Hair cortisol as a predictor of quality of life among children with mental disorder

by

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AUTHORS DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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ABSTRACT

Children living with mental disorder are at risk for lower health-related quality of life (HRQoL) than their healthy peers. Although hair cortisol concentration (HCC) is found to be elevated among individuals subjected to chronic stress, blunted HCC levels are associated with mental disorders in children. Understanding ways in which mental disorder translates into psychosocial outcomes will help to inform the development of effective interventions and services tailored to specific populations.

This study aimed to determine whether physiological stress was associated with HRQoL in children with mental disorder. Data from 100 children, aged 4-17 years, was collected from tertiary care clinics in south-western Ontario, Canada. The Mini International Neuropsychiatric Interview for Children and Adolescents was administered to measure the presence of eight common mental disorders in childhood; the KIDSCREEN-27 was used to assess HRQoL across five domains, and cortisol was extracted from hair samples collected from children a standard ELISA procedure. Multiple regression analyses were conducted to test the association between HCC and HRQoL.

Results demonstrated that there were no differences in HCC across type of mental disorder, child age, or sex. High HCC was significantly associated with low parent-reported psychological wellbeing HRQoL [β=-0.17; CI: -0.34, -0.00] and school environment HRQoL [β=-0.25; CI=-0.48, -0.03]. The presence of a chronic physical condition and high parental stress scores were found to moderate the relationship between HCC and HRQoL in the domains of peers and social support [β=-0.79; CI=-1.30, -0.28] and physical well-being [β=-0.01; CI=-0.03,-0.00] respectively. These results demonstrate that high HCC is associated with lower reports of HRQL in children with mental disorder. Furthermore, the presence of a physical illness and environments high in parental stress augment the nature of the association between HCC and HRQoL. Thus, approaches that reduce stress and increase coping in children with mental disorder may be helpful in promoting optimal well-being. This study provides compelling evidence that supports the need for further investigation into the links between physiological stress and psychosocial outcomes in children with mental disorder.

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LIST OF ABBREVIATIONS

Hair cortisol concentration ……..……(HCC)

Health-related quality of life ……...……(HRQoL)

Chronic physical illness …….(CPI)

Hypothalamic-pituitary adrenal axis ……(HPA)

Major depressive disorder ……....(MDD)

Attention deficit/hyperactivity disorder ……(ADHD)

Mini International Neuropsychiatric Interview for Children and Adolescents ……(MINI-KID)

Child-reported health-related quality of life ……..(CRHRQoL)

State Trait Anxiety Inventory …….…..(STAI)

Centre for Epidemiologic Studies Depression Scale …….(CESD)

Parental Stress Scale ……..…….(PSS)

SECTION ONE: Introduction

Over the course of the past few decades, with advancements in modern medicine, patterns of illness have shifted from infectious diseases to primarily chronic diseases, including mental disorders (1). Mental disorders are defined as syndromes characterized by disturbances in an individual's cognition, emotion regulation, or behavior (2). According to the DSM-5, mental disorders reflect dysfunction in the "psychological, biological, or developmental processes underlying mental functioning" (2). Due to the nature of psychiatric illness, co-occurring mental disorders are fairly common (3). Mental disorders have negative consequences on an individual's daily life, including but not limited to, loss of economic productivity, relationships, and physical wellness (4).

Recently, childhood mental health has become an increasing concern, as rates of hospitalization soar as a result of mental disorders (5). Mental disorders affect between 10-20% of children worldwide (6). Mental disorders in children aged 5-14 years, ranked second among the causes of disability-adjusted life years in 2015 (7) and accounted for nearly half of all patient days in Canadian hospitals in 2013-2014 (5). Childhood mental disorders have a substantial impact on both the functioning of the individual, and their families (8). Not only are childhood mental disorders having a significant impact on the child's development, but in fact, children with a history of psychiatric illness were three times more likely than their healthy counterparts to have a subsequent diagnosis later in life(3). Due to the persistent nature of mental disorders, many of the problems associated with these disorders continue into adulthood (4,9-10). Adults with a history of childhood mental disorders are more likely to have a lower income, experience unemployment, and be involved in the criminal system (8,11-12).

Childhood mental disorders influence the productivity, health, and the social and economic burden of disease in both childhood and adulthood (13). There is growing recognition that further research into the understanding and the treatment of childhood mental health is essential for the success of future generations. Of particular interest is how mental disorder in children is tied to physiological stress and quality of life. Understanding the mechanisms through which mental disorder translates into

psychosocial outcomes will help to inform the development of effective interventions and services tailored to specific populations. Intervening during these critical stages of development is imperative in order to help children achieve the best possible health outcomes.

SECTION TWO: Literature Review

2.1 Paediatric mental disorders

Roughly 20% of Canadians will experience some form of mental disorder in their lifetime, majority of which have its onset during childhood or adolescence (5). The social determinants of health could explain why some children develop mental illness. Early life experiences have continuously been shown to influence a child's mental health (13-14). Stressors such as abuse and neglect can negatively impact a child's development and often leads to mental health issues. Other risk factors for mental health problems include low socio-economic status, bullying and presence of a chronic physical illness (CPI) (15-18). The presence of a childhood mental disorder in itself is a stressor that can lead to other adverse health outcomes. Children with mental disorders often experience developmental disruptions, stigmatization, and low quality of life (19-21).

2.1.1 Quality of life among children with mental disorders

Health-related quality of life in children is subjective, multidimensional and constantly evolving (22). It must take into consideration aspects of an individual's physical, psychological, and social functioning. Health-related quality of life can be influenced by several aspects of a child's life, including their stage of development and unique individual experiences. Children with mental disorders must also consider their illness and its trajectory when reporting their health-related quality of life (22). Children living with a mental disorder have repeatedly been shown to present with lower health-related quality of life than healthy controls (21,23-24). A systematic review demonstrated that children with mental disorders have compromised health-related quality of life, with the largest effect sizes seen in the psychological and the family-related domains (21).

The health-related quality of life was examined among 45,398 children across England (24). Nearly one third (29%) of the participating children presented with mental health problems. Children were reported to have either internalizing problems, externalizing problems or both. Health-related quality of life was measured using the self-report KIDSCREEN-10 questionnaire. Children who presented with

mental health problems had significantly lower health-related quality of life than the children who were reported to have no mental health problems. The lowest levels of HRQoL were seen among children who had both internalizing and externalizing problems. Only 12% of the children with reported mental health problems were found to have high health-related quality of life. In accordance with these findings, another study examined parent-reported quality of life in 3,597 children, aged 6-17 years, across Australia (23). Children were diagnosed with one of three mental disorders, major depressive disorder, attention deficit/hyperactivity disorder (ADHD), and conduct disorder. Their results showed that children with a mental disorder had significantly lower parent-reported quality of life than healthy controls. These children were reported to have lower self-esteem, and a greater number of behavioural and emotional problems. Interestingly, children diagnosed with MDD were reported to have greater impairments in their overall health perceptions and higher reported levels of pain and discomfort than children diagnosed with ADHD and conduct disorder. Preliminary research is beginning to suggest that children with mental disorders have lower health-related quality of life than children with some chronic conditions, such as, asthma or diabetes (25-26). These findings highlight the critical need for new approaches to support children at risk of low quality of life.

2.1.2 Stress associated with paediatric mental disorders

Parents of children with a mental disorder often perceive that their child's health problems interfere with their peer relationships and with family functioning (23). It was reported that children with depression saw greater impacts on child and peer activities, while children with conduct disorder or ADHD had greater impacts on their relationship with their caregivers (23). Childhood mental disorders place great strain on both the child and their family. Many mental disorders are associated with impairments in many aspects of a child's daily life, including academic performance, relationships, both with their peers and their families, and behaviour at school (26). Many of these children require a higher level of support from their families and the educational system, and as a result suffer from greater stress than their healthy peers.

2.2 The human physiological stress response

The human body has developed a complex set of physiologically adaptive processes that occur in response to stress (27). The hypothalamus is the main regulator of the body's endocrine response to stress, and operates through the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus collects information from its environment through the continuous monitoring of several physiological processes to maintain homeostasis (27). Any deviation from physiological set points initiates a cascade of responses in an attempt to return to homeostasis, resulting in the release of glucocorticoids (27-28). Glucocorticoids and androgenic steroids induce physiological changes in the body, such as increased glucose and fat metabolism (29). The most common glucocorticoid in humans is cortisol, which is known to induce a variety of different physiological and behavioural adaptations that prepare the body to respond to challenging, or threatening situations (28). Behavioural adaptations include increased alertness, arousal and attention, as well as decreased appetite and reproduction (27). These adaptations occur in response to several physiological changes – such as increased blood pressure, heart rate, and blood glucose and fat concentrations – that increase substrate availability to target organs through increased blood delivery (27).

2.2.1 Physiological stress associated with paediatric mental disorders

The HPA axis, is thought to play a critical role in the pathophysiology of mental disorders (30). Altered activity of the HPA axis has been linked to chronic stress and the development of mental disorders in children, specifically anxiety and depressive disorders (30-31). HPA axis dysregulation can be the result of prolonged exposure to stress, traumatic events, genetic factors, and gene-environment interactions (31-32). Children with anxiety disorders have perceptions of the world, such that their everyday lives are filled with numerous stressors (33). This condition of persistent stress can lead to a chronic activation of the HPA axis and can result in a maladaptive stress response.

2.2.2 Attenuation hypothesis

The human stress response serves as the process of returning to homeostasis following a stimulus that the brain perceives as a challenge (29). The stimulus may take the form of a threat to either an

individual's physical or mental capacity. The cumulative wear of several highly stressful experiences on their bodily systems is termed allostatic load (29). According to the attenuation hypothesis, after exposure to the initial stressor, stress levels are elevated as the body is responding to the new stimulus, however, if exposure to the stressor is prolonged, the body may develop a down-regulated stress response (30). This down-regulation results in a lower basal cortisol output and a blunted response to additional acute stressors (34).

2.3 Measurement of cortisol

Physiological levels of stress have typically been quantified using blood, saliva, and urine levels of cortisol. These measures have provided useful for measuring acute stressors. Resting cortisol levels follow a diurnal rhythm (35). Cortisol secretion peaks approximately 30 minutes after waking and decrease over the course of 24 hours until the following waking period when they spike once again (35). When in a condition of stress, the HPA axis produces and releases additional cortisol into the circulation to overcome the stressor. This concentration of cortisol is higher than resting levels and peaks roughly 15-30 minutes after encountering the stressor (36). Although blood, salivary, and urine measurements of cortisol provide accurate and point-specific concentrations for cortisol, they do not provide accurate measures of long-term stress due to the high variability induced from individual and environmental characteristics (37-38).

2.3.1 Hair analysis / new science of hair cortisol

It has recently been established that cortisol concentrations found in human hair provide an alternative measure to the blood, saliva, and urine measurements (39). Hair cortisol concentration (HCC) has been proven to reflect long-term stress placed on the body and is thus thought to be a useful biomarker for chronic stress (39). HCC measurements correlate well with the average of 3 intrapersonal salivary cortisol measurements and are non-invasive (40). Hair typically grows approximately 1 cm/month and cortisol secretion can be accurately backdated, up to 6 months, to reflect the months prior to sampling (41). Any measurements prior to 6 months have been shown to be less accurate, likely do to

shampooing and other damage (42). Due to the chronic nature of mental disorders in youth, a more stable measure of cortisol concentration is required (43). HCC provides a promising biomarker for chronic stress.

