159,161–167]. However, I am only aware of one study that has explored the between- and within-dyad effects of parenting stress on child psychopathology. Van Dijk et al. (2022) found significant positive between- and within-dyad effects of parenting stress on internalizing and externalizing symptoms in children from 3-9 years of age [168]. To date, no study has explored the between- and within-dyad effects of parent distress on psychopathology in children with a CPI. Such effects may be especially important to explore in this population as parents of a child with a CPI may experience greater fluctuations in depressive and anxiety symptoms, as well as parenting stress, due to acute illness-related events (e.g., hospitalizations, complications, symptom exacerbations) [143]. Moreover, the disaggregation of these effects may be particularly important for guiding prevention and intervention efforts.

2.5.2 The Moderating Role of Child Cortisol

Not all children appear to be equally impacted by parent distress, and there is substantial variability in the association between parent distress and child psychopathology [13]. Research that elucidates factors that explain such variability has the potential to advance developmental

theory and support the development of more targeted prevention and intervention strategies. The diathesis-stress/dual-risk model is often used to explain individual variability in parent-child psychopathology transmission, and suggests that not all children are equally susceptible to the adverse influences of environmental stressors [169]. Specifically, dysregulated or maladaptive HPA-axis functioning may be an underlying biological marker of diathesis or vulnerability, rendering some children more vulnerable to psychopathology when exposed to parent distress [169]. Such effects may arise from “vulnerable” children being particularly sensitive to the adverse environments associated with parent distress (i.e., negative parenting practices, reduced parental support, poor parent-child relationships, etc.) [170]. Conversely, normative or adaptive HPA-axis functioning may be an underlying marker of resilience, and “resilient” children may be better able to adapt and cope with the adverse environments associated with parent distress [169]. Overall, the dual-risk designation comes from the effect of a vulnerability factor inherent within the individual interacting with the stress from their environment [170].

In line with the diathesis-stress model, a wide body of literature has shown that child salivary cortisol (basal levels and reactivity) moderates associations between environmental stressors (e.g., harsh parenting, parental hostility, home chaos, family stress, negative family environment, stressful life events, and trauma/abuse) and child psychopathology. Specifically, some studies indicate that higher child cortisol intensifies the adverse effects of environmental stressors on child psychopathology [171–176], whereas other studies suggest that these associations are more pronounced among children with low cortisol [177–180]. However, far less work has explored the interactive effects of parent distress and child cortisol on child psychopathology. Black et al. (2019) found a significant interactive effect of parent depression and child salivary cortisol awakening response (CAR) on child internalizing, but not

externalizing, symptoms. They found a positive association between CAR and internalizing symptoms in children with a mother having a history of depression, but not in children with no parent having a history of depression [181]. However, Kushner et al. (2016) found that child salivary cortisol reactivity did not moderate associations between maternal depression exposure and child internalizing and externalizing symptoms [182]. Similarly, Simons et al. (2017) found no interactive effects between parenting stress and child salivary cortisol (reactivity and total output in response to stress) on child internalizing or externalizing symptoms [183].

Studies examining diathesis-stress effects using child HCC are scarce, but have found some support for child HPA-axis dysregulation conferring vulnerability to the adverse influences of environmental stressors. Shan et al. (2024) found an interactive effect between positive parent-child interactions and child HCC in 6-year-old children. Specifically, higher HCC was associated with greater psychosocial difficulties in the group of children with lower positive parent-child interactions, but no association was found in the group of children with higher positive parent-child interactions [87]. Similarly, Shapero et al. (2019) found a positive association between recent life stress and depressive symptoms in adolescents with high and average HCC, but no association in adolescents with low HCC [92]. Conversely, Fuchs et al. (2018) found no association between HCC and psychopathology in a group of high-risk children (5-12 years) whose mothers reported experiences of early life maltreatment (ELM), but found a positive association in the low-risk group whose mothers did not report any ELM [124]. I am only aware of one study that has explored the interactive effects of parent distress and child HCC on child psychopathology. Specifically, Agapaki et al. (2022) examined associations between child HCC and anxiety/depressive symptoms in children (aged 1.5-4 years) of mothers with and without perinatal mental disorders (PMD). They found a significant positive association between

child HCC and anxiety/depressive symptoms in the PMD group, but no association in the control group [184]. No prior study has explored the interactive effects of parent distress and child HCC on psychopathology in children with a CPI. This knowledge can clarify whether HPA-axis dysregulation in children with a CPI is associated with greater vulnerability to the adverse effects of parent distress, and could support the identification of children with a CPI who may benefit the most from interventions that target parent distress.

It is also possible that child HPA-axis dysregulation might interact with parent distress at both levels of the longitudinal framework. Specifically, child HCC may magnify the between-dyad and/or the within-dyad associations between parent distress and child psychopathology. The former effect would suggest that child HPA-axis dysregulation intensifies the stable parent-child transmission pathway, whereas the latter would suggest that it intensifies the dynamic parent-child transmission pathway. To explore this, Laurent et al. (2013) examined interactions between adoptive parent depressive symptoms and child salivary cortisol on child internalizing and externalizing symptoms at both the between- and within-dyad levels. At the between-dyad level, they found that the combination of a mother or father with higher average depressive symptoms and a child with high evening basal cortisol predicted greater child externalizing, but not internalizing, symptoms over 54 months [185]. At the within-dyad level, fluctuations in maternal depressive symptoms predicted greater child internalizing and externalizing symptoms regardless of child basal cortisol levels. However, the within-dyad effect of paternal depressive symptoms was moderated by child cortisol, such that fluctuations in paternal depressive symptoms predicted greater internalizing symptoms, but only for children with high evening basal cortisol [185]. This finding is consistent with the hypothesis that child HPA-axis dysregulation may heighten risk for the within-dyad transmission of internalizing symptoms

[185]. No prior study has examined whether child HCC moderates associations between parent distress, at both the between- and within-dyad levels, and child psychopathology in healthy or chronically ill children. Examining moderation at both levels provides a more nuanced understanding of how biological vulnerability shapes children's responses to both stable and fluctuating levels of parent distress.

2.6 Health-related Quality of Life

Health-related quality of life (HRQoL) in children is a multidimensional construct that captures a child's physical, psychological, and social well-being [186]. Specific to the measure used in this dissertation (i.e., KIDSCREEN-27), HRQoL in children is measured across five domains: physical well-being, psychological well-being, parents and autonomy, social support and peers, and school environment [187]. Having a CPI during childhood can affect a child's ability to interact with their physical, social, and school environment, and may be associated with significant psychological distress [3]. A wide body of literature has shown that children with a CPI experience lower HRQoL across all domains compared to their healthy peers [188,189]. Specifically, the physical symptoms associated with CPIs (e.g., pain, fatigue), the psychological burden of managing a CPI (e.g., distress, family conflicts), the loss of autonomy due to the condition (e.g., reduced social/leisure time and independence), as well as restrictions to participating in life activities (e.g., school absenteeism, fewer peer relationships) may contribute to poor HRQoL in this population [190–192]. Despite the growing recognition of the impacts of childhood CPI on HRQoL, there remains a need to better understand the mechanisms linking childhood CPI to poor HRQoL. This understanding is crucial for the development of targeted and effective prevention and intervention initiatives to improve HRQoL in children with a CPI.

As previously established, CPIs are often primary sources of chronic stress for children [3], and stress has been identified as a key predictor of poor HRQoL in children. Numerous studies have provided evidence of an inverse association between perceived stress [193,194], stress symptoms [195,196], adverse childhood experiences [197], and stressful/negative life events [196,198–201] and HRQoL in children. The allostatic load model highlights the cumulative *wear and tear* on the body and brain caused by chronic stress exposure [15]. In children, chronic stress can negatively impact regions of the brain responsible for learning and memory, decision-making, emotional regulation, and social behaviour [63]. However, few studies have examined the relationship between biomarkers of chronic stress, such as HCC, and HRQoL in children.

2.6.1 Hair Cortisol and HRQoL

Studies examining the relationship between HCC and HRQoL in children are scarce, and the available studies have been limited to cross-sectional designs. Gerber et al. (2017) found no association between HCC and HRQoL across several domains in Swiss first-grade schoolchildren (6-8 years) [202]. Similarly, Angelhoff et al. (2023) found no association between HCC and any of the KIDSCREEN-27 domains in children aged 3-5 years [203]. Fuchs et al. (2018), however, found a positive association between HCC and global HRQoL in children (5-12 years), but only among a high-risk group of children whose mothers reported experiences of early life maltreatment [124]. I am only aware of one study that has explored the relationship between HCC and HRQoL in children with a CPI. Buchan et al. (2021) found a negative association between HCC and HRQoL in children (4-17 years) with physical-mental multimorbidity, but only in the domains of peers and social support, and school environment. To

date, no prior study has examined the longitudinal relationship between HCC and HRQoL in healthy or chronically ill children.

2.6.2 Psychopathology and HRQoL

As previously established, children with a CPI are at a greater risk of developing psychopathology compared to their healthy peers [5,6]. Experiencing psychopathology during childhood can significantly impair emotional well-being, life satisfaction, participation in daily activities, peer and family relationships, and school performance, which may negatively impact HRQoL [204]. A wide body of literature has demonstrated that children with a mental disorder experience worse HRQoL compared to healthy controls [205–207], and several studies have reported negative associations between psychopathology symptoms and HRQoL in children [195,208–211]. The impact of psychopathology on HRQoL may be further exacerbated in children with a CPI given the compounding burden of living with a physical illness and mental disorder. In fact, several studies show that children with multimorbidity have worse HRQoL compared to children with a physical illness or mental disorder only [11,212,213].

Given the preliminary evidence linking HCC to psychopathology in children with a CPI [129], and robust evidence linking psychopathology to reduced HRQoL, psychopathology may be a key mechanism through which HCC influences HRQoL in this population. In support of this, several studies have found a significant mediating effect of internalizing psychopathology symptoms on the relationship between illness-related stressors (e.g., disease activity/severity, pain intensity, presence of symptoms) and HRQoL in children with a CPI [214–218]. Specifically, these studies found that greater disease activity/severity, pain intensity, and symptoms were associated with greater internalizing symptoms, which in turn led to reduced HRQoL. To my knowledge, no prior study has examined the mediating impact of

psychopathology on the relationship between HCC and HRQoL in children with a CPI.

Clarifying these pathways can inform the development of interventions to improve HRQoL in children with a CPI.

Additionally, there is a lack of literature exploring change in psychopathology as a predictor of change in HRQoL in both healthy and chronically ill children. Otto et al. (2017) found that increasing mental health problems over two years were associated with decreasing HRQoL in children and adolescents (7 to 17 years) [219]. Studies examining bidirectional relationships between psychopathology and HRQoL over time in children have found some support for greater psychopathology predicting worse HRQoL at a later time point [220,221]. Longitudinal studies in children with a CPI have also reported that greater psychopathology is associated with worse HRQoL over time [222,223], and illness-specific studies have reported that increases in depressive symptoms predict decreases in HRQoL over periods of 6-18 months [224,225]. However, no previous study has examined whether changes in psychopathology are linked to changes in HRQoL among children with diverse CPIs over several years. From a clinical perspective, clarifying the longitudinal relationship between psychopathology and HRQoL may help to elucidate whether psychopathology represents a modifiable intervention target for improving HRQoL in children with a CPI.

Chapter 3 – Dissertation Rationale and Study Objectives

3.1 Rationale and Purpose of Dissertation

This dissertation contributes to the scarcity of literature exploring longitudinal associations between HCC and health outcomes in children with a CPI. As established in Chapter 2, the chronic stress associated with a childhood CPI may lead to HPA-axis dysregulation and an increased risk of psychopathology and poor HRQoL. Over the past two decades, HCC has been identified as a valuable biomarker of chronic HPA-axis dysregulation and has been increasingly explored as a predictor of psychopathology and negative health outcomes in children. However, evidence linking HCC to psychopathology and poor HRQoL in children is mixed, and very few studies have examined these associations in children with a CPI. Existing studies in samples of children with a CPI are often small, cross-sectional, and illness-specific. This dissertation addresses these knowledge gaps through three complementary studies, and is the first to examine longitudinal associations between HCC, psychopathology, and HRQoL in a large sample of children with diverse CPIs. The objectives, research questions, and hypotheses of the three studies that comprise this dissertation are described in the following sections.

3.2 Study 1 - Objectives and Hypotheses

The objectives of Study 1 were to identify trajectories of HCC in children with a CPI over time, identify predictors of HCC trajectory group membership, and examine associations between HCC trajectories and child psychopathology. Specifically, this study addressed the following research questions:

1. What HCC trajectory patterns emerge among children with a CPI over 48 months?
2. What baseline factors are associated with HCC trajectory group membership?

3. What is the association between HCC trajectory group membership and child internalizing and externalizing psychopathology symptoms over 48 months?

Based on previous research [134,226,227], I hypothesized that there would be three distinct trajectories of HCC over time: hypersecretion, medium secretion, and hyposecretion. Predictors of trajectory group membership were hypothesized to be child sex, child age, time since CPI diagnosis, child race, parent age, parent race, and household income. Finally, I hypothesized that children following a maladaptive or dysregulated HCC trajectory would exhibit higher internalizing and externalizing psychopathology symptoms compared to children following an adaptive or normative trajectory [136].

3.3 Study 2 - Objectives and Hypotheses

The objectives of Study 2 were to examine the between-dyad and within-dyad effects of parent distress on child psychopathology over time, and explore if these associations are moderated by child HCC trajectory. Specifically, this study addressed the following research questions:

1. What is the association between parent internalizing symptoms and parenting stress, at both the between- and within-dyad levels, and child internalizing and externalizing psychopathology symptoms over 48 months?
2. Are these associations moderated by child HCC trajectory group membership?

Based on previous research, I hypothesized significant positive between- and within-dyad effects from parenting internalizing symptoms and parenting stress to child internalizing and externalizing psychopathology symptoms [159,164,166,168]. Additionally, I hypothesized that child HCC trajectory group membership would moderate these associations, such that these

associations would be strengthened for children following a maladaptive or dysregulated HCC trajectory [87,92,181,185].

3.4 Study 3 - Objectives and Hypotheses

The objectives of Study 3 were to examine associations between child HCC trajectories and child HRQoL over time, and examine child psychopathology as a potential mediator of these relationships. Specifically, this study addressed the following research questions:

1. What is the association between HCC trajectory group membership and child HRQoL over 48 months?
2. Are these associations mediated by child psychopathology symptoms?

Based on previous research [228], it was hypothesized that children following a maladaptive or dysregulated HCC trajectory would exhibit lower HRQoL. Additionally, it was hypothesized that greater child psychopathology symptoms would mediate these associations [214,215,218].

Chapter 4 – Methodologies and Analytical Approaches

4.1 Data Source: MY LIFE

The data for this dissertation come from the Multimorbidity in Children and Youth across the Life-course (MY LIFE) study [60]. MY LIFE is an ongoing prospective study designed to document the course of psychopathology in children diagnosed with a CPI, identify predictors of psychopathology and HRQoL, and examine the biological and psychosocial factors that are implicated in these relationships [60].

4.1.1 Participants

Participants in MY LIFE include 263 children, aged 2-16 years at the time of recruitment, who have been diagnosed with one CPI, as well as their primary caregiver (herein parent) [60]. CPIs were defined as physician-diagnosed conditions that are expected to last ≥ 1 year and result in one or more of the following: (1) physical or functional limitations, (2) dependencies (i.e., medication, special equipment) to compensate for functional limitations, and (3) increased healthcare service use [229]. Children with multiple physical illnesses (i.e., medically complex) were excluded from the sample, as mental health outcomes in these children are likely to differ from children with one CPI [230]. In addition, children and parents without sufficient English language skills were excluded from the sample, as some of the selected outcome measures have not been validated in other languages. Eligible children and their families were recruited from the pediatric outpatient clinics of dermatology, endocrinology, gastroenterology, haematology, neurology, respirology, and rheumatology at McMaster Children's Hospital in Hamilton, Ontario [60]. The recruitment strategy for the sample was intentionally broad to increase the generalizability of the results across various physical illnesses. In addition, the design of MY

LIFE was informed by a pilot study, which suggested that the risk for physical-mental multimorbidity in children across different CPIs is negligible [7].

4.1.2 Study Procedures

Health professionals at the participating clinics worked together with research assistants to identify eligible children and their families. Eligible families were then contacted by the research assistant, who verified eligibility, described the purpose of the study, and obtained informed consent. Written informed consent was obtained from all parents and children aged ≥ 16 years, written assent was obtained from children 7-15 years, and oral assent was obtained from children < 7 years. Data collection included structured interviews, self-report measures, and the collection of biological samples that took place in a private research office located within the hospital prior to the COVID-19 pandemic. In March 2020, data collection for MY LIFE switched to mail-in surveys and telephone interviews in accordance with public health directives to limit the risk of exposure to COVID-19. Parent reports from the child's primary caregiver were collected for all children, and children ≥ 10 years provided additional self-reports. Baseline assessments were taken between August 2017 and November 2019, and follow-up assessments occurred at 6, 12, 24, and 48 months [231]. Study approval was obtained from the Waterloo Human Research Ethics Board (ORE-22183) and Hamilton Integrated Research Ethics Board (2797).

4.2 Study Measures

4.2.1 Child Hair Cortisol Concentration

At each assessment, hair samples were collected from children to measure hair cortisol concentration. Hair was collected using a standardized procedure by cutting approximately 80 strands of hair (~ 4 mm diameter) from the back of the head, as close to the scalp as possible.

Samples were attached to a piece of paper with a paper clip, which indicated the scalp end. Parents also provided information about factors that may affect HCC levels (e.g., corticosteroid medication use, hair colour, hair dyes/treatments, hair wash frequency, and household smoking status) using a standardized form [232]. Items on the hair questionnaire are provided in Supplementary Table 1. After March 2020, hair sample collection occurred in participants' homes. Parents were provided with detailed written instructions for collection, and samples were placed in an envelope and sent to the investigators by mail. Previous research has shown that samples collected by participants at home do not differ significantly from samples collected by research staff in a clinic [233].

Hair samples were processed using a standardized protocol for washing, steroid extraction, and cortisol assay [234]. The first 3 cm of each hair sample (proximal to the scalp) was cut with scissors and placed into a Falcon 50 mL conical centrifuge tube. Samples were washed twice with 12 mL of isopropanol for two minutes and left to air-dry for 48 h. Dried samples were pulverized using the Retsch CryoMill at 25 Hz for 3 min. Approximately 30-35 mg of ground hair was transferred to a 2 mL Eppendorf tube, and 1 mL of 100% ethanol was added before it was shaken by hand and rotated at 45 rpm on the RPI Mix-All Laboratory Tube Mixer for 24 to 72 h at room temperature. Samples were vortexed for 5 s and centrifuged at 2800 rpm for 15 min, and 0.8 mL of supernatant was aliquoted into a new 2 mL Eppendorf tube (supernatant tube). The supernatant was left to air-dry for 48 h, after which another 1 mL of 100% ethanol was added to the tube, and it was rotated at 45 rpm on the RPI Mix-All Laboratory Tube Mixer for 24 to 72 h at room temperature. Samples were vortexed for 5 s and centrifuged at 2800 rpm for 15 min. During this final extraction stage, 1 mL of the supernatant was aliquoted into the supernatant tube, and it was left to air-dry for 48 h. It was then reconstituted with 150 μ L

of Salimetrics Salivary Cortisol Assay Diluent, vortexed for 5 s, and centrifuged for 10 min. Samples were then assayed in duplicate by high-sensitivity enzyme-linked immunosorbent assays using the High Sensitivity Salivary Cortisol Immunoassay Kit (Cat# 1-3002, Salimetrics, Pennsylvania), according to the manufacturer's instructions. The intra- and inter-assay coefficients of variation were 8.2% and 6.2%, respectively. Cortisol concentration is expressed as picograms per milligram (pg/mg) of hair. A natural log-transformation (ln) was applied to account for positive skew in the HCC values.

4.2.2 Child Psychopathology

Child psychopathology symptoms were measured at each assessment using the parent-reported Ontario Child Health Study Emotional Behavioural Scales (EBS) [235,236]. The EBS is a 52-item checklist that measures symptoms of MDE, GAD, SAD, SP, ADHD, ODD, and CD in children aged 4 to 17 years over the past six months using a 3-point scale. Scale items are scored as 0, 1, or 2, corresponding to responses of “never or not true”, “sometimes or somewhat true”, and “often or very true”, respectively. Raw scores were summed to generate a subscale score for internalizing symptoms (e.g., MDD, GAD, SAD, SP; range: 0–54) and externalizing symptoms (e.g., ADHD, ODD, CD; range: 0–50), as well as a total score across all items (range: 0–104). Higher scores on the EBS indicate a greater severity or frequency of symptoms. The EBS has demonstrated strong reliability and validity in clinical and general population samples [235,236]. Missingness at the item level was handled with mean imputation by averaging the available items when up to 50% of items were left unanswered. Internal consistency in this sample was excellent (internalizing $\alpha = 0.93$; externalizing $\alpha = 0.90$; total $\alpha = 0.94$). The survey items for the EBS are provided in Supplementary Table 2.

4.2.3 Child Health-related Quality of Life

Child health-related quality of life (HRQoL) was measured at each assessment using the parent-reported KIDSCREEN-27 [237]. The KIDSCREEN-27 is a 27-item scale designed to measure HRQoL over the past week across five domains: physical well-being (i.e., physical activity and energy), psychological well-being (i.e., mood and life satisfaction), parents and autonomy (i.e., free time and parental support), social support and peers (i.e., interactions and support from friends), and school environment (i.e., school enjoyment and cognitive capacity) [187]. Items are scored on a 5-point scale, corresponding to responses of “Never” to “Always”, respectively. Summed scores for each domain are transformed into T-scores ($M=50$, $SD=10$), where higher scores indicate better HRQoL. The KIDSCREEN-27 has been validated in children with a physical illness and demonstrates adequate parent-child agreement [238]. Internal consistency in this sample ranged from acceptable to good (physical well-being $\alpha=0.89$; psychological well-being $\alpha=0.87$; parents and autonomy $\alpha=0.77$; social support and peers $\alpha=0.88$; school environment $\alpha=0.82$). The survey items for the KIDSCREEN-27 are provided in Supplementary Table 3.

4.2.4 Parent Distress

4.2.4.1 Parent Internalizing Symptoms

Parent internalizing symptoms were assessed using self-report measures of depression and anxiety (see below). Because parent depression and anxiety scores were highly correlated across the study ($r_s \geq 0.74$), their scores at each assessment were summed to create an overall measure of parent internalizing symptoms.

4.2.4.1.1 Parent Depression

Parent depression was measured at each assessment using the Center for Epidemiological Studies Depression Scale (CES-D) [239]. The CES-D is a 20-item self-report scale that measures the frequency of depressive symptoms over the past week across four domains (depressed affect, positive affect, somatic activity, and interpersonal relations). Items are scored from 0-3, corresponding to responses of “Rarely or None of the Time (Less than 1 Day)” to “Most or All of the Time (5-7 Days)”, respectively. Scores are summed to calculate a total score (range: 0-60), where higher scores indicate greater depressive symptomatology. Based on developer instructions [239], missingness at the item level was handled with mean imputation by averaging the available items when up to four items were left unanswered. The CES-D has been validated in parents of children with physical and mental health conditions [240,241], and internal consistency in our sample was excellent ($\alpha=0.92$). The survey items for the CES-D are provided in Supplementary Table 4.

4.2.4.1.2 Parent Anxiety

Parent anxiety was measured at each assessment using the Generalized Anxiety Disorder-7 Scale (GAD-7) [242]. The GAD-7 is a 7-item self-report scale that measures the frequency of symptoms relating to generalized anxiety disorder over the past two weeks. Items are scored from 0-3, corresponding to responses of “Not at all” to “Nearly every day”, respectively. Scores are summed to calculate a total score (range: 0-21), where higher scores indicate higher levels of anxiety and impairment. Missingness at the item level was handled with mean imputation by averaging the available items when up to four items were left unanswered. The GAD-7 has demonstrated robust psychometric properties [242], and internal consistency in our sample was good ($\alpha=0.87$). The survey items for the GAD-7 are provided in Supplementary Table 5.

4.2.4.2 Parenting Stress

Parenting stress was measured at each assessment using the 18-item Parental Stress Scale (PSS) [243]. The PSS is a self-report scale that assesses stress over the past month across four parenting domains: rewards, stressors, loss of control and satisfaction. Items are scored on a 5-point scale, from Strongly Disagree (1) to Strongly Agree (5). Scores are summed to calculate a total score (range: 18-90), where higher scores indicate higher levels of parenting stress. Missingness at the item level was handled with mean imputation by averaging the available items when up to three items were left unanswered. The PSS has demonstrated robust psychometric properties [243], and internal consistency in our sample was good ($\alpha=0.85$). The survey items for the PSS are provided in Supplementary Table 6.

4.2.5 Clinical Characteristics

Several variables were measured to assess the clinical characteristics of children in the MY LIFE study. Parents reported the time since their child's CPI diagnosis (years), and body mass index (BMI) percentiles were calculated at each assessment from child height and weight measurements, adjusted for child sex and age [60]. Child disability was measured at each assessment using the 12-item parent-reported World Health Organization Disability Assessment Schedule (WHODAS) 2.0 [244]. The WHODAS 2.0 measures difficulty in functioning over the past month across the domains of cognition, mobility, self-care, getting along, life activities and participation (e.g., 'Getting dressed', 'Standing for long periods') on a five-point scale from '0 = none' to '4 = extreme or cannot do'. Scores were summed to create a total score (range: 0–48), where higher scores indicate more impairment and disability. Based on developer instructions, missingness at the item level was handled with mean imputation by averaging the available items when one item was left unanswered [244]. The WHODAS 2.0 has been validated in children

with a CPI [245], and internal consistency in our sample was good (WHODAS 2.0 $\alpha = 0.87$). The survey items for the WHODAS 2.0 are provided in Supplementary Table 7.

4.2.6 Sociodemographics

Sociodemographic variables were collected through a parent-reported questionnaire that included select questions from the Canadian Census. Data were collected on child and parent age (years), sex (male or female), race (white or not), and country of birth (born in Canada or not), as well as parental relation (biological parent or not), marital status (married/common law or not), education level (post-secondary graduate or not), and annual household income (<\$90,000 or $\geq$ \$90,000 CAD). Annual household income was dichotomized according to the 2021 median household income before taxes in Ontario (\$90,000 CAD). Information on child gender was not collected during the 48-month follow-up period, but was introduced at the six-year follow-up.

4.3 Statistical Analysis

This section provides an overview and rationale for the statistical analyses used in each study; specific details of their application are described in chapters 5-7. For each study, descriptive statistics for the overall sample and each HCC trajectory group were presented as means (M) and standard deviations (SD) for continuous variables, and frequencies and percentages for categorical variables. All data were analyzed in R version 4.5.1.

4.3.1 Study 1

4.3.1.1 Objective 1: Identify trajectories of HCC in children with a CPI over time

Latent class growth analysis (LCGA), also known as group-based trajectory modelling, was used to identify trajectories of HCC in MY LIFE children over 48 months [130,131]. Unlike variable-centered approaches (e.g., linear mixed-effects models, growth curve models) that aim to predict outcomes based on relationships among variables, LCGA is a person-centered

approach that focuses on relationships among individuals [131,246]. This modelling approach aims to identify homogeneous subgroups of individuals within the population who follow similar trajectories over time [130,246]. Specifically, LCGA uses a single outcome variable measured at multiple time points to identify classes that correspond to different growth trajectories for the outcome variable, so that individuals within the same class are more similar than individuals between classes [246]. The results are separate fixed-effects growth models for each class, which can vary in their initial level and growth in the outcome over time (i.e., linear, quadratic, cubic) [130,246]. Under the LCGA framework, the variances of intercept and slope within each class are fixed to zero, and therefore individuals assigned to the same class are assumed to follow the same trajectory [130]. This approach is well-suited to examining HCC over time, as it captures the heterogeneous nature of HPA-axis functioning in children, and can be used to identify children with a CPI who exhibit maladaptive or dysregulated HCC patterns over time [132].

Growth mixture modelling (GMM) is another person-centered modelling approach that is often used to identify and describe distinct trajectory classes within a population [130]. Unlike LCGA, GMM allows for within-class variation by introducing random effects to capture individual differences in trajectories within each class [246]. Specifically, GMMs estimate the variance around the intercept and slope within each class, providing information about how closely individuals within a class follow the mean trajectory [130,247]. Thus, using GMM, researchers can examine differences between and within classes, whereas using LCGA, researchers can only examine differences between classes [247]. Although GMM is a more flexible modelling approach, it estimates more parameters than LCGA and can result in complex models that are difficult to interpret [130]. Additionally, GMM assumes that the subgroups represent distinct populations of individuals within the sample with different trajectories of the

outcome, and is more suitable when the research questions involve examining differences within classes [247]. In contrast, LCGA assumes that classes within the sample represent subgroups of individuals that share similar trajectories of the outcome, but it does not assume that the subgroups represent distinct populations [247]. It is more suitable when the research questions involve identifying and describing classes, and examining differences between classes. Thus, LCGA was chosen over GMM to identify trajectories of HCC.

4.3.1.2 Objective 2: Identify predictors of HCC trajectory group membership

Once the optimal number and shape of the trajectories have been identified with LCGA, further analysis can examine predictors of trajectory group membership [133]. A multinomial logistic regression model was used to identify baseline sociodemographic and clinical predictors of HCC trajectory group membership. This approach is well-suited to examining predictors of change in HCC over time, and can identify potential risk or resilience factors that contribute to the expression of maladaptive or dysregulated HCC patterns in children with a CPI. Specifically, the use of LCGA to identify distinct trajectories of HCC overcomes the limitations of variable-centered approaches. As discussed previously, variable-centered approaches estimate a single average trajectory, where predictors can only explain deviation around the average pattern of change and are assumed to have uniform effects across all individuals (i.e., the same predictor influences change in HCC in the same way and to the same extent for all individuals) [131]. Such models that aggregate predictor effects across all individuals in the population may result in misleading or inaccurate conclusions [248]. In contrast, person-centered approaches that allow researchers to explore predictors of membership in distinct trajectory groups can better inform tailored interventions by linking predictors to clinically meaningful patterns of change in HCC.

