Title: Cumulative exposure to socioeconomic and psychosocial adversity and hair cortisol concentration: a longitudinal study from 5 months to 17 years of age.

Running head: Cumulative adversity and hair cortisol concentration

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ABSTRACT

Background: Exposure to early adversity has been associated with long-lasting risks for poor health and functioning. Prior research suggests that the hypothalamic-pituitary-adrenal (HPA) axis, and its main end-product glucocorticoid hormone cortisol, may be at play. This study tested whether an index of cumulative socioeconomic and psychosocial adversity assessed prospectively, from infancy to adolescence, was associated with hair cortisol concentration (HCC), and if this association differed by sex. **Methods**: The sample comprised 556 adolescents (42.0% males) who provided hair for cortisol measurement at 17 years of age. Adversity indicators (young and single motherhood, low socioeconomic status (SES), maternal alcohol use, hostile-reactive parenting, and depressive symptoms, as well as peer victimization and neighborhood dangerousness) were repeatedly reported by mothers or youths between the ages of 5 months and 15 years. **Results**: Chronic adversity was non-linearly associated with HCC; youth exposed to lower *and* higher levels of adversity had moderate-to-higher HCC compared to lower HCC noted in participants with moderate levels of adversity, for both males and females. None of the indicators taken separately, except the perception of neighborhood dangerousness, were significantly associated with HCC. **Conclusion**: Our findings support the hypothesis that HPA axis activity varies according to cumulative adversity, albeit non-linearly, which may bear consequences for later health and functioning.

Keywords: Early-life adversity; HPA-axis; Hair cortisol; Longitudinal study; Non-linear models.

Abbreviations: HPA axis = hypothalamic-pituitary-adrenal; HCC = hair cortisol concentration; SES = socioeconomic status.

1) INTRODUCTION

Children growing up in environments characterized by socioeconomic (e.g., low family income and parents' educational attainment) and psychosocial adversity (e.g., maternal depression, coercive parenting practices) are more likely to experience health and behavioral problems (Hunt et al., 2017; Oh et al., 2018). While the causal chain of events underlying this vulnerability is yet to be specified, many physiological systems are thought to be implicated, including inflammation, cellular aging, epigenetic mechanisms, and brain functioning and connectivity (Danese and McEwen, 2012; McCrory et al., 2017). The hypothalamic-pituitary-adrenal (HPA) axis and end-product glucocorticoid stress hormone cortisol have also been proposed to represent a key pathway by which early adversity induces health and behavioral disparities, namely because of their role in mobilizing energy required to cope with stressors and maintain homeostasis (Koss and Gunnar, 2018). Specifically, it has been argued that disrupted salivary cortisol responses to stress (i.e. higher, prolonged, repeated or blunted responses) and diurnal salivary cortisol secretion (flattened circadian rhythm, higher or lower levels at specific times of the day) may signal the wear and tear of the HPA axis following adversity, which could jeopardize other physiological systems, health and behavior over time, a phenomenon known as allostatic load (McEwen et al., 2015).

The association between childhood adversity and HPA axis functioning has, to date, mainly been investigated through the lenses of salivary cortisol. While experiences of abuse and parental loss were not associated with disrupted patterns of salivary cortisol secretion in basal or stressful contexts in a meta-analysis (Fogelman and Canli, 2018), participants maltreated as children were shown in another meta-analysis to be more likely to have blunted awakening cortisol levels, especially among agency-referred study samples (Bernard et al., 2017). Child

maltreatment has also been associated with blunted cortisol responses to social stress in adulthood, albeit weakly so (Bunea et al., 2017). The evidence for a robust association thus still awaits, although blunted secretion across diverse indicators is not uncommon. The large heterogeneity noted between the studies included in these meta-analyses also raises the possibility that other factors may obscure this association, including the assessment of cortisol and adversity. For example, indicators of salivary cortisol are known to be sensitive to time-varying confounders (e.g., allergies, unexpected acute stressors, and time of saliva sampling) and poor adherence to saliva collection protocols. Differences across studies in the measurement of salivary cortisol may thus affect, to some degree, the accuracy of the cortisol indicators used, and thus the statistical power to detect significant associations with early adversity.