2.3.2 Determinants of hair cortisol in children

Several variables have been proposed to be related to HCC in humans. Due to the relatively limited quantity of research surrounding this topic, there is insufficient evidence to determine whether several individual characteristics influence HCC in children.

Age

The existing literature into the influence of age on HCC has reported mixed results. It is suspected that age may influence cortisol levels, particularly during adolescence as a result of pubertal hormone changes (44). A meta-analysis examining determinants of HCC in children and adolescents found inconclusive results as to whether age has an effect on HCC (45). Ten studies were identified that found no significant association between age and HCC (46-55). Of the four studies that found significant associations, the findings were mixed, with two reporting a positive association (56-57) and two a negative association (42,58). It is important to note that several of the studies examined the associations within very narrow age ranges and thus results could present differently if all samples followed similar methodology.

Sex

Similar to the results found with age, there were inconclusive results as to whether sex influences HCC. It is suspected that HCC could differ by sex as a result of sex-linked differences in cortisol responses. Females have been shown to have higher free salivary cortisol levels (59) and a more prolonged cortisol awakening response while males have been shown to have an increased cortisol reactivity to daily stressors (60). Previous research, however, has failed to conclusively quantify the relationship between sex and HCC. The majority of studies have found no significant associations

between sex and HCC in children (48-50,54,56-58,61-64). Multiple studies have found that boys had higher HCC than girls of the same age (46-47,51,65), however, no studies have reported higher HCC in girls than boys. One study examining HCC across a large, diverse sample found that sex and HCC were associated in children up to the age of 10, but became non-significant in children aged 10-17 years (42). Their findings suggested that boys had higher HCC than their female counterparts. Based on available evidence, it is clear that further research is required to solidify the association between sex and HCC in children.

Hair colour

The majority of research conducted to date has not found any significant differences in HCC among various natural hair colours (42,59,64). There have been, however, differences seen in HCC among individuals who artificially colour their hair (66-68). HCC were found to be significantly lower in these individuals.

Hair washing

Certain alcohols, such as those found in many shampoos, have been found to penetrate the hair shaft, possibly leading to the loss of certain substances from the hair (69). It is unclear based on existing research what the impact of hair washing has on HCC. After analyzing multiple 3-cm hair segments (proximal, middle, and distal) of the same hair, there was not found to be a notable difference in the amount of times per week individuals washed their hair for the first two segments (42). There was however, a decrease in HCC in the most distal segment of the hair. This suggests that after a certain period of time, the hair begins to be altered by hair cleansing products. In accordance with these findings, several other studies found no significant differences in HCC depending on hair wash frequency in the first 3 cm or less of hair in children (56,61,63-64,70). Only one study was identified that found a significant relationship between HCC and hair wash frequency. They identified a significant negative relationship, however, it was only present in females (47). Based on these findings, it is reasonable to assume that frequency of hair washing is likely not a significant determinant of HCC in children.

2.4 Hair cortisol and mental disorders

Although there is preliminary research into the association between HCC and psychiatric disorders in adults, there is a significant gap in the literature with regards to children. In line with results from studies using adult samples, preliminary findings support the notion that hair cortisol could serve as a physiological marker of chronic stress and stressful experiences, such as school entry (61), trauma exposure (52), and number of injury events (54), however, the effects of psychopathology remain unclear. A review concluded that there was insufficient evidence to draw an association between HCC and psychiatric illness in children and highlighted the need for further research (45). Some research has been presented investigating the association between HCC and anxiety, depression and ADHD, however, to the best of our knowledge there have been no studies that have explored the relationship between HCC and separation anxiety, social phobia, conduct disorder or oppositional defiant disorder.

The two main classifications of mental disorders are internalizing disorders, comprising mood and anxiety disorders, and externalizing disorders include disorders, such as ADHD, oppositional defiant disorder, and conduct disorder (71). Previous research has demonstrated that a non-categorical approach can be applied when considering children with chronic conditions (72). In this analysis, we will test for differences in hair cortisol concentrations across mental disorder classifications in an effort to support or refute the non-categorical approach when considering mental disorder in this sample of children.

2.4.1 Anxiety disorders

Although the literature has presented some discrepancies with regards to the association between HCC and anxiety, it is suspected that individuals with anxiety have lower HCC than their healthy counterparts. One identified study found that adults with generalized anxiety disorder had 50-60% lower HCC than age and gender matched controls (11.3 pg/mg vs 21/2 pg/mg) (73). By contrast, they found no significant differences in salivary cortisol measurements between adults with and without generalized anxiety disorder, suggesting that despite having a blunted daily cortisol pattern, their response to acute stressors remains the same, supporting the attenuation hypothesis. To date there have only been two

studies that investigate the association between HCC and anxiety in children. The first found a negative association between symptoms of anxiety and HCC among girls aged 10-12 (ß=-0.570 pg/mg SE=0.005) and a negative association between anxiety symptoms and salivary reactivity (ß=-0.427 ng/ml SE=0.118) (74). Interestingly, these associations were not found among boys of the same age. The second found contrasting results in that no significant associations between anxiety and HCCs were presented among their sample of girls. Based on these mixed findings, it is clear that further research is required to define the relationship between anxiety and HCC in children (75).

2.4.2 Depression

Nine studies have been identified that investigate the association between cortisol concentrations and depression in children. Six of the studies specifically examined the association between hair cortisol and depressive symptoms, while the other three examined acute measures of cortisol in children with depression. The existing evidence linking depression and cortisol concentrations has been inconsistent, likely as a result of differing methodology, sample characteristics, and outcome measures. Three of the studies examining HCC and depressive symptoms in children found no significant association (53,64,75). By contrast, one study found a significant positive association in boys (ß=0.553 (SE=0.010)) (74) and the final study found a modest positive association in girls (r=0.33) (76). It is important to note that these associations are found with respect to depressive symptoms in otherwise healthy children. To the best of our knowledge there have yet to be any studies examining HCC in children diagnosed with depression. Evidence from studies using acute cortisol measurements suggests that the HPA axis is dysregulated in children with depression. A study found that circulating (blood or saliva) or secreted (urine) cortisol levels were elevated in 64% of patients diagnosed with depression compared to healthy controls (77). Although the effect size was reduced when the sample was restricted to participants under the age of 18 years, a meaningful difference remained. Results from another study corroborated these findings, in that children with depression had higher baseline cortisol values and overactive cortisol responses to psychological stressors (78). In addition, research into the association between HCC and depression in adults has also produced mixed findings. Two studies found elevated HCC in patients with depression

(24.3 pg/mg vs 16.0 pg/mg; 19.24 pg/mg vs 13.54 pg/mg) (42,79) while a third found no significant association between the two (80). It is clear from the existing literature that further research is required to explore the association between HCC and depression in children.

2.4.3 ADHD

The link between HCC and ADHD appears to be relatively consistent. Two studies were identified that examined the relationship between ADHD and HCC in children. One investigated child HCC in boys aged 4-5 years with ADHD (81). They found that boys presenting with elevated ADHD symptomology had lower HCC than those with lower levels of ADHD symptoms (F_{change}=3.97, p=0.049). The results from their analysis held true when they controlled for co-morbid mental disorder symptoms. The second study found that low HCC predicted an increase in ADHD symptoms over a 12-month period in children aged 4-5 years (82). These findings in addition to the evidence presented using circulating cortisol levels suggests that there is a negative correlation between ADHD and HCC.

2.5 Hair cortisol and health-related quality of life

Two studies have been identified that have examined the relationship between HCC and health-related quality of life in children. The first study, examined the links between HCC, perceived stress and health-related quality of life among healthy children (47). Hair samples from 318 healthy 6- to 8-year-old children in Switzerland found no significant association between HCC and health-related quality of life. They also found no relationship between HCC and stress exposure. Despite these findings, preliminary research into this relationship in children diagnosed with a mental disorder suggests otherwise. The link between hair cortisol and psychopathology or quality of life was explored in a sample of 5-12-year-old children in Germany (83). The children were divided into two groups, the first being a “high-risk” group, consisting of children whose mothers were subjected to early life maltreatment, and the second being a healthy, “low-risk” comparison group. It was found that within the high-risk group, high HCCs were associated with higher levels of quality of life. It was also found that children in the low-risk group with high HCC have a higher number of behavioural problems. These findings support the attenuation

hypothesis in that children who are subjected to higher levels of chronic stress have a maladaptive HPA axis. Children exposed to high levels of stress have a chronically activated stress-system resulting in a blunted diurnal cortisol pattern. Of these children, those with higher HCC reflect the children with the least blunted stress response. Children not exposed to chronic stress could be considered as having a functioning stress response, and therefore individuals with elevated HCCs were those experiencing abnormal stressful experiences. As there are only two identifiable studies investigating this relationship, it is clear that further research is needed to develop a clear understanding the interplay between chronic stress and health-related quality of life.

SECTION THREE: Study Rationale & Research Objectives

3.1 Study rationale

There is limited research examining the link between cortisol and health-related quality of life. Examining the extent to which HCC is associated with HRQoL will inform the understanding of the natural course of physiological stress in children diagnosed with a mental disorder, as well as provide evidence of the biological mechanisms linking mental illness and psychosocial health outcomes in children. Identifying at-risk children and intervening during the critical period soon after diagnosis will help minimize the individual, social and economic burden associated with childhood mental disorders.

Determining if physiological stress is a mechanism through which mental disorder and HRQoL are associated in children will allow for the development of targeted efforts that provide the required support and promote proper stress management techniques among these children. Furthermore, identifying if co-occurring diagnoses or parental mental disorder result in a greater risk of increased physiological stress and lower perceived quality of life will help focus efforts towards at-risk populations. Identifying vulnerable populations, and intervening during this critical period of development, may allow for the promotion of wellness for all family members throughout the child's illness. Intervention efforts that reduce the perception of stress may minimize the long-term detrimental effects of the diagnosis, thereby decreasing the negative mental health impacts of pediatric mental disorders experienced by the entire family.

3.2 Study objectives

The proposed research seeks to determine the relationship between HCC and HRQoL in children diagnosed with a mental disorder. Specifically, this study aims to determine whether physiological stress is a variable that helps explain the association between presence of a mental disorder and low levels of parent-reported HRQoL in children with a mental disorder.

The proposed study has the following four objectives:

1. To examine whether HCC differ across different mental disorders, age, or sex.

2. To quantify the association between HCC and parent-reported HRQoL in children diagnosed with a mental disorder.
3. To investigate whether age, sex, socio-economic status, child's physical health status, or parental mental disorder, moderate the relationship between HCC and HRQoL in children with a mental disorder.
4. To conduct an exploratory analysis into whether there is an association between HCC and child-reports of HRQoL.