4.3.1.3 Objective 3: Examine associations between HCC trajectories and psychopathology

Finally, trajectory group membership can be explored as a predictor of health outcomes over time [249]. A series of linear mixed-effects (LME) models were used to examine associations between HCC trajectories and internalizing and externalizing psychopathology symptoms over 48 months. Repeated measurements from the same individual are likely to be correlated, and this correlation needs to be considered in the analysis of longitudinal data [250]. To account for the correlation between repeated measurements from the same individual, LME models incorporate both fixed and random effects [251]. Thus, LME models can be used to examine change in an outcome over time and assess how predictors are associated with rates of change over time [250]. These models are well-suited to examining the longitudinal association between HCC trajectory group membership and psychopathology symptoms in children with a CPI. Although LME models are considered a variable-centered approach, the use of LCGA to first identify distinct trajectories of HCC, and then examine their associations with psychopathology, overcomes some of the limitations of variable-centered approaches. Variable-centred approaches overlook the possibility that certain subgroups of children may follow distinct HCC trajectories, which may be uniquely associated with psychopathology [132]. In contrast, this approach makes it possible to compare psychopathology symptoms between groups characterized by different patterns of change in HCC over time, thereby identifying HCC trajectories associated with greater psychopathology.

4.3.2 Study 2

4.3.2.1 Objective 1: Examine the between-dyad and within-dyad effects of parent distress on child psychopathology

A series of LME models were used to examine the between-dyad and within-dyad effects of parent internalizing symptoms and parenting stress on child psychopathology over time, and explore if these associations were moderated by child HCC trajectory. Longitudinal data provide an advantage over cross-sectional data in that they allow researchers to distinguish between effects that are attributable to between-person and within-person processes [160]. As discussed previously, LME models are often used to analyze longitudinal data and examine how variables are related over time. However, variables that are measured repeatedly contain an aggregate of both between- and within-person effects, and failure to disaggregate these effects in LME models can result in inaccurate conclusions [160]. To disaggregate these effects, predictors can be separated into their stable (i.e., between-person) and time-varying (i.e., within-person) components through centering [252].

To examine between-person effects, variables are grand-mean centered by which an individual's mean predictor score across all time points (i.e., person-mean) is centered on the grand-mean (i.e., mean for all individuals across all time points). To examine within-person effects, variables are person-mean centered by which an individual's predictor score at each time point is centered on their own person-mean. These two disaggregated components are included as predictors in the LME model to obtain separate estimates for the between- and within-person effects [160]. In the context of this dissertation, however, the terms between-dyad (BD) and within-dyad (WD) are used instead of between-person and within-person, as the parent-child dyad is the primary unit of analysis for Study 2. This approach is well-suited to examining the

stable and dynamic influences of parent distress on psychopathology in children with a CPI, and the disaggregation of these effects may be particularly relevant for prevention and intervention efforts.

4.3.2.2 Objective 2: Explore if these associations are moderated by HCC trajectory

Researchers are often interested in testing hypotheses of moderation, which occurs when the effect of a predictor (X) on the outcome of interest (Y) depends on the level of another variable (Z: a moderator) [253]. Moderation effects are typically evaluated by including a product interaction term between the predictor and moderator (i.e., $X*Z$) in the model [253]. However, centering remains a critical concern when exploring moderation hypotheses with longitudinal data, and models may produce spurious moderation effects when time-varying predictors are not disaggregated into their between- and within-person components [254]. Specifically, since a time-varying predictor contains a blend of between-person and within-person effects, that blend carries forward to any interactions that include the time-varying predictor [158]. Thus, to test for moderation by HCC trajectory, interaction terms between HCC trajectory group and the between-dyad and within-dyad effects of parent internalizing symptoms and parenting stress (e.g., BD parenting stress*HCC trajectory) were included in subsequent LME models [255]. Exploring moderation at both levels is beneficial for understanding whether child HPA-axis functioning impacts the stable and/or dynamic associations between parent distress and child psychopathology.

4.3.3 Study 3

4.3.3.1 Objective 1: Examine associations between HCC trajectories and HRQoL

A series of latent growth curve models (LGCMs) were used to examine associations between HCC trajectories and HRQoL over 48 months. In the LGCM framework, data from

repeated measurements are used to model change over time, where two parameters are treated as latent variables – the intercept and slope (also referred to as growth factors) [256]. The intercept represents the baseline status of the outcome and the slope represents the rate of change in the outcome over time [257]. The growth factors are estimated based on individual trajectories and provide an estimate of the average trajectory of the outcome over time [256]. Once the growth factors are estimated, additional variables can be included in the model to examine predictors of the baseline status (i.e. intercept) and rate of change (i.e., slope) of the outcome [257]. This approach is well-suited to examining the impact of HCC trajectory group membership on HRQoL over time. Additionally, the LGCM framework is easily extended to evaluate longitudinal mediational processes, which directly aligns with the second objective of Study 3 (described below).

4.3.3.2 Objective 2: Explore psychopathology as a potential mediator of these associations

A series of parallel-process LGCMs were used to examine child psychopathology as a mediator of the associations between HCC trajectories and HRQoL. In its simplest form, a mediator (M) represents a mechanism through which a predictor (X) is able to influence an outcome of interest (Y) [258]. A standard cross-sectional mediation path is presented in Figure 1. Path a represents the effect of X on M, path b represents the effect of M on Y, controlling for the effect of X, and path c' represents the effect of X on Y, controlling for the effect of M [259]. An estimate of the mediated or indirect effect can be calculated by finding the product of the a and b paths, which represents the influence of X on Y through M [259]. Longitudinal data provide several benefits over cross-sectional data and can provide more accurate representations of growth over time and thus more accurate conclusions about mediational processes [259].

Specifically, longitudinal data allows for the examination of whether a predictor influences the growth of a mediator, which influences the growth of an outcome [258,260].

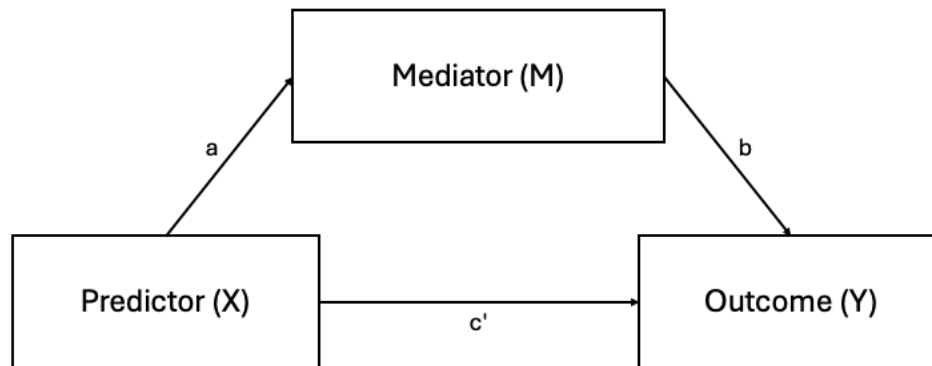


Figure 1. Standard mediation model

The parallel-process LGCM is recommended to evaluate longitudinal mediational processes when both the mediator and the outcome change over time [260]. Once the intercept and slope of the mediator and outcome are separately modelled, and the impact of the predictor on the intercept and slope of the mediator and outcome is examined, the two separate growth models are combined into one parallel-process model [260]. Mediation can then be examined through the intercepts and the slopes of the mediator and outcome (Figure 2) [261]. Since the intercept only provides information about the baseline status of the mediator and outcome, examining mediation through the intercepts is comparable to the cross-sectional mediation model presented above [261]. Specifically, intercept-to-intercept mediation is supported when the predictor significantly affects the baseline status of the mediator, which in turn significantly affects the baseline status of the outcome. In contrast, longitudinal mediation can be explored through the slopes of the mediator and outcome. Specifically, slope-to-slope mediation is supported when the predictor significantly affects the growth of the mediator, which in turn

significantly affects the growth of the outcome [260]. This method is well-suited for examining mediation effects with longitudinal data, and allows for a greater understanding of the complex associations between HCC trajectory, psychopathology, and HRQoL over time.

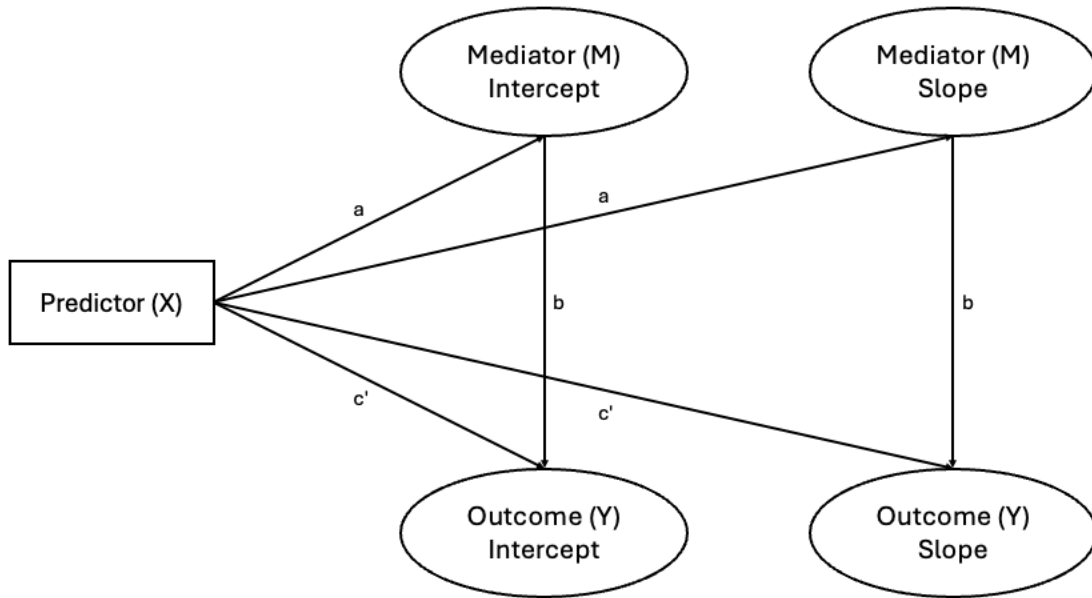


Figure 2. Parallel-process LGCM mediation model

4.4 Missing Data

Retention in MY LIFE over time is high; retention rates across the study were 97.7% at 6 months, 96.2% at 12 months, 93.9% at 24 months, and 89.4% at 48 months. Out of the 263 children enrolled in MY LIFE at baseline, 244 (92.8%) provided at least one valid hair sample during the 48-month follow-up, and were included in the analytic sample for this dissertation. Excluded children ($n = 19$) had lower household income compared to included children, $\chi^2(1)=4.66, p=.031$. There were no other differences between included vs. excluded children.

Out of the 244 children included in the final analytic sample, 79 (32.4%) had complete HCC data at all five assessments, and 165 (67.6%) had some missing data. The following

number of children had valid HCC data at each assessment: baseline ($n = 199$), 6-month ($n = 210$), 12-month ($n = 196$), 24-month ($n = 149$), 48-month ($n = 153$). Missing HCC data were associated with higher disability ($W=7550.5$, $p=.029$), and lower household income ($\chi^2(1)=6.55$, $p=.011$). In Study 1, LCGA with full information maximum likelihood (FIML) estimation handled hair data assumed to be missing at random (MAR). One of the main advantages of LCGA using FIML is that subjects with missing data do not have to be excluded from the analysis, as the model is built using all the available data [131,262]. Specifically, children with complete and partially complete HCC data across the five time points are analyzed together, where the model estimates are adjusted for missingness [263].

Out of the 244 children, 177 (72.5%) had complete EBS data at all five assessments, and 67 (27.5%) had some missing data. Missing EBS data were associated with older child age ($W=4510.5$, $p=.004$), endocrine CPI ($p=.021$), and lower parent education ($\chi^2(1)=8.31$, $p=.004$). Similarly, out of the 244 children, 162 (66.4%) had complete KIDSCREEN-27 data at all five assessments, and 82 (33.6%) had some missing data. Missing KIDSCREEN-27 data were associated with older child age ($W=5483.5$, $p=.026$), lower household income ($\chi^2(1)=14.16$, $p<.001$), and lower parent education ($\chi^2(1)=10.56$, $p=.001$). In Studies 1 and 2, LME models included all children in the analyses by using restricted maximum likelihood (REML) estimation to accommodate missing EBS data over time. In Study 3, LGCMs included all children in the analyses by using FIML estimation to handle missing EBS and KIDSCREEN-27 data over time. These approaches assume that data are MAR and use all available data to produce the maximum likelihood estimation of model parameters [264]. Additionally, they have been shown to outperform mean imputation methods [264] and produce comparable estimates relative to multiple imputation methods [265].

4.5 Sample Size and Power

The final sample for this dissertation includes 244 children who provided at least one valid hair sample, and their parents. Conducting power analyses after study data has already been collected has been widely criticized in the literature [266,267]. Instead, it is recommended that researchers perform analyses and interpret results according to 95% confidence intervals (CIs) for effect sizes [267]. As such, no post-hoc power analyses were conducted for the analyses used in this dissertation. However, power was taken into consideration when selecting appropriate statistical models; the sections below summarize these considerations.

Sample size requirements for LCGA (Study 1) are complex and depend on numerous factors (e.g., true number of classes, class sizes, separation between classes, number of time points), some of which are difficult to know a priori [268]. Larger sample sizes are needed when the number of true classes is higher, class sizes are smaller, separation between classes is lower, and with fewer time points [269]. Simulation studies suggest that a minimum sample size of 200 is required with four time points, when the true number of classes is two, and there is a high degree of separation between classes [269,270]. Previous studies using LCGA have been able to identify three cortisol trajectory classes across four to five time points with sample sizes between $n=79-138$ [132,226,227,271]. Additionally, to maximize statistical power, LGCA was chosen over GMM [272]. Since LCGA assumes no within-class variability (i.e., all individuals within a class have the same intercept and slope), it estimates fewer parameters than GMM and may be more useful in cases with smaller sample sizes [130].

Power analyses for LME models and LGCMs (Studies 1, 2, and 3) are similarly complex because sample sizes are allocated at multiple levels (i.e., the number of individuals and the number of repeated measurements), and there are many types of effects that can be explored (i.e.,

fixed effects, interactions, variance components) [273]. For LME models, simulation studies suggest that a sample size of 100-200 with 5 time points is sufficient for detecting medium to large fixed effects and interaction effects [273,274]. For LGCMs, simulation studies suggest that a sample size between 100-200 with 5 time points is sufficient for detecting medium to large group differences in growth trajectory patterns [275], and a sample size of 200 with 5 time points is sufficient for detecting medium to large mediation effects in parallel-process LGCMs [276]. However, the categorical nature of the HCC trajectory class may have limited the statistical power to detect significant differences between classes. Since two of the classes have relatively small sample sizes (Hyposecretion: $n = 21$; Hyper-to-Hypo: $n = 57$), some of the null effects reported in this dissertation may be attributable to low statistical power. Thus, the analyses can be considered exploratory.

Chapter 5 – Study 1

Association between hair cortisol and psychopathology in children with a chronic physical illness

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5.1 Overview

Children with a chronic physical illness (CPI) experience significant stress and are at a greater risk of psychopathology. However, little is known about chronic stress and its relationship with psychopathology in this population. Over the last decade, hair cortisol concentration (HCC) has emerged as a viable biomarker of chronic stress. This study identified trajectories of HCC in children with a CPI and examined their associations with psychopathology. The study included data from 244 children enrolled in the Multimorbidity in Children and Youth across the Life-course (MY LIFE) study. MY LIFE is a prospective study of children aged 2-16 years with a CPI recruited from outpatient clinics at a Canadian pediatric hospital and followed for 48 months. Children provided 3-cm hair samples for cortisol assay, and parents reported psychopathology symptoms using the Emotional Behavioural Scales. We identified three HCC trajectories: (1) Hypersecretion ($n=166$, 68.03%); (2) Hyposecretion ($n=21$, 8.61%); and (3) Hyper-to-Hypo ($n=57$, 23.36%). When adjusting for sociodemographic and clinical characteristics, children in the Hyper-to-Hypo class had lower internalizing ($\beta=-3.17$, $p=.005$) and externalizing ($\beta=-2.27$, $p=.007$) psychopathology symptoms compared to the Hypersecretion class. This study provides evidence that children with a CPI follow distinct HCC trajectories. Children who followed a decreasing trajectory exhibited lower psychopathology symptoms compared to children who followed a consistently elevated trajectory, indicating that chronically high cortisol levels may contribute to the development of psychopathology.

Keywords: chronic stress, hair cortisol, physical illness, children, psychopathology.

5.2 Introduction

Approximately 15-30% of children globally are affected by a chronic physical illness (CPI) [1]. Childhood CPI refers to a wide range of highly prevalent and often disabling conditions such as asthma, juvenile arthritis, type 1 diabetes, and epilepsy. Children with these conditions experience considerable stress stemming from treatments and symptom management, familial and environmental stressors, as well as restrictions in their daily lives [2,3]. As a result, diagnosis of a CPI during childhood is associated with an increased risk of child psychopathology, such as depression, anxiety, and conduct problems [4–8]. It has been estimated that anywhere from 20-50% of children with a CPI will develop psychopathology [9,10]. Understanding the link between childhood CPI and psychopathology is critical as the proportion of children diagnosed and living with CPIs is steadily increasing [1].

The link between stress biomarkers and psychopathology in children is an emerging area of research largely focused on cortisol, a hormone released by the hypothalamic-pituitary-adrenal (HPA) axis in response to stress [11]. Repeated activation of the HPA-axis can lead to dysregulation and result in increased cortisol secretion (hypersecretion) or decreased cortisol secretion (hyposecretion) over time [11]. Evidence suggests that children who display altered cortisol responses are at an increased risk of developing psychopathology [12–14]. Traditionally, studies have measured cortisol in children through urine, blood or saliva [15]. However, these samples only provide a short-term measure of cortisol secretion (i.e., minutes to hours), limiting their applicability to understanding the impact of chronic stressors [15]. Over the last decade, hair cortisol concentration (HCC) has emerged as a biomarker of long-term cortisol secretion [16,17]. Unlike traditional measures, hair sampling is non-invasive and averages circulating cortisol levels over an extended period (i.e., months) as an indicator of chronic stress [18]. Hair

typically grows at a rate of 1 cm per month, and 3 cm hair samples have been shown to accurately reflect average cortisol secretion in the three months before collection [19–21].

Previous studies have found altered HCC in children exposed to chronic stressors (e.g., maltreatment, traumatic events, CPI) [22–25]. However, the relationship between HCC and psychopathology in children remains unclear. While some studies have reported positive associations [26–28], others have reported inverse associations [29,30], and no associations [22,31–34]. Some previous research suggests that the pattern of HPA dysregulation underlying specific psychopathology symptoms may differ [35,36]. Specifically, higher HCC has been associated with the presence of internalizing symptoms (e.g., depression and anxiety) in children [29,37], whereas lower HCC has been associated with externalizing symptoms (e.g., behavioural and conduct disorders) [24,38]. Further longitudinal research is needed to clarify these relationships before HCC can reliably be used to identify children at an elevated risk of developing psychopathology.

The majority of research exploring longitudinal patterns of cortisol secretion in children utilizes variable-centered approaches that assume population homogeneity (i.e., all individuals follow a similar trajectory over time) [39]. However, variable-centered approaches overlook the possibility that subgroups of children may follow distinct cortisol secretion trajectories, which may be uniquely associated with psychopathology. In contrast, person-centered approaches assume population heterogeneity and aim to identify and describe subgroups within the population that follow distinct trajectories over time [39]. These approaches can be used to identify subgroups of children who follow dysregulated or maladaptive cortisol trajectories in response to stress, and therefore, may be more susceptible to developing psychopathology [40].

Moreover, if these subgroups do exist, their identification can support the implementation of targeted interventions to prevent or reduce the negative effects of chronic stress.

Studies using person-centered analyses of HCC in children are limited and report inconsistent associations between HCC trajectories and psychopathology. Rovnaghi et al. (2021) examined HCC trajectories in children across ages 1-3, and found that children who followed a hypersecretion trajectory exhibited higher internalizing and externalizing behaviours compared to children who followed a decreasing trajectory. Panter-Brick et al. (2020), however, found no significant differences in mental health symptoms across three distinct HCC trajectories (e.g., hypersecretion, medium secretion, and hyposecretion) in war-affected adolescents aged 12-18 years over 11 months. Even though a diagnosis of a CPI in childhood is considered a stressful life event, few studies have examined HCC in children with a CPI, and no previous study has explored trajectories of HCC in this population using a person-centered approach. Thus, our first objective was to examine trajectories of HCC in a large sample of children with a CPI over 48 months, and identify the sociodemographic and clinical predictors of HCC trajectories. Based on previous findings [40,42,43], we expected to identify three distinct HCC trajectories: hypersecretion, medium secretion, and hyposecretion.

Additionally, only one prior study has examined associations between HCC and psychopathology over time in children with a CPI, which was limited to exploring this relationship in a small sample (n=42) over a short follow-up period of 6 months [44]. This study found consistent positive associations between HCC and externalizing symptoms over time, but the positive associations between HCC and internalizing symptoms were only significant at baseline [44]. Thus, our second objective was to investigate associations between HCC trajectories and psychopathology symptoms over 48 months, adjusting for sociodemographic and

clinical characteristics. Given that some previous research suggests that the pattern of HPA dysregulation underlying specific psychopathology symptoms may differ, we conducted separate models for internalizing and externalizing symptoms. In line with previous research, we hypothesized that children who follow a maladaptive or dysregulated HCC trajectory would exhibit higher internalizing and externalizing symptoms compared to children who follow an adaptive or normative trajectory [41].

5.3 Methods

Study Design and Sample

Data come from the ongoing Multimorbidity in Children and Youth across the Life-course (MY LIFE) study, a prospective study of 263 children with a CPI [45,46]. Children (2-16 years) and their primary caregiving parent were recruited from outpatient clinics at a pediatric hospital in Ontario, Canada. Baseline assessments were taken between August 2017 and November 2019, and follow-ups occurred at 6, 12, 24, and 48 months. CPIs were defined as physician-diagnosed conditions expected to last ≥ 1 year and result in one or more of the following: (1) physical or functional limitations, (2) dependencies (e.g., medication), or (3) increased healthcare service use. The most common CPIs in the MY LIFE sample included juvenile arthritis (19%), type 1 diabetes (14.5%), celiac disease (10.6%), cystic fibrosis (8.4%), and haemophilia (7.6%). Families without sufficient English language skills were excluded, as well as children with >1 CPI at baseline. Health professionals at the participating clinics worked together with research assistants to identify eligible children and their families. Eligible families were then contacted by the research assistant, who verified eligibility, described the purpose of the study, and obtained informed consent. Written informed consent was obtained from all parents and children aged ≥ 16 years, written assent was obtained from children 7-15 years, and

oral assent was obtained from children <7 years. Study approval was obtained from relevant research ethics boards.

Measures

Hair Cortisol Concentration

Hair was collected from children at each assessment by cutting approximately 80 strands of hair (~4 mm diameter) from the posterior vertex, as close to the scalp as possible. Children with shorter hair had 15-20 hairs collected from 4-5 different locations on the posterior vertex. Samples were attached to a piece of paper with a clip, which indicated the scalp end. Parents completed a questionnaire about factors hypothesized to influence HCC (e.g., medications, hair colour, hair wash frequency, smoke exposure, etc.) [20]. After March 2020, hair collection occurred in the homes of participants. Parents were provided with detailed instructions for collection, and samples were placed in an envelope and sent to the investigators by mail. Previous research has shown that samples collected by participants at home do not differ from samples collected by research staff [47].

The first 3 cm of each hair sample (proximal to the scalp) were analyzed by enzyme-linked immunosorbent assay (ELISA) using the High Sensitivity Salivary Cortisol Immunoassay Kit (Salimetrics, Pennsylvania), as per the manufacturer's instructions. Insufficient hair samples (e.g., length or amount) were excluded from the analyses. The extraction and assaying of the hair samples followed established procedures, and have been described previously [44]. Cortisol concentration was expressed as pg/mg of hair. Although liquid chromatography-mass spectrometry (LC-MS) has shown higher specificity and sensitivity [48], the Salimetrics ELISA kit has shown strong correlations with LC-MS ($r^2 = 0.98$) [49], validating our assay method.

Some previous research suggests that corticosteroid medication use can suppress HPA-axis activity, resulting in lower HCC levels [50,51]. Given that corticosteroid medications are commonly prescribed for some CPIs in MY LIFE (e.g., intranasal corticosteroids for asthma or topical corticosteroids for eczema), we compared HCC levels between children using corticosteroids and children not using corticosteroids. We found no significant differences in HCC levels at any study time point, thus children using corticosteroids were not excluded from the analyses.

Psychopathology

Psychopathology symptoms were measured at each assessment using the Emotional Behavioural Scales (EBS). The EBS is a 52-item parent-reported checklist that measures symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD), separation anxiety disorder (SAD), social phobia (SP), attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) over the past six months in children <18 years [52,53]. Using a 3-point scale, parents rated symptoms (e.g., “Unhappy, sad or depressed”, “Can’t sit still, restless or hyperactive”) as “never or not true”, “sometimes or somewhat true”, and “often or very true”. Raw scores were summed to generate a subscale score for internalizing symptoms (e.g., MDD, GAD, SAD, SP; range: 0-54) and externalizing symptoms (e.g., ADHD, ODD, CD; range: 0-50). Higher scores on the EBS indicate a greater severity or frequency of symptoms. Internal consistency was excellent (Internalizing EBS $\alpha = 0.93$; Externalizing EBS $\alpha = 0.90$).

Sociodemographic and Clinical Variables

Parents reported the age, sex, race, and country of birth (immigrant or not) of themselves and their child. Parents also reported their marital status, education level, and annual household

income. Several additional variables were measured to assess the clinical characteristics of children in MY LIFE. Parents reported the years since CPI diagnosis, and body mass index (BMI) percentiles were determined based on child height and weight, adjusted for sex and age [45]. The 12-item parent-reported World Health Organization Disability Assessment Schedule (WHODAS) 2.0 was used to measure child disability [54]. The WHODAS 2.0 measures difficulty in functioning across the domains of cognition, mobility, self-care, getting along, life activities and participation (e.g., “Getting dressed”, “Standing for long periods”) on a 5-point scale from “0 = none” to “4 = extreme or cannot do”. Scores were summed to create a total score (range: 0-48), where higher scores indicate more impairment and disability. The WHODAS 2.0 has been validated in children with a CPI [55], and internal consistency was good (WHODAS 2.0 $\alpha = 0.87$).

Statistical Analysis

All statistical analyses were conducted in R version 4.2.1. The final sample for analysis included 244 children who provided at least one valid hair sample during the study. Differences in baseline characteristics between children with valid vs. missing hair data were compared using t-tests for continuous variables and Chi-square (χ^2) or Fisher’s exact tests for categorical variables. HCC values were positively skewed (range 0.05 – 164.18 pg/mg, M=15.01, SD=18.09) and were thus natural log-transformed (ln) for the analyses (range -3.04 – 5.1 ln-pg/mg, M=2.11, SD=1.15). Bivariable analyses (t-tests, ANOVAs, and correlations) were conducted to explore associations between baseline HCC and baseline factors hypothesized to impact cortisol levels. Spearman rank correlations were examined between HCC levels and psychopathology symptoms at each time point to assess associations.

Latent class growth analysis (LCGA) with full information maximum likelihood estimation was used to identify trajectories of HCC over time using the “lcm” package in R [39,56,57]. This approach captures the heterogeneity in how an outcome changes over time, and aims to identify subgroups within the sample that follow distinct trajectories [58]. LCGA estimates a mean growth curve in each class, and assumes that individual growth trajectories within each class are homogeneous [59]. Simulation studies recommend a minimum sample size of 200 for LCGA [60,61], and previous studies examining cortisol trajectories have used samples as small as $n=79$ [62]. Models with 1-5 latent classes were estimated for a variety of trajectories (linear, quadratic, cubic). To determine the optimal shape of the trajectories, non-significant higher-order terms (i.e., quadratic, cubic) were removed, and the model was re-estimated. After the initial series of models were estimated, models were re-specified with child sex and age at baseline included as covariates based on previous literature [63,64].

The final model was selected by comparing the following fit indices: (i) Bayesian Information Criterion (BIC: lower values indicate better model fit), (ii) Lo–Mendell–Rubin likelihood ratio test (LMR-LRT: determines whether a k -class model performs better than a $k-1$ class model), (iii) entropy (values closer to 1 indicate better classification), and (iv) posterior probabilities of group assignment (>0.70 threshold for acceptability) [56,57]. After selecting the optimal model, individuals were assigned to their most likely class. The descriptions of the classes were established by examining the shape of the trajectories, and in the context of HCC reference ranges in healthy children [65,66]. Baseline sociodemographic and clinical characteristics were compared across classes using analysis of variance (ANOVA), χ^2 , and Fisher’s exact tests. A multinomial logistic regression was used to explore the baseline sociodemographic and clinical predictors of class membership. Characteristics associated with

class membership in the bivariate analyses at $p < .20$ were included as predictors in the regression model.

A series of linear mixed-effects (LME) models explored changes in psychopathology symptoms over time, as measured with the EBS. LME models with restricted maximum likelihood estimation (REML) were conducted in R using the “lme4” package [67]. A random coefficient model was specified whereby time (linear and quadratic) was added as a fixed effect to assess the average change in psychopathology symptoms over time. Additional fixed effects included HCC trajectory class, as well as its interaction with time to examine if HCC trajectory class impacts the rate of change in psychopathology symptoms over time. Sociodemographic and clinical characteristics were entered into the models as covariates based on prior literature [68], as well as those significantly associated with psychopathology symptoms at $p < .05$. Model assumptions were assessed graphically, and judged to be acceptable. Model fit was assessed by comparing BIC values during model building. Missing EBS data was minimal, and represented 7.3% and 8% of total observations for internalizing and externalizing symptoms, respectively. Having missing data was associated with older child age, endocrine CPI, and lower parent education. REML was used to account for EBS data assumed to be missing at random, whereas missing data on covariates was handled using complete case analysis. One child (0.4%) had missing household income data, thus the final analytic sample for the LME models was $n=243$ children.

5.4 Results

Sample Characteristics

Baseline characteristics of the sample are presented in Table 1. The mean age of children at baseline was 9.54 years ($SD=4.17$), and 117 (47.95%) were female. The mean time since CPI

diagnosis at baseline was 4.42 years (SD=4.08), and 25% of children represented new-onset cases (e.g., time since diagnosis < 1 year). Nineteen children (7.22%) did not provide a valid hair sample during the study, and these children were less likely to have a household income above the provincial median ($\geq \$90,000$ CAD). There were no other differences between children with valid vs. missing HCC data.