In contrast to salivary cortisol, which captures circulating cortisol secretion according to specific times and contexts, hair cortisol concentration (HCC) is a cumulative index of cortisol secretion that gradually incorporates into the growing hair over extended periods of time, typically 2-3 months (Russell et al., 2012; Stalder et al., 2017). Accordingly, HCC offers a complementary strategy to capture stable patterns of cortisol secreted across a variety of contexts, including in response to acute or repeated stress and throughout the day (Bryson et al., 2018). HCC is also less likely to be affected by time-varying confounders. Despite these potential advantages, however, recent meta-analyses and systematic reviews conducted exclusively on HCC also reported mixed findings with adversity (Gray et al., 2018; Khoury et al., 2019; Stalder et al., 2017), echoing in part what has been noted for salivary cortisol indicators.

It is noteworthy that the association between childhood adversity and HCC have mostly been examined using a cross-sectional research design (Gray et al., 2018). These studies have, for instances, reported higher HCC in young children growing up with less educated parents,

whereas no differences could be detected for family income (Ursache et al., 2017; Tarullo et al., 2020, although see Bryson et al. 2018). Neighborhood disadvantage was also positively associated with HCC in participants of various ages (Tarullo et al., 2020; Ziliolo et al., 2017; Vliegenthart et al., 2016). Alternatively, no HCC differences could be detected between school-aged children who grew up with a mother who experienced child maltreatment (Fuchs et al., 2018), or according to parental stress (Gerber et al., 2017), in comparison to controls. Lifetime exposure to trauma was nonetheless associated with higher HCC in children (Simmons et al., 2016). In their meta-analysis derived from 66 independent studies, Stalder and colleagues (2017) showed that individuals exposed to chronic stress (e.g., unemployment, natural disasters) had higher HCC. Notably, this association was greater in magnitude when the stressors were still present at the time of hair collection, whereas a non-significant trend for lower HCC levels was noted in conditions of past/absent stress (Stalder et al., 2017). An overall positive, but small association between HCC and adversity was also reported in the meta-analysis of 28 study samples aggregating a total of 3,397 participants (Khoury et al., 2019). Building on prior knowledge of hyper- *and* hypo-secretion of cortisol in the literature, Khoury and colleagues (2019) showed that studies who reported lower HCC included participants who were maltreated as children, while those reporting higher HCC comprised participants that had either been victims of child maltreatment or who had experienced trauma as adults.

The findings emerging from these systematic reviews and meta-analyses — and the independent studies comprised in them — raise the possibility that the timing of adversity and the time elapsed from its onset at the time of cortisol measurement could affect the adversity-cortisol association and, thus, partly explain the mixed findings. This falls in line with prior findings indicating that the strength of the association between chronic stressors and multiple indicators of

cortisol secretion (i.e. morning cortisol, daily output, and the adrenocorticotropin hormone or ACTH) decreases as time passes by between the stressors onset and cortisol measurement (Miller et al., 2007). In other words, while recent (or acute) exposure to adversity may co-occur with heightened HPA axis activity, lower levels of HPA axis activity is anticipated as these experiences become more distant (Miller et al., 2007). It has also been argued that adversity may have differential impact on HPA axis activity depending on when it was first encountered (Lupien et al., 2009). That is, variability in the timing of exposure and time elapsed between the onset of adversity and hair collection between and within the studies may obscure the association between childhood adversity and HCC. Studies conducted in large age-homogenous cohorts for which these factors are held constant or systematically set to vary are needed to test more specifically these hypotheses and thus clarify the childhood adversity-HCC association.