3.3 Hypotheses

Based on the literature review and the current research objectives, we hypothesize that HCC will be positively associated with both parent-reported and child-reported HRQoL in children with mental disorder. It is suspected that children with mental disorder are exposed to prolonged periods of elevated physiological stress and as a result, are at-risk for developing a maladaptive HPA axis. A maladaptive HPA axis would result in a blunted daily cortisol pattern, and therefore higher HCC will be associated with positive outcome, in this case, higher HRQoL. The null hypothesis is such that HCC will be inversely associated with HRQoL among children with mental disorder. This hypothesis implies that this sample of children will not have been subjected to high levels of chronic stress for a sufficient enough period of time to experience the attenuation hypothesis. As a result they will have a normal functioning HPA axis with elevated HCC being associated with negative outcome. Therefore, higher HCC will be associated with lower HRQoL. Due to the paucity of previous literature, and inconsistent results in the literature that has been done, it is difficult to hypothesize whether age and sex will moderate the relationship between HCC and HRQoL. We do, however, hypothesize that having a co-morbid CPI and impaired parental mental health will moderate the relationship between HCC and HRQoL.

SECTION FOUR: Methods

4.1 Sample

Data come from two studies examining multimorbidity in children. Multimorbidity is the presence of two or more chronic health conditions, either mental or physical (84). The first, a cross-sectional study conducted from 2015-17, examined the burden and predictors of co-morbid chronic physical illnesses among children with mental disorders who were currently receiving mental health services (85). Children were recruited from the Children and Youth Mental Health Program at McMaster Children's Hospital. To be eligible for the study, children must have met the following criteria: [1] aged 4-17 years at the time of recruitment; [2] were classified as having at least one of generalized anxiety disorder, separation anxiety disorder, major depressive disorder, attention deficit/hyperactivity disorder, conduct disorder, or oppositional defiant disorder; and, [3] have a parent/guardian who was the primary caregiver in the three months prior to referral to the mental health program. This study received ethical approval from the Hamilton Integrated Research Ethics Board (15-197).

Over the study recruitment period, a total of 259 eligible children were identified. Of these children and their families, 144 (56% response rate) were interested in participating and provided consent. One hundred (39% retention) families completed telephone diagnostic interviews, however, six children did not complete the required questionnaires resulting in a final sample of 92 child-parent dyads (36% retention).

The second, a prospective pilot study conducted from 2014-16, examined the prognosis and risk of co-occurring mental disorder in a sample of children with chronic physical illnesses (86). Children were recruited from respiratory, allergy, and endocrinology clinics at McMaster Children's Hospital in Hamilton, Ontario and from neurology and rheumatology clinics at Children's Hospital London Health Sciences in London, Ontario and followed for six months. Children were included in the study if they met the following three eligibility criteria: [1] they were aged 6-16 years at the time of recruitment; [2] have been diagnosis with asthma, diabetes, epilepsy, food allergy, or juvenile idiopathic arthritis, within the previous 6 months; and [3] had at least one parent that could read English. This study received ethical

approval from the Hamilton Integrated Research Ethics Board (14-130) and Western Research Ethics Board (105505).

Over the six-month recruitment period, a total of 62 families were approached. Of these families, four were not interested in participating and two had children who did not meet the eligibility criteria, resulting in 56 (90% response rate) participating families. Fifty families (83%) completed the baseline telephone interview and mail questionnaires. Researchers were unable to contact the six families who agreed to participate but did not return the mail questionnaires. An additional six families were lost to follow-up over the course of the study with forty-four families completing the 6-month follow-up questionnaires (88% retention).

The sample for the proposed study consists of children, aged 4-17 years, who have been diagnosed with one of the eight most common childhood mental disorders: major depressive disorder, generalized anxiety disorder, separation anxiety disorder, social phobia – generalized and non-generalized, specific phobia, ADHD, conduct disorder, and oppositional defiant disorder. The children whose data was considered eligible for use in the current study were all children included in study 1 and those in study 2 who screened positive for a mental disorder either at baseline or at the six-month follow-up. To be included in these analyses, children and their parents must have completed the questionnaire package and provided hair samples. The final sample included 100 children (72 from study 1; 28 from study 2), aged 4-17 years, with a mean age of 13.0 years; 67% of the children were female; and, 47% had a co-morbid chronic physical illness. Characteristics of the sample are shown in Table 1. Because the objective of this thesis was to examine the relationship between HCC and HRQoL among children with a mental disorder, only data from the first instance in which children from study 2 screened positive for mental disorder were included. For example, if a child had a negative screen at recruitment (baseline), but a positive screen at the six-month follow-up, then the follow-up data were used in the analysis. Relatedly, if a child screened positive at both measurement occasions, then baseline data were used. In this regard, 25 children screened positive for a mental disorder at baseline and three children at six months.

The two samples of children were recruited from tertiary care clinics in the same region of south-western Ontario, Canada and followed extremely similar recruitment and data collection procedures.

Statistical testing was completed to ensure that the samples were acceptable to merge for this analysis. Results are presented in Table 1. There was an absence of significant differences in the majority of the sample sociodemographic characteristics including parental education, income, marital status and immigration status. The only significant differences between the two samples were found with child age and sex, with study 1 having a slightly older sample and a greater proportion of females than study 2. In the context of this study, these differences render the sample more inclusive.

4.2 Data collection

Participant recruitment procedures were similar for both studies. Children visiting their clinic who met the inclusion criteria were identified and their families were informed about the study by clinic staff (e.g., clinic nurse). If the children and their families expressed interest in participating, they were provided an overview of the study in the form of a letter and signed a release of information, granting research staff permission to contact them via telephone or email to answer study-related questions and arrange participation.

Data collection procedures differed slightly for the two studies. Data collection for study 1 occurred entirely at the research office or in the clinics. Once participants were identified, research staff scheduled a time for children and their families to complete the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) to screen for mental disorder and the other study questionnaires. All responses were collected electronically on tablets. Hair sampling was completed at the clinic by a member of the research team. Data collection for study 2 occurred primarily by telephone and through mail questionnaires. Telephone interviews were scheduled with participating families to administer the MINI-KID interview. Two mail packages were sent out via post including all necessary self-report questionnaires and detailed instructions for providing the hair sample. The first study package was sent at the time of recruitment into the study (baseline) and again 6-months later (follow-up). A second diagnostic MINI-KID interview was completed at time of follow-up. All parents of recruited children completed the mail questionnaires and the MINI-KID phone interview as a proxy. Children

under the age of 11 did not complete any study questionnaires, while children ≥11 years of age completed the MINI-KID phone interview, and the self-report mail questionnaires.

Table 1: Sample Characteristics

Variable	TOTAL	MY	REACH	T – statistic / chi square / Fisher Exact	P value
Age in years (SD)[a]	13.0 (3.43)	13.69 (3.25)	11.29 (3.23)	3.86	0.000
Sex					
Male	33	18	15	6.03	0.014
Female	67	54	13		
Income					
<$15-29,999	9	9	0		
$30-74,999	31	26	5		0.046
$75-89,999	13	9	4	8.01	
$90,000+	45	28	17		
Parental Education					
≤ Completion of high school	21	18	3		
Completed vocational/technical training/ college/university	66	44	22	-	0.014
Completed graduate/professional school	13	10	3		
Marital Status					
Partnered	66	44	22	-	0.203
Non-partnered	34	28	6		
Major depressive disorder (MDD)	65	54	11	12.05	0.000
Generalized anxiety disorder (GAD)	56	51	5	-	0.001
Separation anxiety disorder (SAD)	30	28	2	-	0.001
Social phobia					
Generalized social phobia (GP)	41	38	3	-	0.001
Non-generalized social phobia (NGP)	10	8	2		0.515
Specific phobia (SP)	25	18	7	0.26	0.613
Attention deficit / hyperactivity disorder (ADHD)	32	25	7	0.60	0.440
Conduct disorder (CD)	22	19	3	-	0.051
Oppositional defiant disorder (ODD)	43	35	8	3.40	0.065
Children with a co-morbid physical illness	43	15	28	-	-

Sample size is 100 therefore values represent both n and percentages.

[a] Data is presented as a mean

4.3 Study measures

All measures outlined in the current study were collected through diagnostic interviews or self-report questionnaires in both pilot studies.

Mental disorder. Child mental disorder was measured using the MINI-KID, a short, structured, diagnostic interview (81). The MINI-KID accurately diagnoses DSM-4 disorders in children up to the age of 17 (87). It has been previously validated against the Schedule for Affective Disorders and Schizophrenia for School Aged Children- Present and Lifetime Version (87). Two versions of the MINI-KID exist, one for children and a proxy version completed by caregivers. Questions on the two versions remain identical aside from the original asking questions *directly to* the child, while the parent version asks *about* the child. Within the MINI-KID there are eight "modules", each focusing on a common childhood mental disorder. Each module begins with screening questions, and progresses based on response patterns. The MINI-KID has demonstrated good concordance between the child and parent versions (87) and strong test retest reliability (88).

Quality of life. The KIDSCREEN-27 is a generic health-related quality of life (HRQoL) measure, previously validated for children and adolescents with and without chronic illnesses (89). The KIDSCREEN-27 assesses HRQoL across 5 dimensions: Physical Well-Being; Psychological Well-Being; Parents & Autonomy; Peers & Social Support; and School Environment. Physical Well-Being assesses the child's physical activities and general health; Psychological Well-Being assesses general mood and feelings about oneself; parents and autonomy assesses the child's family and free time; Peers and Social Support examines the child's relationships with their friends; and School Environment examines the child's school and learning experience. Each domain has between 5-7 items and is scored using a Likert scale. The possible results ranged from: Never [1], Seldom [2], Quite Often [3], Very Often [4], to Always (5). Raw total scores are transformed to T-values with a mean of 50 and a standard deviation of 10. The KIDSCREEN-27 has been previously used in children with mental disorder (90). The KIDSCREEN-27 has been shown to have acceptable parent-child agreement (91-92). Internal consistencies for parent- and child-reported scores, as indicate by Cronbach α, have been reported as

robust in this sample across all domains except physical well-being [Physical Well-Being: 0.65; Psychological Well-Being: 0.80; Parents & Autonomy: 0.80; Peers & Social Support: 0.87; and School Environment:0.84] (93).

Hair cortisol concentration (HCC). Hair cortisol was collected as the measure of chronic physiological stress in children. Parents collected hair samples from their children and returned them to study investigators in person in study 1 or with the mail questionnaires in study 2. Roughly 50-60 dry hairs were collected from the posterior vertex of each child. If the child had shorter hair, 15-20 hairs were collected from 4-5 different locations along the posterior vertex. Hair samples were attached to a sheet of paper with a paper clip and were aligned with a mark to indicate the scalp end. A hair sampling questionnaire was completed by parents that included variables hypothesized to affect HCC, such as medication use, hair length and colour, hair washing and treatments, smoke exposure, and ethnicity (42,45). Hair samples were analyzed using high-sensitivity enzyme-linked immunosorbent assays protocol and HCC were measured and reported using units of pg/mg.