Associations between baseline HCC and factors hypothesized to impact cortisol levels are presented in Supplementary Table S1. Males had higher HCC than females ($M=2.7$, $SD=1.14$ vs. $M=2.33$, $SD=1.04$; $p=.018$). Older children ($r=-0.414$, $p<.001$) and children with higher BMIs ($r=-0.156$, $p=.031$) had lower HCC. Children with treated/dyed hair had lower HCC ($M=2.19$, $SD=0.71$ vs. $M=2.56$, $SD=1.14$; $p=.029$), and HCC was lower in children with brown hair compared to blonde hair ($M=2.24$, $SD=1.14$ vs. $M=2.89$, $SD=0.95$; $p<.001$). Medication use, smoking status, hair wash frequency, and child race did not impact HCC levels. Correlations between HCC and psychopathology symptoms at each time point are presented in Supplementary Table S2. There were no associations between HCC levels and internalizing symptoms across the study time points. Only 6-month HCC levels were significantly positively associated with externalizing symptoms at baseline, 12, 24, and 48 months, and these associations were weak in magnitude ($p\leq 0.19$).

Trajectories of Hair Cortisol Concentration

A three-class conditional model was selected based on superior fit indices (see Supplementary Table S3). The trajectories for the three-class conditional model are illustrated in Figure 1, and were characterized as follows: (1) Hypersecretion ($n=166$, 68.03%); (2) Hyposecretion ($n=21$, 8.61%); and (3) Hyper-to-Hypo ($n=57$, 23.36%). Children in the Hypersecretion class had high HCC levels at baseline (ln-HCC pg/mg: $M=2.73$, $SD=0.88$), that

fluctuated but remained high over time. Children in the Hyposecretion class had low HCC levels at baseline (ln-HCC pg/mg: $M=0.72$, $SD=1.17$), that did not increase significantly over time. Children in the Hyper-to-Hypo class had high HCC levels at baseline (ln-HCC pg/mg: $M=2.68$, $SD=0.9$), which rapidly decreased over the first 12 months, and remained low afterwards. Across all trajectory classes, older children and females had lower HCC levels. Parameter estimates for the selected model are presented in Table 2.

A comparison of baseline sociodemographic and clinical characteristics across the trajectory classes is presented in Supplementary Table S4. Characteristics associated with class membership in the bivariate analyses were years since CPI diagnosis, parent age, and parent immigration status. Post-hoc comparisons showed that children in the Hyposecretion class had less recent CPI diagnoses and an older primary caregiving parent, compared to children in the Hypersecretion class. Additionally, there were more children with a parent born outside of Canada in the Hyposecretion class compared to the Hypersecretion class.

Results of the multinomial logistic regression for class membership are presented in Table 3. Female children ($OR=4.25$, 95% CI [1.36 , 13.31], $p=.013$), children with less recent CPI diagnoses ($OR=1.19$, 95% CI [1.04 , 1.37], $p=.011$), and children with an older primary caregiving parent ($OR=1.13$, 95% CI [1.03 , 1.24], $p=.013$) were more likely to be in the Hyposecretion class compared to the Hypersecretion class. Additionally, older children ($OR=0.88$, 95% CI [0.79 , 0.97], $p=.015$) were less likely to be in the Hyper-to-Hypo class compared to the Hypersecretion class.

Associations Between HCC Trajectories and Psychopathology

Results of the models examining changes in EBS psychopathology symptoms are presented in Table 4 and Figure 2. There was a significant effect for quadratic change over time

in internalizing symptoms ($\beta=0.46$, 95% CI [0.26, 0.67], $p<.001$), suggesting that symptoms decreased from baseline to 24 months, and increased from 24 months to 48 months (Figure 2a). There was a significant effect for the Hyper-to-Hypo class ($\beta=-3.17$, 95% CI [-5.40, -0.94], $p=.005$); children in this class had lower average internalizing symptoms compared to the Hypersecretion class. There was no difference in symptoms between the Hyposecretion and Hypersecretion classes ($\beta=0.19$, 95% CI [-3.22, 3.60], $p=.912$). Higher levels of disability ($\beta=0.57$, 95% CI [0.49, 0.64], $p<.001$) and having a primary caregiving parent who is female ($\beta=3.03$, 95% CI [0.26, 5.81], $p=.032$) and a postsecondary graduate ($\beta=1.90$, 95% CI [0.36, 3.44], $p=.016$) were associated with higher average internalizing symptoms.

There was a significant effect for quadratic change over time in externalizing symptoms ($\beta=0.19$, 95% CI [0.05, 0.33], $p=.009$), suggesting that symptoms decreased from baseline to 24 months, and increased from 24 months to 48 months (Figure 2b). There was a significant effect for the Hyper-to-Hypo class ($\beta=-2.27$, 95% CI [-3.92, -0.62], $p=.007$); children in this class had lower average externalizing symptoms compared to the Hypersecretion class. There was no difference in symptoms between the Hyposecretion and Hypersecretion classes ($\beta=-1.02$, 95% CI [-3.56, 1.51], $p=.427$). Female children had lower average externalizing symptoms compared to male children ($\beta=-2.26$, 95% CI [-3.52, -1.00], $p<.001$). Higher levels of disability ($\beta=0.30$, 95% CI [0.24, 0.35], $p<.001$) and having a primary caregiving parent who is not a biological parent ($\beta=10.62$, 95% CI [6.02, 15.22], $p<.001$) were associated with higher average externalizing symptoms.

Interactions between HCC trajectory class and time were non-significant for both internalizing and externalizing psychopathology symptoms. Thus, HCC trajectory class did not influence the rate of change in psychopathology symptoms over time.

5.5 Discussion

To our knowledge, this is the first study to estimate trajectories of HCC in children with a CPI, and investigate associations between HCC trajectories and psychopathology. We identified three HCC trajectory classes using LCGA, suggesting that children with a CPI exhibit inter-individual differences in the HPA-axis stress response. These trajectories were distinct with respect to both initial levels of HCC and change over time, and were uniquely associated with psychopathology. Additionally, we found no associations between HCC levels and internalizing symptoms, and inconsistent associations between HCC and externalizing symptoms, across the study time points. This finding suggests that identifying distinct HCC trajectories using a person-centered approach provides additional value above and beyond simple correlations between HCC levels and psychopathology.

Most children (68.03%) followed a Hypersecretion trajectory with consistently elevated HCC compared to reference levels in healthy children [65,66], which suggests that a diagnosis of a CPI in childhood is a significant chronic stressor for children. The Hypersecretion class may identify children with maladaptive or dysregulated HPA-axis functioning. A failure to habituate or adapt to chronic stressors can result in prolonged HPA-axis activity, leading to a hyperactive state, and a greater risk of developing psychopathology [69].

Nearly a quarter of children (23.36%) followed a Hyper-to-Hypo trajectory, displaying initially elevated HCC that decreased over time to normative levels. This class potentially identifies children with an adaptive profile of HPA-axis functioning who have habituated to chronic stressors and returned to normal functioning [69]. Consistent with this notion, we found that children in the Hyper-to-Hypo class had lower internalizing and externalizing psychopathology symptoms over time, compared to children in the Hypersecretion class. This is

consistent with a previous study that found that elevated HCC was associated with greater psychopathology symptoms in children with a CPI over 6 months [44]. These findings also align with the results from Rovnaghi et al. (2021), who found that children following a decreasing HCC trajectory exhibited lower internalizing and externalizing behaviours compared to children following a hypersecretion trajectory.

We also found that older children were less likely to belong to the Hyper-to-Hypo class compared to the Hypersecretion class. This finding may suggest that older children with a CPI are at a greater risk of exhibiting maladaptive HPA-axis stress responses. Adolescence is an especially sensitive period of development that is associated with heightened stress-induced HPA-axis activity [70]. Previous research has shown that adolescents and older children exhibit heightened cortisol responses and slower recovery following a laboratory stressor, compared to younger children [40,71,72]. The results from this study add to the growing literature suggesting that HPA-axis stress reactivity heightens as children age [71], and further highlight that older children may be particularly susceptible to the stressful impacts of chronic illness. Although we found that older children had lower HCC levels in the bivariable analyses, the relationship between age and HCC in children (with or without a CPI) is not well-established [63]. Future research is required to clarify how age impacts HCC levels across childhood.

Fewer than one-in-ten children (8.61%) exhibited a Hyposecretion trajectory, with low levels of HCC that did not significantly increase over time. Given that children in this class had less recent CPI diagnoses, this class may also represent a healthy adaptation group who habituated to the chronic stressors at an earlier point. However, low levels of HCC do not necessarily reflect a healthy adaptation profile, as hypocortisolism has also been associated with psychopathology [73]. Thus, the trajectory of HCC in this class may also be explained by

maladaptive or dysregulated HPA-axis functioning, whereby exposure to chronic stressors impairs HPA-axis function over time leading to a hypoactive state [74]. Indeed, we found no difference in internalizing or externalizing symptoms between the Hyposecretion and Hypersecretion classes. Given the small sample size in the Hyposecretion class (n=21), this finding should be interpreted with caution.

Although evidence suggests that HCC is higher in male children [63], female children tend to exhibit heightened cortisol reactivity in response to stressors [75]. Additionally, previous studies exploring cortisol trajectories in children exposed to stressors have found that females are more likely to follow a hypersecretion trajectory [40,76]. In contrast, we found that female children were more likely to belong to the Hyposecretion class compared to the Hypersecretion class. This paradoxical finding could be explained by the greater HPA-axis variability that female children exhibit in response to stress [75]. Specifically, the Hyposecretion class may identify a small subgroup of primarily female children (71%) who exhibit blunted cortisol responses.

Some research suggests that the pattern of HPA-axis dysregulation underlying specific psychopathology symptoms may differ [35,36]. Specifically, hypersecretion has been associated with internalizing symptoms in children [29,37], whereas hyposecretion has been associated with externalizing symptoms [24,38]. In contrast, our findings did not suggest that high and low HCC levels are differentially associated with internalizing and externalizing symptoms. Instead, both hypersecretion and hyposecretion could be adaptive or maladaptive, depending on various external factors (e.g., genetics, timing, context) [77]. We encourage additional research in this area.

Strengths and Limitations

This study has several methodological strengths. First, the prospective design of MY LIFE allowed us to identify trajectories of HCC in a large sample of children with a CPI, and examine their associations with psychopathology over 48 months. Previous studies in this area have been limited to cross-sectional designs, or longitudinal designs with small samples and short follow-up periods. Second, using a person-centred modelling approach like LCGA allowed us to capture the heterogeneity of HCC patterns and identify both adaptive and maladaptive patterns of HPA-axis activity within our sample. These HCC trajectories were uniquely associated with psychopathology, further highlighting that person-centered approaches are beneficial for identifying subgroups of children who may be at high-risk. Variable-centered approaches that estimate an average trajectory across all individuals may not sufficiently capture heterogeneity, and may be limited for understanding the influence of HCC on psychopathology in children [40]. Finally, we used a symptom checklist to assess psychopathology, rather than a diagnostic interview. The symptoms that encompass psychopathology in children exist on a continuum of frequency and severity, and imposing binary notions of psychopathology as being “present” versus “absent” can reduce reliability and validity [78]. Moreover, the symptom checklist used in this study has demonstrated strong psychometric properties against diagnostic interviews for psychopathology in children [52,53].

Our findings should be considered in the context of the following limitations. First, most of MY LIFE children are White, and come from socioeconomically advantaged families [45]. Additionally, families were recruited from one pediatric hospital, and only families with sufficient English language skills were included [45]. Although the socioeconomic characteristics of MY LIFE families are similar to families of children with CPI in the general population [79], these factors may limit the generalizability of the results to diverse populations.

Second, because the MY LIFE sample does not include a control group, we could not examine and compare HCC trajectories between children with a CPI and healthy children. Current studies reporting HCC reference ranges in healthy children are cross-sectional, and have utilized small samples [65,66]. Thus, the comparisons made in this study to healthy children should be interpreted with caution, and future research should aim to examine and compare HCC trajectories between these populations. Third, this study included children across a broad age range that encompasses several developmental periods, and could not examine how HCC trajectories might differ across these periods. Additionally, while we adjusted for child age in all models, we could not account for the effect of pubertal status on HPA-axis responses, as this was not measured in our study. Fourth, psychopathology symptoms were measured using the parent-reported EBS; parent-child agreement is typically low, and parents tend to overreport symptoms of psychopathology [80]. Finally, we did not measure perceived stress levels, and previous studies have reported weak to no associations between perceived stress and HCC in children [28,81]. However, given that children often struggle to reliably self-report their levels of stress, HCC may hold utility as an objective indicator of chronic stress in children [16].

5.6 Conclusions

This study is the first to provide evidence that children with a CPI follow distinct HCC trajectories, with many children displaying elevated HCC compared to healthy norms. Children who followed a Hyper-to-Hypo trajectory exhibited lower psychopathology symptoms compared to the Hypersecretion trajectory, indicating that chronically high cortisol levels may play a role in the development of psychopathology. Given the increase in the proportion of children diagnosed and living with CPIs, our findings can support the early identification and treatment of children experiencing chronic stress. Preliminary research suggests that mindfulness-based

interventions for children and their parents can reduce HCC levels in healthy children [82,83].

Future research can explore windows of opportunity for interventions to reduce the negative impacts of stress and the incidence of psychopathology in children with a CPI.

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5.8 Tables and Figures

Table 1. Characteristics of the study sample at baseline

Characteristic	Analytic sample (n=244)	Excluded sample (n=19)	<i>p</i> -value
Child			
Age (years), mean (SD)	9.54 (4.17)	8.63 (4.7)	.423
Female, n (%)	117 (47.95%)	8 (42.11%)	.800
Years since CPI diagnosis, mean (SD)	4.42 (4.08)	3.66 (3.71)	.405
BMI percentile, mean (SD)	58.44 (29.73)	61.28 (33.78)	.763
WHODAS 2.0, mean (SD)	19.31 (6.69)	19.21 (8.02)	.957
Born in Canada, n (%)	230 (94.26%)	18 (94.74%)	.999
CPI Type, n (%)			.198
Dermatological	19 (7.79%)	4 (21.05%)	
Endocrine	34 (13.93%)	4 (21.05%)	
Gastroenterological	33 (13.52%)	1 (5.26%)	
Hematological	27 (11.07%)	2 (10.53%)	
Neurological	10 (4.1%)	2 (10.53%)	
Respiratory	51 (20.9%)	3 (15.79%)	
Rheumatological	70 (28.69%)	3 (15.79%)	
White, n (%)	198 (81.15%)	15 (78.95%)	.766
Parent			
Age (years), mean (SD)	40.55 (6.34)	40.1 (8.79)	.829
Female, n (%)	219 (89.75%)	18 (94.74%)	.704
Biological parent, n (%)	240 (98.36%)	19 (100%)	.999
Born in Canada, n (%)	209 (85.66%)	14 (73.68%)	.181
Household income ≥ \$90,000, n (%)	151 (61.89%)	6 (31.58%)	.031
Postsecondary graduate, n (%)	189 (77.46%)	11 (57.89%)	.089
Married/Common law, n (%)	212 (86.89%)	16 (84.21%)	.726
White, n (%)	210 (86.07%)	16 (84.21%)	.737

Table S1. Associations between baseline characteristics and baseline HCC

Characteristic	Ln-HCC pg/mg, mean (SD) (n=199)	Test statistic and <i>p</i> -value
Age (years)		$r=-0.414, p<.001$
Sex		$t=-2.38, p=.018$
Female	2.33 (1.04)	
Male	2.7 (1.14)	
BMI percentile		$r=-0.156, p=.031$
Corticosteroid medication use		$t=-1.05, p=.295$
No	2.47 (1.11)	
Yes	2.66 (1.08)	
Household smoking Status		$t=0.046, p=.964$
No	2.51 (1.11)	
Yes	2.5 (1.15)	
Natural Hair Colour		$F=5.61, p=.001$ Blonde > Brown [$p<.001$]
Blonde	2.89 (0.95)	
Brown	2.24 (1.14)	
Red	2.8 (1.12)	
Black	2.73 (0.87)	
Hair Dye/Treatments		$t=2.25, p=.029$
No	2.56 (1.14)	
Yes	2.19 (0.71)	
Hair wash frequency		$F=1.91, p=.130$
< 1 time per week	3.64 (0.26)	
1-2 times per week	2.69 (0.95)	
3-4 times per week	2.49 (1.03)	
> 4 times per week	2.35 (1.29)	
Child Race		$t=1.34, p=.185$
White	2.47 (1.15)	
Non-white	2.69 (0.85)	

Notes: For ANOVA's, pairwise contrasts with the Bonferroni adjustment were examined when the overall test was statistically significant. *P*-values were calculated as = unadjusted *p*-value * number of pairwise contrasts.

Table S2. Correlations between HCC and psychopathology symptoms

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Ln-HCC T1	1													
2. Ln-HCC T2	0.52***	1												
3. Ln-HCC T3	0.31***	0.39***	1											
4. Ln-HCC T4	0.21*	0.41***	0.47***	1										
5. Ln-HCC T5	0.14	0.27**	0.29***	0.35***	1									
6. INT T1	-0.01	0.05	-0.05	-0.02	0.06	1								
7. INT T2	0.06	0.05	0.01	0	0.04	0.80***	1							
8. INT T3	0.08	0.07	0.01	0.04	0.04	0.75***	0.81***	1						
9. INT T4	0.07	0.08	0.05	-0.04	0	0.65***	0.71***	0.71***	1					
10. INT T5	-0.03	0.01	-0.05	0.04	-0.01	0.57***	0.57***	0.62***	0.66***	1				
11. EXT T1	0.1	0.15*	0.09	0.07	0.12	0.59***	0.49***	0.47***	0.39***	0.32***	1			
12. EXT T2	0.05	0.08	0.01	0.01	0.08	0.51***	0.60***	0.48***	0.45***	0.32***	0.78***	1		
13. EXT T3	0.11	0.17*	0.07	0.06	0.13	0.44***	0.50***	0.54***	0.43***	0.29***	0.77***	0.81***	1	
14. EXT T4	0.08	0.19**	0.12	0.02	0.15	0.30***	0.39***	0.38***	0.50***	0.30***	0.63***	0.72***	0.78***	1
15. EXT T5	0.04	0.17*	0.07	-0.07	0.12	0.27***	0.29***	0.30***	0.39***	0.46***	0.55***	0.58***	0.62***	0.72***

Notes. INT = EBS Internalizing Symptoms; EXT = EBS Externalizing Symptoms; T1 = Baseline; T2 = 6 months; T3 = 12 months; T4 = 24 months; T5 = 48 months.

* $p < .05$, ** $p < .01$, *** $p < .001$

Table S3. Latent class growth analysis (LCGA) model selection criteria

Trajectory	Classes	Order	AIC	BIC	sBIC	Entropy	LMR-LRT	Relative class size (%)					Posterior classification probabilities	
								Class 1	Class 2	Class 3	Class 4	Class 5	Min	Max
Linear	1 ^a	(1)	2802.60	2813.09	2803.58	1		100						
	2 ^a	(1,1)	2730.17	2751.15	2732.13	0.57	$p<.001$	63.93	36.07				0.86	0.88
	3 ^a	(1,1,1)	2733.23	2764.71	2736.18	0.42	$p=.429$	50.41	18.44	31.15			0.65	0.82
	4 ^a	(1,1,1,1)	2720.60	2762.57	2724.53	0.54	$p<.001$	18.44	50	1.64	29.92		0.66	0.82
	5 ^a	(1,1,1,1,1)	2720.61	2773.07	2725.52	0.56	$p=.130$	40.16	40.57	1.64	14.75	2.87	0.63	0.81
	1 ^b	(1)	2666.01	2683.50	2667.65	1		100						
	2 ^b	(1,1)	2640.26	2668.23	2642.87	0.39	$p<.001$	33.61	65.39				0.78	0.81
	3 ^b	(1,1,1)	2631.97	2670.44	2635.57	0.61	$p=.004$	29.92	1.64	68.44			0.76	0.83
	4 ^b	(1,1,1,1)	2632.83	2681.79	2637.41	0.49	$p=.183$	62.3	1.64	24.18	11.89		0.67	0.80
	5 ^{b,c}													
Quadratic	1 ^a	(2)	2757.03	2771.02	2758.34	1		100						
	2 ^a	(2,2)	2670.59	2698.57	2673.21	0.59	$p<.001$	39.75	60.25				0.86	0.88
	3 ^a	(1,2,2)	2658.23	2696.69	2659.50	0.66	$p<.001$	4.51	43.03	52.46			0.80	0.85
	4 ^a	(2,2,1,1)	2642.63	2691.59	2644.88	0.71	$p<.001$	45.9	47.54	1.23	5.33		0.81	0.95
	5 ^a	(2,2,2,1,2)	2645.15	2711.59	2649.04	0.59	$p=.217$	46.72	2.46	23.36	4.92	22.54	0.60	0.85
	1 ^b	(2)	2605.35	2626.34	2607.32	1		100						
	2 ^b	(2,2)	2571.01	2606.06	2574.36	0.46	$p<.001$	31.15	68.85				0.79	0.84
	3^b	(2,1,2)	2560.24	2605.70	2562.16	0.56	$p=.001$	68.03	8.61	23.36			0.71	0.83
	4 ^b	(2,1,1,2)	2564.73	2620.68	2567.64	0.73	$p=.700$	27.87	1.23	0.82	70.08		0.55	0.93
	5 ^b	(1,2,1,2,1)	2564.66	2631.11	2568.55	0.58	$p=.126$	27.05	57.79	1.23	13.11	0.82	0.60	0.96
Cubic	1 ^{a,d}													
	2 ^{a,d}													
	3 ^a	(2,2,3)	2657.62	2703.09	2659.55	0.69		52.87	43.44	3.69			0.83	0.87
	4 ^{a,d}													
	5 ^{a,d}													
	1 ^{b,d}													
	2 ^{b,d}													
	3 ^{b,d}													
	4 ^{b,d}													
	5 ^{b,d}													

Notes: Order indicates the shape of the trajectory in each class (1=Linear, 2=Quadratic, 3=Cubic), AIC: Akaike Information Criterion, BIC: BIC Bayesian Information Criterion, sBIC: sample size adjusted BIC, LMR-LRT: Lo-Mendell-Rubin Likelihood Ratio Test. Significant LMR-LRT suggests better model fit than a k-1 class model. Bold indicates selected model.

^aUnconditional models (i.e., no covariates).

^bConditional models (child age at baseline and child sex included as covariates).

^cModel identified a class with 0% group membership.

^dCubic term was non-significant in all classes

Figure 1. Plot of mean ln-HCC values over time for each HCC trajectory class. The shaded areas around each trajectory represent 95% confidence intervals.

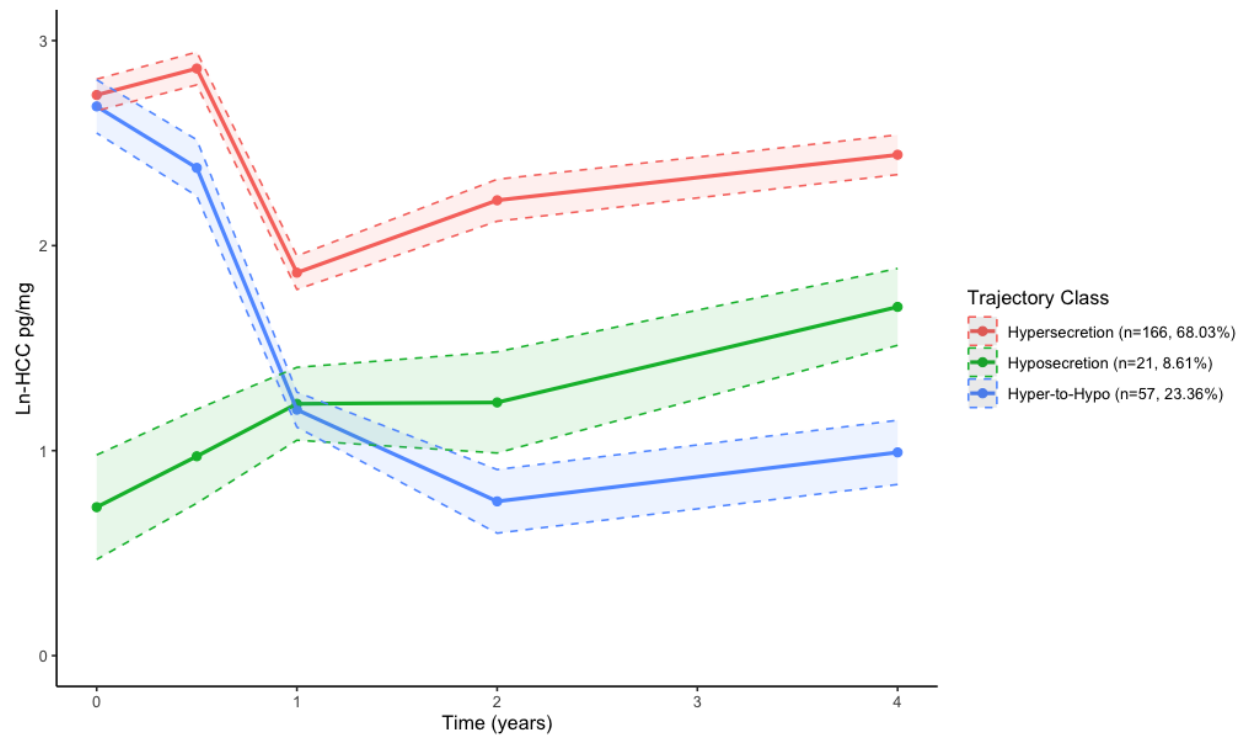


Table 2. Parameter estimates and descriptive statistics for the selected 3-class conditional LCGA model

	n (%)	Parameter	β	SE	p-value	Ln-HCC pg/mg, mean (SD)				
						Baseline	6 months	12 months	24 months	48 months
Class 1: Hypersecretion	166 (68.03%)	Intercept	3.06	0.09	< .0001	2.73 (0.88)	2.86 (0.95)	1.87 (0.92)	2.22 (1.00)	2.44 (0.93)
		Time	-0.80	0.13	< .0001					
		Time ²	0.17	0.03	< .0001					
Class 2: Hyposecretion	21 (8.61%)	Intercept	1.38	0.26	< .0001	0.72 (1.17)	0.97 (0.97)	1.23 (0.69)	1.24 (0.92)	1.7 (0.73)
		Time	0.12	0.14	.384					
Class 3: Hyper-to-Hypo	57 (23.36%)	Intercept	2.83	0.22	.0001	2.68 (0.9)	2.38 (0.98)	1.2 (0.64)	0.75 (0.98)	0.99 (1.05)
		Time	-1.53	0.28	.0001					
		Time ²	0.28	0.06	.0001					
Covariates		Sex [Female]	-0.26	0.08	.0009					
		Child Age at Baseline	-0.10	0.009	.0001					

Notes. Child age at baseline is centered at the mean value. Ln-HCC values were compared across trajectory classes at each time point using analysis of variance tests. Pairwise contrasts, with the Bonferroni adjustment, were examined when the overall difference was statistically significant. *P*-values were calculated as = unadjusted *p*-value * number of pairwise contrasts. Baseline: $F(2,196) = 44.49$, $p < .001$ (contrasts: 1 > 2 [$p < .001$], 3 > 2 [$p < .001$]), 6 months: $F(2,207) = 32.61$, $p < .001$ (contrasts: 1 > 2 [$p < .001$], 1 > 3 [$p = .006$], 3 > 2 [$p < .001$]), 12 months: $F(2,193) = 14.38$, $p < .001$ (contrasts: 1 > 2 [$p = .024$], 1 > 3 [$p < .001$]), 24 months: $F(2,146) = 33.18$, $p < .001$ (contrasts: 1 > 2 [$p = .002$], 1 > 3 [$p < .001$]), 48 months: $F(2,150) = 35.75$, $p < .001$ (contrasts: 1 > 2 [$p = .017$], 1 > 3 [$p < .001$], 2 > 3 [$p = .041$]).

Table S4. Comparison of baseline characteristics across trajectory classes

Characteristic	Trajectory class			<i>p</i> -value	Contrasts
	Class 1: Hypersecretion (n=166)	Class 2: Hyposecretion (n=21)	Class 3: Hyper-to-Hypo (n=57)		
Child					
Age (years), mean (SD)	9.65 (4.24)	10.68 (4.23)	8.79 (3.88)	.171	
Female, n (%)	78 (46.99%)	15 (71.43%)	24 (42.11%)	.065	
Years since CPI diagnosis, mean (SD)	4.13 (4.06)	6.78 (3.82)	4.38 (4.02)	.019	2 > 1 [<i>p</i> =.015]
BMI percentile, mean (SD)	57.8 (28.95)	68.56 (28.26)	56.35 (32.2)	.251	
Born in Canada, n (%)	159 (95.78%)	18 (85.71%)	53 (92.98%)	.113	
WHODAS 2.0, mean (SD)	19.82 (7.05)	18.19 (5.02)	18.26 (6.07)	.232	
White, n (%)	139 (83.73%)	17 (80.95%)	42 (73.68)	.251	
Parent					
Age (years), mean (SD)	40.08 (6.2)	43.91 (7.69)	40.69 (5.92)	.032	2 > 1 [<i>p</i> =.027]
Female, n (%)	148 (81.16%)	19 (90.48)	52 (91.23%)	.942	
Biological parent, n (%)	164 (98.8%)	20 (95.23%)	56 (98.25%)	.480	
Born in Canada, n (%)	147 (88.55%)	14 (66.67%)	48 (84.21%)	.029	2 < 1 [<i>p</i> =.006]
Household income ≥ \$90,000, n (%)	101 (60.84%)	14 (66.67%)	36 (63.16%)	.814	
Postsecondary graduate, n (%)	128 (77.11%)	15 (71.43%)	46 (80.7%)	.645	
Married/Common law, n (%)	145 (87.35%)	20 (95.23%)	47 (82.46%)	.356	
White, n (%)	146 (87.95%)	18 (85.71%)	46 (80.7%)	.365	

Notes: For ANOVA's, pairwise contrasts with the Bonferroni adjustment were examined when the overall test was statistically significant. *P*-values were calculated as = unadjusted *p*-value * number of pairwise contrasts.