Second, the association between adversity and HCC has been investigated across a variety of adversity indicators, from parental education, housing problems, and maltreatment to neighborhood insecurity, which may bring about inconsistency if these experiences or contexts differentially relate to HCC (Tarullo et al., 2020). Also, importantly, these distinct forms of adversity often congregate within the same families. For example, children growing up in families headed by less educated parents or those earning a lower family income are disproportionally exposed to harsh parenting practices (Shaw and Shelleby, 2014) and peer victimization (Arseneault, 2018). Beyond the investigation of the unique associations between HCC and each indicator, we must test whether the *accumulation* of adversity across multiple socioeconomic and psychosocial adversity indicators affects chronic cortisol secretion. Preliminary evidence suggests that cumulative stress indexes are positively associated with HCC (Karlén et al., 2011; Simmons et al., 2016, O'Brien et al., 2013), although Bryson et al. (2018)

did not detect a significant association between a cumulative index of 17 indicators of socioeconomic and psychosocial adversity and HCC among two-year-old toddlers (Bryson et al., 2018). To the best of our knowledge, no studies have yet tested whether the cumulative experience of multiple forms of socioeconomic and psychosocial adversity, from infancy to adolescence, is associated with HCC.

Third, accumulating evidence suggests that the association between childhood adversity and HPA axis activity may not always follow a linear function. That is, individuals who grew up in increasingly severe adverse environments may not necessarily show incrementally higher HPA axis activity, such as it is expected in a dose-response association. Attention in capturing severity in adversity is thus warranted. Indeed, while exposure to moderate stressors has been linked to lower HPA axis activity, more severe experiences of childhood adversity have been associated with heightened secretion (Gunnar, 2020; Boyce and Ellis, 2005). For example, 10-12-year-old children adopted internationally early in life from foster care systems had lower salivary cortisol responses to psychosocial stress than children who were adopted later on, suggesting a blunted HPA axis responsiveness at moderate levels of adversity (Gunnar et al. 2009). Notably, however, children who remained in institutions for a longer period did not differ from children reared with their biological parents, thus pointing to a U-shaped non-linear association between severity of adversity and salivary cortisol response to stress. Our team also reported a shift from moderate to lower to *higher* salivary cortisol responses to a psychosocial stress test in young adults who reported increasingly severe child maltreatment, indicating a J-shaped non-linear association (Ouellet-Morin et al., 2018).

Growing evidence also suggests that non-linear associations are also detected between childhood adversity and HCC. We have previously shown that persistent peer victimization was

non-linearly associated with HCC among 17-year-old boys. While lower HCC was noted for participants who experienced moderate levels of peer victimization, moderate-to-higher HCC were noted for both youths who had been more victimized and those who had not been victimized by their peers (Ouellet-Morin et al., 2020). Non-linear associations were also reported in adults between HCC and SES, as derived from income and levels of education, pointing to inverted and non-inverted U-shaped functions according to the minority group of the participants (O'Brien, Tronick & Moore, 2012). Interestingly, the Adaptive calibration model (Del Giudice et al., 2011) proposes four prototypical patterns of responsiveness according to increasing levels of adversity/trauma, which captures and expands on these findings. While moderate-to-high responsiveness is anticipated in lower stress or safe environments, a buffered pattern of responsiveness is expected in the context of moderate stress. Notably, a point of inflection toward an enhanced pattern of responsiveness is proposed for individuals confronted with dangerous and unpredictable environments, once more suggesting a U-shaped function. However, females exposed to even more severe and traumatic stress are expected to show even higher responsiveness to stress (i.e. J-shaped function), whereas males are expected to revert to unresponsive patterns of response under the same conditions (Del Giudice et al., 2011). Altogether, theorization and preliminary findings suggest that non-linear functions (i.e., U-shaped, inverted U-shaped, J-shaped) may help to capture the variation in HCC across increasingly severe adverse context. Although most evidence points to a U-shaped association between adversity and HCC, the possibility that an inverted U-shaped or J-shaped functions may also be detected cannot yet be discarded.