The protocol for the hair processing was based on that of Vaghri & Hertzman (94) and followed standard procedures for washing, extraction and cortisol assays. The hair samples were measured from the end proximal to the scalp and cut into 3cm segments. The hair was washed twice in 12.0mL of isopropanol. The hair and isopropanol were placed in an enclosed Falcon 50.0mL Conical Centrifuge tube and the mixture was shaken by hand for 2min. After the first wash, the isopropanol was discarded while after the second wash, the top of the tube was wiped and the tube was left open for 48hrs to air dry. Following the wash, the hair was ground using a ball mill. Four stainless steel ball bearings were placed in a grinding jar with the dried hair samples. The jar was run in a Retsch CryoMill at a frequency of 25Hz for three minutes. After being ground, 30-35mg of the sample was placed in a 2.0mL Eppendorf tube with 1.0mL of 100% ethanol. The tube was shaken and then placed on the Mix-All Laboratory Tube Mixer for 24hrs at 22rpm. The hair was extracted from the ethanol solution using two-step procedure and a centrifuge. During the first extraction, the samples were vortexed for 2-3 seconds and then centrifuged at 3500rpm for 15 minutes. Next, 0.8mL of the supernatant was pipetted into a clean 2.0mL conical tube. The tubes were left open to air dry for 48 hours to allow for the supernatant to evaporate completely.

Once dried, 10mL of 100% ethanol was added to the original tubes which were then placed on the Mix-All for an additional 48hours. The same extraction process was repeated except with 1.0mL of the supernatant extracted. The supernatant was reconstituted with 150 μL of Salimetrics Salivary Cortisol Assay Diluent. The mixture was vortexed for five seconds, and then centrifuged for 10 minutes. The samples were then assayed by ELISA using the High Sensitivity Salivary Cortisol Immunoassay Kit (Cat# 1-3002, Salimetrics, Pennsylvania), as per manufacturer instructions. The current protocol opted to use 100% ethanol as opposed to methanol as per the Vaghri & Hertzman procedures. A pilot test was run and determined that the values were highly correlated and therefore laboratory technicians opted for the less toxic and abrasive ethanol. Cortisol levels are expressed as pg/mg of hair. Intra and inter-assay coefficients of variance were below 10% in the present study.

Sociodemographic Characteristics. Sociodemographic information was collected through a parent-report questionnaire. Information included child and parent age, sex, and immigration status, parental education, parental marital status, and annual household income.

4.4 Data analysis

Descriptive statistics calculated the frequencies of each mental disorder among the sample, the proportion of children with physical-mental multimorbidity, and various other relevant sample characteristics The independent variable for this analysis was child HCC. HCC was coded as a continuous variable with higher values representing higher concentrations. The dependent variables were the HRQoL scores for each of the five domains on the KIDSCREEN-27. Multiple regression analyses were conducted to test the association between HCC and HRQoL, adjusted for child age and sex. Product-term interactions were used to determine if age, sex, socioeconomic status, presence of a physical illness or parental mental disorder moderated the association between HCC and HRQoL or self-concept.

Selection of variables. Because only the subset of children >10 years provided self reports, these analyses used parent-reported data to maximize the sample available for analysis. An exploratory analysis was completed using the subset of the sample that completed the child-reported HRQoL questionnaire to explore the association between HCC and child-reported HRQoL. Because children under the age of 10

did not complete the MINI-KID diagnostic interview or any mail questionnaires, the analysis was carried out using the results from the parental MINI-KID, and KIDSCREEN-27.

4.5 Effect moderators

There are several variables that could have acted as effect moderators in the association between HCC and quality of life. Effect modifiers are any additional variable that may affect the strength of the association between the independent and dependent variables (95). Effect modifiers have the potential to increase, decrease, or mask a true association. The primary variables that we tested for effect modification were child's sex, child's age, socioeconomic status – specified through parental income and parental diagnosis with a mental disorder, and child physical health status.

4.6 Modelling

Given that the analysis uses both continuous and binary predictor variables, we used the following general linear model, given by:

$$Y_i = \beta_0 + \beta_1 X_{1i} + \cdots + \beta_k X_{ki} + \varepsilon_i \; ; \; i = 1, \dots , n$$

where

Y_i is the continuous outcome for subject i;

$X_{1i,} \dots , X_{ki}$ are (fixed) k explanatory variables for subject i;

$\beta_0, \beta_{1,} \dots , \beta_k$ are the (fixed) unknown regression coefficients for each of the predictor variables.

ε_i are *i.i.d* from Normal with mean zero and constant variance σ^2,

i.e. $\varepsilon_i \overset{iid}{\sim} N(0, \sigma^2)$ and for any $i \neq j, \; (X_i, Y_i) \perp \left(X_j, Y_j\right)$.

4.6.1 Objective 1

Objective 1 examined if HCC differs across the different mental disorders (Model 1), age (Model 2), or sex (Model 3). HCC data were tested for normality using the Shapiro-Wilk test. Results indicated that data were not normally distributed and skewed to the right [W=0.843; p=<0.0001]. As a result the

nonparametric Kruskal-Wallis and Mann-Whitney U tests were used to determine whether HCC differs depending on the child's age, sex, or mental disorder.

4.6.2 Objective 2

Objective 2 examined the association between HCC and HRQoL scores while controlling for age and sex using general linear regression models. Five separate models (Models 4-8) were run, one for each of the specific HRQoL domains (Physical, Psychological, Peers, Parents, and School). A multivariable linear regression model was run for the continuous outcome variable of HRQoL (one specific domain) with the predictor variable of HCC while controlling for age and sex.

$$HRQoL_i = \beta_0 + \beta_1\, HCC_i + \beta_2 AGE_i + \beta_3 SEX_i + \varepsilon_i\ ;\ i = 1, \dots, n$$

β_1 is the effect of HCC on HRQoL; β_2 is the effect of age on HRQoL, β_3 is the effect of the sex on HRQoL, β_0 is the intercept and ε_i is the residual in the equation.

4.6.3 Objective 3

Objective 3 examined which variables moderated the association between HCC and HRQoL scores. Moderators included age, sex, socioeconomic status, chronic physical illness, parental stress and parental mental disorder. Five separate models (Models 9-13) were run, one for each of the specific HRQoL domains (Physical, Psychological, Peers, Parents, and School). A multivariable linear regression model was run for the continuous outcome variable of HRQoL (one specific domain) with the predictor variable of HCC while testing for effect modification for AGE, SEX, Socioeconomic status, Parental MD, and Physical health status.

$$\begin{aligned} HRQoL_i = {} & \beta_0 + \beta_1\, HCC_i + \beta_2 AGE_{ki} + \beta_3 SEX_i + \beta_4 SES_i + \beta_5 Parental\ MD_i \\ & + \beta_6 Physical\ Health\ Status_i + \beta_7 HCC * AGE_{\ i} + \beta_8 HCC * SEX_{\ i} + \beta_9 HCC * SES_{\ i} \\ & + \beta_{10} HCC * Parental\ MD_{\ i} + \beta_{11} HCC * Phsyical\ Health\ Status_{\ i} + \varepsilon_i\ ;\ i = 1, \dots, n \end{aligned}$$

β_1 is the effect of HCC on HRQoL; β_2 is the effect of age on HRQoL, β_3 is the effect of the sex on HRQoL, β_4 is the effect of the socioeconomic status on HRQoL, β_5 is the effect of presence of a parental mental disorder on HRQoL, β_6 is the effect of the child's physical health status on HRQoL, β_7 is the effect of the product of HCC and age on HRQoL, β_8 is the effect of the product of HCC and sex on HRQoL, β_9 is the effect of the product of HCC and socioeconomic status on HRQoL, β_{10} is the effect of the product of HCC and the presence of a parental mental disorder on HRQoL, β_{11} is the effect of the product of HCC and the child's physical health status on HRQoL, β_0 is the intercept and ε_i is the residual in the equation. The regression coefficients $\beta_{7\text{-}11}$ provided an estimate of the effect of the moderating variables; if any of $\beta_{7\text{-}11}$ were found to be statistically different from zero, the corresponding moderator would significantly moderate the association between HCC and HRQoL.

4.6.4 Objective 4

Objective 4 was an exploratory analysis of the association between HCC and child-reported HRQoL scores while controlling for age and sex. Five separate models (Models 14-18) were run, one for each of the specific HRQoL domains (Physical, Psychological, Peers, Parents, and School). A multivariable linear regression model was run for the continuous outcome variable of child-reported HRQoL (one specific domain) with the predictor variable of HCC while controlling for AGE and SEX. Since this is an exploratory data analysis, the analysis was carried out at an alpha of 0.2.

$$child - reported\ HRQoL_i = \beta_0 + \beta_1\ HCC_i + \beta_2 AGE_i + \beta_3 SEX_i + \varepsilon_i\ ;\ i = 1, \dots, n$$

β_1 is the effect of HCC on child-reported HRQoL; β_2 is the effect of age on child-reported HRQoL, β_3 is the effect of the sex on child-reported HRQoL, β_0 is the intercept and ε_i is the residual in the equation.

4.7 Ethics

This thesis project has received approval by the Office of Research Ethics at the University of Waterloo (23025).

SECTION FIVE: Results

5.1 Sample characteristics

A total of 100 children, ranging in age from 5-17 years, provided complete hair samples along with all other essential study outcomes. The participating children had a mean age of 13.0 (standard deviation (SD) 3.43) years, and over two-thirds were female (67%). The majority (65%) of children had brown hair, 26% had blonde hair, 6% had red hair, and 2% had black hair. Roughly one-third of the children (30%) were exposed to household smoke, either from their parents or being smokers themselves. Fifty-two percent of children screened positive for an internalizing disorder only, 7% with an externalizing disorder, and 41% screen positive for both an internalizing and externalizing disorder. Approximately half (47%) of children had a co-morbid chronic physical illness. Most children (45%) came from families whose household income was ≥$90,000 per year. Additional sample characteristics are presented in Table 2.

Table 2: Sample characteristics

Variable	% of sample
Age in years[a]	13.0 (3.43)
Sex	
Male	33
Female	67
Hair Colour	
Blonde	25
Brown	65
Black	2
Red	6
Hair Washing (# per week) (SD)[a]	3.8 (1.89)
Smoke Exposure	
Not exposed	66
Exposed	29
Income	
<$15-29,999	9
$30-74,999	31
$75-89,999	13
$90,000+	45
Parental Education	
≤ Completion of high school	21
Completed vocational/technical training/ college/university	66
Completed graduate/professional school	13
Marital Status	
Partnered	66
Non-partnered	34
Mental Disorder	
Internalizing Disorder	52
Externalizing Disorder	7
Both Internalizing & Externalizing Disorders	41
Children with a co-morbid physical illness	43

[a] Data is presented as a mean

5.2 Hair cortisol and sample characteristics

Nonparametric tests did not find statistically significant differences in HCC between child age (Kruskal-Wallis Test: p=0.065) or sex (Mann-Whitney U test: p=0.188). Similarly, there were no statistically significant differences in HCC depending on whether the child was diagnosed with internalizing mental disorder, externalizing mental disorder, or both (Kruskal-Wallis test: p=0.401). The results from these tests are presented in Table 3. Figures 1,2, and 3 illustrate the distributions of HCC across child age, sex and mental disorder.