Table 3. Multinomial logistic regression for HCC trajectory class membership

Trajectory Class	Predictor	OR	95% CI		p-value
Hyposecretion	Child Sex [Female]	4.25	1.36	13.31	.013
	Child Age	0.84	0.69	1.01	.063
	Years Since CPI Diagnosis	1.19	1.04	1.37	.011
	Child Born Outside Canada	3.33	0.48	23.31	.225
	Parent Age	1.13	1.03	1.24	.013
	Parent Born Outside Canada	3.08	0.85	11.20	.087
Hyper-to-Hypo	Child Sex [Female]	0.90	0.48	1.68	.743
	Child Age	0.88	0.79	0.97	.015
	Years Since CPI Diagnosis	1.05	0.96	1.15	.258
	Child Born Outside Canada	1.99	0.44	8.92	.370
	Parent Age	1.06	0.99	1.13	.085
	Parent Born Outside Canada	1.15	0.43	3.11	.776

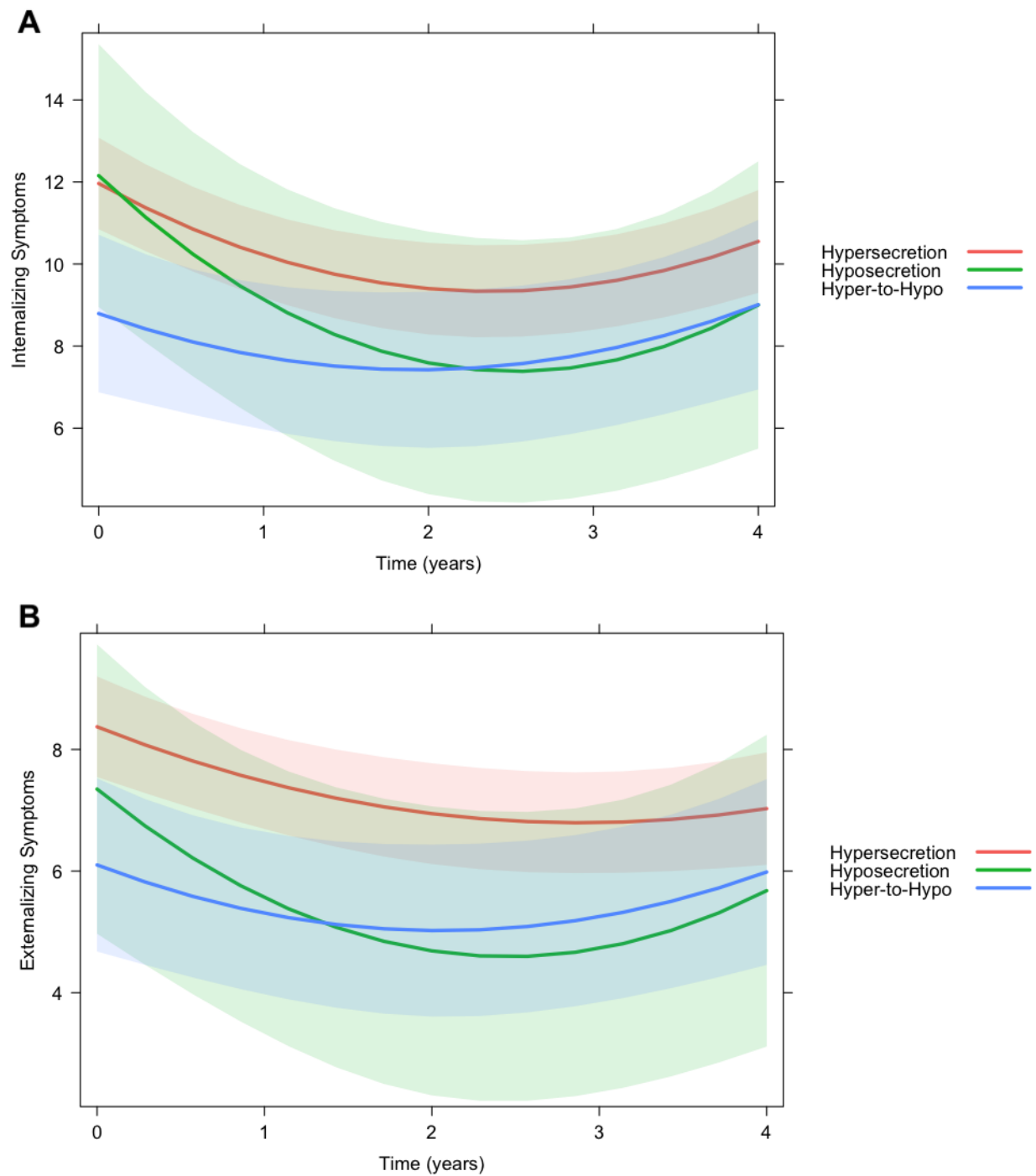
Notes: Reference class is Class 1: Hypersecretion. OR = Odds Ratio

Table 4. Linear mixed-effects models for EBS psychopathology symptoms

	Model A: Internalizing			Model B: Internalizing			Model C: Externalizing			Model D: Externalizing		
Predictors	β	CI	<i>p</i> -value	β	CI	<i>p</i> -value	β	CI	<i>p</i> -value	β	CI	<i>p</i> -value
Intercept	6.73	3.71, 9.74	<.001	6.68	3.65, 9.70	<.001	7.72	5.46, 9.98	<.001	7.66	5.40, 9.92	<.001
Child Sex [Female]	1.46	-0.20, 3.13	.085	1.47	-0.20, 3.13	.084	-2.27	-3.53, -1.00	<.001	-2.26	-3.52, -1.00	<.001
Child Age at Baseline	0.24	-0.04, 0.51	.095	0.24	-0.04, 0.52	.090	0.08	-0.13, 0.29	.475	0.08	-0.13, 0.29	.464
Time Since CPI Diagnosis at Baseline	-0.05	-0.28, 0.18	.670	-0.05	-0.28, 0.18	.672	0.07	-0.11, 0.24	.453	0.07	-0.11, 0.24	.452
WHODAS 2.0	0.57	0.49, 0.64	<.001	0.57	0.49, 0.64	<.001	0.30	0.24, 0.35	<.001	0.30	0.24, 0.35	<.001
Parent Sex [Female]	3.05	0.28, 5.83	.031	3.03	0.26, 5.81	.032	1.90	-0.20, 4.01	.076	1.88	-0.22, 3.98	.079
Parent Age at Baseline	-0.15	-0.33, 0.03	.096	-0.16	-0.34, 0.02	.085	-0.11	-0.25, 0.02	.105	-0.11	-0.25, 0.02	.098
Parent Relation [Other]	3.72	-2.36, 9.80	.231	3.89	-2.20, 9.97	.210	10.51	5.91, 15.11	<.001	10.62	6.02, 15.22	<.001
Education Level [Postsecondary Graduate]	1.77	0.23, 3.31	.024	1.90	0.36, 3.44	.016	0.01	-1.09, 1.11	.991	0.10	-1.01, 1.20	.862
Household Income [$\geq$ 90K]	0.30	-0.76, 1.37	.576	0.37	-0.70, 1.43	.499	-0.34	-1.08, 0.40	.367	-0.31	-1.05, 0.43	.410
Time	-2.16	-2.88, -1.45	<.001	-2.21	-3.08, -1.34	<.001	-1.19	-1.67, -0.70	<.001	-1.09	-1.68, -0.50	<.001
Time ²	0.47	0.30, 0.64	<.001	0.46	0.26, 0.67	<.001	0.23	0.12, 0.35	<.001	0.19	0.05, 0.33	.009
HCC Class												
Hyposecretion	-0.90	-3.98, 2.18	.576	0.19	-3.22, 3.60	.912	-1.61	-3.94, 0.72	.177	-1.02	-3.56, 1.51	.427
Hyper-to-Hypo	-2.44	-4.44, -0.44	.017	-3.17	-5.40, -0.94	.005	-1.97	-3.49, -0.46	.011	-2.27	-3.92, -0.62	.007
Time*HCC Class												
Time*Hyposecretion				-1.57	-4.13, 1.00	.231				-1.15	-2.89, 0.59	.194
Time*Hyper-to-Hypo				0.79	-0.92, 2.49	.366				0.04	-1.11, 1.20	.943
Time ² *HCC Class												
Time ² *Hyposecretion				0.28	-0.33, 0.89	.362				0.27	-0.14, 0.68	.203
Time ² *Hyper-to-Hypo				-0.09	-0.50, 0.31	.644				0.07	-0.21, 0.34	.635
Random Effects												
Residual (Within-Child)	20.25 (4.5)			20.21 (4.50)			9.25 (3.04)			9.24 (3.04)		
Intercept	37.51 (6.13)			37.47 (6.12)			22.04 (4.69)			22.00 (4.69)		
ICC	0.65			0.65			0.70			0.70		
N	243			243			243			243		
Marginal R ² /Conditional R ²	0.267 / 0.743			0.268 / 0.743			0.248 / 0.778			0.249 / 0.778		

Notes. Reference group for HCC class is Hypersecretion. Child Age, Time Since CPI Diagnosis, WHODAS 2.0, and Parent Age are centred at the mean value.

Figure 2. Model predicted (A) internalizing psychopathology symptoms and (B) externalizing psychopathology symptoms over time for each HCC trajectory class.



Chapter 6 – Study 2

Stable and dynamic influences of parent internalizing symptoms and parenting stress on psychopathology in children with a chronic physical illness: The moderating role of child hair cortisol

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6.1 Overview

Children with a chronic physical illness (CPI), such as diabetes, asthma, and epilepsy, experience significant stress and are at a greater risk of psychopathology. Parent distress strongly influences child psychopathology, and understanding stable and dynamic paths of transmission is critical for developing effective interventions. This study examined the between-dyad (stable) and within-dyad (dynamic) effects of parent internalizing symptoms and parenting stress on psychopathology in children with a CPI. Additionally, we examined whether these associations were moderated by child hair cortisol concentration (HCC). Data come from 244 children (2-16 years at baseline) with a CPI, and their parents, who were followed for 48 months (assessments at baseline, 6, 12, 24, and 48 months). Parent internalizing symptoms and parenting stress were assessed using self-report measures. Hair samples were collected from children, and parents reported child psychopathology symptoms. Previous work identified three HCC trajectories among children in this sample: Hypersecretion (68.0%), Hyposecretion (8.6%), and Hyper-to-Hypo (23.4%). There were significant between- and within-dyad effects of parent internalizing symptoms and parenting stress on child internalizing and externalizing symptoms. Child HCC moderated the between-dyad effects of parent internalizing symptoms and parenting stress on child internalizing symptoms. The combination of high average levels of parent internalizing symptoms or parenting stress and cortisol hypersecretion predicted greater child symptoms. Findings highlight the importance of considering parent distress, paired with child cortisol, to understand psychopathology risk in children with a CPI. Overall, HCC may be a promising biomarker for understanding heterogeneity in associations between parent distress and child psychopathology. *Keywords:* parent internalizing, parenting stress, child psychopathology, physical illness, hair cortisol

6.2 Introduction

Over the past two decades, the prevalence of childhood-onset chronic physical illnesses (CPI) has increased, with estimates suggesting that 30-50% of children in North America are affected by a CPI [1,2]. Childhood CPI encompasses a broad range of conditions resulting in functional limitations, dependencies, and high health care needs, such as juvenile arthritis, epilepsy, and asthma [3]. These illnesses can be significant sources of stress for children, who often must navigate the prolonged and repeated demands of living with a CPI (e.g., treatments, symptoms) [4]. As a result, children with a CPI exhibit an elevated risk of developing psychopathology [5]. The prevalence of psychopathology in children in the general population is estimated to be approximately 20% [1,6]. In comparison, anywhere from 20-50% of children with a CPI will develop psychopathology, which can lead to worse physical health, poor quality of life, and suicidality [7,8]. Thus, understanding risk factors for psychopathology in children with a CPI is important for informing prevention and treatment strategies.

Parents strongly influence child psychopathology, and two potential factors found to influence child psychopathology symptoms include parent internalizing symptoms and parenting stress. The link between parent internalizing symptoms, herein defined as symptoms of depression and anxiety, and child internalizing and externalizing symptoms is well-established [9,10]. Parenting stress, defined as the stress experienced by parents related to their parenting role, has also shown strong associations with child psychopathology symptoms [11]. Moving forward, parent distress is used as an overarching term encompassing both parent internalizing symptoms and parenting stress. Parent distress has been linked to negative parenting practices and reduced parental support [12,13], and theoretical models suggest that this adverse environment may place children at high risk for psychopathology [14]. Previous studies have

shown that greater parent distress is associated with greater psychopathology symptoms in children with a CPI [15–18]. In fact, children with a CPI may be particularly vulnerable to the effects of parent distress due to the compounding influences of managing illness-related and parent distress-related stressors. In addition to the impact on the child, managing a CPI is often stressful for the parent-child dyad. Specifically, parents of children with a CPI often report greater internalizing symptoms and parenting stress due to the additional challenges of caring for a chronically ill child [17,19]. Understanding paths from parent distress to child psychopathology is crucial for developing effective interventions, particularly in children with a CPI who may be especially vulnerable [20].

While parent distress exhibits relative stability across adulthood, parents may experience fluctuations due to environmental changes, including positive and negative life events [21]. In addition, acute illness-related events (e.g., exacerbations, hospitalizations, complications) may further contribute to fluctuations in parent distress in parents of a child with a CPI [22]. Children are not only impacted by the level of distress their parent experiences on average (between-dyad effects), but also by deviations from these averages (within-dyad effects) [23]. For example, a child may exhibit greater psychopathology symptoms at times when their parent is experiencing higher levels of distress compared to their own average. No prior study has explored the between- and within-dyad effects of parent distress on psychopathology symptoms in children with a CPI, and longitudinal designs can separate these sources of variation [24]. Disentangling these effects can add to our understanding of how these factors influence psychopathology in children with a CPI, and may be relevant for guiding intervention and prevention efforts.

Although the link between parent distress and child psychopathology is well-established, not all children are equally susceptible, and studies are increasingly investigating moderators that

might be implicated in this relationship [25,26]. In particular, individual differences in the relationship between parent distress and child psychopathology may be accounted for by variations in child cortisol, a hormone involved in stress regulation. Cortisol is the main hormone secreted by the hypothalamic-pituitary-adrenal (HPA) axis in response to stress [27]. Although this process is adaptive acutely, chronic exposure to stress can lead to HPA-axis dysregulation, resulting in high (i.e., hypersecretion) or low (i.e., hyposcretion) cortisol levels over time [28,29]. Vulnerability stress models, such as diathesis-stress/dual-risk, suggest that HPA-axis dysregulation may be a risk marker conferring vulnerability to the effects of adverse environments [30]. In children, cortisol is most commonly measured in saliva, which can be used to measure cortisol reactivity in response to stressors as well as non-stressed basal (diurnal) cortisol throughout the day [31]. Several studies have demonstrated that higher basal cortisol levels and higher cortisol reactivity are associated with greater psychopathology in children exposed to adverse environments (e.g., parental hostility, maltreatment, stressful events) [32–35]. However, very few studies have examined the moderating impacts of child cortisol on the relationship between parent distress and child psychopathology, and none have examined this relationship in children with a CPI. Black et al. (2019) found that the relationship between maternal depression and internalizing symptoms was moderated by child salivary cortisol awakening response (CAR), such that higher CAR predicted greater internalizing symptoms in children with a mother having a history of depression, but not in children with no parents having a history of depression. Simons et al. (2017), however, found no interactive effects between maternal parenting stress and child salivary cortisol (reactivity and basal levels) on child psychopathology symptoms.

Additionally, it is possible that child HPA-axis dysregulation may influence the strength of the between-dyad and within-dyad associations between parent distress and child psychopathology. Specifically, elevated cortisol may strengthen the association between average levels of parent distress and child psychopathology symptoms (i.e., between-dyad moderation), or strengthen the coupling between fluctuations in parent distress and child psychopathology symptoms (i.e., within-dyad moderation). In line with this, Laurent et al. (2013) reported that child salivary cortisol moderated the association between average depressive symptoms among adoptive parents and child externalizing symptoms. Specifically, the combination of high average parental depressive symptoms and high child basal cortisol predicted greater child externalizing symptoms over 54 months. At the within-dyad level, fluctuations in maternal depressive symptoms predicted greater child internalizing and externalizing symptoms regardless of child basal cortisol levels [26]. However, fluctuations in paternal depressive symptoms predicted greater internalizing symptoms, but only for children with high basal cortisol. This finding suggests that elevated child cortisol may heighten risk for the within-dyad transmission of internalizing symptoms [26]. Examining moderation at both levels is critical for understanding whether child cortisol influences stable parent-child risk pathways, dynamic parent-child risk pathways, or both.

More recently, hair cortisol concentration (HCC) has been used as a biomarker of chronic HPA-axis dysregulation in children [37,38]. Unlike traditional biomarkers (e.g., saliva), hair collection is non-invasive, and represents average cortisol secretion over several months as a biomarker of long-term cortisol secretion [37]. Hair typically grows 1 cm per month, and 3 cm hair samples can be used to measure average cortisol secretion in the preceding 3 months [39]. Previous research has found higher HCC in children exposed to adverse environments and

chronic stressors [40–42], including parent distress [43,44], and childhood CPI [45,46]. Previous work also suggests that high child HCC may confer vulnerability to the adverse influences of environmental stressors [47,48]. Specifically, Shapero et al. (2019) found a positive association between recent life stress and depressive symptoms in adolescents with high and average HCC, but no association in those with low HCC. However, no prior study has examined whether chronic HPA-axis dysregulation, indexed by HCC, influences the between- or within-dyad effects of parent distress on child psychopathology. Given the acute and invasive nature of traditional cortisol biomarkers (i.e., saliva), HCC could be a promising biomarker for understanding heterogeneity in the association between parent distress and child psychopathology.

The current study aimed to build upon existing research by exploring associations between parent distress and psychopathology in children with a CPI, and examining whether child HCC alters children's vulnerability to the effects of parent distress. While parent internalizing symptoms and parenting stress are related constructs, they represent distinct aspects of parent distress [49], and thus were examined separately. Specifically, the objectives of the study were to 1) disentangle the between- and within-dyad effects of parent internalizing symptoms and parenting stress on psychopathology symptoms in children with a CPI; and 2) examine if these associations are moderated by child HCC. We used HCC trajectories established in our previous work [50]. It was hypothesized that there would be significant between- and within-dyad effects from parent internalizing symptoms and parenting stress to child psychopathology symptoms, and that these effects would be strengthened for children with high HCC.

6.3 Methods

Participants

Participants were from the ongoing Multimorbidity in Children and Youth Across the Life-course (MY LIFE) study, a longitudinal cohort of children (2-16 years) with a CPI. Methodological details of the MY LIFE sample have been described in detail previously [51]. Chronic physical illnesses were defined as physician-diagnosed physical conditions expected to last for ≥ 12 months and result in ≥ 1 of: functional limitations; dependencies (e.g., assistive devices), or need for additional health services. Children and their primary caregiving parent/guardian (herein parent) were recruited from outpatient clinics at a pediatric hospital in Ontario, Canada, and followed for 48 months (assessments at baseline, 6, 12, 24, and 48 months). Informed consent was obtained from all participants, and study approval was obtained from the University of Waterloo Human Research Ethics Board (#31010) and Hamilton Integrated Research Ethics Board (#2797).

Measures

Parent Internalizing Symptoms: Parent depression was measured at each assessment using the Center for Epidemiological Studies Depression Scale (CES-D) [52]. The CES-D is a 20-item self-report scale that measures the frequency of depressive symptoms over the past week. Items are scored on a 4-point scale and are summed to calculate a total score, where higher scores indicate greater depressive symptomatology. The CES-D has been validated in parents of children with physical and mental health conditions [53,54], and internal consistency in our sample was excellent ($\alpha=0.92$). Parent anxiety was measured at each assessment using the Generalized Anxiety Disorder-7 Scale (GAD-7) [55]. The GAD-7 is a 7-item self-report scale that measures the frequency of symptoms relating to generalized anxiety disorder over the past

two weeks. Items are scored on a 4-point scale and are summed to calculate a total score, where higher scores indicate higher levels of anxiety. The GAD-7 has demonstrated robust psychometric properties [55], and internal consistency in our sample was good ($\alpha=0.87$). Parent depression (CES-D) and anxiety (GAD-7) scores were highly correlated across the study ($rs \geq 0.74$), and their scores were summed to create an overall measure of parent internalizing symptoms (P-INT).

Parenting Stress: Parenting stress was measured at each assessment using the 18-item Parental Stress Scale (PSS) [56]. The PSS is a self-report scale that assesses stress over the past month across four parenting domains: rewards, stressors, loss of control and satisfaction. Items are scored on a 5-point scale and are summed to calculate a total score, where higher scores indicate higher levels of parenting stress. The PSS has demonstrated robust psychometric properties [56], and internal consistency in our sample was good ($\alpha=0.85$).

Child Psychopathology Symptoms: Child psychopathology symptoms were measured at each assessment using the parent-reported Emotional Behavioural Scales (EBS) [57]. The EBS is a 52-item checklist that measures symptoms of internalizing (INT; generalized anxiety disorder, separation anxiety disorder, social phobia, major depressive disorder) and externalizing (EXT; attention-deficit hyperactivity disorder, conduct disorder, oppositional defiant disorder) disorders in children over the past 6 months. Items are rated on a 3-point scale, where higher scores indicate greater symptomatology. Internal consistency in our sample was excellent (INT $\alpha=0.93$; EXT $\alpha=0.90$).

Child Hair Cortisol: Research staff collected hair from children at each assessment by cutting approximately 80 strands of hair from the posterior vertex, as close to the scalp as possible. Due to the COVID-19 pandemic, hair samples were collected by parents in the homes

of participants beginning in March 2020. Detailed collection instructions were sent to participants, and hair samples were placed in a bag and sent back by mail. Of the 263 children enrolled in MY LIFE, 244 provided at least one valid hair sample across the study, and are included in the analyses. Missing hair data was associated with lower household income ($\chi^2(1)=4.66, p=.031$), but was not associated with any of the other variables in this study. The first 3-cm of each sample were analyzed by enzyme-linked immunosorbent assay using the High Sensitivity Salivary Cortisol Immunoassay Kit (Salimetrics, Pennsylvania), according to the manufacturer's instructions. The process for collection and extraction followed previously published procedures [43]. The intra- and inter-assay coefficients of variation were 8.2% and 6.2%, respectively. Cortisol levels are expressed as pg/mg hair. A natural log-transformation ($\ln$) was applied to account for positive skew in the HCC values. Previous work identified distinct trajectories of HCC over 48 months among the 244 children in this sample using latent class growth analysis (LCGA) [50]. Methodological details for the identification of the HCC trajectory classes have been described in detail previously [50]. Three HCC trajectory classes were identified in this sample: Hypersecretion (68.0%), Hyposecretion (8.6%), and Hyper-to-Hypo (23.4%). Previous analyses examining correlates of child HCC (e.g., age, sex, CPI type, BMI, ethnicity, corticosteroid medication use, smoking status, hair colour, hair treatments, hair washing frequency) found that only child age and sex were associated with HCC over time. Accordingly, these variables were included as covariates in the LCGA model and are included as covariates in all subsequent models. The three-class LCGA model is shown in Figure 1.

Sociodemographic and clinical characteristics: At each assessment, data were collected on child and parent age, sex, race, and country of birth, as well as parental relation, marital status, education level, and annual household income. Parents reported the time since their

child's CPI diagnosis (years), and body mass index (BMI) percentiles were calculated from child height and weight measurements, adjusted for child sex and age. The 12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0 was used to measure child disability at each assessment [58]. Parents rated items on a 5-point scale, and items were summed to calculate a total score, whereby higher scores indicate greater disability. The WHODAS 2.0 has demonstrated excellent psychometric properties in children with a CPI [59], and internal consistency in our sample was good ($\alpha=0.87$).

Statistical Analysis

Linear mixed-effects (LME) models, conducted using the “lme4” package in R [60], examined child psychopathology symptoms over time. Out of the 244 participants, 177 (72.5%) had complete EBS data at all five time points, and 67 (27.5%) had some missing data. Missing data were associated with older child age ($W=4510.5, p=.004$), endocrine CPI ($p=.021$), lower parent education ($\chi^2(1)=8.31, p=.004$), and higher parent internalizing symptoms ($W=4660.5, p=.015$). Models included all children by using restricted maximum likelihood estimation to account for EBS data assumed to be missing at random. Missing covariate data (one child had missing household income data), were handled using complete case analysis.

Models included random intercepts and slopes, and fixed effects for follow-up time (linear and quadratic), parent internalizing symptoms, parenting stress, and HCC class. All models were adjusted for child sex and age, years since CPI diagnosis, child disability (WHODAS 2.0), parent sex and age, parent relation, household income, and parent education. Centering was used to disentangle the between- and within-dyad effects of parent internalizing symptoms and parenting stress on child psychopathology symptoms [24]. To assess between-dyad (BD) effects, we used grand-mean centering by which a parent's mean score across all time

points (i.e., their person-mean) was centered and standardized on the grand-mean (i.e., mean for entire sample across all time points). Because these variables vary across parents, and not time, they represent only BD effects (i.e., average differences between parents). To assess within-dyad (WD) effects, we used person-mean centering by which a parent's score at a particular time point was centred and standardized on their person-mean. Because these variables vary within-parents across time, and do not include any between-parent variation, they represent only WD effects (i.e., time-specific fluctuations from a parent's mean score).

Model building followed an iterative process. To address objective one, we first examined the between- and within-dyad effects of parent internalizing symptoms and parenting stress on child internalizing and externalizing symptoms. Next, interactions with time were explored to examine if these factors influence the rate of change in internalizing or externalizing symptoms over time. Next, to address objective two, we explored all possible two- and three-way interactions between the BD and WD effects of parent internalizing symptoms and parenting stress, HCC class, and time on internalizing and externalizing symptoms. Significant interactions were decomposed using simple slopes analysis [61], with p -values adjusted using the Sidak correction for multiple comparisons. Non-significant interactions were excluded from the models for parsimony. Simulation studies suggest that sample sizes between 100-200 with five time points are sufficient for detecting medium to large fixed effects in LME models [62,63]. However, small sample sizes within two of the HCC trajectory classes (Hyposecretion: $n=21$; Hyper-to-Hypo: $n=57$), may have influenced power to detect significant interaction effects.

6.4 Results

Sample Characteristics

Sample characteristics are summarized in Table 1. Children had a mean age of 9.5 years (SD=4.2), and 117 (48.0%) were female. One-quarter of children (25%) represented new-onset cases of CPI (duration <1 year), and the mean time since CPI diagnosis was 4.4 years (SD=4.1). Parents had a mean age of 40.6 years (SD=6.3), and 219 (89.8%) were female. Most parents were married/common law (86.9%), post-secondary graduates (77.5%), and had a household income equal to or above the provincial median of \$90,000 CAD (61.9%). Descriptive statistics and correlations between parent internalizing symptoms, parenting stress, and child internalizing and externalizing symptoms are presented in Supplementary Table 1. A comparison of parent internalizing symptoms and parenting stress across HCC trajectory classes is presented in Supplementary Table 2. There were no significant differences in scores across HCC trajectories at any time point.

Internalizing Symptoms

Results of the LME models predicting child internalizing symptoms are presented in Table 2. Model 1 tested the between- and within-dyad effects of parent internalizing symptoms and parenting stress on child internalizing symptoms. The significant quadratic time effect showed that child internalizing symptoms followed a U-shaped trajectory ($\beta=0.35, p<.001$) (Figure 2). Average parent internalizing symptoms, but not parenting stress, were significantly associated with child internalizing symptoms (BD effects). Specifically, higher mean parent internalizing symptoms were associated with greater child internalizing symptoms ($\beta=2.31, p<.001$). The significant WD effect of parent internalizing symptoms also showed that children exhibited greater internalizing symptoms at times when their parent reported higher than usual internalizing symptoms compared to their own mean ($\beta=0.63, p<.001$). There was no difference in child internalizing symptoms between the Hyposecretion and Hypersecretion HCC classes

($\beta=-0.87, p=.556$), but children in the Hyper-to-Hypo class had fewer internalizing symptoms compared to the Hypersecretion class ($\beta=-2.36, p=.014$). Greater child disability was also associated with greater child internalizing symptoms ($\beta=0.47, p<.001$). In Model 2, the significant interaction between WD parent internalizing symptoms and quadratic time suggested that the within-dyad association between parent internalizing symptoms and child internalizing symptoms followed a U-shaped trajectory ($\beta=0.30, p=.005$).

Model 3 tested all possible two- and three-way interactions between the BD and WD effects of parent internalizing symptoms, HCC class, and time on child internalizing symptoms. Main effects were consistent with Model 1. HCC class significantly moderated the effect of BD parent internalizing symptoms on child internalizing symptoms for the Hyposecretion vs. Hypersecretion class ($\beta=-3.21, p=.040$), and the Hyper-to-Hypo vs. Hypersecretion class ($\beta=-2.28, p=.024$) (Figure 3a). Specifically, the negative interactions suggest that the association between average parent internalizing symptoms and child internalizing symptoms was weaker for children in the Hyposecretion and Hyper-to-Hypo classes, compared to the Hypersecretion class. Decomposing these interactions using simple slopes analysis showed no association between average parent internalizing symptoms and child internalizing symptoms for children in the Hyposecretion class ($\beta=-0.23, 95\% \text{ CI } [-3.25, 2.80], p=.998$) or the Hyper-to-Hypo class ($\beta=0.70, 95\% \text{ CI } [-1.18, 2.58], p=.846$), but having a parent with higher mean internalizing symptoms was associated with greater internalizing symptoms for children in the Hypersecretion class ($\beta=2.98, 95\% \text{ CI } [1.91, 4.05], p<.001$).

Model 4 tested all possible two- and three-way interactions between the BD and WD effects of parenting stress, HCC class, and time on child internalizing symptoms. Main effects were consistent with Model 1. HCC class moderated the effect of BD parenting stress on child

internalizing symptoms for the Hyposecretion compared to the Hypersecretion class ($\beta=-3.24$, $p=.045$) (Figure 3b). Specifically, the negative interaction suggests that the association between average parenting stress and child internalizing symptoms was weaker for children in the Hyposecretion class compared to the Hypersecretion class. However, decomposing the interaction using simple slopes analysis showed no association between average parenting stress and child internalizing symptoms for children in the Hyposecretion class ($\beta=-2.32$, 95% CI [-5.46, 0.82], $p=.146$) or the Hypersecretion class ($\beta=0.92$, 95% CI [-0.12, 1.96], $p=.084$).