Finally, several studies suggested that males display higher HCC than females (Gray et al., 2018; Rippe et al., 2016), although not consistently (Prado-Gascó et al., 2019). For instance,

higher HCC was associated with person-related adverse life events (e.g., loss of a relationship) for males (12-18 years), but not female adolescents (van Dammen et al., 2020). Higher daily salivary cortisol levels were also reported for boys exposed to more pervasive maltreatment in comparison to girls (Doom et al., 2013), although it is uncertain whether these differences would be detected in hair. Several lines of evidence support a sex-moderation hypothesis, including sex or gender differences in sensitivity to stress, coping mechanisms, timing of puberty or hormonal changes occurring during puberty (Del Giudice et al., 2011; Negriff et al., 2015; Shirtcliff et al., 2012). It is also hypothesized that males and females differentially respond to stress, starting in adolescence, with males being more sensitive to stressors of a competitive nature and females to social exclusion (Stroud et al. 2009). Sexual dimorphic associations may, however, not be present across the distribution of adversity, but uniquely arise in severely adverse and traumatic contexts, as argued in the Adaptive calibration model (Del Giudice et al., 2011). For the most part, however, HCC studies have not tested (or reported) sex-moderation analyses and sex was not detected as a significant moderator in Khoury and colleagues' (2019) recent meta-analysis. Systematic tests of this hypothesis are thus needed.

The present study aimed to test whether a cumulative index of persistent socioeconomic (e.g., low family income, young and single motherhood) and psychosocial (e.g., maternal depression, hostile-reactive parenting, peer victimization) adversity, measured between 5 months and 15 years of age, was associated with HCC measured two years later, at 17 years of age. To do so, we estimated group-based trajectories to capture distinct-but-homogenous levels of persistent adversity for each indicator and derived a cumulative score of adversity. We expected that the association between cumulative adversity and HCC would be best described non-linearly, as previously suggested in the Adaptive Calibration Model (Del Giudice et al., 2011) and reported

in this cohort in regards to peer victimization (Ouellet-Morin et al., 2020). Finally, we explored whether these patterns of findings differed for boys and girls, but did not articulate specific hypotheses as for whom, males or females, stronger associations with HCC are expected to arise considering previous mixed findings.

2) METHODS

Participants were members of the Quebec Longitudinal Study of Child Development (QLSCD), a population-based cohort of 2,120 children born in 1997-98 in all administrative regions of the Province of Quebec (Canada), except the First Nations' Territories, and followed up by the Institut de la Statistique du Québec (ISQ) and a team of researchers. Children were included in the original sample if the mother's pregnancy had lasted 24 to 42 weeks (i.e. 99.9% of all registered birth) and the mother could speak French or English. Extremely preterm (<24 weeks of gestation) and post-term (>42 weeks of gestation) babies were excluded. At the time of the study's inception, the Quebec population was 7 million, of which nearly 20% was rural. French was the first language for nearly 80% of the population. The QLSCD cohort was representative of the population in this respect. When the child was 5 months of age, most were living with their two biological parents (95.7%), who were on average in their late twenties or early thirties [mothers: mean (standard deviation or SD)=29.8 (5.1) years; fathers: 32.5 (5.5)], in majority Caucasian White (96% and 97%, mothers and fathers respectively) who had completed a high school diploma (85% and 79%, mothers and fathers respectively) and for whom the family income was, for the majority, deemed sufficient (83.2%) according to the size of the family and the region of residence (Statistics Canada, 1998). At age 17, a sample of 1,150 youths, who still participated in the study lived in the province of Quebec and could be contacted, were invited to collect hair for cortisol measurement. A total of 556 participants (42.0%; 231 males) provided

enough hair for analysis. Compared to the initial cohort (n=2,120), fewer non-Caucasian (χ^2=6.35, p<.01) males (χ^2=17.56, p<.001) from lower SES families (r_{pb}=-.09, p<.001) participated. To account for this selective attrition, we used inverse probability weights in the analyses. The QLSCD protocol was approved by the ISQ and the University of Montreal ethics committees. Informed consent was obtained at each data collection.