Table 3: Hair cortisol concentrations across child's age, sex, and type of mental disorder

Variable	# of children	Median value for HCC (Quartile 1; Quartile 3)	p-value
Age in years			
5-7 years	14	11.61 (Q1 6.61; Q3 27.71)	
8-10 years	8	9.87 (Q1 7.30; Q3 24.73)	0.065
11 -13 years	27	7.34 (Q1 6.18; Q3 15.22)	
14-17 years	51	6.58 (Q1 3.56; Q3 10.96)	
Sex			
Male	33	9.10 (Q1 6.25 ; Q3 15.42)	0.188
Female	67	7.23 (Q1 3.65; Q3 12.60)	
Mental Disorder			
Internalizing	52	8.76 (Q1 3.95; Q3 12.48)	
Externalizing	7	7.88 (Q1 6.45; Q3 15.42)	0.708
Internalizing & Externalizing	41	8.03 (Q1 5.27; Q3 12.84)	

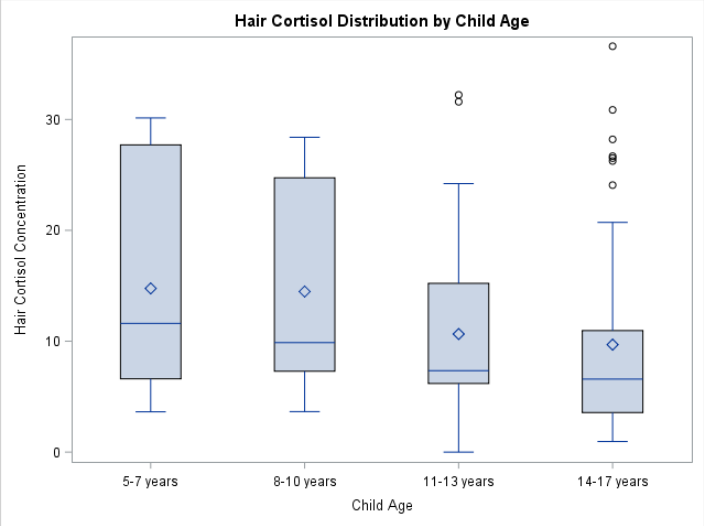

Figure 1: Distribution of hair cortisol concentration by child age

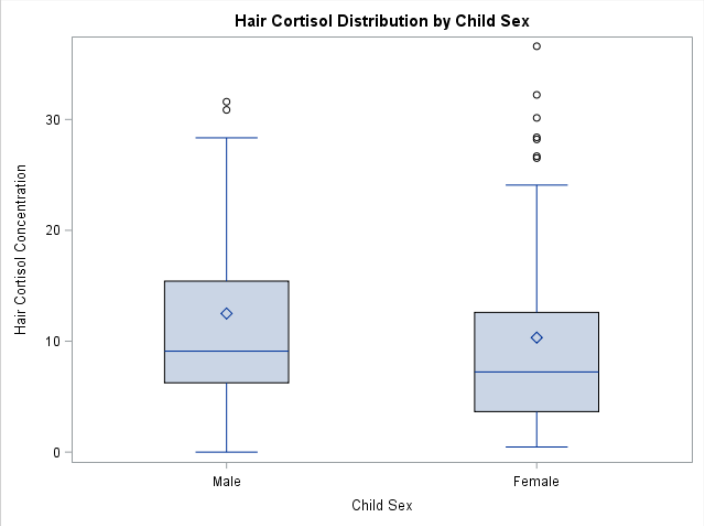

Figure 2: Distribution of hair cortisol concentration by child sex

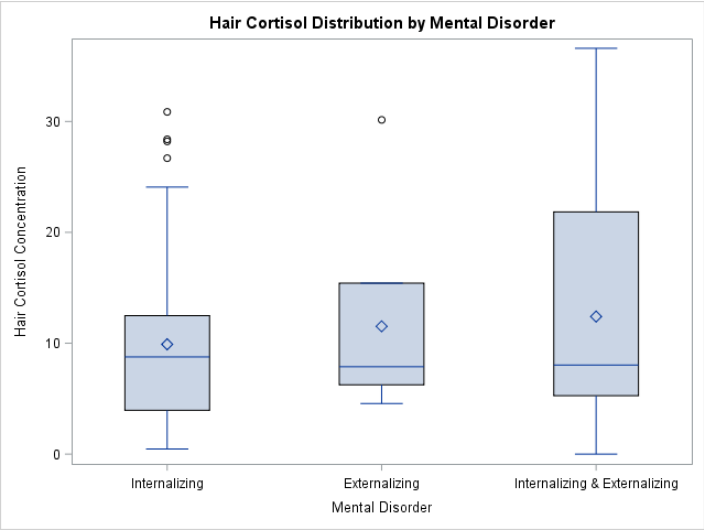

Figure 3: Distribution of hair cortisol concentration by child mental disorder

5.3 Hair cortisol and health-related quality of life analysis

Multivariable analyses show that HCC was significantly associated with parent-reported HRQoL in children with a mental disorder. The results of the HCC and HRQoL analysis are presented in Table 4. Adjusting for child age and sex, aligning with the hypotheses, higher HCC was associated with lower scores of psychological well-being [β=-0.17, p=0.048]. Similarly, higher HCC was associated with lower scores of HRQoL regarding school environment [β=-0.25, p=0.029]. HCC was not significantly associated with HRQoL scores in the domains of physical well-being [β=0.05, p=0.580] parents & autonomy (β=-0.04, p=0.678), and peers and social support (β=-0.16, p=0.208).

Table 4: Association between hair cortisol concentrations and parent-reported health-related quality of life

Health Related Quality of Life Domain	**Unadjusted**		**Adjusted**	
	β	**95% CI**	**β**	**95% CI**
Physical Well-being	0.19	-0.03, 0.41	0.05	-0.13, 0.24
Psychological Well-being	-0.08	-0.27, 0.10	-0.17*	-0.34, -0.00
Parents & Autonomy	-0.00	-0.18, 0.18	-0.04	-0.22, 0.15
Peers & Social Support	-0.12	-0.38, 0.14	-0.17	-0.43, 0.10
School Environment	-0.14	-0.39, 0.11	-0.25*	-0.48, -0.03

* Denotes significant at p<0.05.

5.4 Hair cortisol and HRQoL effect modifiers

Multivariable regression models were used to test potential effect modifiers in the relationship between HCC and HRQoL. Effect modifiers that were tested included child age, sex, presence of any co-morbid physical illness, type of mental disorder, parental mental health status, and household income. All models were adjusted for child age and sex.

5.4.1 Child age and sex

As shown in Model 1 found in Table 5, child age was not found to moderate the association between HCC and any of the five HRQoL domains [physical well-being (β=-0.03, p=0.189), psychological well-being (β=0.01, p=0.837), peers & social support (β=0.01, p=0.738), school environment (β=0.04, p=0.225), or parents & autonomy (β=-0.01, p=0.655)].

Similarly, child sex was not found to be a significant moderator in the association between HCC and HRQoL [physical well-being (β=0.31, p=0.110), psychological well-being (β=0.14, p=0.413), peers & social support (β=0.24, p=0.381), school environment (β=0.26, p=0.271), and parents & autonomy (β=0.19, p=0.094)]. Results from the regression analysis are presented in Model 2 in Table 5.

5.4.2 Co-morbid physical illness

The presence of a chronic physical illness was found to moderate the association between HCC and HRQoL in the domain of peers and social support [β=-0.79, p=0.003]. As shown in Figure 1, parent-reported HRQoL scores in the domain of peers and social support were lower at higher HCC in children with a co-morbid chronic physical illness [t=-3.09, p=0.003]. The presence of a co-morbid physical illness was not found to moderate the association between HCC and any of the other four HRQoL domains [physical well-being (β=-0.13, p=0.488), psychological well-being (β=-0.08, p=0.629), school environment (β=-0.18, p= 0.436), and parents & autonomy (β=-0.08, p=0.670)]. Results from the regression analysis are presented in Model 3 in Table 5.

The moderating effects of having a comorbid CPI were further explored using a post-hoc probing technique previously described (96). Conditional moderator variables centered around zero were calculated to allow for post-hoc regression sets to be run. This examined two-way interaction effects of the moderating variable on the relationship between the independent (HCC) and dependent (HRQoL) variables. Figure 4 illustrates the regression lines at high (1 SD above the mean) and low (1 SD below the mean) values of the moderating variable, in this case HCC.

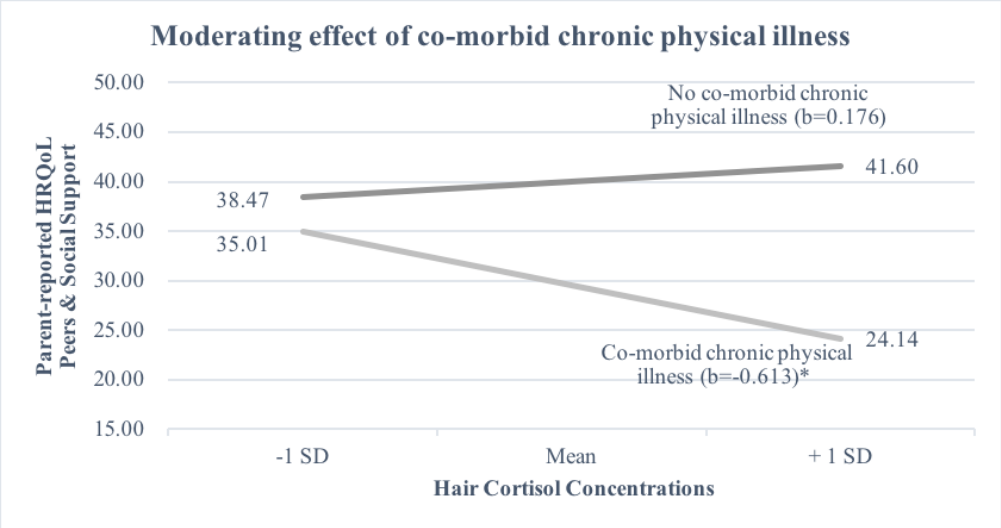

Figure 4: Effect modification of having a co-morbid physical illness (* $p<0.05$)

5.4.3 Mental disorder

The type of mental disorder was tested as a potential effect modifier, comparing children with internalizing disorder to those with externalizing disorder, and to those with both internalizing and externalizing disorder. As shown in Model 4 found in Table 5, mental disorder was not found to moderate the association between cortisol and any of the five HRQoL domains [physical well-being (β=-0.05, p=0.621), psychological well-being (β=0.09, p=0.311), peers & social support (β=-0.17, p=0.235), school environment (β=-0.00, p=0.988), and parents & autonomy (β=-0.03, p=0.754)].

5.4.4 Parental mental health status

Parental mental health status was examined as a possible effect modifier in the relationship between HCC and HRQoL. Specifically, parental scores on the State Trait Anxiety Inventory (STAI), Centre for Epidemiologic Studies Depression Scale (CESD), and the Parental Stress Scale (PSS) were used. Parental scores on the STAI measure were not found to moderate the relationship between HCC and any of the five HRQoL domains [physical well-being (β=-0.01, p=0.554), psychological well-being (β=-0.01, p=0.570), peers & social support (β=-0.02, p=0.373), school environment (β=-0.02, p=0.261), and parents & autonomy (β=-0.00, p=0.868)]. Results from the moderation analysis are presented in Model 5 in Table 5.