Externalizing Symptoms

Results of the LME models predicting child externalizing symptoms are presented in Table 3. Model 1 tested the between- and within-dyad effects of parent internalizing symptoms and parenting stress on child externalizing symptoms. The significant quadratic time effect showed that child externalizing symptoms followed a U-shaped trajectory ($\beta=0.17$, $p=.001$) (Figure 2). Average parent internalizing symptoms and parenting stress were significantly associated with child externalizing symptoms (BD effects). Specifically, higher mean parent internalizing symptoms ($\beta=1.23$, $p=.001$) and parenting stress ($\beta=0.92$, $p=.013$) were associated with greater child externalizing symptoms. The significant WD effect of parenting stress also showed that children exhibited greater externalizing symptoms when their parent reported higher than usual parenting stress compared to their own mean ($\beta=0.34$, $p=.001$). There was no difference in child externalizing symptoms between the Hyposecretion and Hypersecretion HCC classes ($\beta=-1.55$, $p=.176$), but children in the Hyper-to-Hypo class had fewer externalizing symptoms compared to the Hypersecretion class ($\beta=-1.92$, $p=.010$). Female children had fewer externalizing symptoms ($\beta=-2.82$, $p<.001$), greater child disability was associated with greater

child externalizing symptoms ($\beta=0.23, p<.001$), and children with non-biological parents had greater externalizing symptoms ($\beta=9.03, p<.001$).

Subsequent models tested all possible two- and three-way interactions between the BD and WD effects of parent internalizing symptoms and parenting stress, HCC class, and time on child externalizing symptoms. No significant interactions were found.

6.5 Discussion

The current study investigated relationships between parent distress, child HCC, and psychopathology symptoms in children with a CPI. Consistent with previous literature in both healthy and chronically ill children [9,15,20], higher average levels of parent internalizing symptoms were associated with greater child internalizing and externalizing symptoms. Interestingly, fluctuations in parent internalizing symptoms were only associated with greater child internalizing, but not externalizing, symptoms. This finding may suggest that fluctuations in child psychopathology symptoms are primarily influenced by congruent symptom-specific fluctuations in parent symptoms. This aligns with findings from Schulz et al. (2021), who found that when parents reported higher internalizing symptoms, their children also reported higher internalizing, but not externalizing, symptoms at the same assessment.

Both average levels and fluctuations in parenting stress were associated with greater child externalizing, but not internalizing, symptoms. This contrasts with previous literature that has shown strong associations between parenting stress and child internalizing psychopathology [65–67]. However, some studies report stronger associations between parenting stress and child externalizing symptoms [66,68,69]. Parents of children who exhibit difficult externalizing behaviours (e.g., oppositionality) often report increased levels of parenting stress [66,67]. Thus, these findings may reflect the strong bidirectional relationship between parenting stress and child

externalizing symptoms [67]. Moreover, this bidirectional relationship may be intensified in parents of children with a CPI, who often report increased levels of parenting stress [17].

The mechanisms underlying these associations likely involve a complex interplay of genetic and environmental influences [70]. In addition to the role of shared genetic vulnerability [70,71], parent distress has been linked to negative parenting practices, reduced parental support, and poorer parent-child relationships [12,13], which may heighten risk for psychopathology symptoms in children [70,72]. Families of a child with a CPI are also more likely to exhibit less positive parent-child relationships, lower parental responsiveness, and higher levels of neglectful parenting [73]. Parent distress may also interfere with the management of their child's CPI, which can negatively affect child psychological well-being [16,74].

A more nuanced picture emerged when considering interactions between parent distress and child HCC. More specifically, we found that higher average parent internalizing symptoms were associated with greater child internalizing symptoms, but only among children following a hypersecretion HCC trajectory. Conversely, average parent internalizing symptoms were not associated with child internalizing symptoms among children following a hyposecretion or hyper-to-hyposecretion HCC trajectory. The association between average parenting stress and child internalizing symptoms was also moderated by child HCC. Although the significant interaction suggested that the positive association between average parenting stress and child internalizing symptoms was weaker among children following a hyposecretion compared to a hypersecretion HCC trajectory, decomposing this interaction further showed no association in either HCC class. These findings are consistent with previous studies indicating that the combination of exposure to negative parent/family environments and high cortisol (salivary reactivity and HCC) is associated with greater child internalizing symptoms [25,32,35,47].

However, the current study extends this previous work by using HCC trajectories that reflect long-term patterns of cortisol secretion over several years. Although cortisol is a dynamically fluctuating hormone, repeated HCC assessments over time may capture trait-like individual differences in stress physiology that shape children's vulnerability to the effects of parent distress.

In the context of childhood CPI, these results may be attributable to compounding negative influences. Specifically, children with a CPI following a hypersecretion HCC trajectory may be particularly vulnerable to developing psychopathology when exposed to high average levels of parent distress, due to their compounding negative effects on child mental health. Importantly, we found no differences in parent internalizing symptoms or parenting stress between HCC classes, suggesting that these factors are not simply impacting child psychopathology through their association with cortisol. Overall, results are consistent with context-dependent theories of psychopathology, such as diathesis-stress/dual-risk [75]. These models propose that children with vulnerability markers are disproportionately likely to be affected by negative environments [30]. These markers can be physiological in nature (e.g., high HCC) and confer vulnerability to psychopathology when exposed to high average levels of parent distress [76]. Current results also suggest that some cortisol trajectories may be protective and confer resilience to high parent distress. This is central to the diathesis-stress framework, which posits that vulnerable and resilient children develop differently under adverse environmental conditions [77]. Accordingly, cortisol hypersecretion may be a marker of vulnerability in children with a CPI, whereas more adaptive cortisol trajectories (e.g., hyposecretion and hyper-to-hyposecretion) may be a marker of resilience.

However, HCC class did not moderate the effects of average parent internalizing symptoms or parenting stress on child externalizing symptoms; a finding consistent with Black et al. (2019), who reported that interactions between parental depression and child salivary cortisol were significant for child internalizing, but not externalizing, symptoms. These results suggest that children with a CPI exposed to high average levels of parent distress may be at a greater risk of externalizing symptoms, even if they are following a more adaptive cortisol trajectory. Additionally, the within-dyad effects of parent internalizing symptoms and parenting stress on child internalizing and externalizing symptoms were not moderated by child HCC. This suggests that the coupling between fluctuations in parent distress and child psychopathology symptoms occurs independently of child cortisol. This is consistent with Laurent et al. (2013), who found that fluctuations in maternal depressive symptoms predicted greater child internalizing and externalizing symptoms, regardless of child salivary cortisol reactivity. It is also possible that within-dyad effects are more strongly influenced by acute fluctuations in cortisol that may occur proximal to the assessments of parent distress, rather than the long-term patterns captured by the HCC trajectories. Taken together, findings highlight the importance of considering environmental contexts, such as parent distress, in conjunction with child cortisol to identify children with a CPI at high risk of psychopathology.

This research contributes to the growing literature examining the influence of parent distress on psychopathology in children with a CPI. Our results suggest that parents strongly influence child psychopathology, and interventions targeting parent distress may have beneficial downstream effects on child mental health. Specifically, findings support the implementation of family-centered care models that consider parents in the context of pediatric healthcare [78]. Screening parents for internalizing symptoms and parenting stress should be integrated into

pediatric care to facilitate the provision of resources that support parent mental health [79]. Moreover, screening should occur routinely, as our findings show that in addition to average levels, fluctuations in parent distress have a significant impact on child psychopathology symptoms.

Several meta-analyses have suggested that psychological interventions for parents (i.e., psychotherapy, psychoeducation) can lead to decreases in child psychopathology [80,81]. However, far less work has explored the effectiveness of psychological interventions in parents of a child with a CPI, and the effects on child mental health in this population have been mixed [82,83]. Bennett et al. (2021) investigated the impact of a drop-in centre for treating psychopathology symptoms in children with a CPI. Parents attending the centre reported reductions in internalizing symptoms at follow-up, however, improvements in parent symptoms were not accompanied by improvements in child symptoms [15]. Future research is needed to examine the effectiveness of interventions for parent distress on psychopathology in children with a CPI. Additionally, HCC may be a promising biomarker to identify children with a CPI who could benefit the most from supports and interventions that target parent distress. However, because this study examined trajectories over time as opposed to HCC measurements at a single time point, the clinical utility of HCC as an early screening tool remains to be established. Future research is needed to establish the predictive value of single HCC measurements and determine whether they can be used to identify children with a CPI at elevated risk.

Strengths, Limitations and Future Directions

The current study has several strengths, including the use of a large sample of children with diverse CPIs, increasing the generalizability of the results across a range of illnesses. The longitudinal design allowed us to disentangle the between- and within-dyad effects of parent

distress on child psychopathology. Separating these sources of variation provides important context for prevention and intervention efforts. Additionally, the longitudinal design allowed us to use previously identified HCC trajectories in this sample [50], and explore interactions between parent distress and HCC trajectory class. Previous studies exploring interactions between parent factors and child cortisol have been primarily cross-sectional, or limited to prospective designs with small samples and/or short follow-ups. Moreover, the person-centered nature of the HCC classes captures long-term heterogeneity in cortisol secretion, and is beneficial for identifying subgroups of children who may be the most responsive to interventions that target parent distress.

This study also has limitations. First, recruitment occurred at a single site, and the sample was relatively homogeneous with respect to socioeconomic indicators and ethnicity. Thus, findings may not be generalizable to diverse populations. Second, parents were predominantly mothers, which may limit the generalizability of findings to fathers. Relatedly, parent reports of child psychopathology were used, and research suggests that parent reports may differ from child self-reports [84]. In particular, depressed/anxious mothers often rate their children as having more psychopathology symptoms, and thus shared informant variance may have influenced reporting [85]. Future studies should utilize a multi-informant approach, including child, coparent, and teacher reports. Third, our sample included children as young as two years old, and the intended age range for the EBS is 4-17 years. However, previous work has validated the EBS Brief Version in the sample used in this study, and found no differences in psychometric properties when excluding children <4 years of age [86]. Fourth, because missing EBS data were associated with greater parent internalizing symptoms, the association between parent internalizing symptoms and child psychopathology may be underestimated. Fifth, sample sizes

within two of the HCC classes were small, which may have influenced our power to detect significant interactions. Future person-centered research should utilize larger samples to explore effects within smaller HCC trajectories. Finally, although findings align with traditional diathesis-stress/dual-risk models, more recent context-dependent theories, such as differential susceptibility [76] and biological sensitivity to context [87], have received considerable support. Both theories converge on the idea that vulnerability markers in children are not inherently maladaptive. Rather, children with high HCC may respond in a “for better and for worse” manner, experiencing worse outcomes when exposed to negative environments, but better outcomes when exposed to positive environments [76]. Thus, future work should explore how positive environmental influences, such as interventions for parent distress, may benefit children with a CPI following a hypersecretion trajectory.

6.6 Conclusions

Collectively, findings from this study support the examination of associations between parent distress and psychopathology in children with a CPI at multiple levels by exploring both between- and within-dyad effects. We found that higher average levels and fluctuations in parent internalizing symptoms and parenting stress were associated with greater child psychopathology symptoms. Additionally, child HCC moderated associations between average parent internalizing symptoms and parenting stress on child internalizing symptoms. Results suggest that children with a CPI following a cortisol hypersecretion trajectory may be particularly vulnerable when exposed to high average levels of parent internalizing symptoms and parenting stress, and that some cortisol trajectories may be protective. This work highlights the importance of examining parent distress, paired with child cortisol, to understand psychopathology risk in children with a CPI.

6.7 References

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6.8 Tables and Figures

Figure 1. Plot of mean ln-HCC values over time for each HCC trajectory class.

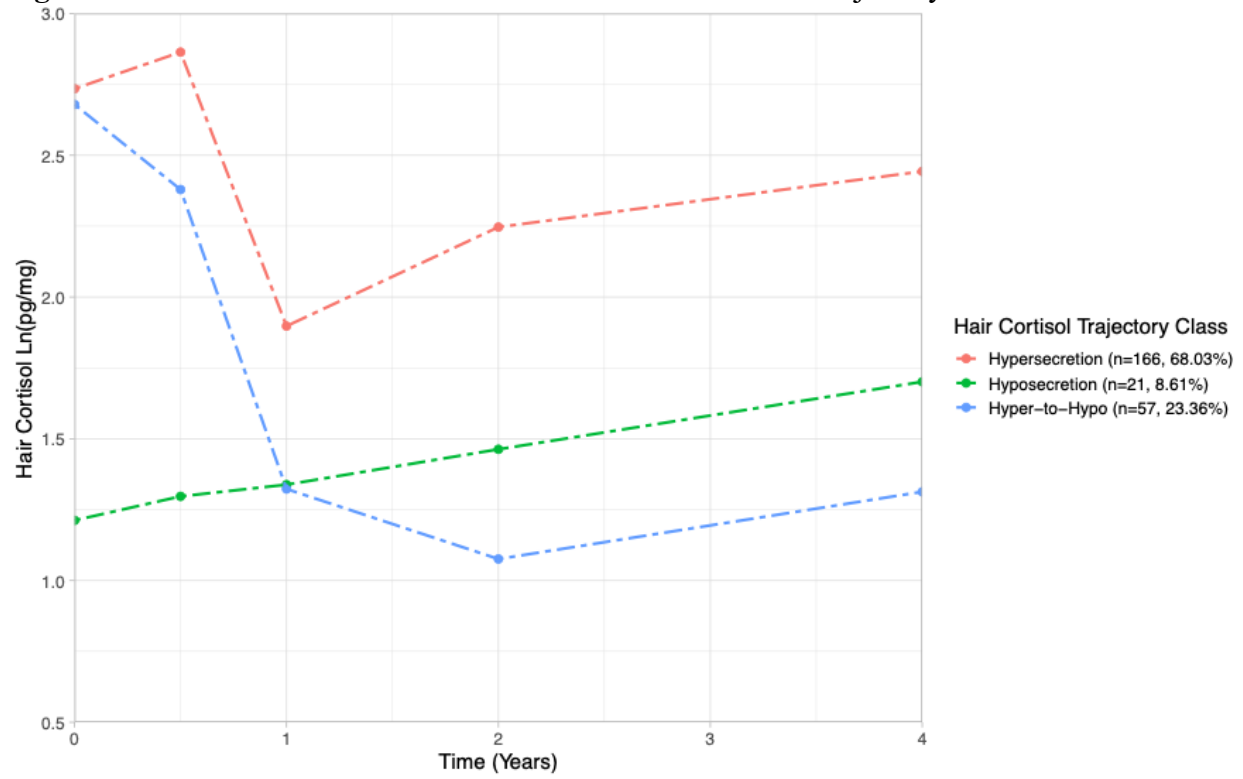


Table 1. Sample characteristics at baseline.

Characteristic	Total (n=244)
Child	
Age (years), mean (SD)	9.54 (4.17)
Female, n (%)	117 (47.95%)
CPI Type, n (%)	
Dermatological	19 (7.79%)
Endocrine	34 (13.93%)
Gastroenterological	33 (13.52%)
Hematological	27 (11.07%)
Neurological	10 (4.1%)
Respiratory	51 (20.9%)
Rheumatological	70 (28.69%)
Years since CPI diagnosis, mean (SD)	4.42 (4.08)
BMI percentile, mean (SD)	58.44 (29.73)
WHODAS 2.0, mean (SD)	19.31 (6.69)
Born in Canada, n (%)	230 (94.26%)
White, n (%)	198 (81.15%)
Internalizing Symptoms, mean (SD)	11.12 (9.32)
Externalizing Symptoms, mean (SD)	7.71 (6.69)
Parent	
Age (years), mean (SD)	40.55 (6.34)
Female, n (%)	219 (89.75%)
Biological parent, n (%)	240 (98.36%)
Born in Canada, n (%)	209 (85.66%)
Household income ≥\$90,000, n (%)	151 (61.89%)
Postsecondary graduate, n (%)	189 (77.46%)
Married/Common law, n (%)	212 (86.89%)
White, n (%)	210 (86.07%)
Parent Internalizing Symptoms, mean (SD)	14.93 (12.97)
Parenting Stress, mean (SD)	36.14 (8.72)

Supplementary Table 1. Descriptive statistics and correlations between variables across study time points.

Variable	N	Mean (SD)	Median [range]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. P-INT T1	243	14.9 (13.0)	11 [0-59]	1																		
2. P-INT T2	239	15.0 (14.1)	11 [0-70]	0.74***	1																	
3. P-INT T3	235	15.4 (13.7)	12 [0-74]	0.69***	0.71***	1																
4. P-INT T4	222	16.2 (13.1)	13 [0-56]	0.65***	0.72***	0.75***	1															
5. P-INT T5	191	16.5 (13.9)	13 [0-62]	0.57***	0.64***	0.65***	0.73***	1														
6. PSS T1	243	36.1 (8.7)	35 [18-65]	0.46***	0.38***	0.35***	0.38***	0.28***	1													
7. PSS T2	239	36.6 (9.3)	35 [18-73]	0.45***	0.51***	0.40***	0.45***	0.42***	0.74***	1												
8. PSS T3	235	36.4 (9.1)	36 [18-65]	0.42***	0.40***	0.46***	0.46***	0.37***	0.74***	0.76***	1											
9. PSS T4	222	35.4 (8.9)	34 [18-66]	0.39***	0.39***	0.41***	0.53***	0.47***	0.65***	0.75***	0.78***	1										
10. PSS T5	193	36.2 (9.7)	36 [18-64]	0.41***	0.43***	0.39***	0.53***	0.60***	0.62***	0.73***	0.68***	0.81***	1									
11. INT T1	243	11.1 (9.3)	9 [0-42]	0.48***	0.40***	0.34***	0.33***	0.25***	0.32***	0.31***	0.30***	0.24***	0.23**	1								
12. INT T2	239	10.2 (9.3)	7 [0-38]	0.38***	0.43***	0.36***	0.35***	0.26***	0.25***	0.29***	0.29***	0.23***	0.22**	0.80***	1							
13. INT T3	235	9.3 (9.1)	7 [0-46]	0.44***	0.45***	0.42***	0.47***	0.34***	0.30***	0.33***	0.34***	0.34***	0.31***	0.75***	0.81***	1						
14. INT T4	222	8.8 (8.0)	7 [0-42]	0.34***	0.35***	0.34***	0.41***	0.37***	0.20**	0.28***	0.24***	0.29***	0.31***	0.64***	0.70***	0.70***	1					
15. INT T5	192	10.1 (9.7)	7 [0-38]	0.31***	0.29***	0.25***	0.36***	0.38***	0.11	0.21**	0.16*	0.23**	0.30***	0.56***	0.57***	0.62***	0.66***	1				
16. EXT T1	243	7.7 (6.7)	6 [0-32]	0.35***	0.24***	0.23***	0.23***	0.16*	0.31***	0.26***	0.26***	0.24***	0.20**	0.57***	0.49***	0.45***	0.37***	0.30***	1			
17. EXT T2	239	7.3 (6.9)	6 [0-38]	0.34***	0.32***	0.32***	0.31***	0.26***	0.23***	0.32***	0.27***	0.27***	0.25***	0.50***	0.59***	0.46***	0.44***	0.31***	0.78***	1		
18. EXT T3	235	6.7 (6.2)	5 [0-33]	0.32***	0.30***	0.30***	0.34***	0.23**	0.29***	0.32***	0.33***	0.37***	0.28***	0.43***	0.50***	0.53***	0.42***	0.29***	0.77***	0.81***	1	
19. EXT T4	222	6.1 (6.2)	4 [0-38]	0.24***	0.26***	0.29***	0.34***	0.31***	0.27***	0.34***	0.30***	0.41***	0.37***	0.28***	0.38***	0.36***	0.49***	0.29***	0.63***	0.72***	0.78***	1
20. EXT T5	183	6.5 (6.3)	5 [0-40]	0.20**	0.27***	0.20**	0.30***	0.31***	0.17*	0.32***	0.19**	0.30***	0.32***	0.24**	0.27***	0.29***	0.37***	0.45***	0.53***	0.57***	0.62***	0.72***

Notes. P-INT = Parent Internalizing Symptoms; PSS = Parenting Stress; INT = Child Internalizing Symptoms; EXT = Child Externalizing Symptoms; T1 = Baseline; T2 = 6 months; T3 = 12 months; T4 = 24 months; T5 = 48 months.

* $p < .05$, ** $p < .01$, *** $p < .001$

Supplementary Table 2. Comparison of parent internalizing symptoms and parenting stress across HCC trajectory classes.

	HCC Trajectory Class			<i>p</i> -value
	Hypersecretion (n=166)	Hyposecretion (n=21)	Hyper-to-Hypo (n=57)	
	M (SD), Median [range]			
Parent Internalizing Symptoms (P-INT)				
Baseline	15.6 (13.6), 12 [0, 59]	14.3 (11.6), 9 [3, 47]	13.3 (11.6), 10 [0, 54]	.702
6 months	15.2 (14.6), 11 [0, 70]	15.0 (11.3), 12 [3, 50]	14.3 (13.6), 8 [0, 57]	.701
12 months	15.7 (14.2), 12 [0, 74]	14.0 (12.0), 13 [0, 38]	15.2 (12.9), 11 [0, 52]	.925
24 months	16.4 (13.9), 12.5 [0, 56]	15.6 (11.5), 13 [3, 44]	15.6 (11.6), 14 [0, 45]	.993
48 months	16.3 (14.6), 11 [0, 62]	18.1 (13.7), 13 [3, 51]	16.6 (12.4), 15 [0, 54]	.620
Parenting Stress (PSS)				
Baseline	36.5 (9.17), 36 [18, 65]	35.0 (9.22), 34 [21, 59]	35.5 (7.13), 35 [20, 51]	.546
6 months	36.9 (9.80), 36 [18, 73]	35.5 (9.05), 34 [20, 57]	36.2 (7.76), 34 [22, 55]	.800
12 months	36.9 (9.58), 37 [18, 65]	34.1 (8.00), 33 [19, 47]	35.9 (8.02), 36 [18, 56]	.378
24 months	36.1 (9.06), 35 [18, 66]	32.4 (8.33), 32 [19, 49]	34.4 (8.62), 32 [18, 53]	.160
48 months	36.6 (9.85), 36 [18, 64]	35.5 (5.89), 35 [24, 46]	35.6 (10.4), 34 [20, 63]	.689

Notes. *P*-values are from Kruskal-Wallis tests.

Figure 2. Model predicted evolution of child internalizing and externalizing symptoms over time. The shaded areas represent 95% confidence intervals.

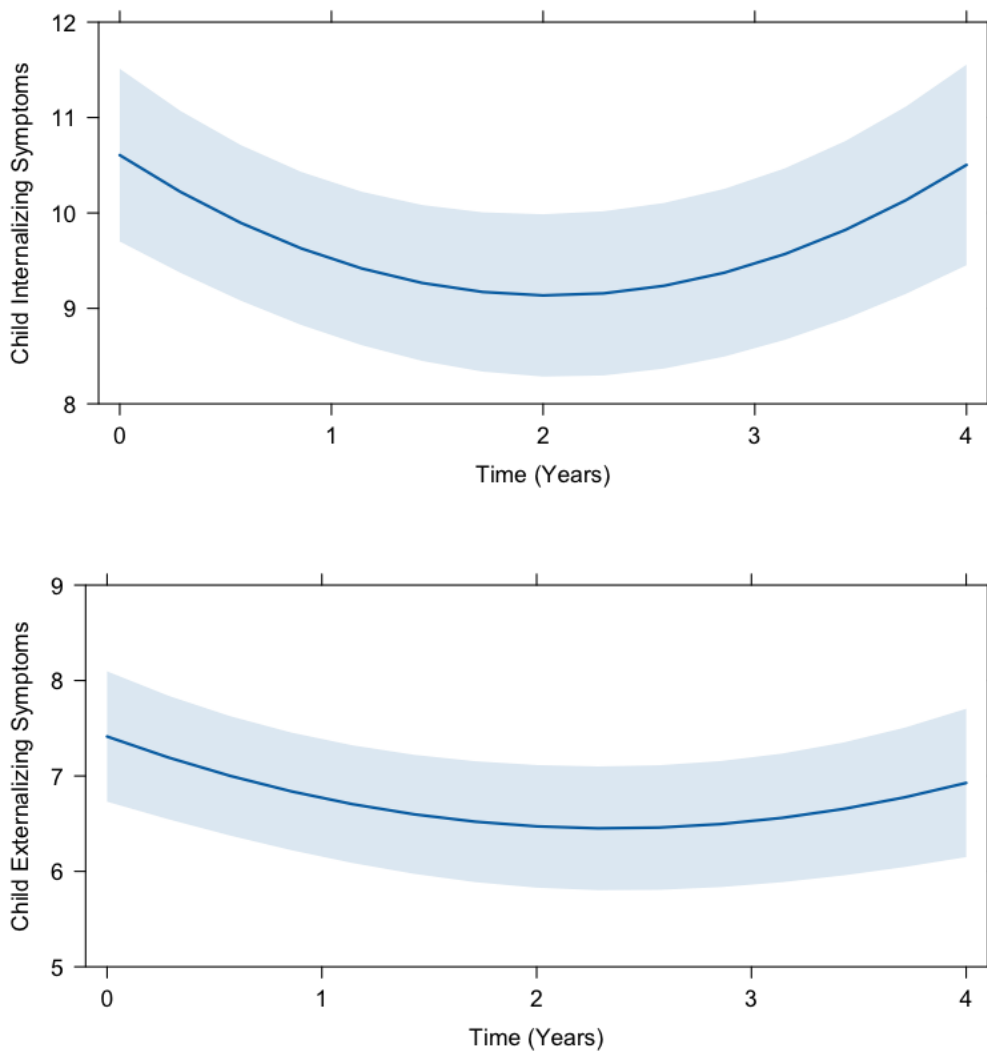


Table 2. LME models for internalizing symptoms.

	Internalizing, Model 1			Internalizing, Model 2			Internalizing, Model 3			Internalizing, Model 4		
Predictor	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
(Intercept)	7.60	4.72, 10.48	<.001	7.48	4.61, 10.36	<.001	7.22	4.36, 10.07	<.001	7.33	4.47, 10.20	<.001
Child Sex [Female]	0.57	-1.03, 2.17	.482	0.60	-1.00, 2.20	.463	0.70	-0.88, 2.28	.383	0.50	-1.11, 2.10	.544
Child Age	0.17	-0.09, 0.43	.205	0.17	-0.09, 0.43	.202	0.17	-0.09, 0.43	.206	0.14	-0.12, 0.40	.282
WHODAS 2.0	0.47	0.40, 0.55	<.001	0.47	0.40, 0.54	<.001	0.47	0.40, 0.54	<.001	0.47	0.40, 0.54	<.001
Years Since CPI Diagnosis	-0.03	-0.25, 0.19	.809	-0.02	-0.24, 0.20	.858	-0.04	-0.26, 0.17	.705	-0.02	-0.24, 0.20	.862
Parent Sex [Female]	2.13	-0.51, 4.77	.113	2.18	-0.46, 4.82	.105	2.37	-0.24, 4.97	.075	2.35	-0.28, 4.97	.080
Parent Age	-0.05	-0.22, 0.12	.557	-0.06	-0.22, 0.11	.523	-0.03	-0.20, 0.13	.692	-0.04	-0.21, 0.13	.669
Parent Relation [Non-biological]	-0.04	-6.43, 6.35	.990	0.14	-6.25, 6.52	.966	-0.80	-7.15, 5.54	.804	-0.68	-7.09, 5.73	.835
Parent Education [Postsecondary Graduate]	1.26	-0.23, 2.76	.097	1.39	-0.10, 2.88	.068	1.44	-0.04, 2.92	.056	1.46	-0.03, 2.95	.055
Household Income [$\geq 90K$]	0.65	-0.35, 1.66	.203	0.62	-0.39, 1.63	.227	0.62	-0.38, 1.62	.226	0.61	-0.40, 1.61	.235
BD P-INT	2.31	1.34, 3.29	<.001	2.35	1.37, 3.32	<.001	2.98	1.92, 4.04	<.001	2.37	1.39, 3.34	<.001
WD P-INT	0.63	0.33, 0.93	<.001	1.08	0.48, 1.68	<.001	1.09	0.49, 1.69	<.001	1.08	0.48, 1.68	<.001
BD PSS	0.50	-0.43, 1.43	.295	0.50	-0.44, 1.43	.297	0.48	-0.44, 1.40	.308	0.92	-0.12, 1.95	.082
WD PSS	0.18	-0.11, 0.48	.223	0.16	-0.13, 0.46	.282	0.16	-0.13, 0.46	.284	0.16	-0.13, 0.46	.283
HCC Class [Hyposecretion]	-0.87	-3.79, 2.04	.556	-0.91	-3.82, 2.00	.539	-0.89	-3.76, 1.98	.542	-1.48	-4.45, 1.49	.328
HCC Class [Hyper-to-Hypo]	-2.36	-4.24, -0.48	.014	-2.35	-4.23, -0.47	.014	-2.41	-4.26, -0.56	.011	-2.43	-4.30, -0.56	.011
Time	-1.44	-2.10, -0.79	<.001	-1.42	-2.07, -0.76	<.001	-1.42	-2.08, -0.76	<.001	-1.42	-2.08, -0.76	<.001
Time ²	0.35	0.20, 0.51	<.001	0.34	0.18, 0.49	<.001	0.34	0.19, 0.49	<.001	0.34	0.18, 0.49	<.001
WD P-INT x Time				-1.09	-1.96, -0.22	.014	-1.10	-1.97, -0.22	.014	-1.09	-1.96, -0.22	.015
WD P-INT x Time ²				0.30	0.09, 0.51	.005	0.30	0.09, 0.51	.005	0.30	0.09, 0.51	.005
BD P-INT x HCC Class [Hyposecretion]							-3.21	-6.27, -0.14	.040			
BD P-INT x HCC Class [Hyper-to-Hypo]							-2.28	-4.26, -0.30	.024			
BD PSS x HCC Class [Hyposecretion]										-3.24	-6.41, -0.07	.045
BD PSS x HCC Class [Hyper-to-Hypo]										-1.16	-3.20, 0.87	.263
Random Effects												
Intercept	39.25			39.01			37.73			38.14		
Slope (Time)	1.89			1.85			1.86			1.85		
Residual	15.27			15.20			15.20			15.20		
ICC	0.71			0.71			0.70			0.71		
Marginal R ² /Conditional R ²	0.349 / 0.810			0.353 / 0.812			0.366 / 0.812			0.360 / 0.812		

Notes. BD = Between-dyad; WD = Within-dyad; P-INT= Parent Internalizing Symptoms; PSS = Parenting Stress. Reference group for HCC Class is Hypersecretion. Child Age, WHODAS 2.0, Years Since CPI Diagnosis, and Parent Age are centred at the mean value.