Prior to the present hair collection, our team conducted a pilot study (Ouellet-Morin et al., 2016) to validate a home-based adaptation to the widely used lab-based collection protocol for which the hair sample is collected by a trained research assistant (Kirschbaum et al., 2009). In this pilot study, we invited 34 youth matched on age, sex, and SES to the present population-based cohort to ask a family member or a friend to collect hair at home and send it back to our laboratory by mail. One week later, they also came to our laboratory where a research assistant collected a second hair sample (Ouellet-Morin et al., 2016). A strong correlation was noted between the two samples (r=0.91, p< 0.001) and no mean difference in cortisol levels could be detected between the two samples (t=0.06, p=0.95). Accordingly, we used this adapted protocol and invited the participants to collect a sample of their hair at home. We sent by regular mail the required materials (curved scissors, hair clamps, collection cardboard, etc.) and the paper instructions, which detailed how to collect a 1 cm wide (and at least 3 cm long) sample of their hair from the posterior vertex area of the scalp at home, as indicated in photos included in the instructions. Once the collection was completed, the participants sent the material and the hair sample (stored in a Ziploc bag) back to our lab using a prepaid and pre-addressed envelope. Importantly, most participants (n=489 or 89.1%) asked a parent to perform the hair collection. The weight of 4 hair samples (.7%) was insufficient for conducting the laboratory analysis according to the original protocol (Kirschbaum et al., 2009), thus leading to our final study

sample of 556. Wash and steroid extraction procedures were conducted at the Centre for Studies on Human Stress, Canada (Ouellet-Morin et al., 2020). The first 3 cm long segment of the samples were assayed in duplicate using a luminescence immunoassay (detection range: .005-4 µg/dl; intra-assay coefficient of variation=7.24%; inter-assay coefficient of variation=10.13). The participants had a mean cortisol level of 16.19 pg/mg (*SD*=14.84; 3*SD*-winsorized) and the scores were log10-transformed. A wide range of information about the natural state of the hair (e.g., color, curvature), usual care (e.g., frequency of washing, treatments), and health (e.g., medications, physical activity, sleeping habits, body mass index (BMI), tobacco, drug and alcohol consumption, allergies, head injuries, and a wide range of health problems, from cardiovascular to inflammatory diseases) hypothesized to covary with HCC or HPA axis activity (Russell et al., 2012; Stalder et al., 2017) were reported by the participants using a questionnaire. Only the following factors uniquely predicted HCC: smoking, month of collection, hair washing 24 hours before sampling, natural hair color and BMI. Standardized residuals of HCC were used to account for these confounders.

A total of eight indicators of adversity were considered because of their prior association to poor health (Oh et al., 2018). When the participating children were 5 months old, the information about *Young motherhood* was coded as present if the mother gave birth to her first child before 21 years of age, the same threshold used to ensure the recruitment of more families at risk (Moffitt and E-Risk Study Team, 2002). *Single-headed family* was present if reported by the mothers at least once in the preschool years, that is, at any time when the children were 5 months, 1½, 2½, 3½, 4½, or 5 years. *SES* included information about family annual income, mothers' and fathers' education and occupational prestige collected on up to 11 occasions between 5 months and 15 years (peak missingness at 13 years: 9.1% of this sample). *Maternal alcohol use* was