Similarly, parental scores on the CESD measure were not found to moderate the relationship between HCC and any of the five HRQoL domains [physical well-being (β=-0.39, p=0.60), psychological well-being (β=-0.32, p=0.092), peers & social support (β=-0.18, p=0.44), school environment (β=-0.27, p=0.75), and parents & autonomy (β=-0.03, p=0.37)]. Results from the moderation analysis are presented in Model 6 in Table 5.

As shown in Model 7 found in Table 5, parental scores on the PSS measure were not found to moderate the relationship between HCC and HRQoL in the domains of psychological well-being (β=-0.00, p=0.529), peers & social support (β=-0.00, p=0.923), school environment (β=-0.01, p=0.467), and parents & autonomy (β=-0.01, p=0.273)]. PSS scores were, however, found to be a significant effect moderator in the domain of physical well-being (β=-0.01, p=0.034). Figure 1 illustrates the relationship between HCC and HRQoL at different levels of parental stress scores. Results indicated that parent-reported HRQoL scores in the domain of physical well-being tended to be higher at higher HCC when scores on the parental stress scale are low [t=2.38,p=0.0195]. A similar procedure for the post-hoc probing of the moderating effect of parental stress score was followed as used in the analysis of comorbid chronic physical condition.

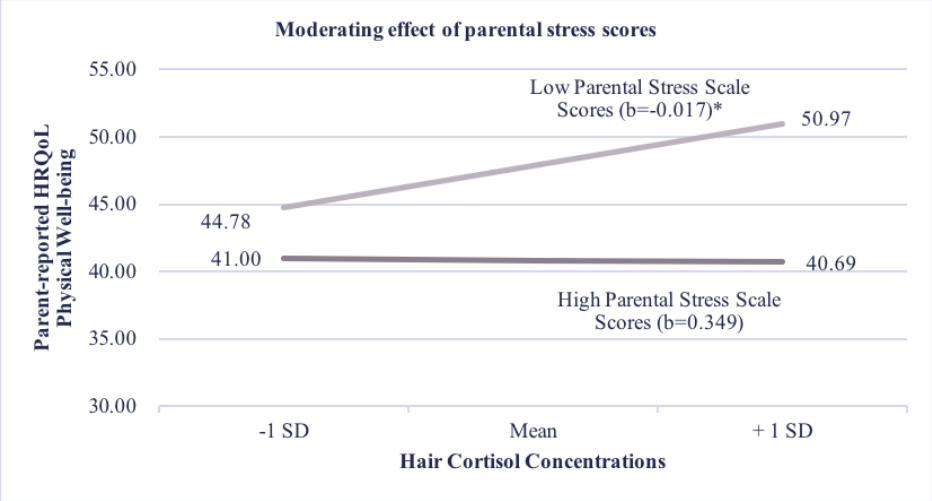

Figure 5: Effect modification of parental stress scores (*p<0.05)

5.4.5 Socioeconomic status

In this analysis, socioeconomic status was represented by total household income. Socioeconomic status was not found to moderate the association between cortisol and any of the five HRQoL domains [physical well-being (β=-0.12, p=0.261), psychological well-being (β=-0.17, p=0.092), peers & social support (β=-0.27, p=0.085), school environment (β=-0.15, p=0.274), and parents & autonomy (β=-0.09, p=0.392)]. Results from the moderation analysis are presented in Model 8 in Table 5.

Table 5: Effect modification in the relationship between hair cortisol concentrations and parent-reported child health-related quality of life

Health Related Quality of Life Domain	ß	95% CI		P-value
MODEL 1: Effect modification of child's age				
Physical Well-being	-0.03	-0.08	0.02	0.189
Psychological Well-being	0.01	-0.04	0.05	0.837
Peers & Social Support	0.01	-0.06	0.08	0.738
School Environment	0.04	-0.02	0.10	0.225
Parents & Autonomy	-0.01	-0.06	0.04	0.655
MODEL 2: Effect modification of child's sex				
Physical Well-being	0.31	-0.07	0.68	0.110
Psychological Well-being	0.14	-0.20	0.49	0.413
Peers & Social Support	0.24	-0.30	0.77	0.381
School Environment	0.26	-0.20	0.72	0.271
Parents & Autonomy	0.19	-0.06	0.69	0.094
MODEL 3: Effect modification of having a co-morbid chronic physical illness				
Physical Well-being	-0.13	-0.50	0.24	0.488
Psychological Well-being	-0.08	-0.38	0.23	0.629
Peers & Social Support	-0.79	-1.30	-0.28	0.003

School Environment	-0.18	-0.64	0.28	0.436
Parents & Autonomy	-0.08	-0.46	0.30	0.670
MODEL 4 : Effect modification of type of mental disorder				
Physical Well-being	-0.05	-0.23	0.14	0.621
Psychological Well-being	0.09	-0.09	0.27	0.311
Peers & Social Support	-0.17	-0.44	0.11	0.235
School Environment	-0.00	-0.23	0.22	0.988
Parents & Autonomy	-0.03	-0.22	0.16	0.754
MODEL 5: Effect modification of parental scores on the state trait anxiety inventory				
Physical Well-being	-0.01	-0.03	0.02	0.554
Psychological Well-being	0.01	-0.03	0.02	0.570
Peers & Social Support	-0.02	-0.05	0.02	0.373
School Environment	-0.02	-0.05	0.01	0.261
Parents & Autonomy	-0.00	-0.03	0.02	0.868
MODEL 6: Effect modification of parental scores on the center of epidemiologic studies depression scale				
Physical Well-being	0.39	-0.80	0.02	0.059
Psychological Well-being	-0.32	-0.69	0.05	0.092
Peers & Social Support	-0.18	-0.75	0.40	0.546
School Environment	-0.27	-0.77	0.26	0.294
Parents & Autonomy	-0.03	-0.48	0.42	0.881
MODEL 7: Effect modification of parental scores on the parental stress scale				
Physical Well-being	-0.01	-0.03	-0.00	0.034
Psychological Well-being	-0.00	-0.02	0.01	0.529
Peers & Social Support	-0.00	-0.02	0.02	0.923
School Environment	0.01	-0.01	0.02	0.467
Parents & Autonomy	0.01	-0.01	0.02	0.273
MODEL 8: Effect modification of familial socioeconomic status				
Physical Well-being	-0.12	-0.34	0.09	0.261
Psychological Well-being	-0.17	-0.36	0.03	0.092
Peers & Social Support	-0.28	-0.59	0.04	0.085
School Environment	-0.15	-0.42	0.12	0.274
Parents & Autonomy	-0.09	-0.31	0.12	0.392

5.5 Exploratory analysis into HCC and child-reported HRQoL

An exploratory analysis was conducted to examine the relationship between HCC and child-reported HRQoL in children with mental disorder. Multivariable models were computed to examine the associations while controlling for child age and sex. Higher HCC were seen among individuals with lower HRQoL scores in the domains of physical well-being [β=-0.05, p=0.57], psychological well-being [β=-0.09, p=0.20], parents & autonomy [β=-0.06, p=0.61], and peers and social support [β=-0.20, p=0.18]. In contrast higher HCC levels were associated with higher HRQoL scores in the domain of school environment [β=-0.04, p=0.78]. Results from the exploratory analysis are presented in Table 6.

Table 6: Association between hair cortisol concentrations and child-reported health-related quality of life

Health Related Quality of Life Domain	Unadjusted		Adjusted	
	β	95% CI	β	95% CI
Physical Well-being	0.02	-0.22, 0.25	-0.05	-0.26, 0.16
Psychological Well-being	-0.05	-0.23, 0.13	-0.09	-0.26, 0.08
Peers & Social Support	-0.09	-0.47, 0.28	-0.20	-0.54, 0.15
School Environment	-0.11	-0.22, 0.43	0.04	-0.27, 0.34
Parents & Autonomy	-0.02	-0.30, 0.27	-0.06	-0.34, 0.22

5.6 Mediation analysis

In addition to the analysis outlined in the research objectives, an exploratory mediation analysis was conducted to determine if HCC mediated the relationship between parental mental health status and parent-reported child HRQoL (Figure 3). Following standard procedures, each mediator was tested using three models (97). The first model tested the association of the independent variable (parental mental health status) with the dependent variable (HRQoL). The second model tested the association between the independent variable (parental mental health status) and the dependent variable (HRQoL) with the possible mediator (HCC) included in the model. The third and final model tested the association between the independent variable (parental mental health status) and the possible mediator (HCC). Results from these regression sets are presented in Tables 7-9. The important conditions for mediation are that the â (Model 2) and $\hat{b}$ (Model 3) coefficients are statistically significant (97). As seen in tables 6-8, these conditions were not met for any of the regression sets. The mediation effect was, therefore, not further explored.

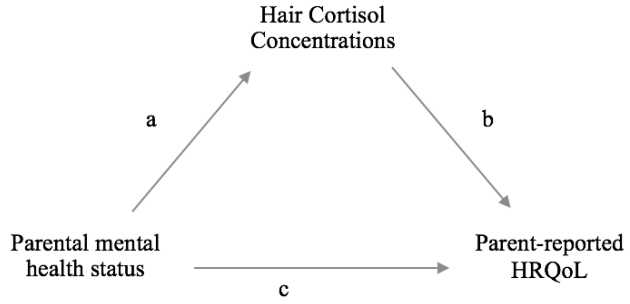

Figure 6: HCC as a mediator between Parental Mental health status and HRQoL

Table 7: Mediation analysis of parental state trait anxiety inventory scores

Model	ß	p-value	95% CI	
Physical Well-being				
Model 1	-0.06	0.522	-0.26	0.13
Model 2	0.08	0.434	-0.12	0.27
Model 3	0.31	0.002	0.11	0.51
Psychological Well-being				
Model 1	-0.07	0.433	-0.34	-0.00
Model 2	-0.17	0.069	-0.21	0.17
Model 3	0.31	0.002	0.11	0.48
Parents & Autonomy				
Model 1	0.09	0.007	-0.48	-0.03
Model 2	-0.04	0.654	-0.49	0.02
Model 3	0.32	0.002	0.11	0.47
Peers & Social Support				
Model 1	-0.19	0.166	-0.34	-0.00
Model 2	-0.12	0.377	-0.21	0.17
Model 3	0.31	0.002	0.11	0.48
School Environment				
Model 1	-0.29	0.017	-0.34	-0.00
Model 2	0.19	0.122	-0.21	0.17
Model 3	0.33	0.002	0.11	0.48

Table 8: Mediation analysis of parental scores on the center for epidemiologic studies depression scale

Model	ß	p-value	95% CI	
Physical Well-being				
Model 1	-0.19	0.011	-0.34	-0.04
Model 2	0.08	0.389	-0.37233	-0.07
Model 3	0.30	0.000	0.20300	0.67
Psychological Well-being				
Model 1	0.07	0.001	-0.37	-0.02
Model 2	-0.10	0.279	-0.37	-0.07
Model 3	0.30	0.000	0.20	0.67
Parents & Autonomy				
Model 1	-0.30048	<0.0001	-0.37	-0.02
Model 2	0.10758	0.246	-0.37	-0.07
Model 3	0.29835	0.000	0.20	0.67
Peers & Social Support				
Model 1	-0.37	0.001	-0.37	-0.02
Model 2	0.01	0.931	-0.37	-0.07
Model 3	0.30	0.000	0.20	0.67
School Environment				
Model 1	-0.40	<0.0001	-0.47	0.01
Model 2	-0.07	0.553	-0.58	-0.19
Model 3	0.29	0.001	0.18	0.65