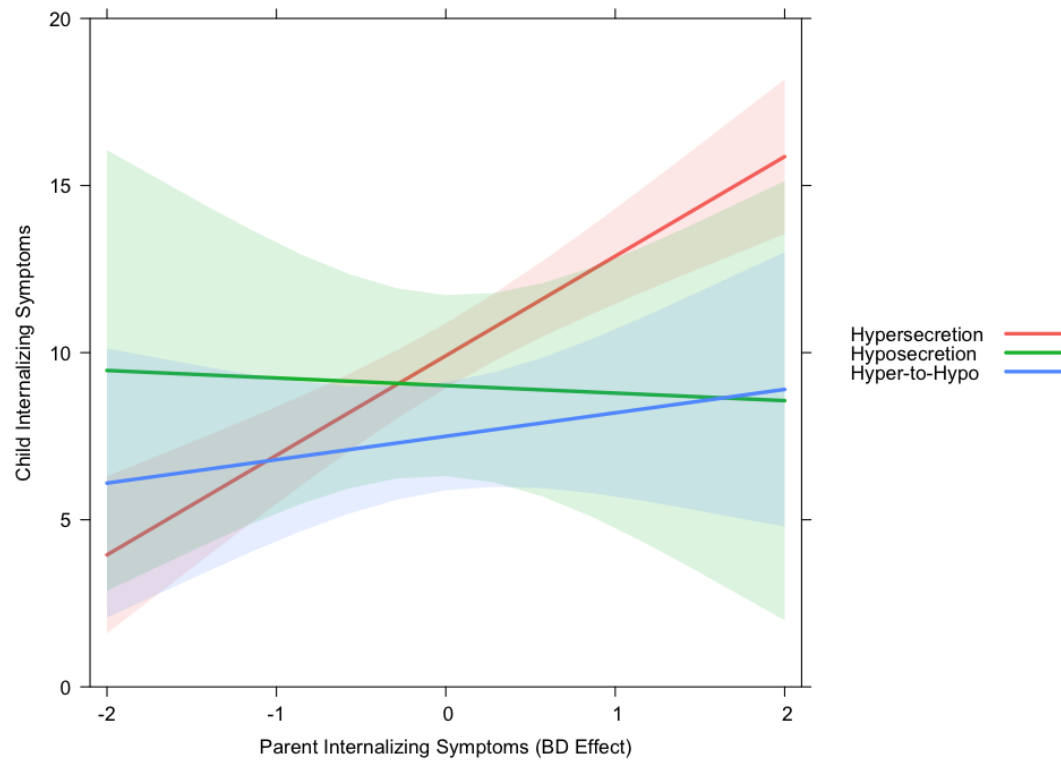
Table 3. LME models for externalizing symptoms.

Predictor	Externalizing, Model 1		
	B	95% CI	p-value
(Intercept)	8.45	6.25, 10.65	<.001
Child Sex [Female]	-2.82	-4.05, -1.58	<.001
Child Age	0.05	-0.15, 0.25	.637
WHODAS 2.0	0.23	0.18, 0.28	<.001
Years Since CPI Diagnosis	0.09	-0.08, 0.26	.284
Parent Sex [Female]	1.20	-0.84, 3.24	.247
Parent Age	-0.05	-0.18, 0.08	.475
Parent Relation [Non-biological]	9.03	4.10, 13.95	<.001
Parent Education [Postsecondary Graduate]	-0.25	-1.34, 0.84	.655
Household Income [$\geq 90K$]	-0.21	-0.92, 0.50	.554
BD P-INT	1.23	0.48, 1.99	.001
WD P-INT	0.16	-0.05, 0.37	.133
BD PSS	0.92	0.20, 1.64	.013
WD PSS	0.34	0.14, 0.54	.001
HCC Class [Hyposecretion]	-1.55	-3.80, 0.70	.176
HCC Class [Hyper-to-Hypo]	-1.92	-3.37, -0.47	.010
Time	-0.82	-1.27, -0.37	<.001
Time ²	0.17	0.07, 0.28	.001
Random Effects			
Intercept	23.62		
Slope (Time)	0.93		
Residual	7.09		
ICC	0.76		
Marginal R ² /Conditional R ²	0.304 / 0.832		

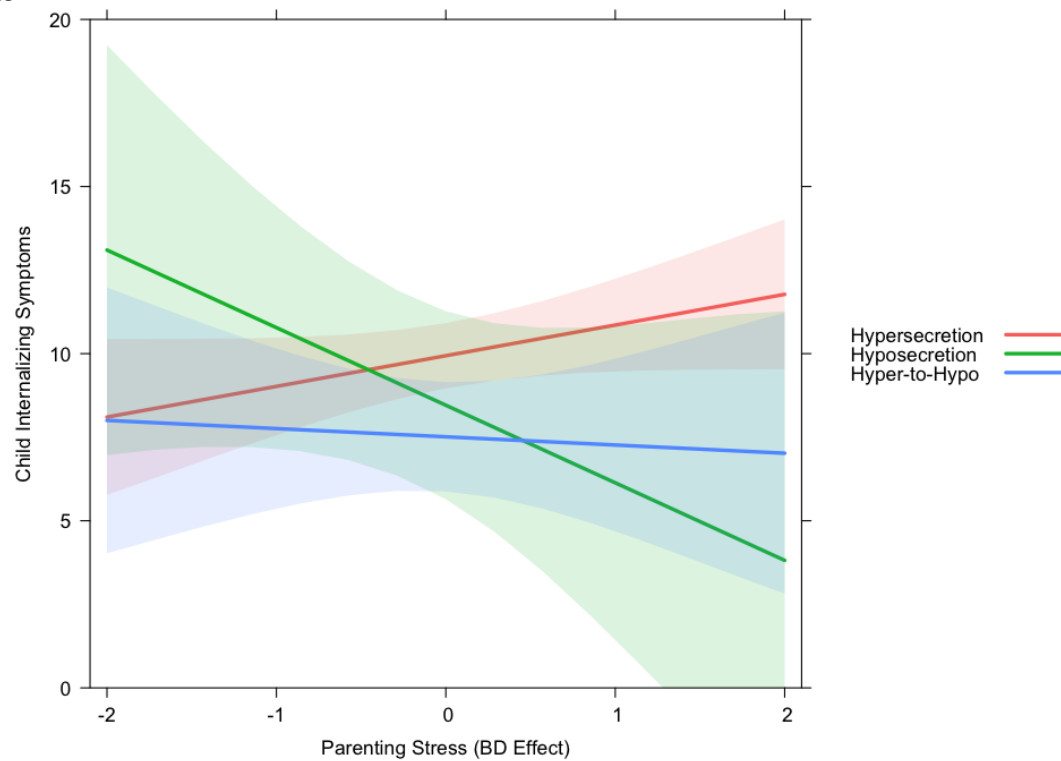
Notes. BD = Between-dyad; WD = Within-dyad; P-INT= Parent Internalizing Symptoms; PSS = Parenting Stress. Reference group for HCC Class is Hypersecretion. Child Age, WHODAS 2.0, Years Since CPI Diagnosis, and Parent Age are centred at the mean value.

Figure 3. Interactions between HCC class and parent internalizing symptoms and parenting stress (BD effects) on child internalizing symptoms. The shaded areas represent 95% confidence intervals.

a



b



Chapter 7 – Study 3

Longitudinal relationship between hair cortisol and quality of life in children with a chronic physical illness: The mediating role of psychopathology

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7.1 Overview

Purpose: Chronic physical illnesses (CPIs) affect nearly half of children. Managing a CPI may be stressful and can lead to psychopathology and poor health-related quality of life (HRQoL). Hair cortisol concentration (HCC) is a biomarker of chronic stress, and evidence suggests that cortisol hypersecretion is associated with psychopathology. However, the extent to which HCC is associated with HRQoL is unclear. This study investigated associations between HCC and HRQoL in children with a CPI, and examined mediating effects of psychopathology. **Methods:** Data come from 244 children (2-16 years) with a CPI who were followed for 48 months. Children provided hair samples, and parents reported child psychopathology (Emotional Behavioural Scales) and five domains of HRQoL (KIDSCREEN-27). Previous work identified three HCC trajectories among children: Hypersecretion (68.0%), Hyposecretion (8.6%), and Hyper-to-Hypo (23.4%). Latent growth curve models estimated associations between HCC trajectories and HRQoL and potential mediating effects of psychopathology. **Results:** Children following a Hyper-to-Hypo trajectory had lower psychopathology compared to the Hypersecretion trajectory, which in turn was associated with higher HRQoL in the domains of parents and autonomy ($\beta=0.102, p<.001$), social support and peers ($\beta=0.069, p=.011$), and school environment ($\beta=0.098, p=.001$). Children following a Hyposecretion trajectory had higher HRQoL in the physical well-being domain ($\beta=0.142, p=.024$), compared to the Hypersecretion trajectory. **Conclusions:** Findings suggest that cortisol hypersecretion may be linked to lower HRQoL in children with a CPI, with greater psychopathology acting as a potential mediating mechanism. Interventions aimed at reducing stress and psychopathology may be effective at improving HRQoL in this population.

Keywords: hair cortisol, children, physical illness, psychopathology, quality of life

7.2 Introduction

Chronic physical illnesses (CPIs; e.g., epilepsy, asthma, diabetes) affect approximately 30-50% of children, and are often associated with diverse functional limitations and psychosocial consequences [1]. Having a CPI during childhood impacts a child's ability to interact with their physical and social environment, which can lead to impaired health and well-being, including health-related quality of life (HRQoL) [2]. HRQoL in children is a multidimensional construct that encompasses perceived physical and psychological well-being, level of autonomy, and feelings of acceptance by society and peers [2]. It is well-known that children with a CPI experience worse HRQoL compared to healthy children [3,4]. As a result, HRQoL in pediatric healthcare has been increasingly recognized as an important clinical outcome, and its assessment is fundamental for monitoring health and treatment effects, understanding illness-related burdens, and guiding medical decision-making [3,5]. Thus, exploring predictors of HRQoL in children with a CPI is critical to the development of targeted and effective interventions for improving HRQoL [3].

Children living with a CPI may be exposed to significant illness-related stressors (e.g., exacerbations, treatments, hospitalizations) [6], and childhood stress (e.g., negative life events, adverse experiences, perceived stress) has been identified as a risk factor for impaired HRQoL [7–10]. Cortisol is a glucocorticoid hormone secreted by the hypothalamic-pituitary adrenal (HPA) axis in response to stress [11]. Chronic stress exposure can lead to HPA-axis dysregulation and result in hypersecretion or hyposecretion of cortisol over time [12]. Hair cortisol concentration (HCC) has been identified as a valuable biomarker of chronic HPA-axis dysregulation in children, as the most proximal 3 cm of hair to the scalp reflects average cortisol secretion over the past three months [13,14]. Previous research has found evidence of HPA-axis

dysregulation, as quantified by HCC, in children exposed to chronic stressors [15–17], including childhood CPI [18]. However, very few studies have examined the relationship between HCC and HRQoL in children. Fuchs et al. (2020) found no association between HCC and HRQoL in healthy children aged 5 to 12 years [19]. Similarly, Geber et al. (2017) found no association between HCC and HRQoL in 6- to 8-year-old schoolchildren [19,20]. Buchan et al. (2021), however, found a negative association between HCC and HRQoL in children with a CPI experiencing comorbid psychopathology, but only in the domain of social support and peers [21].

Robust evidence shows that children with a CPI exhibit an elevated risk of developing psychopathology compared to their healthy peers [22–25]. Psychopathology in children is strongly linked to impaired HRQoL [26–28], and studies suggest that children with a CPI experiencing comorbid psychopathology experience worse HRQoL compared to children with a physical illness only [29–32]. Dysregulation of the HPA-axis has been reported in children with a mental disorder [33–35], and HCC has been increasingly explored as an early risk factor for the development of child psychopathology. Preliminary evidence suggests that cortisol hypersecretion, as quantified by HCC, is associated with increased psychopathology in children with a CPI [18,36]. Thus, these findings may suggest that HPA-axis dysregulation in children with a CPI contributes to increased psychopathology, which in turn leads to impaired HRQoL.

Previous studies have found significant mediating effects of internalizing psychopathology symptoms (i.e., depression and anxiety) on the relationship between illness-related stressors (i.e., disease severity, pain intensity, presence of symptoms) and HRQoL in children with a CPI [37–41]. To date, however, no studies have explored the mediating role of psychopathology on the longitudinal relationship between HPA-axis dysregulation and HRQoL

in healthy or chronically ill children. Clarifying these associations can inform the development of interventions to improve HRQoL in children with a CPI. Thus, the aims of this study were to (1) explore longitudinal associations between HCC and HRQoL in children with a CPI, and (2) examine psychopathology as a potential mechanism through which HCC influences HRQoL in this population.

7.3 Methods

Study Sample and Procedures

Data come from the Multimorbidity in Children and Youth Across the Life-course (MY LIFE) study, a prospective study of 263 children (2 to 16 years old at enrolment) with a CPI. Methodological details of the MY LIFE sample have been described previously [42,43]. Chronic physical illnesses were defined as physician-diagnosed conditions expected to last for ≥ 12 months and result in ≥ 1 of: functional limitations, dependencies, or additional healthcare use. Children and their primary caregiving parent/guardian were recruited from outpatient clinics at a pediatric hospital in Canada and followed for 48 months (assessments at baseline, 6, 12, 24, and 48 months). Informed consent was obtained from all participants, and study approval was obtained from the relevant research ethics boards.

Measures

Hair cortisol: Initially, research staff collected hair from children by cutting approximately 80 strands from the posterior vertex, as close to the scalp as possible. Due to the COVID-19 pandemic, hair samples were collected by parents in the homes of participants beginning in March 2020 and continued thereafter. Detailed collection instructions were sent to participants, and hair samples were placed in a bag and sent to the investigators by mail. The first 3 cm of each sample was analyzed by enzyme-linked immunosorbent assays using the High

Sensitivity Salivary Cortisol Immunoassay Kit (Salimetrics, Pennsylvania), according to the manufacturer's instructions. The process for collection and extraction followed previously published procedures [44]. The intra- and inter-assay coefficients of variation were 8.2% and 6.2%, respectively. Cortisol levels are expressed as pg/mg hair. A natural log-transformation was applied to account for positive skew. Of the 263 children enrolled in MY LIFE, 244 provided at least one valid hair sample and were included in the analyses. Missing hair data was associated with lower household income ($\chi^2(1)=4.66, p=.031$), but was not associated with any of the other variables in this study.

Health-related Quality of Life: Child HRQoL was assessed using the parent-reported KIDSCREEN-27 [45]. The KIDSCREEN-27 is a 27-item scale designed to measure HRQoL across five domains: physical well-being (i.e., physical activity and energy), psychological well-being (i.e., mood and life satisfaction), parents and autonomy (i.e., free time and parental support), social support and peers (i.e., interactions and support from friends), and school environment (i.e., school enjoyment and cognitive capacity) [46]. Items are scored on a 5-point scale, and scores are summed to obtain a score for each domain. Domain scores are transformed into T-scores ($M=50, SD=10$), where higher scores indicate better HRQoL [45]. The KIDSCREEN-27 has been validated in children with a physical illness and demonstrates adequate parent-child agreement [47]. Internal consistency in our sample ranged from $\alpha=0.77$ for parents and autonomy to $\alpha=0.89$ for physical well-being.

Psychopathology: Child psychopathology was measured using the Emotional Behavioural Scales (EBS) [48,49]. The EBS is a 52-item parent-report checklist that measures symptoms of major depressive disorder, generalized anxiety disorder, separation anxiety disorder, social phobia, attention-deficit hyperactivity disorder, oppositional defiant disorder, and

conduct disorder over the past six months. Items are scored on a 3-point scale, and scores are summed to generate a total psychopathology score. Higher scores on the EBS indicate a greater severity or frequency of symptoms. Internal consistency in our sample was excellent ($\alpha=0.94$).

Sociodemographic and clinical characteristics: Data were collected on child and parent age, sex, race, and country of birth, as well as parental marital status, education level, and annual household income. Parents also reported the time since their child's CPI diagnosis (years). The 12-item World Health Organization Disability Assessment Schedule (WHODAS) 2.0 was used to measure child disability [50]. Parents rated items on a 5-point scale, and items were summed to calculate a total score, whereby higher scores indicate greater disability. The WHODAS 2.0 has demonstrated excellent psychometric properties in children with a CPI [51], and internal consistency in our sample was good ($\alpha=0.87$).

Statistical Analyses

This study is an extension of previous work using MY LIFE data that identified trajectories of HCC among children with a CPI using latent class growth analysis [18]. Methodological details for the identification of the HCC trajectory classes have been described previously [18]. Three HCC trajectories were identified: Hypersecretion (68.0%), Hyposecretion (8.6%), and Hyper-to-Hypo (23.4%) (see Fig. 1).

Latent growth curve models (LGCs) were used to examine the longitudinal relations between study variables. This analysis allowed us to examine the growth trajectories of psychopathology and HRQoL simultaneously, and is recommended to evaluate mediational processes when the mediator and outcome variables change over time [52]. In general, LGCs consist of a latent intercept and a latent slope factor. In the current study, scores at baseline, 6, 12, 24, and 48 months were rescaled to be 0, 0.5, 1, 2, and 4, respectively. Thus, the latent

intercepts represented mean scores at baseline, and the latent slopes represented change in scores from baseline to 48 months. Longitudinal mediation was investigated using the steps suggested by Cheong et al. (2003).

First, unconditional LGCMs for psychopathology and HRQoL were specified to determine the optimal shape of the trajectories (i.e., linear or quadratic). Once the best-fitting unconditional models were chosen, HCC trajectory class (dummy-coded) and relevant baseline covariates were included as predictors of each latent growth factor to estimate the conditional models. Baseline covariates included child sex and age, years since CPI diagnosis, disability (WHODAS 2.0), parent sex and age, household income, and parent education. Second, the conditional LGCMs of psychopathology and HRQoL were combined into five parallel process models for each HRQoL domain to examine covariances between the latent growth factors of psychopathology and HRQoL. Finally, the parallel process models were used to test for mediation, such that HCC class predicted the psychopathology intercept or slope factor, which then predicted the HRQoL intercept or slope factor (see Fig. 2). Separate mediation models were tested for each of the five HRQoL domains, and indirect effects were tested using the product of coefficients method [53].

Models were fit with a robust maximum likelihood estimator, which accounts for non-normality. Missing data were accommodated with full-information maximum likelihood estimation, which uses all available data under the assumption of missing at random. Out of the 244 participants, 157 (64.3%) had complete data at all five time points, and 87 (35.7%) had missing psychopathology or HRQoL data. Missing data were associated with older child age ($W=5456.5, p=.009$), lower household income ($\chi^2(1)=10.17, p=.001$), and lower parent education ($\chi^2(1)=12.13, p<.001$). Models were considered to have good fit to the data if the

Comparative Fit Index (CFI) ≥ 0.90 , and Root Mean Square Error of Approximation (RMSEA) and Standardized Root Mean-square Residual (SRMR) ≤ 0.08 [54]. Model fit was considered adequate if two of the three fit indices met the pre-defined thresholds. All analyses were conducted in R version 4.5.1 using the “lavaan” package [55].

7.4 Results

Sample Characteristics

The baseline characteristics of the sample are presented in Table 1. Children had a mean age of 9.5 years (SD=4.2), and 117 (48.0%) were female. One-quarter of children (25%) represented new-onset cases of CPI (duration <1 year), and the mean time since CPI diagnosis was 4.4 years (SD=4.1). Parents had a mean age of 40.6 years (SD=6.3), and 219 (89.8%) were female. Most parents were married/common law (86.9%), post-secondary graduates (77.5%), and had a household income equal to or above the provincial median of \$90,000 CAD (61.9%). Descriptive statistics and correlations between psychopathology and HRQoL are presented in Supplementary Table S1.

Unconditional LGCMs

Unconditional LGCMs suggested that a quadratic growth curve was the best-fitting model for all variables, other than psychological well-being and school environment. Quadratic growth models were able to converge and fit best when the variance of the quadratic slopes were set to 0. The results from the increasingly complex unconditional models are presented in Supplementary Table S2.

Conditional LGCMs

The values for the latent growth factors along with the fit statistics for the conditional models are presented in Table 2. Model fit for all variables was good, except for the model for

social support and peers, which did not meet the cutoff criteria for CFI. However, both the RMSEA and SRMR indicated good fit, suggesting that the model provided an adequate fit to the data.

Associations between HCC class and the latent growth factors of each variable are presented in Table 3. There was a significant effect of the Hyper-to-Hypo class on the psychopathology intercept ($\beta=-0.179, p<.001$), suggesting that children in this class had lower psychopathology at baseline compared to the Hypersecretion class. There was a significant effect of the Hyposecretion class on the physical well-being intercept ($\beta=0.144, p=.026$), suggesting that children in this class had higher HRQoL at baseline compared to the Hypersecretion class. There were significant effects of the Hyper-to-Hypo class on the intercepts of psychological well-being ($\beta=0.141, p=.011$), social support and peers ($\beta=0.236, p=.008$), and school environment ($\beta=0.150, p=.013$), suggesting that children in this class had higher HRQoL at baseline compared to the Hypersecretion class. There was also a significant effect of the Hyper-to-Hypo class on the linear ($\beta=-0.589, p=.049$) and quadratic ($\beta=0.807, p=.045$) slopes of social support and peers, suggesting that children in this class, after an initial period of steeper decline, experienced greater increases in HRQoL compared to the Hypersecretion class. There were no other significant effects of HCC class on the intercepts or slopes of psychopathology and HRQoL. Covariate effects from the conditional models are presented in Supplementary Table S3.

Parallel Process Models

Covariances between each of the latent growth factors of psychopathology and HRQoL from the parallel process models are presented in Table 4. There was significant misspecification in the parallel process model of psychopathology and psychological well-being due to the high

covariance between the latent slope factors (i.e., the correlation between latent slopes was below -1). Thus, the model was re-specified by restricting the covariance between the latent slopes to zero (see Table 4). Model fit was good for all variables, except for psychological well-being, which did not meet the cutoff criteria for CFI and RMSEA. Thus, we proceeded to the final step to test for mediation in all HRQoL domains, except for psychological well-being.

The psychopathology intercept was negatively associated with the intercepts of physical well-being ($Est. = -0.168, p = .035$), psychological well-being ($Est. = -0.515, p < .001$), parents and autonomy ($Est. = -0.515, p < .001$), social support and peers ($Est. = -0.339, p = .001$), and school environment ($Est. = -0.511, p < .001$), indicating that higher baseline psychopathology was associated with lower baseline HRQoL. The psychopathology intercept was positively associated with the parents and autonomy slope ($Est. = 0.359, p = .030$), indicating that higher baseline psychopathology was associated with increases in HRQoL. The parents and autonomy intercept was positively associated with the psychopathology slope ($Est. = 0.255, p = .011$), indicating that higher baseline HRQoL was associated with increases in psychopathology. Finally, the psychopathology slope was negatively associated with the slopes of physical well-being ($Est. = -0.493, p = .002$), parents and autonomy ($Est. = -0.875, p < .001$), social support and peers ($Est. = -0.922, p < .001$), and school environment ($Est. = -0.799, p < .001$), indicating that increases in psychopathology were associated with decreases in HRQoL.

Mediation Models – Indirect Effects Through Psychopathology

Model fit information and parameter estimates from the mediation models are presented in Table 5. All mediation models resulted in good fit to the data. There were significant indirect effects of the Hyper-to-Hypo class on the intercepts of parents and autonomy ($\beta = 0.102, p < .001$), social support and peers ($\beta = 0.069, p = .011$), and school environment ($\beta = 0.098, p = .001$), through

the psychopathology intercepts. This suggests that being in the Hyper-to-Hypo class is associated with lower baseline psychopathology, which in turn is associated with higher baseline HRQoL compared to the Hypersecretion class. There were no significant indirect effects of HCC class on the intercept of physical well-being through the intercept of psychopathology. However, there was a significant direct effect of the Hyposecretion class on the physical well-being intercept ($\beta=0.142$, $p=.024$), suggesting that children in this class had higher baseline HRQoL compared to the Hypersecretion class, controlling for psychopathology. There were no significant indirect effects of HCC class on the slopes of HRQoL through the slopes of psychopathology.

Sensitivity Analysis

Two sensitivity analyses were conducted to support the main findings. First, to examine reverse mediated effects, model mediation paths were respecified (i.e., HCC class $\rightarrow$ HRQoL $\rightarrow$ Psychopathology). There were no statistically significant indirect effects in any of the reverse mediation models. Second, to examine if the mediated effects persisted over 48 months and to establish temporal precedence, models were respecified where the psychopathology intercepts represented the mean value at 24 months, and the HRQoL intercepts represented the mean value at 48 months. The sensitivity analysis yielded results that were consistent with the main analyses. Specifically, the indirect effects of the Hyper-to-Hypo class on the HRQoL intercepts through the psychopathology intercepts remained significant for parents and autonomy ($\beta=0.048$, 95% CI [0.003, 0.093], $p=.038$), social support and peers ($\beta=0.062$, 95% CI [0.001, 0.122], $p=.042$), and school environment ($\beta=0.072$, 95% CI [0.003, 0.140], $p=.046$), and remained non-significant for physical well-being ($\beta=0.033$, 95% CI [0.000, 0.067], $p=.054$).

7.5 Discussion

To our knowledge, this is the first study to examine longitudinal associations between HCC and HRQoL in children with a CPI, and explore the potential mediating role of psychopathology. We found that children following a decreasing HCC trajectory (i.e., Hyper-to-Hypo) had higher HRQoL at baseline compared to children following a consistently elevated HCC trajectory (i.e., Hypersecretion) in the domains of parents and autonomy, social support and peers, and school environment. Moreover, these effects were mediated by psychopathology. Specifically, lower baseline psychopathology contributed to higher baseline HRQoL for children in the Hyper-to-Hypo versus the Hypersecretion HCC class. Additional findings from the sensitivity analyses supported the temporal precedence of the mediation pathway, and confirmed that the mediated effects were not restricted to the baseline assessment, and persisted across the duration of the study.

These findings are consistent with and expand upon previous work that found that higher HCC was associated with lower HRQoL in the domain of social support and peers in children with a CPI experiencing comorbid psychopathology [21]. Children with a CPI exposed to repeated stressors may develop maladaptive HPA-axis stress responses that can result in cortisol hypersecretion over time. Previous research has shown that cortisol hypersecretion in children, as measured through HCC, is associated with greater psychopathology [56–59]. Experiencing psychopathology during childhood can have a considerable impact on children's emotional well-being, life satisfaction, participation in activities, social relationships, and school performance, which can negatively impact HRQoL [60]. A wide body of literature has reported that psychopathology has detrimental effects on children's HRQoL, especially in children with a CPI [29–32].

Overall, these results suggest that cortisol hypersecretion may be associated with lower HRQoL in children with a CPI, and psychopathology may be a key mechanism through which cortisol hypersecretion is linked to impaired HRQoL in this population. Conversely, children with a CPI following a more adaptive decreasing cortisol trajectory may be at a reduced risk of psychopathology, and thus experience better HRQoL. This adaptive profile of HPA-axis functioning may be a marker of underlying genetic or physiological resilience to stress [61,62]. Such underlying resilience may help to explain why children in the Hyper-to-Hypo class already exhibited lower psychopathology, and thus higher HRQoL, at baseline before the decline in HCC was observed.

Additionally, we found that children following a consistently low HCC trajectory (i.e., Hyposecretion) had higher baseline HRQoL in the physical well-being domain compared to children in the Hypersecretion class, an effect not mediated by psychopathology. This finding suggests that while psychopathology explains part of the association between HPA-axis dysregulation and HRQoL, cortisol hypersecretion is also linked to lower HRQoL in some domains through mechanisms independent of psychopathology. Theoretical models suggest that chronically elevated cortisol levels lead to *wear and tear* on the body and brain, which can negatively impact physical health, cognitive performance, social engagement, and emotional regulation [35,63]. Cumulatively, these effects may explain part of the association between cortisol hypersecretion and lower HRQoL in children with a CPI, independent of its association through psychopathology.

Although we did not find that HPA-axis dysregulation was associated with change over time in HRQoL, findings of this study indicate that increases in psychopathology over 48 months were associated with decreases in HRQoL in children with a CPI. This aligns with findings from

Otto et al. (2017), who found that increasing mental health problems over 2 years was associated with decreasing overall HRQoL in a population-based study of children aged 7 to 17 years [26]. These findings underscore the importance of considering psychopathology as a key risk factor for impaired HRQoL in children with a CPI. Future research should explore whether interventions aimed at treating symptoms of psychopathology may lead to improvements in HRQoL in this population.

Clinically, the findings of this study have practical implications for the development of interventions to improve HRQoL in children with a CPI. Meta-analyses have suggested that psychological interventions, such as cognitive behavioural therapy, may be effective in reducing symptoms of anxiety and depression in children with a CPI [64,65]. Importantly, some psychological interventions have been shown to improve HRQoL in children with a CPI, in addition to reducing symptoms of psychopathology [66,67]. However, the results of this study suggest that interventions aimed at improving HRQoL in children may be the most effective when psychopathology and HPA-axis dysregulation are jointly addressed. Specifically, interventions aimed at reducing stress levels in children with a CPI may lead to reductions in psychopathology and improvements in HRQoL. Preliminary research has shown that meditation and mindfulness-based training for children and their parents can reduce HCC levels in healthy children [68,69]. Studies in children with chronic illnesses have shown that nature-based and guided imagery interventions can reduce salivary cortisol levels in the short-term [70,71]. Future research should examine whether stress-reduction interventions can reduce hair cortisol levels in children with a CPI, and whether these changes are linked to improvements in mental health and HRQoL.