Table 9: Mediation analysis of scores on the parental stress scale

Model	ß	p-value	95% CI	
Physical Well-being				
Model 1	-0.09	0.152	-0.34	-0.00
Model 2	0.11	0.259	-0.30	-0.06
Model 3	0.23	0.000	0.24	0.81
Psychological Well-being				
Model 1	-0.19	0.001	-0.34	-0.00
Model 2	-0.08	0.359	-0.30	-0.06
Model 3	0.23	0.000	0.24	0.81
Parents & Autonomy				
Model 1	-0.14	0.025	-0.48	-0.03
Model 2	-0.05	0.628	-0.31	0.01
Model 3	0.25	0.000	0.22	0.79
Peers & Social Support				
Model 1	-0.16	0.064	-0.34	-0.00
Model 2	-0.09	0.506	-0.30	-0.06
Model 3	0.23	0.000	0.24	0.81
School Environment				
Model 1	-0.19	0.015	-0.34	-0.00
Model 2	-0.18	0.143	-0.29	-0.06
Model 3	0.23	0.001	0.24	0.81

SECTION SIX: Discussion

Despite the alarming increase of reported mental disorder in children, there remains a paucity of evidence surrounding important psychosocial outcomes in this population. There is a critical need for a deeper understanding of the impact mental disorder has on children both physiologically and psychologically. Determining how public health practice can mitigate these potentially negative physical and psychological outcomes will promote the foundations for lifelong health in the coming generations. The aim of this study was to help extend the state of knowledge surrounding the psychosocial effects of physiological stress by examining the relationship between HCC and HRQoL among children with mental disorder. Not only is this the first study to examine this relationship in this population, but to the best of our knowledge this is the only the third study to examine the relationship between HCC and HRQoL in any population of children. This thesis aims to extend the limited research base regarding HCC and provide solid foundations for future in-depth research.

6.1 Hair cortisol and parent-reported health-related quality of life

The results from our multivariable regression analyses suggest that HCC was associated with parent-reported HRQoL in children with mental disorder. These results indicate that children experiencing higher levels of physiological stress, evident from high HCC, experience impaired quality of life, as reported by their parents or guardians. As the science of hair cortisol remains relatively new and unexplored, there is limited existing research connecting HCC and HRQoL. The findings from this study appear to contrast the two previously published studies in the field. One study found no association between HCC and HRQoL in a sample of Swiss children (46). One important distinguishing factor between these results and the present study, is that study was conducted on 6- to 8-year-old healthy children and our study population included children of a wider age range who were diagnosed with mental disorder. The second study identified that has examined the relationship between HCC and HRQoL in children found that higher HCC was associated with less impaired HRQoL in children whose mothers experienced early life maltreatment (83). The results from the current study do however, fit well within the literature surrounding childhood mental disorder and quality of life.

HCC was found to be associated with the parent-reported psychological well-being HRQoL domain amongst children diagnosed with mental disorder. These results indicate that among children diagnosed with mental disorder, those with higher levels of physiological stress, measured through HCC, experience lower levels of psychological well-being. The psychological well-being domain of the KIDSCREEN-27 examines the mental health, emotions, and satisfaction with life in children. It is therefore not surprising that children with high levels of physiological stress scored lower regarding their experiences of positive feelings. These findings contrast those found when investigating the link between HCC and well-being in women (98). Smyth et al. found that there was no association between ill-being and HCC, however, this study examined the association in healthy females without mental disorder. Worsening mental health in children has been shown to be associated with lower scores in the psychological well-being HRQoL domain (99). Moreover, childhood stress has been found to be associated with low psychological and physical well-being in children (100). Our results support previous work using salivary cortisol measures which found an inverse correlation between psychological well-being and cortisol levels (101), although the reported effect size [-0.98 (-1.36, -0.61)] was substantially larger than that seen in the present study [-0.17 (-0.34,-0.00)].

HCC was also found to be associated with the school environment HRQoL domain amongst our sample of children diagnosed with mental disorder. Children with higher HCC were found to have lower scores of HRQoL in their school environment than their counterparts with lower HCC. It has previously been demonstrated that children diagnosed with mental disorder have lower HRQoL in their school environment than their healthy counterparts (21). Existing literature suggests that children with mental disorder experience higher levels of stigmatization and discrimination than their healthy peers (20). This stigmatization is through the assumptions and treatment by school staff, peers, and family and may lead to an increase in already heightened social anxiety levels (102). It is plausible to speculate that children with increased levels of anxiety surrounding their school environment experience higher levels of physiological stress. Many of these negative experiences are explored in the School Environment portion of the KIDSCREEN-27 and are likely reflected in the low scores reported by the children's parents. Another possible explanation for these results is that roughly one third (32%) of our study population was

diagnosed with ADHD. This could partially explain our results as ADHD has been shown to impact a child's capacity to learn and concentrate at school (21) and has been associated with lower quality of life in school-related subscales (103-104).

6.2 Impact of a co-morbid chronic physical illness

Results from our effect modification analysis indicate a significant moderating effect of having a co-morbid CPI, specifically in the domain of peers and social support HRQoL. Among the children in this study with a co-morbid CPI, higher HCC was found to be associated with lower HRQoL in the domain of peers and social support. No significant association was found between HCC and HRQoL in the domain of peers and social support for children without a co-morbid CPI. Research demonstrates that children with co-morbid CPI and mental disorder have greater impairments in HRQoL than children with either CPI or mental disorder independently (105-106). To the best of our knowledge there has yet to be research conducted examining the relationship between having co-morbid physical-mental disorders and specific HRQoL domains in children. Our results are in accordance with existing research conducted among adults with co-morbid disorders which suggests that CPIs negatively impact HRQoL with regards to physical well-being while their mental disorder negatively impacted other domains of HRQoL including social well-being (107). The added burden associated with having a co-morbid CPI could help to explain the moderating effect of co-morbid disorders seen in this study. Children with more severe physical impairments have been shown to have difficulty building or maintaining social relationships with other children (108). We could speculate that this would become a substantial stressor for the child, and as a result, it would not be surprising that among children diagnosed with co-morbid CPI, there was a significant inverse relationship between physiological stress and HRQoL in the domain of peers and social support. These findings do not support the attenuation hypothesis seen in previous HCC research. This could be attributed to the fact that there was no temporal variable included in this study and it is therefore unknown how long the children had been experiencing these elevated levels of physiological stress.

6.3 Impact of parental stress

Parental stress had a moderating effect on the relationship between HCC and HRQoL in the domain of physical well-being. Among children whose parents experienced low levels of parental stress, high levels of HCC were significantly associated with high levels of HRQoL in the domain of physical well-being. In the portion of children whose parents were experiencing high levels of parental stress, there was no statistically significant association between HCC and HRQoL in the domain of physical well-being. Although these results support the notion that a child's social environment has a significant moderating effect on the relationship between HCC and child HRQoL (83), the direction of effect is surprising as it is not consistent with previous literature. Children raised in low-risk environments, such as those free of impaired parental mental health, have been found to have normal functioning HPA axis, resulting in higher HCC being associated with lower levels of HRQoL (83). Even more intriguing, is HRQoL, in the domain of physical well-being, in children whose parents reported high levels of stress, appeared to remain the same at different levels of HCC. Although the relationship between HCC and HRQoL in these children was not statistically significant, it suggests that children exposed to stressful social environments are resistant to the effects of additional physiological stress. The lack of a significant relationship could be due to the low to moderate agreement between parent-reported and child-reported scores on the KIDSCREEN-27 (91). Parents who report higher levels of stress are often found to report lower HRQoL scores for their children across all domains (108). This suggests that parents may be reporting a function of their own quality of life rather than that of their child. In a post-hoc analysis, we found that children of parents with high reports of stress had lower parent-reported HRQoL than children of parents with low reports of stress. These results were found specifically for the peers and social support, and psychological well-being HRQoL domains. As this was a post-hoc analysis, we did not formally examine informant discrepancies and therefore there is potential that these findings are the result of other factors or chance. Previous literature has indicated that informant discrepancies have been found in HRQoL measures as a result of parental mental health status (109), suggesting that this is a worthwhile area of future investigation. Despite these limitations, research has consistently demonstrated that caregiving behaviour has a profound impact on a child's developing HPA axis (110-111). It has been shown that children who experience low levels of caregiving and maternal care are at risk for epigenetic

changes that render them at increased likelihood for negative mental health later in life (112). It is conceivable that this partially explains the results seen in this study. Higher levels of parental stress might have a similar impact on the HPA axis as caregiving which may result in a decreased sensitivity to physiological stress. These complex findings highlight the critical need for further research examining the impact of parental stress on children's HCC and HRQoL.

6.4 Implications for research

Since this study is the first to examine the relationship between HCC and HRQoL in children with a mental disorder, it has several important implications for the relatively new field of hair cortisol research.

6.4.1 Longitudinal analysis

While this research has produced informative insight into the complex relationship between physiological stress and psychosocial outcomes, the association remains relatively unknown. This research provides exciting preliminary evidence suggesting that physiological stress could partially explain the low reports of HRQoL seen among children with mental disorder. These findings highlight the need for the replication of this study including a larger sample of children and using a longitudinal design.

The use of a prospective longitudinal design would allow for exploration of how changes in HCC over time impact HRQoL. One study found that decreases in mental disorder severity were associated with improvements in HRQoL in children, while increasing severity of mental disorder was associated with deteriorating HRQoL (99). Replication of this study using longitudinal data would provide the opportunity to explore the relationship between HCC and HRQoL while controlling for mental disorder severity. There would be substantial value in exploring how changes in physiological processes over time impact important clinical outcomes in this vulnerable population of children. Longitudinal data would also provide insight into whether negative parental mental health precedes or follows child mental disorder. If negative parental mental health appears following the diagnosis of their child's mental disorder, this could inform public health practice to provide support and counselling to parents.

6.4.2 Sample Size

The inclusion of larger sample size would allow for comparisons to be drawn between specific mental disorders rather than between the more general categories of internalizing and externalizing disorders. This could lead to more accurate and specific conclusions. The use of a larger sample size could confirm the moderating effect of child's sex on the relationship between HCC and HRQoL. Results presented in Models 2 and 3 (Table 5) demonstrate that although the relationship is not statistically significant, the regression coefficients for child's sex are substantially larger than those found in the moderating analysis of child's age. We could speculate that there might be true relationship and the lack of significance in these findings is due to a lack of power as a result of a small sample size. Previous research into the impact of age on HCC has found mixed results (45), which suggests that methodology and sample size and characteristics should be considered when reviewing the literature.

6.4.3 HCC and child-reported HRQoL

The results from our exploratory analysis did not find any statistically significant associations between HCC and HRQoL among any of the five domains. The lack of statistically significant results could also be attributed to a lack of power in the analysis as previous studies have found significant associations between HCC and self-reported HRQoL in children (83). Due to the wide age range included in our sample, not all children completed the self-report study questionnaires. Data from children under the age of 11 relied solely on proxy-reports, greatly reducing the sample size included in this exploratory analysis. Quality of life is highly subjective and therefore relying on proxy reports likely does not provide a completely accurate depiction of the true levels (24). As such it would be beneficial to replicate this research using a larger sample of children in order to explore this relationship further and draw more reliable conclusions.

6.4.4 Circulating cortisol

HCC has been shown to provide accurate measures of long term stress (39), which are suspected to be associated with mental disorder (73-74,76), however, they likely do not reflect more recent, acute stressors that could be impacting the child's HRQoL. Including acute levels of cortisol in addition to HCC could provide a more in depth analysis of the relationship between the levels of physiological stress axis and mental disorder in children. The literature surrounding circulating cortisol, measured either through saliva, blood, or urine, and psychiatric disorder is slightly more established than that surrounding HCC. It could be beneficial to explore the relationship between circulating cortisol and HRQoL in children with mental disorder and investigate whether those results differ from what is found with HCC measurements.

6.4.5 Cortisol reactivity

The attenuation hypothesis suggests that dysregulation of the HPA axis may lower basal cortisol levels, and could also influence cortisol reactivity, resulting in a blunted response to acute stressors (34). HCC does not allow for the analysis of cortisol reactivity as a 1cm sample of hair provides an average measure of physiological stress over a 1 month period (41). It would be interesting to determine if cortisol reactivity is associated with HRQoL among children with mental disorder and how these relationships compare to those found in this study using HCC. Cortisol reactivity, in addition to HCC, would provide a more in-depth analysis of HPA axis functioning among children with mental disorder. HCC indicates basal cortisol levels reflecting chronic stress and overall HPA axis dysregulation, and cortisol reactivity would provide insight into how the HPA axis responds to acute stressors (113). Together they would provide data that could help clarify the ambiguity in the results produced by research surrounding the relationship between physiological and perceived stress. Furthermore, parental mental health and chronic stress have been shown to be predictive of cortisol reactivity in children (114). This could partially explain the lack of many significant findings in the analysis of the moderating effect of parental mental health in this study.

6.4.6 Coping mechanisms

The majority of research investigating stress and psychosocial outcomes in children with mental disorder have placed a focus on the negative implications of the diagnoses. Examining how individual coping characteristics, such as resiliency and flourishing, impact the relationship between HCC and HRQoL in at-risk children could provide interesting findings that inform public health interventions. Research surrounding stress and HPA axis reactivity has found that coping style, including an individual's temperament and personality, and skills they acquired through cognitive behaviour therapy, have a significant influence on their ability to critically appraise stressors (115). It is possible that these findings could be reflected in the results from this study's effect modification analysis into the effects of parental stress. Some children might have better coping abilities than others which could be the outcome of being raised in higher-risk social environments. Figure 5 demonstrates that among children living in high stress environments, additional physiological stress does not seem to translate to impaired HRQoL, whereas children living in low stress environments appear to be sensitive to the negative implications of additional physiological stress. This could suggest that children exposed to chronic stress in their environment develop coping mechanisms to become resistant to the negative implications associated with stress. These findings provide compelling evidence that assessment of coping skills should be included in future research using cortisol measurements.

6.5 Implications for practice and prevention

In order to strengthen the foundations for lifelong health, extra focus and resources must be directed towards critical periods of development, specifically childhood and adolescence. This study aimed to help identify children at risk impaired quality of life, with the hope that efforts can be put in place to minimize these detrimental outcomes. Although there are many positive aspects of the current healthcare system, there remains significant room for improvement, specifically when considering mental health services. The importance of mental health is becoming more apparent as the Government has made mental health a priority in the new 2017 Health Accord (116). Despite these advances, mental health care remains neglected and underfunded. Only 7% of health care dollars are allotted to mental health services, despite mental illness accounting for roughly 10% of the burden of disease on the healthcare system

(117). The current mental health system in Canada requires faster and higher quality services, better coordination with physical health-care services, and appropriate funding (118). In order to effectively treat and support all children, it is essential that proper policies and programs are developed to break the cycle between negative mental health, high physiological stress, and poor quality of life in children.

6.5.1 Mental health services and service use

The results from this study are evidence that public health must intervene to improve the HRQoL of children with mental disorder through the reduction of physiological stress levels. The first key step in this process is through improved access to specialized care and treatment. 75% of children with mental disorder have not accessed specialized services (119). This is devastating, considering the long-term consequences associated with childhood mental disorder (120). It is not abnormal for wait times for children to see specialists or psychiatrists to reach 6 months to 1 year (118). Findings from previous studies show that the earlier that children receive treatment for mental disorder, the better the outcomes will be (120). Early intervention has been shown to result in more favourable health outcomes, including psychological well-being, academic attendance and achievement, and a smaller burden on the social justice and healthcare systems (120).

Improved coordination between mental and physical healthcare services in Ontario will allow for better treatment and services (116). It would also allow for heightened monitoring of at-risk populations. Children with co-morbid mental disorder and physical illness in this study had greater impairments in HRQoL in the domain of peers and social support at higher levels of HCC than their counterparts suffering from mental disorder independently. This indicates that children with co-morbid disorders are at greater risk of negative health outcomes associated with physiological stress. This population of children are accessing specialized services in both the physical and mental healthcare systems and therefore their healthcare providers should be aware of treatment plans in both systems in order to provide the most appropriate care. With increased coordination of care, children can be identified and directed towards services that meet their specific needs. Children with co-morbid conditions were found to have low HRQoL in the domain of peers and social support. There is the opportunity for specialized services that

help build and maintain social relationships. Promoting the development of meaningful relationships would likely mitigate some of the negative consequences of having co-morbid disorders that children often face.

6.5.2 Stress Reduction

Looking further upstream, public health must work to reduce physiological stress levels in children with mental disorder. This study adds to the growing body of evidence suggesting that mental disorder results in both physiological and psychosocial impairments in children and youth. The findings suggest that increased physiological stress is associated with negative psychosocial outcomes, including low HRQoL. In order to mitigate the impact on HRQoL, we must decrease the high levels of physiological stress experienced by children with mental disorder. This will concomitantly work to reduce stress-related health disorders later in life associated with childhood mental disorder (13). Public health must develop programs that promote stress reduction techniques in children.

Relaxation techniques, social and emotional learning, and problem solving training, have all been shown to be effective at reducing stress among children (121). Mind-body integration practices and cooperative activities have been shown to reduce salivary cortisol levels in children (122). These practices involved a combination of breathing techniques, tai-chi, and activities that required collaboration to achieve group goals. Results indicated that cortisol levels were significantly reduced after participation in the intervention. It was also found that 85% of children had incorporated these practices into their lives to overcome stressful situations 5 months after completion of the intervention. Elementary and high schools could be one environment in which these programs can be implemented. School-based stress management programs have been proven to be effective in reducing stress and increasing coping skills in children (123). If we can make these programs widespread and accessible, it is plausible that significant reductions in the detrimental impairments in HRQoL associated with childhood mental disorder would be seen.

6.5.3 School environments

Research indicates that children with mental disorder experience negative health implications extending beyond their disorder-related symptoms (8,11-13,23). Our results provide preliminary evidence suggesting that school environments could be critical for children suffering from mental disorder. This study supports the importance of improving this environment. Mental health training should be provided to school staff as a step towards ameliorating the environment for children with mental disorder. Bringing together key staff in schools, healthcare providers, and community-based organizations for specialized training in early identification and intervention will better support and serve children and youth (120). Elements that could be covered in this training include stress lessons for, and tools to identify and support children with mental disorder. Training could hopefully decrease some of the stigmatization and discrimination felt by children at school. In addition to heightened training for school staff, the addition of educational supports and expert assistance in schools would provide teachers with the support they require to help children with mental disorder (13). Placing mental health workers in schools will have a significant impact on an additional 9,000 children and youth each year (120). Although these programs will be costly to implement, the long term benefits, seen through greater academic achievement, decreased healthcare costs, and increased productivity, both in children and their parents, will greatly outweigh the initial costs (120).

6.5.4 Social environment

Stressful home environments appear to have a negative impact on children's HPA axis functioning and psychosocial outcomes. Although this relationship is extremely complex and the current findings, both from this study and previous literature, do not sufficiently explain the association, it is evident that social environment plays a role in the development of children (124). Programs and services should be developed to decrease stress in both children and their families. Combined therapy has been proven effective to improve outcomes in both parents and their children (125). Combined therapy pulls from attachment and social learning principles to foster authoritative parenting with good nurturing and communication. Additionally, parental education programs could help inform parents on how to cope with their child's health problems and mitigate the harmful impacts that they may have on their own

mental health (13). Impacts would be two-fold as these programs would decrease the burden on parents and guardians while increasing the likelihood of safe and supportive environments for children.

6.6 Strengths and limitations

This study is the first to examine the association between HCC and HRQoL in children with mental disorder. The findings provide preliminary evidence into this complex relationship that warrant further exploration. The results must be considered within the context of several limitations. Firstly, the data used in this study did not have a variable indicating time since diagnosis or onset of symptoms in each child. This is an important limitation when considering the attenuation hypothesis. If a subset of the children included in this study had been experiencing symptoms for a prolonged period of time prior to recruitment into the study, it is possible that they have already adapted to chronic HPA axis activation and therefore were releasing lower levels of cortisol. This could have potentially skewed the results in our analysis. Secondly, a control group was not included in the study population. This rendered it impossible to test whether HCC in children with mental disorder differed significantly from HCC of healthy children. It is conceivable that the relationships found in this study could also be found among health children free of mental disorder. Thirdly, hair samples were collected by the children's parents or guardians. Despite detailed instructions being provided in the study kits, there remains the possibility of human error when cutting or marking hair samples.

Fourthly, it is important to acknowledge that the participants included in this study likely do not reflect the broader population of children with mental disorder. Our study population was recruited out of tertiary care clinics and therefore may reflect children experiencing severe symptoms, as they would be most likely to be referred to specialized care. Future studies should recruit study participants from a variety of locations, such as schools and community centres, to provide a sample more representative of children with mental disorder as a whole.

Lastly, due to the cross-sectional nature of this study, I was unable to determine whether high levels of physiological stress precede impaired quality of life, or whether low quality of life is the cause

of high levels of physiological stress. This furthers the importance of replicating the results using a longitudinal design.

SECTION SEVEN: Conclusion

Although the research in this field is limited and inconsistent, hair cortisol provides valuable information allowing for better understanding of the long term functioning of the HPA axis. The non-invasive and simple nature of the measurements renders HCC a viable option for researching the connections between the HPA axis and psychopathology. The link between how mental disorder negatively impacts quality of life remains unclear, however, the results of this study are a promising first step into disentangling the interplay between physiological stress and psychosocial outcomes. Higher levels of physiological stress seem to be associated with lower health related quality of life children with mental disorder. This relationship is significant in the domains of psychological well-being and school environment, suggesting that school-based interventions could have a profound impact on the quality of life of children with negative mental health. This study highlights the need for additional research to further explore the preliminary findings outlined in this study. There is substantial room for improvement when considering the child and youth mental health system in Canada. As mental health becomes a priority in the Canadian healthcare system, there is the opportunity for programs, policies, and services that target and support this growing population of children. The long-term benefits of early identification and intervention of mental disorder and stress reduction in children extend across the lifespan, far beyond the improvement of psychosocial outcomes.

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