Strengths and Limitations

This study has several important strengths. First, this study included a large sample of children with diverse CPIs, increasing the generalizability of the findings across a range of chronic illnesses. Second, measurement of cortisol from hair overcomes the inherent limitations and burdens of using subjective stress questionnaires or invasive short-term stress biomarkers (e.g., urine, saliva) [13]. Third, the person-centered nature of the HCC trajectories accounts for heterogeneity in HCC patterns over time, and is beneficial for identifying subgroups of children who may be at high risk of experiencing poor HRQoL. Finally, the longitudinal data from this study covered a period of four years, and longitudinal studies investigating predictors of change in HRQoL in children are scarce.

The results of this study must be interpreted in light of the following limitations. First, the lack of ethnic and sociodemographic diversity within the sample may limit the generalizability of the results to diverse and marginalized populations. Second, only parent-reported data were used, and previous studies have reported discrepancies between parent- and child-reported psychopathology and some domains of HRQoL in children with a CPI [29,72]. Thus, future research would benefit from using a multi-informant approach. Third, the small sample size of the Hyposecretion HCC class ($n=21$) may have influenced our power to detect significant mediating effects for this group. Fourth, it was not possible to explore the distinct mediating effects of internalizing and externalizing psychopathology due to nonconvergence of the LGCMs when these domains were considered separately (data not shown). Finally, the present findings are not sufficient to establish causal relations among variables, and it is possible that other unmeasured mediators may better explain the relationship between HCC and HRQoL in children.

7.6 Conclusions

Overall, the findings from this study highlight the importance of considering HPA-axis dysregulation and psychopathology as key risk factors for impaired HRQoL in children with a CPI. Specifically, cortisol hypersecretion may contribute to poor HRQoL in this population, with greater psychopathology acting as a potential mediating mechanism. As such, it is crucial to routinely screen for psychopathology and monitor stress levels in children with a CPI. Given that children are often unreliable self-reporters of their stress, HCC could be used to identify those in need of intervention, though further research is needed to clarify its clinical utility. Holistic interventions aimed at reducing stress and symptoms of psychopathology may be the most effective at improving HRQoL in children with a CPI.

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7.8 Tables and Figures

Figure 1. Mean HCC over time for each trajectory class

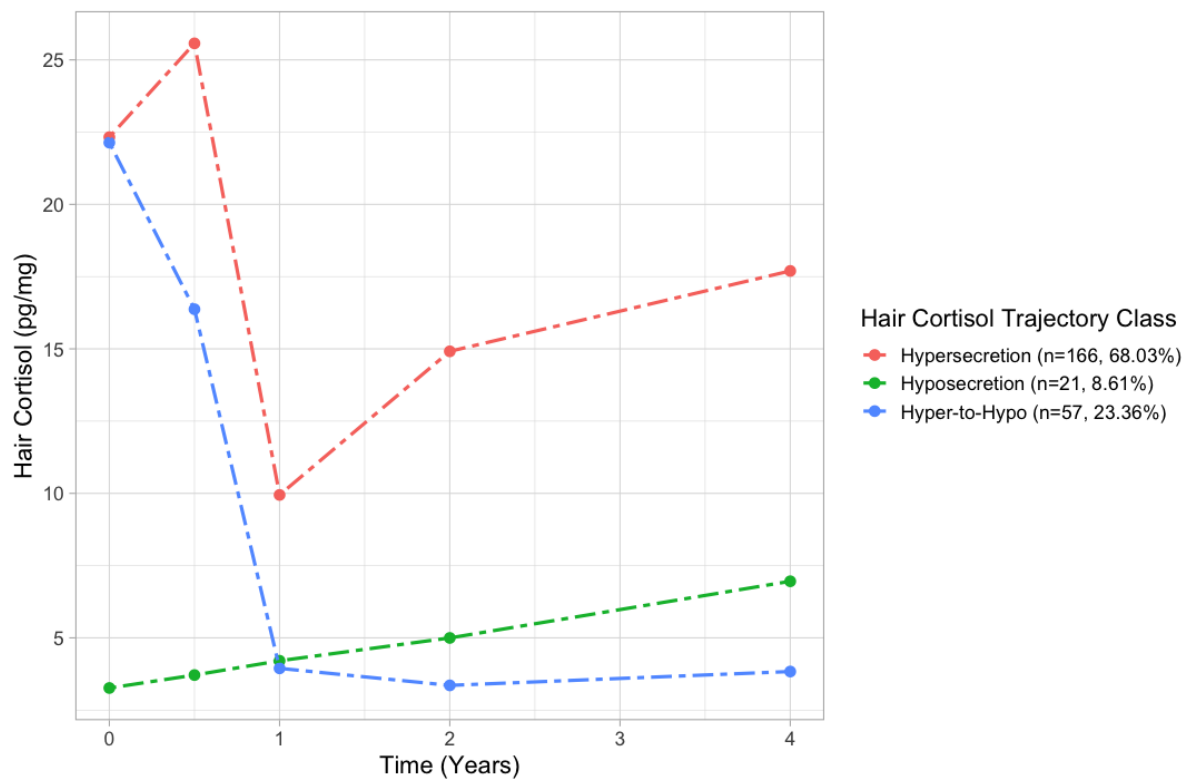


Figure 2. Mediation model

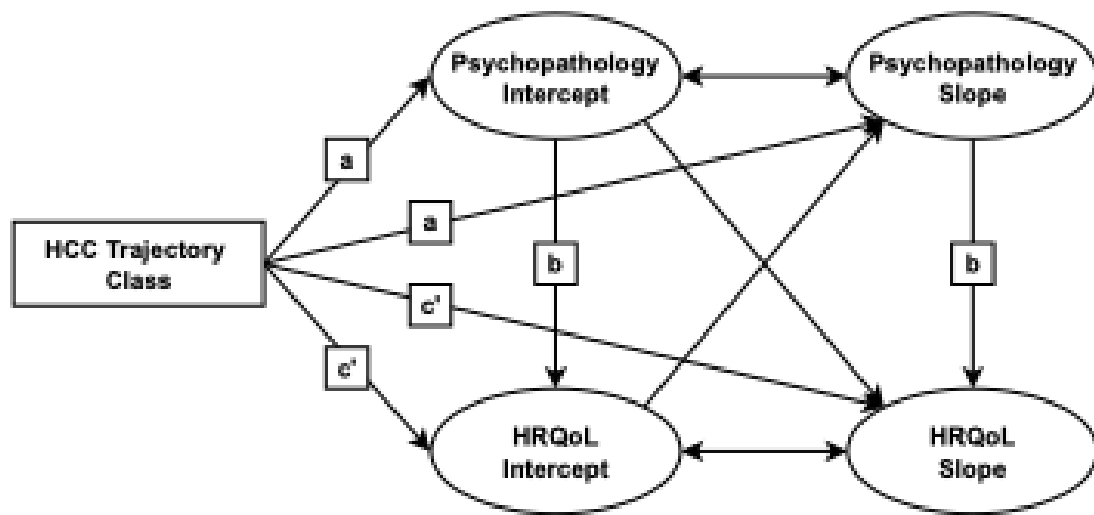


Table 1. Sample descriptives

Characteristic	Overall (n=244)	HCC Trajectory Group		
		Hypersecretion (n=166)	Hyposecretion (n=21)	Hyper-to-Hypo (n=57)
Child				
Age (years), mean (SD)	9.54 (4.17)	9.65 (4.24)	10.68 (4.23)	8.79 (3.88)
Female, n (%)	117 (47.95%)	78 (46.99%)	15 (71.43%)	24 (42.11%)
CPI Type, n (%)				
Dermatological	19 (7.79%)	15 (9.04%)	2 (9.52%)	2 (3.51%)
Endocrine	34 (13.93%)	24 (14.46%)	2 (9.52%)	8 (14.04%)
Gastroenterological	33 (13.52%)	24 (14.46%)	2 (9.52%)	7 (12.28%)
Hematological	27 (11.07%)	16 (9.64%)	3 (14.29%)	8 (14.04%)
Neurological	10 (4.1%)	6 (3.61%)	0 (0.00%)	4 (7.02%)
Respiratory	51 (20.9%)	29 (17.47%)	7 (33.33%)	15 (26.32%)
Rheumatological	70 (28.69%)	52 (31.33%)	5 (23.81%)	13 (22.81%)
Years since CPI diagnosis, mean (SD)	4.42 (4.08)	4.13 (4.06)	6.78 (3.82)	4.38 (4.02)
WHODAS 2.0, mean (SD)	19.31 (6.69)	19.82 (7.05)	18.19 (5.02)	18.26 (6.07)
Born in Canada, n (%)	230 (94.26%)	159 (95.78%)	18 (85.71%)	53 (92.98%)
White, n (%)	198 (81.15%)	139 (83.73%)	17 (80.95%)	42 (73.68)
Parent				
Age (years), mean (SD)	40.55 (6.34)	40.08 (6.2)	43.91 (7.69)	40.69 (5.92)
Female, n (%)	219 (89.75%)	148 (81.16%)	19 (90.48)	52 (91.23%)
Biological parent, n (%)	240 (98.36%)	164 (98.8%)	20 (95.23%)	56 (98.25%)
Born in Canada, n (%)	209 (85.66%)	147 (88.55%)	14 (66.67%)	48 (84.21%)
Household income $\geq$ \$90,000, n (%)	151 (61.89%)	101 (60.84%)	14 (66.67%)	36 (63.16%)
Postsecondary graduate, n (%)	189 (77.46%)	128 (77.11%)	15 (71.43%)	46 (80.7%)
Married/Common law, n (%)	212 (86.89%)	145 (87.35%)	20 (95.23%)	47 (82.46%)
White, n (%)	210 (86.07%)	146 (87.95%)	18 (85.71%)	46 (80.7%)

Supplementary Table S1. Descriptive statistics and correlations between study variables

Variable	N	M	SD	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	26	27	28	29
1. Physical T1	243	47.63	11.62	1																												
2. Physical T2	239	49.37	11.33	0.67***	1																											
3. Physical T3	235	49.9	12.21	0.59***	0.61***	1																										
4. Physical T4	221	48.77	11.23	0.62***	0.63***	0.68***	1																									
5. Physical T5	190	48.07	10.73	0.55***	0.57***	0.52***	0.63***	1																								
6. Psychological T1	243	48.38	10.22	0.62***	0.51***	0.46***	0.43***	0.40***	1																							
7. Psychological T2	237	49.21	10.72	0.45***	0.64***	0.48***	0.49***	0.45***	0.63***	1																						
8. Psychological T3	233	49.28	11.03	0.45***	0.46***	0.56***	0.45***	0.33***	0.56***	0.65***	1																					
9. Psychological T4	220	47.78	10.91	0.47***	0.42***	0.47***	0.61***	0.44***	0.43***	0.58***	0.60***	1																				
10. Psychological T5	191	47.85	10	0.44***	0.43***	0.40***	0.46***	0.64***	0.41***	0.49***	0.46***	0.50***	1																			
11. Autonomy T1	243	51.39	9.63	0.31***	0.34***	0.32***	0.33***	0.31***	0.51***	0.46***	0.45***	0.37***	0.37***	1																		
12. Autonomy T2	239	52.44	10.43	0.33***	0.41***	0.37***	0.40***	0.42***	0.45***	0.44***	0.38***	0.63***	1																			
13. Autonomy T3	234	53.23	10.47	0.27***	0.34***	0.42***	0.32***	0.32***	0.38***	0.48***	0.57***	0.38***	0.32***	0.58***	0.65***	1																
14. Autonomy T4	219	53.26	10.18	0.28***	0.32***	0.33***	0.39***	0.35***	0.35***	0.45***	0.48***	0.53***	0.40***	0.51***	0.67***	0.62***	1															
15. Autonomy T5	190	53.23	10.25	0.27***	0.22**	0.24**	0.23**	0.27***	0.32***	0.28***	0.40***	0.30***	0.47***	0.48***	0.52***	0.55***	0.63***	1														
16. Social T1	243	48.34	11.12	0.35***	0.24***	0.27***	0.23***	0.22**	0.45***	0.32***	0.32***	0.29***	0.28***	0.52***	0.42***	0.32***	0.35***	0.30***	1													
17. Social T2	238	49.76	12.21	0.32***	0.33***	0.30***	0.26***	0.38***	0.36***	0.45***	0.33***	0.32***	0.36***	0.33***	0.50***	0.32***	0.35***	0.26***	0.50***	1												
18. Social T3	232	46.83	14.7	0.16*	0.20**	0.30***	0.15*	0.16*	0.25***	0.36***	0.44***	0.29***	0.18*	0.29***	0.37***	0.38***	0.33***	0.25***	0.30***	0.42***	1											
19. Social T4	220	43.41	14.02	0.25***	0.18**	0.28***	0.38***	0.21**	0.18**	0.26***	0.31***	0.49***	0.25***	0.18**	0.22**	0.28***	0.31***	0.14	0.26***	0.28***	0.28***	1										
20. Social T5	191	49.2	10.86	0.27***	0.27***	0.27***	0.24***	0.39***	0.33***	0.33***	0.30***	0.35***	0.53***	0.27***	0.30***	0.35***	0.37***	0.37***	0.28***	0.44***	0.22**	0.29***	1									
21. School T1	241	50.47	11.07	0.32***	0.16*	0.20**	0.24***	0.29***	0.42***	0.34***	0.27***	0.31***	0.30***	0.39***	0.36***	0.23***	0.31***	0.26***	0.38***	0.27***	0.15*	0.16*	0.26***	1								
22. School T2	238	51.76	11.35	0.33***	0.35***	0.34***	0.34***	0.33***	0.46***	0.56***	0.41***	0.37***	0.36***	0.35***	0.48***	0.38***	0.39***	0.31***	0.31***	0.43***	0.25***	0.18**	0.33***	0.67***	1							
23. School T3	232	51.4	10.88	0.20**	0.21**	0.35***	0.25***	0.24***	0.38***	0.42***	0.49***	0.38***	0.28***	0.29***	0.35***	0.47***	0.41***	0.33***	0.19**	0.27***	0.43***	0.27***	0.26***	0.54***	0.66***	1						
24. School T4	221	51.14	11.02	0.25***	0.21**	0.32***	0.38***	0.31***	0.27***	0.37***	0.35***	0.52***	0.32***	0.27***	0.33***	0.34***	0.42***	0.22**	0.15*	0.30***	0.30***	0.38***	0.28***	0.51***	0.60***	0.62***	1					
25. School T5	188	49.89	10.01	0.18*	0.16*	0.20**	0.26***	0.32***	0.22**	0.23**	0.29***	0.40***	0.41***	0.25***	0.29***	0.40***	0.40***	0.33***	0.16*	0.22**	0.17*	0.25***	0.42***	0.42***	0.55***	0.50***	0.65***	1				
26. Psychopathology T1	243	18.84	14.36	-0.28***	-0.22***	-0.28***	-0.19**	-0.26***	-0.53***	-0.49***	-0.46***	-0.32***	-0.33***	-0.43***	-0.42***	-0.40***	-0.40***	-0.36***	-0.26***	-0.33***	-0.32***	-0.11	-0.33***	-0.43***	-0.50***	-0.42***	-0.30***	-0.26***	1			
27. Psychopathology T2	239	17.43	14.68	-0.27***	-0.33***	-0.34***	-0.22**	-0.30***	-0.49***	-0.60***	-0.51***	-0.39***	-0.35***	-0.39***	-0.47***	-0.40***	-0.38***	-0.26***	-0.25***	-0.40***	-0.31***	-0.1	-0.32***	-0.36***	-0.55***	-0.47***	-0.40***	-0.29***	0.81***	1		
28. Psychopathology T3	235	16.01	13.64	-0.25***	-0.27***	-0.32***	-0.17*	-0.23**	-0.39***	-0.51***	-0.55***	-0.37***	-0.35***	-0.37***	-0.41***	-0.40***	-0.39***	-0.28***	-0.26***	-0.33***	-0.33***	-0.1	-0.30***	-0.35***	-0.49***	-0.52***	-0.36***	-0.30***	0.78***	0.83***	1	
29. Psychopathology T4	222	14.86	12.31	-0.23***	-0.25***	-0.32***	-0.28***	-0.29***	-0.34***	-0.47***	-0.46***	-0.55***	-0.40***	-0.31***	-0.42***	-0.36***	-0.47***	-0.32***	-0.19**	-0.32***	-0.26***	-0.27***	-0.34***	-0.37***	-0.47***	-0.47***	-0.51***	-0.39***	0.63***	0.73***	0.75***	1
30. Psychopathology T5	183	16.7	14.01	-0.22**	-0.22**	-0.22**	-0.19*	-0.35***	-0.27***	-0.36***	-0.33***	-0.44***	-0.54***	-0.23**	-0.38***	-0.33***	-0.43***	-0.40***	-0.12	-0.26***	-0.22**	-0.17*	-0.47***	-0.27***	-0.44***	-0.36***	-0.39***	-0.49***	0.55***	0.58***	0.61***	0.68***

Note. Physical = Physical Well-being, Psychological = Psychological Well-being, Autonomy = Parents and Autonomy, Social = Social Support & Peers, School = School Environment, T1 = Baseline, T2 = 6 months, T3 = 12 months, T4 = 24 months, T5 = 48 months.

*p<.05, **p<.01, ***p<.001

Supplementary Table S2. Unconditional models

Variable	Growth	CFI	RMSEA	SRMR	BIC	χ^2	Intercept	Slope	Quadratic	Change in χ^2
Psychopathology	Linear	0.932	0.149	0.071	8173.748	83.64	17.620 (0.886)***	-0.462 (0.219)*		
	Quadratic^a	0.971	0.102	0.056	8143.398	47.80	18.839 (0.933)***	-3.206 (0.570)***	0.699 (0.134)***	$p<.001$
	Quadratic	0.985	0.083	0.046	8141.802	29.71	18.841 (0.933)***	-3.217 (0.572)***	0.702 (0.134)***	$p=.012$
Physical Well-being	Linear	0.982	0.067	0.041	8214.677	20.81	48.783 (0.671)***	-0.098 (0.167)		
	Quadratic^a	0.988	0.057	0.035	8215.084	15.72	48.247 (0.696)***	1.094 (0.575)	-0.293 (0.137)*	$p=.035$
	Quadratic	0.987	0.073	0.034	8229.087	13.23	48.221 (0.702)***	1.053 (0.567)	-0.281 (0.135)*	$p=.457$
Psychological Well-being	Linear	0.986	0.048	0.068	8051.080	23.70	48.874 (0.620)***	-0.314 (0.176)		
	Quadratic ^a	0.984	0.053	0.068	8056.536	23.66	48.920 (0.633)***	-0.417 (0.575)	0.026 (0.135)	$p=.849$
	Quadratic	0.998	0.021	0.031	8062.595	13.22	48.918 (0.633)***	-0.417 (0.576)	0.026 (0.135)	$p=.027$
Parents & Autonomy	Linear	0.979	0.068	0.055	7982.146	24.14	52.054 (0.5820)***	0.345 (0.174)*		
	Quadratic^a	0.985	0.062	0.050	7983.293	19.79	51.603 (0.5980)***	1.354 (0.554)*	-0.248 (0.129)	$p=.036$
	Quadratic	0.996	0.039	0.024	7989.946	9.95	51.582 (0.596)***	1.292 (0.543)*	-0.234 (0.126)	$p=.067$
Social Support & Peers	Linear	0.643	0.161	0.115	8831.060	67.25	48.203 (0.659)***	-0.068 (0.226)		
	Quadratic^a	0.778	0.134	0.085	8814.054	44.74	49.576 (0.686)***	-4.244 (0.793)***	1.012 (0.189)***	$p<.001$
	Quadratic	0.771	0.166	0.081	8828.633	42.83	49.486 (0.700)***	-4.162 (0.801)***	0.979 (0.189)***	$p=.683$
School Environment	Linear	0.965	0.089	0.067	8100.803	29.12	51.386 (0.666)***	-0.384 (0.184)*		
	Quadratic ^a	0.970	0.087	0.064	8102.889	25.71	50.898 (0.697)***	0.636 (0.606)	-0.240 (0.136)	$p=.083$
	Quadratic	0.982	0.083	0.047	8109.131	15.46	50.835 (0.696)***	0.656 (0.606)	-0.242 (0.136)	$p=.029$

Note. Unstandardized estimates (standard errors) are displayed. The selected model is bolded.

^a the variance of the quadratic slopes were set to zero

* $p<.05$, ** $p<.01$, *** $p<.001$

Table 2. Conditional models

Variable	Intercept (I)	Slope (S)	Quadratic (Q)^a	I:S Covariance	CFI	RMSEA	SRMR
Psychopathology	0.835 (0.409)*	-0.610 (1.358)	1.604 (2.679)	-0.362 (0.095)**	0.976	0.061	0.022
Physical Well-being	6.409 (0.451)***	1.197 (1.681)	-2.227 (1.956)	-0.297 (0.182)	0.966	0.061	0.023
Psychological Well-being	6.967 (0.534)***	0.478 (1.022)	NA	-0.328 (0.135)	0.950	0.055	0.035
Parents & Autonomy	7.813 (0.596)***	-0.194 (1.861)	0.889 (2.686)	-0.123 (0.146)	0.983	0.038	0.024
Social Support & Peers	6.864 (0.659)***	-0.087 (1.090)	0.093 (1.396)	-0.395 (0.191)	0.859	0.065	0.038
School Environment	6.178 (0.574)***	-0.976 (0.685)	NA	-0.380 (0.099)*	0.984	0.032	0.030

Note. Standardized estimates (standard errors) are displayed.

^a the variance of the quadratic slopes were set to 0

* $p < .05$, ** $p < .01$, *** $p < .001$

Table 3. HCC trajectory class effects

Variable	HCC Trajectory Class (ref = Hypersecretion)					
	Hyper-to-Hypo			Hyposecretion		
	β	95% CI	p	β	95% CI	p
Psychopathology						
Intercept	-0.179	-0.276, -0.082	<.001	-0.016	-0.107, 0.075	.729
Slope	0.225	-0.092, 0.541	.182	-0.213	-0.542, 0.117	.222
Quadratic	-0.240	-0.909, 0.430	.493	0.434	-0.134, 1.003	.160
Physical Well-being						
Intercept	0.086	-0.031, 0.204	.148	0.144	0.019, 0.270	.026
Slope	-0.217	-0.619, 0.186	.299	-0.086	-0.437, 0.265	.638
Quadratic	0.180	-0.301, 0.661	.468	-0.016	-0.428, 0.395	.938
Psychological Well-being						
Intercept	0.141	0.034, 0.247	.011	0.100	-0.024, 0.225	.114
Slope	-0.069	-0.314, 0.176	.564	-0.151	-0.393, 0.092	.208
Parents & Autonomy						
Intercept	0.088	-0.047, 0.223	.202	-0.023	-0.152, 0.106	.726
Slope	0.177	-0.354, 0.708	.511	0.306	-0.117, 0.729	.171
Quadratic	-0.319	-1.116, 0.478	.449	-0.411	-1.138, 0.315	.271
Social Support & Peers						
Intercept	0.236	0.055, 0.417	.008	0.069	-0.090, 0.229	.391
Slope	-0.589	-1.057, -0.121	.049	-0.100	-0.836, 0.636	.791
Quadratic	0.807	0.330, 1.285	.045	0.001	-0.988, 0.990	.999
School Environment						
Intercept	0.150	0.032, 0.269	.013	0.079	-0.036, 0.194	.182
Slope	-0.080	-0.244, 0.083	.331	-0.094	-0.279, 0.090	.314

Note. Standardized estimates are displayed.

Supplementary Table S3. Covariate effects from the conditional models

Variable	Covariate															
	Child Sex [Female]		Child Age		Years Since CPI Diagnosis		WHODAS 2.0		Parent Sex [Female]		Parent Age		Parent Education [Postsecondary Graduate]		Household Income [≥90K]	
	<i>β</i>	<i>p</i>	<i>β</i>	<i>p</i>	<i>β</i>	<i>p</i>	<i>β</i>	<i>p</i>	<i>β</i>	<i>p</i>	<i>β</i>	<i>p</i>	<i>β</i>	<i>p</i>	<i>β</i>	<i>p</i>
Psychopathology																
Intercept	-0.103	.071	0.095	.191	0.032	.645	0.572	<.001	0.117	.001	-0.077	.308	-0.020	.747	0.063	.251
Slope	0.295	.090	-0.141	.458	-0.061	.732	-0.476	.022	0.024	.869	0.015	.941	0.006	.971	-0.416	.023
Quadratic	-0.346	.321	0.285	.510	-0.188	.615	0.652	.118	-0.182	.530	0.123	.797	0.126	.725	0.502	.170
Physical Well-being																
Intercept	-0.209	.001	-0.450	<.001	0.235	<.001	-0.434	<.001	-0.131	.016	-0.063	.400	0.029	.643	0.021	.744
Slope	-0.018	.928	-0.341	.209	-0.545	.006	0.546	.012	-0.079	.735	0.313	.262	-0.257	.231	0.212	.363
Quadratic	0.068	.775	0.300	.342	0.756	.002	-0.511	.048	0.205	.432	-0.336	.307	0.261	.288	-0.208	.431
Psychological Well-being																
Intercept	-0.061	.321	-0.382	<.001	0.097	.226	-0.443	<.001	-0.185	.012	0.038	.646	0.033	.616	-0.017	.784
Slope	-0.242	.048	0.086	.629	0.257	.067	0.291	.005	0.037	.785	-0.167	.342	-0.189	.155	0.157	.183
Autonomy & Parent Relations																
Intercept	-0.111	.089	-0.223	.019	-0.012	.886	-0.301	<.001	-0.183	.003	-0.014	.883	-0.087	.205	0.208	.004
Slope	0.102	.677	0.010	.976	0.274	.334	0.092	.714	0.180	.502	0.075	.805	-0.139	.598	-0.425	.083
Quadratic	-0.308	.422	0.142	.791	-0.356	.434	-0.049	.900	-0.253	.540	-0.144	.771	0.358	.408	0.378	.322
Social Support & Peers																
Intercept	0.019	.832	0.086	.539	0.091	.389	-0.292	.002	-0.160	.060	-0.302	.013	-0.045	.653	0.197	.057
Slope	-0.133	.675	-0.636	.151	0.232	.484	-0.117	.711	0.018	.952	0.468	.269	-0.214	.503	-0.393	.270
Quadratic	0.267	.527	0.515	.395	-0.098	.832	0.073	.866	0.092	.810	-0.501	.378	0.263	.531	0.309	.519
School Environment																
Intercept	0.158	.014	-0.076	.425	-0.001	.992	-0.394	<.001	-0.241	<.001	-0.106	.221	0.022	.757	0.102	.134
Slope	-0.023	.801	-0.063	.615	0.117	.240	0.243	.046	0.196	.002	-0.121	.347	-0.148	.130	0.085	.418

Note. Standardized estimates are displayed.

Table 4. Covariances between latent growth factors of Psychopathology and HRQoL

HRQoL Latent Factors	Psychopathology Latent Factors						Fit Statistics		
	Intercept			Slope			CFI	RMSEA	SRMR
	<i>Estimate</i>	95% CI	<i>p</i>	<i>Estimate</i>	95% CI	<i>p</i>			
Physical Well-being							0.960	0.063	0.028
Intercept	-0.168	-0.322, -0.014	.035	0.054	-0.172, 0.280	.636			
Slope	-0.009	-0.255, 0.237	.942	-0.493	-0.835, -0.150	.002			
Psychological Well-being							0.878	0.104	0.040
Intercept	-0.515	-0.652, -0.378	<.001	-0.070	-0.278, 0.138	.523			
Slope	0.014	-0.286, 0.314	.927	NA	NA	NA			
Parents & Autonomy							0.965	0.057	0.030
Intercept	-0.515	-0.634, -0.396	<.001	0.255	0.070, 0.440	.011			
Slope	0.359	0.074, 0.643	.030	-0.875	-1.287, -0.463	<.001			
Social Support & Peers							0.948	0.062	0.041
Intercept	-0.339	-0.519, -0.159	.001	0.243	-0.013, 0.499	.076			
Slope	0.082	-0.225, 0.389	.594	-0.922	-1.627, -0.217	<.001			
School Environment							0.959	0.060	0.036
Intercept	-0.511	-0.645, -0.377	<.001	0.183	-0.025, 0.390	.101			
Slope	0.193	-0.057, 0.442	.127	-0.799	-1.055, -0.542	<.001			

Note. Standardized estimates are displayed.

Table 5. Mediation models

Model/Path	Effect	HCC Trajectory Class (ref = Hypersecretion)						
		Hyper-to-Hypo			Hyposecretion			
		β	95% CI	p	β	95% CI	p	
Physical Well-being (CFI = 0.960, RMSEA = 0.063, SRMR = 0.028)								
HCC Class→Psychopathology Intercept→HRQoL Intercept	Indirect (ab)	0.028	-0.002, 0.058	.069	0.002	-0.012, 0.017	.738	
	Direct (c')	0.059	-0.064, 0.183	.347	0.142	0.020, 0.265	.024	
	Total (ab+c')	0.087	-0.031, 0.205	.146	0.145	0.020, 0.270	.025	
HCC Class→ Psychopathology Slope→HRQoL Slope	Indirect (ab)	-0.068	-0.179, 0.042	.222	0.066	-0.050, 0.182	.249	
	Direct (c')	-0.144	-0.548, 0.260	.492	-0.152	-0.484, 0.179	.379	
	Total (ab+c')	-0.212	-0.612, 0.188	.307	-0.086	-0.434, 0.262	.633	
Parents & Autonomy (CFI = 0.965, RMSEA = 0.057, SRMR = 0.030)								
HCC Class→ Psychopathology Intercept→HRQoL Intercept	Indirect (ab)	0.102	0.046, 0.157	<.001	0.009	-0.043, 0.061	.735	
	Direct (c')	-0.013	-0.147, 0.122	.854	-0.032	-0.160, 0.095	.622	
	Total (ab+c')	0.089	-0.046, 0.225	.199	-0.023	-0.152, 0.105	.724	
HCC Class→ Psychopathology Slope→HRQoL Slope	Indirect (ab)	-0.164	-0.420, 0.092	.200	0.166	-0.095, 0.427	.219	
	Direct (c')	0.357	-0.237, 0.952	.232	0.162	-0.263, 0.588	.463	
	Total (ab+c')	0.193	-0.368, 0.755	.498	0.328	-0.120, 0.776	.169	
Social Support & Peers (CFI = 0.948, RMSEA = 0.062, SRMR = 0.041)								
HCC Class→ Psychopathology Intercept→HRQoL Intercept	Indirect (ab)	0.069	0.019, 0.118	.011	0.006	-0.029, 0.042	.732	
	Direct (c')	0.169	-0.012, 0.350	.057	0.064	-0.090, 0.218	.417	
	Total (ab+c')	0.238	0.056, 0.419	.008	0.070	-0.089, 0.229	.386	
HCC Class→ Psychopathology Slope→HRQoL Slope	Indirect (ab)	-0.151	-0.387, 0.084	.205	0.146	-0.100, 0.393	.227	
	Direct (c')	-0.442	-0.947, 0.064	.146	-0.251	-0.943, 0.440	.483	
	Total (ab+c')	-0.593	-1.056, -0.129	.048	-0.105	-0.845, 0.636	.783	
School Environment (CFI = 0.959, RMSEA = 0.060, SRMR = 0.036)								
HCC Class→ Psychopathology Intercept→HRQoL Intercept	Indirect (ab)	0.098	0.042, 0.155	.001	0.009	-0.042, 0.059	.737	
	Direct (c')	0.050	-0.069, 0.169	.411	0.072	-0.035, 0.178	.187	
	Total (ab+c')	0.148	0.030, 0.267	.014	0.081	-0.035, 0.197	.176	
HCC Class→ Psychopathology Slope→HRQoL Slope	Indirect (ab)	-0.215	-0.550, 0.121	.201	0.217	-0.138, 0.571	.232	
	Direct (c')	0.158	-0.209, 0.525	.394	-0.315	-0.662, 0.032	.077	
	Total (ab+c')	-0.056	-0.213, 0.100	.477	-0.098	-0.272, 0.075	.265	

Note. Standardized estimates are displayed.

Chapter 8 – General Discussion

8.1 Overview

It is well established that children with a CPI are at a greater risk of psychopathology (i.e., multimorbidity) and poor HRQoL [5,6,188]; however, very few studies have examined underlying mechanisms linking childhood CPI to negative health outcomes. Children with a CPI may experience significant chronic stress due to their illness, stemming from treatments and symptoms, daily-life restrictions, and the psychological burden of managing health challenges [3]. Chronic exposure to stress can lead to HPA-axis dysregulation [14], which may be implicated in the development of psychopathology and contribute to poor HRQoL in this population [129,228]. In recent years, HCC has been identified as a valuable biomarker for chronic HPA-axis dysregulation in children, but despite its promising utility, no previous research has examined longitudinal associations between HCC and health outcomes in children with a CPI [18]. This dissertation addressed these knowledge gaps through three interconnected studies that examined the complex longitudinal associations between HCC, psychopathology, and HRQoL in children with a CPI. Specifically, the studies examined trajectories of HCC and their associations with psychopathology (Study 1), the moderating role of HCC on associations between parent distress and child psychopathology (Study 2), and the mediating role of psychopathology on associations between HCC and HRQoL (Study 3). The findings from this dissertation contribute to a greater understanding of the mechanisms underlying child multimorbidity, and can be used to improve health and well-being for children with a CPI and their families.

The following sections of this chapter will describe the key findings from each study in this dissertation (section 8.2), integrated findings that emerged across studies (section 8.3),

implications for clinical practice, policy, and future research (section 8.4), strengths and limitations of this dissertation (section 8.5), and overall conclusions (section 8.6).

8.2 Summary of Key Findings

Study 1 (Chapter 5) delineated 48-month trajectories of HCC in children with a CPI, identified predictors of HCC trajectory group membership, and explored associations between HCC trajectories and psychopathology symptoms over 48 months. Results indicated that a three-class model was optimal, and the HCC trajectories were labelled as Hypersecretion, Hyposecretion, and Hyper-to-Hypo. Child sex, child age, parent age, and time since CPI diagnosis were significant predictors of HCC trajectory group membership. These findings are consistent with previous studies that have identified persistently elevated (i.e., hypersecretion), declining (i.e., hyper-to-hyposecretion), and persistently low (i.e., hyposecretion) HCC trajectories in children [134,136]. Most notably, over two-thirds of the sample followed a Hypersecretion trajectory, with persistently elevated HCC compared to reference levels in healthy children [277,278]. This suggests that living with and managing a CPI may be a significant chronic stressor for children. Specifically, the Hypersecretion class may identify children with increased allostatic load and maladaptive or dysregulated HPA-axis functioning, whereas the Hyper-to-Hypo class may identify children with adaptive HPA-axis functioning [69]. In line with this, we found that children in the Hyper-to-Hypo class exhibited lower internalizing and externalizing symptoms compared to the Hypersecretion class. Additionally, the Hyposecretion class may identify children who have developed blunted HPA-axis responses following prolonged exposure to stress [69]. Consistent with this interpretation, children in this class had less recent CPI diagnoses. However, it remains unclear whether cortisol hyposecretion reflects an adaptive or maladaptive response to chronic stress. Given that psychopathology

symptoms did not differ between the Hyposecretion and Hypersecretion classes, it is possible that cortisol hyposecretion reflects increased allostatic load rather than healthy adaptation [71]. Overall, this study is novel in its use of LCGA to identify trajectories of HCC in children with a CPI, and demonstrates that HPA-axis dysregulation may be implicated in the development of psychopathology in this population.

Study 2 (Chapter 6) examined the between- and within-dyad effects of parent distress on child psychopathology over 48 months, and explored whether these associations were moderated by child HCC trajectory. Higher average parent internalizing symptoms were associated with greater child internalizing and externalizing symptoms (BD effects). However, fluctuations in parent internalizing symptoms only predicted greater child internalizing, not externalizing, symptoms (WD effects). Higher average parenting stress was associated with greater child externalizing, but not internalizing, symptoms (BD effects). Similarly, fluctuations in parenting stress only predicted greater child externalizing, not internalizing, symptoms (WD effects). These findings are consistent with previous studies that have demonstrated significant between- and within-dyad effects from parenting internalizing symptoms and parenting stress to child psychopathology [159,161,165–168]. This study is the first to examine these effects in children with a CPI, and highlights that both average levels and fluctuations in parent distress may be risk factors for child psychopathology in this population. Study findings also suggest that parent internalizing symptoms may be more strongly linked to child internalizing symptoms, whereas parenting stress may be more strongly linked to child externalizing symptoms. Child HCC trajectory moderated the between-dyad effects of parent internalizing symptoms and parenting stress on child internalizing, but not externalizing, symptoms. Specifically, the combination of high average parent internalizing symptoms or parenting stress and cortisol hypersecretion

predicted greater child internalizing symptoms. These findings align with diathesis-stress/dual-risk theories [170,279], and suggest that child HPA-axis dysregulation may confer vulnerability to the negative impacts of environmental stressors. Overall, this study highlights the strong link between parent and child mental health in families of a child with a CPI, and suggests that interventions targeting parent distress may have beneficial downstream effects on child mental health. Moreover, child HCC may help to explain heterogeneity in parent-child associations, and may be a valuable biomarker for identifying children with a CPI who may benefit the most from interventions that target parent distress.

Study 3 (Chapter 7) examined associations between HCC trajectories and HRQoL over 48 months, and explored psychopathology as a mediator of these associations. Children in the Hyper-to-Hypo trajectory had lower psychopathology symptoms compared to the Hypersecretion trajectory, which in turn was associated with higher HRQoL in the domains of parents and autonomy, social support and peers, and school environment. Children in the Hyposecretion trajectory had higher HRQoL in the physical well-being domain compared to the Hypersecretion trajectory, an effect not mediated by psychopathology. These findings are consistent with the only previous study that has examined associations between HCC and HRQoL in children with a CPI [228], and suggest that high HCC may be associated with poor HRQoL across several domains. Moreover, greater psychopathology may act as a potential mediating mechanism linking high HCC to poor HRQoL. However, results also suggest that high HCC may be associated with poor HRQoL in some domains independent of its association through psychopathology. Child HCC trajectory was not associated with change over time in any HRQoL domain; however, increases in psychopathology symptoms were associated with decreases in HRQoL over 48 months. This aligns with previous research in both healthy and chronically ill

children [219,224,225], and suggests that psychopathology is a key risk factor for poor HRQoL in children with a CPI. Overall, these findings suggest that HPA-axis dysregulation may be a distinct mechanism linking childhood CPI to poor HRQoL, and interventions for reducing stress and psychopathology may lead to improvements in HRQoL in this population.

8.3 Integrated Findings

Several integrated themes emerged from the findings of this dissertation. First, living with a CPI during childhood is a significant chronic stressor, and the cumulative physiological effects of chronic stress exposure may be a key mechanism linking childhood CPI to negative health outcomes. Children with a CPI are often exposed to persistent illness-related burdens (e.g., distressing symptoms, painful or invasive treatments, disruptions to daily-life routines, etc.), which may be significant sources of chronic stress [3]. Exposure to chronic stress during childhood can disrupt the body's stress response pathways and lead to HPA-axis dysregulation [14]. More specifically, the findings from this dissertation suggest that HPA-axis dysregulation, indexed by HCC, may be an important mechanism linking childhood CPI to psychopathology and poor HRQoL. This aligns with the Allostatic Load model, which posits that prolonged exposure to stress and subsequent dysregulation of the HPA-axis leads to *wear and tear* on the body and brain, which increases vulnerability to adverse health outcomes [15]. Findings from this dissertation also align with diathesis-stress models, suggesting that HPA-axis dysregulation in children with a CPI may function as a vulnerability factor that heightens risk for psychopathology when exposed to environmental stressors, such as parent distress [279]. Together, these findings underscore the importance of HPA-axis dysregulation as a key mechanism through which the stress of living with and managing a childhood CPI becomes biologically embedded and contributes to adverse health outcomes. Importantly, disruptions in

HPA-axis functioning during this sensitive developmental period may have lasting implications for child health and well-being, and contribute to adverse health outcomes across the lifespan for children with a CPI.

Second, findings point to heterogeneity in long-term cortisol patterns in children with a CPI that are uniquely associated with health outcomes. Some children exhibited relatively stable HCC patterns over time characterized by persistently high (i.e., Hypersecretion) or persistently low (i.e., Hyposecretion) levels, while others exhibited change in HCC over time, characterized by a shift from high to low levels (i.e., Hyper-to-Hypo). These diverse HCC patterns cannot be observed with single HCC measurements or longitudinal variable-centered approaches, and have important implications for understanding health outcomes in children with a CPI. Specifically, these HCC trajectories were uniquely associated with psychopathology and HRQoL above and beyond simple correlations with HCC levels. This underscores the added predictive value of person-centered approaches, and highlights that chronically high or low HCC levels in children with a CPI may be more important in relation to health outcomes than one-time measurements of HCC. This may help explain the inconsistent cross-sectional associations observed between HCC and child psychopathology and HRQoL across previous studies. Taken together, these findings highlight the heterogeneous nature of HPA-axis functioning in children exposed to stress, and suggest that the traditional focus on cortisol hyper- vs. hyposecretion may not fully capture variability. Moreover, approaches that aim to identify and characterize this variability may be important for understanding paths to psychopathology and informing prevention and intervention approaches.

Third, findings from this dissertation support the adoption of a non-categorical framework for understanding the stress experienced by children with a CPI, and for identifying

children with CPI at high risk for psychopathology and poor HRQoL. The non-categorical framework emphasizes that children with a CPI face similar experiences and burdens related to the broad aspects of their condition, and these similarities outweigh the differences due to the characteristics of specific illnesses [280]. In support of the non-categorical framework, previous research demonstrates small to negligible differences in multimorbidity risk and HRQoL between children with different CPIs [7,11]. Specific to this dissertation, CPI type and child disability were not significant predictors of HCC levels, nor were they predictors of membership in the HCC trajectory groups. These findings suggest that living with and managing a CPI during childhood may be stressful, regardless of the type or severity of the condition. Moreover, associations between HCC trajectories and psychopathology and HRQoL persisted after controlling for the effect of child disability. This highlights the importance of considering HPA-axis dysregulation as a distinct mechanism linking childhood CPI to psychopathology and poor HRQoL, independent of the influence of condition-related functional impairment. However, greater disability was associated with greater internalizing and externalizing symptoms and worse HRQoL across all domains, aligning with previous work suggesting that disability is a key predictor of health outcomes in children with a CPI [222,281,282].

Finally, the findings of this dissertation highlight three promising intervention targets for improving health outcomes in children with a CPI: stress/cortisol levels, psychopathology symptoms, and parent distress. Given that children with a CPI may experience significant chronic stress, interventions to improve stress management and reduce HCC levels in children with a CPI may have positive implications for health outcomes [283]. Preliminary work suggests that psychological interventions for children [134,284], mindfulness-based training for children and their parents [285,286], as well as interventions to promote positive parenting [287] can

reduce HCC levels in children. Notably, a recent study found that children (10-18 years) receiving inpatient psychosomatic therapy experienced reductions in HCC from admission to discharge, and such reductions were accompanied by reductions in internalizing symptoms [284]. No previous study has examined the effectiveness of interventions for reducing HCC levels in children with a CPI. However, previous work has demonstrated that nature-based [288] and mindfulness-based [289] interventions can reduce salivary cortisol levels in children with chronic illnesses. Findings also suggest that interventions targeting psychopathology may be effective in improving HRQoL in children with a CPI. Previous research has demonstrated that psychological interventions, such as cognitive behavioural therapy, can reduce psychopathology symptoms and improve HRQoL in children with a CPI [290–292].

Findings from this dissertation also suggest that interventions for parent distress may have positive implications for mental health outcomes in children with a CPI. This aligns with the objectives of family-centered care, which recognizes that the family is the primary unit of support for a child with a CPI, and emphasizes that care and services should be organized around the whole family, not just the child [293,294]. Children with a CPI benefit significantly when their primary caregiver is emotionally stable, enabling them to better navigate the stressors associated with their condition. Therefore, it is crucial to consider the mental health of children and their parents in pediatric healthcare settings, and parents experiencing distress (i.e., depression, anxiety, parenting stress) should be supported. Several systematic reviews and meta-analyses have suggested that psychological interventions for parents can reduce psychopathology symptoms and lead to reductions in child psychopathology symptoms [295–297]. However, studies examining the effectiveness of parent psychological interventions for improving mental health outcomes in children with a CPI have yielded mixed results [153,298,299]. Given the

strong link between parent distress and child psychopathology observed in Study 2 of this dissertation, further research is needed to identify parent-focused interventions that can improve child outcomes in this population.

8.4 Implications for Clinical Practice, Policy, and Future Research

This dissertation has implications for clinical practice, public health policy, and future research. From a clinical perspective, these findings support the adoption of integrated physical-mental healthcare models in pediatric healthcare [300–302]. Key components of this approach should include regular mental health screening for children with a CPI to facilitate early identification and intervention, access to mental health supports and interventions, and referrals to mental health practitioners (e.g., psychiatrists, social workers) to facilitate psychological or pharmacological treatments, when appropriate [300–305]. Additionally, integrated physical-mental healthcare for children with a CPI should be adopted into clinical practice using a non-categorical approach. In particular, regular mental health screening for children in pediatric care settings should be adopted hospital- or clinic-wide, and treatments and supports should be available to all children with a CPI regardless of illness type or severity. The organization of services around particular diagnoses is not necessary or optimal, as it may result in some children receiving the care they need while others are overlooked. While preliminary, findings from this dissertation also indicate that HCC may be a promising biomarker for identifying children with a CPI who are experiencing chronic stress and may be at heightened risk for psychopathology and poor HRQoL. However, much more work is needed to establish the clinical utility of HCC in pediatric populations, and its use as an early screening tool remains a long-term prospect.

Implementing family-centered care models, specific to addressing parent distress, should also be a priority for clinical practice in pediatric healthcare. Pediatric healthcare teams are well

positioned to identify parents experiencing, or at risk of experiencing, high levels of parent distress given their frequent contacts with parents during medical appointments. Standards of care that include regular mental health screening for parents and referral or access to mental health treatment should be developed and implemented [306,307]. One example is the Caring for the Caregiver (C4C) model that is being piloted at SickKids Hospital in Toronto, which provides support to caregivers of children with medical complexity in three steps: 1) early identification of distress, 2) social work assessment, intervention and psychotherapy, and 3) psychiatric care [308]. Esser et al. (2026) conducted a retrospective review of parents referred to psychiatric care and found 79% received a new mental disorder diagnosis, further highlighting the value of family-centered care models that consider parent mental health in the context of pediatric healthcare [309].

From a policy perspective, these findings highlight opportunities to improve public health strategies to optimize health outcomes for children with a CPI and their parents. This dissertation highlights that living with and managing a CPI during childhood is a significant chronic stressor, and should therefore be recognized within policies and programs designed to support children exposed to adversity. Canadian public health frameworks addressing childhood adverse experiences emphasize the need to identify children experiencing chronic stress and intervene early, yet children with a CPI are not included in these approaches [310–313]. Including children with a CPI in these frameworks could strengthen prevention and intervention initiatives by recognizing the diversity of childhood experiences that contribute to the biological embedding of stress and impact health outcomes across the lifespan. In addition, findings support greater investment and funding into integrated physical-mental and family-centered care in pediatric healthcare. Funding for programs that include regular mental health screening for children and

their parents, as well as funding for public and accessible mental health services, may help to mitigate the negative impacts of multimorbidity on children, their families, and society. These recommendations align with Canadian public health frameworks that aim to prevent and mitigate the negative impacts of adverse childhood experiences [310–313].

Finally, this dissertation highlights several avenues for future research. First, larger samples of children with a CPI are needed to identify smaller HCC trajectory groups that may exist within this population, and to increase power to detect differences between groups. Studies with larger samples may also be able to utilize more flexible person-centered modelling approaches, such as GMM, to not only explore differences between HCC trajectory groups, but also within them [247]. Second, future work should focus on children newly diagnosed with a CPI, as the period immediately following the initial diagnosis may be particularly stressful for children and their parents [3]. Examining HCC trajectories during and after this period may provide a more nuanced understanding of the stress experienced by children with a CPI, and help establish the temporal relationship between HCC and psychopathology or HRQoL. Such research could also identify critical windows for interventions to reduce HCC levels and psychopathology symptoms, and improve HRQoL in this population. Relatedly, future work is needed to establish the clinical utility of HCC as an early screening tool, and explore whether interventions for reducing HCC are effective in reducing psychopathology symptoms and improving HRQoL. Third, the relationship between parent distress and child psychopathology is likely bidirectional, and future studies should utilise modelling approaches capable of capturing bidirectional relationships over time (e.g., cross-lagged panel models). Additionally, future work should aim to explore other factors implicated in this relationship (e.g., parent-child relationship quality, parenting practices, parental support), especially considering that some of these may act

as protective factors and could be modifiable intervention targets. Fourth, future research should investigate whether interventions for parent distress can lead to reductions in psychopathology in children with a CPI. This work will be central to informing family-centred approaches to pediatric healthcare. Finally, future work should examine a broader range of allostatic load biomarkers in children with a CPI, such as immune, inflammatory, and other neuroendocrine indicators. Preliminary work in MY LIFE suggests that some inflammatory biomarkers are associated with greater psychopathology symptoms [314]. Since cortisol only captures one aspect of the body's response to stress, using a composite index of allostatic load that incorporates several biomarkers may improve our understanding of the mechanisms linking childhood CPI to negative health outcomes [315].

8.5 Strengths and Limitations

This dissertation has numerous methodological strengths in its examination of the complex relationships between HCC and psychopathology in children with a CPI. First, the use of HCC as an objective measure of chronic stress overcomes the limitations and burdens of using subjective self-report stress questionnaires or invasive short-term stress biomarkers (e.g., saliva). Second, the use of longitudinal data collected at five time points over 48 months allowed for the identification of HCC trajectories in children with a CPI. The person-centered nature of the HCC trajectories captures individual heterogeneity, and is beneficial for identifying children with a CPI who exhibit maladaptive or dysregulated HCC patterns over time. Moreover, the findings from this dissertation suggest that these trajectories may be uniquely associated with health outcomes above and beyond what is captured by individual HCC measurements. The longitudinal nature of the data also allowed for the disaggregation of between- and within-dyad effects of parent distress on child psychopathology. Such effects are often confounded in

longitudinal studies [160], and may be particularly important for guiding prevention and intervention efforts. Third, consistent with previous work demonstrating minimal differences in multimorbidity risk across different illnesses [7], MY LIFE recruited children with diverse CPIs. This non-categorical approach increases the generalizability of the findings across a range of illnesses, and supports the implementation of hospital- or clinic-wide screening, prevention, and intervention programs, rather than illness-specific approaches. Finally, this dissertation takes a dimensional approach to conceptualizing psychopathology, and moves beyond traditional classifications of mental disorders as being either “present” or “absent”. Psychopathology is not an all-or-none phenomenon, and is better conceptualized along continuous dimensions. Imposing binary classifications on a dimensional construct reduces reliability and validity [316], and consequently, many children experiencing distressing psychopathology symptoms may not meet diagnostic thresholds, despite having a clear need for care.

This dissertation is not without limitations. First, MY LIFE recruited from a single pediatric hospital, and the sample is relatively homogeneous with respect to socioeconomic indicators and ethnicity. This may limit the generalizability of the findings to diverse and marginalized populations of children with a CPI. However, previous work suggests that the characteristics of MY LIFE families are consistent with the characteristics of families of children with a CPI in the general Ontario population [22]. Second, MY LIFE did not recruit a healthy comparison group, limiting our ability to compare HCC trajectories between children with a CPI and healthy children. Any comparisons made in this dissertation between these populations should be interpreted cautiously, as available studies reporting HCC reference ranges in healthy children are small and cross-sectional [277,278]. Third, although the wide age range of children included in MY LIFE is a notable strength, we did not have sufficient power to conduct age-

stratified analyses to examine how findings might differ across developmental periods. Additionally, while child age was included as a covariate in all models, pubertal status was not measured, limiting our ability to account for developmental factors that may influence HCC levels beyond age. Fourth, since MY LIFE does not include measures of child perceived stress or stressful life events, it was not possible to examine their associations with HCC levels. Previous work has demonstrated inconsistent associations between HCC and measures of perceived stress and stressful life events in children [92,95,278,317]. It is also possible that perceived or experienced stress influence psychopathology and HRQoL through pathways that are distinct from those captured by physiological stress indicators, like HCC.

Fifth, to maximize statistical power, only parent-reports of child psychopathology and HRQoL were used. Previous research has shown poor-to-moderate parent-child agreement on the EBS and KIDSCREEN-27 in children with a CPI [11,238,318,319], thus the current findings may not reflect those obtained from child self-reports. Future research would benefit from using a multi-informant approach, including child, coparent, and teacher reports. Shared informant variance may have also influenced parent-reports of child outcomes, as evidence suggests that parents experiencing psychological distress may overestimate psychopathology symptoms in their children [320]. However, a recent study conducted using the MY LIFE sample showed that parents experiencing psychological distress did not overestimate psychopathology in their children [319]. In fact, greater parent distress was associated with better parent-child agreement in several EBS domains [319]. Sixth, parent distress was only measured in primary caregiving parents, who were predominantly mothers. This limits our understanding of how paternal distress impacts child outcomes, and does not provide a complete picture of the influence of parent distress on psychopathology in children with a CPI. Finally, this dissertation only examined

unidirectional effects of parent distress on child psychopathology, and this relationship is likely bidirectional. Future work should model bidirectional parent-child pathways, and examine other potential moderating and mediating factors not measured in MY LIFE (e.g., parent-child relationship quality, parenting practices, parental support).

8.6 Conclusions

Collectively, the three studies that make up this dissertation advance our understanding of the complex associations between HCC, psychopathology, and HRQoL in children with a CPI. Three distinct HCC trajectories were identified, which were uniquely associated with psychopathology and HRQoL. These findings suggest that HPA-axis dysregulation may be an important mechanism linking childhood CPI to negative health outcomes. Further, findings indicated that parent and child mental health are strongly linked, and child HPA-axis dysregulation may function as a vulnerability factor that heightens risk for psychopathology when exposed to high levels of parent distress. To effectively support children with a CPI and their parents, integrated physical-mental and family-centered care should be adopted into clinical practice. Ultimately, this dissertation contributes to a greater understanding of the mechanisms underlying child multimorbidity, and the findings can be used to inform future research and clinical practice at all healthcare stages. Specifically, at the primary level, focusing on preventing multimorbidity in children with a CPI; at the secondary level, focusing on treating and reducing the negative impacts of multimorbidity; and at the tertiary level, focusing on improving quality of life and long-term functioning for children with a CPI and their families.

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Appendix A

Supplementary Table 1

Items on the child hair sample questionnaire

Item
Is your child currently on any medications? If yes, please write them down below:
Does your child smoke?
Does anybody in the household smoke?
What is your child's natural hair colour?
Does your child dye his/her hair or have any other treatments (relaxer/perm?) If yes, please write the treatment and tell us when was the last time your child dyed it/had the treatment?
On average, how many times per week does your child wash his/her hair?
When was the last time your child had a haircut? (please be as precise as possible)

Supplementary Table 2

Survey items for the 52-item EBS

Symptoms/Disorder	Survey Item
Internalizing Symptoms	
Major Depressive Disorder (MDE)	Changes in appetite
	Deliberately harms self or attempts suicide
	Feels worthless or inferior
	Gets no pleasure from usual activities
	Has trouble enjoying self
	Overtired or lacks energy
	Talks about killing self
	Trouble sleeping
	Unhappy, sad, or depressed
Generalized Anxiety Disorder (GAD)	Anxious or on edge
	Finds it hard to stop worrying
	Nervous, high-strung or tense
	Too fearful or anxious
	When anxious, his/her mind goes blank
	Worries about doing better at things
Separation Anxiety Disorder (SAD)	Avoids school because of fear of separation from loved ones
	Complains of feeling sick before separating from loved ones
	Has nightmares about being separated from loved ones
	Overly upset when leaving loved ones
	Scared to go to sleep without parents being near
	Worries that bad things will happen to loved ones
	Worries that something bad will cause separation from loved ones
Social Phobia (SP)	Afraid of doing things in front of others
	Avoids social situations
	Doesn't like to be with people he/she doesn't know
	Gets anxious about meeting new people
	Is nervous with people he/she doesn't know
Externalizing Symptoms	
Attention Deficit Hyperactivity Disorder (ADHD)	Can't concentrate, can't pay attention for long
	Can't stay seated when required to do so
	Distractible, has troubles ticking to any activity
	Fails to finish things he/she starts
	Fidgets
	Has difficulty awaiting turn in games or groups
	Impulsive or acts without thinking
	Makes careless mistakes
Oppositional Defiant Disorder (ODD)	Angry and resentful

	Argues a lot with adults
	Blames others for own mistakes
	Easily annoyed by others
	Gets back at people
	Loses temper
Conduct Disorder (CD)	Cruelty, bullying, or meanness to others
	Destroys things belonging to his/her family or other children
	Gets in many fights
	Has been physically cruel to others
	Has broken into someone else's house, building, or car
	Runs away from home
	Sets fires
	Stays out at night despite being told not to
	Steals outside the home
	Truancy, skips school
	Uses weapons when fighting

Supplementary Table 3

Survey items for the 27-item KIDSCREEN 27

Domain	Survey Item
Physical Well-being	Has your child felt fit and well?
	Has your child been physically active (e.g., running, climbing, biking)?
	Has your child been able to run well?
	Has your child felt full of energy?
Psychological Well-being	Has your child felt life was enjoyable?
	Has your child been in a good mood?
	Has your child had fun?
	Has your child felt sad?
	Has your child felt so bad that he/she didn't want to do anything?
	Has your child felt lonely?
	Has your child been happy with the way he/she is?
Parents and Autonomy	Has your child had enough time for him/herself?
	Has your child been able to do the things that he/she wants to do in his/her free time?
	Has your child felt that his/her parent(s) had enough time for him/her?
	Has your child felt that his/her parent(s) treated him/her fairly?
	Has your child been able to talk to his/her parent(s) when he/she wanted to?
	Has your child had enough money to do the same things as his/her friends?
	Has your child had enough money for his/her expenses?
Social Support and Peers	Has your child spent time with his/her friends?
	Has your child had fun with his/her friends?
	Has your child and his/her friends helped each other?
	Has your child been able to rely on his/her friends?
School Environment	Has your child been happy at school?
	Has your child been doing well at school?
	Has your child been able to pay attention?
	Has your child got along well with his/her teacher(s)?

Supplementary Table 4

Survey items for the 20-item CES-D

Survey Item
I was bothered by things that usually don't bother me.
I did not feel like eating; my appetite was poor.
I felt that I could not shake off the blues even with help from my family or friends.
I felt that I was just as good as other people.
I had trouble keeping my mind on what I was doing.
I felt depressed.
I felt that everything I did was an effort.
I felt hopeful about the future.
I thought my life had been a failure.
I felt fearful.
My sleep was restless.
I was happy.
I talked less than usual.
I felt lonely.
People were unfriendly.
I enjoyed life.
I had crying spells.
I felt sad.
I felt that people dislike me.
I could not get "going".

Supplementary Table 5

Survey items for the 7-item GAD-7

Survey Item
Feeling nervous, anxious, or on edge
Not being able to stop or control worrying
Worrying too much about different things
Trouble relaxing
Being so restless that it is hard to sit still
Becoming easily annoyed or irritated
Feeling afraid as if something awful might happen

Supplementary Table 6

Survey items for the 18-item PSS

Survey Item
I am happy in my role as a parent.
There is little or nothing I wouldn't do for my child(ren) if it was necessary.
Caring for my child(ren) sometimes takes more time and energy than I have to give.
I sometimes worry whether I am doing enough for my child(ren).
I feel close to my child(ren).
I enjoy spending time with my child(ren).
My child(ren) is (are) an important source of affection for me.
Having children gives me a more certain and optimistic view for the future.
The major source of stress in my life is my child(ren).
Having children leaves little time and flexibility in my life.
Having children has been a financial burden.
It is difficult to balance different responsibilities because of my child(ren).
The behaviour of my child(ren) is often embarrassing or stressful to me.
If I had it to do over, I might decide not to have children.
I feel overwhelmed by the responsibility of being a parent.
Having children has meant having too few choices and too little control over my life.
I am satisfied as a parent.
I find my child(ren) enjoyable.

Supplementary Table 7

Survey items for the 12-item WHODAS 2.0

Survey Item
Standing for long periods such as 30 minutes?
Taking care of your household responsibilities/chores?
Learning a new task, for example, learning how to get to a new place?
How much of a problem did you have in joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?
How much have you been emotionally affected by your health problems?
Concentrating on doing something for ten minutes?
Walking a long distance such as a kilometre or equivalent?
Washing your whole body?
Getting dressed?
Dealing with people you do not know?
Maintaining a friendship?
Your day-to-day work/school?