reported by the mothers on six occasions between 5 months and 15 years according to an 8-point Likert scale varying from "never" to "every day" (peak missingness at 10 years: 12.9% of this sample). The original distribution of the variable, derived by summing up the scores on all items, were redistributed according to a new scale (i.e. rescaled) varying between 0 and 20. *Hostile-reactive parenting* referred to power-assertive behaviors reported by the mothers on 10 occasions between 2.5 and 15 years (4-8 items, the number of items depended on the age of the child when these parenting behaviors were assessed to reflect age normative changes in the children's behavior occurring from toddlerhood to adolescence, e.g. *How often did you hit your child when he/she was difficult?*; rescaled between 0-10; Cronbach's alphas (α_s)=.63-.75; peak missingness at 10 years: 13.7% of this sample). *Maternal depressive symptoms* in the past week were assessed 7 times between 5 months and 13 years using a shortened version of the Center for Epidemiologic Studies Depression Scale completed by mothers (Radloff, 1977). The scale included 6 to 13 questions scored from "never" to "often" (rescaled between 0-10; $\alpha_{s=}$ .79-.83; peak missingness at 10 years: 22.6% of this sample). *Peer victimization* was reported by the youth themselves on seven occasions between ages 6 and 15 using seven items from the Self-Report Victimization Scale (Ladd and Kochenderfer-Ladd, 2002), measuring perceived occurrence of physical, verbal, relational and cybervictimization and answered according to a 3-point Likert scale from "never" to "often or very often" (rescaled between 0-10; α_s=.70-.80; peak missingness at 6 years: 18.3% of this sample). *Neighborhood Dangerousness* was reported by mothers on eight occasions between 5 months and 15 years, in regard to where the family lived, using five items drawn from the Simcha-Fagan Neighbourhood Questionnaire, to capture a perceived lack of security and social cohesion (e.g., "*Around here, when there is a problem, neighbors get together to find a solution*"; α_s = .86-.91; peak missingness at 10 years: 14.2% of this sample). Figure 1 presents an overview of the timeline of the main study variables.

Socioemotional and behavioral problems, such as depression/anxiety, hyperactive, aggression and oppositional behaviors, known to co-occur with socioeconomic and psychosocial adversity (Hunt et al., 2017) and with higher and lower HPA axis activity (Koss and Gunnar, 2018), were rated by the participating children's teachers on 6 occasions, when they were between 6 and 13 years of age (see Online Supplement 1).

2.1) Statistical Analyses

Preliminary analyses. Considering that each adversity indicator had been measured on several occasions between 5 months and 15 years, we estimated growth mixture models using all the available information. This analytic strategy allowed to capture homogenous patterns of persistent exposure to each adversity indicator. The best-fitting models were selected according to the Bayesian Information Criterion (BIC), LoMendell-Rubin likelihood ratio test (LMR-LRT), entropy estimates, and class membership. These groupings were later summed up to derive the cumulative index of adversity. In the case that the best-fitting model for an indicator included two groups, a score of 0 was assigned for participants belonging to the lowest adversity group, whereas those belonging to the highest adversity group received a score of 2 for that indicator. When a 3-group model was selected, the lowest adversity group had a score of 0, whereas those exposed to the moderate and highest levels had a score of 1 and 2, respectively. Because they relied on a single measure (mother's age at first birth) or the presence of at least one occurrence of single parenthood, the participants of young mothers or of single-headed families were assigned a score of 2, respectively, whereas the remaining participants received a score of 0.

Main analyses. We first tested whether the developmental trajectories of depression/anxiety, social withdraw, inattentive, hyperactive, aggression and oppositional

behaviors were uniquely associated with the cumulative index of adversity using stepwise regressions. These results determined whether these variables were included as confounders in the subsequent analyses. Second, we tested the associations between HCC and the cumulative index of adversity using hierarchical regressions, by including successively and cumulatively the linear, quadratic effects (i.e., squared linear terms) and the confounders. We also explored the association between HCC and each indicator of adversity to detect unique patterns of association, if any. Next, we tested whether these associations varied according to the sex of the participants by including the main effects (e.g., sex and SES) and interaction terms of the variables (sex x SES) subsequently into the previously described regression models. All analyses controlled for non-random attrition.

3) Results

The growth mixture models that estimated increasing number of trajectories for each adversity indicator are presented in Table 1. Figure 2 shows that some youth persistently experienced lower family SES levels (29.7%), higher hostile-reactive parenting (14.6%), grew up with a mother who consumed alcohol more often in comparison to the remaining sample (17.6%), had higher levels of depressive symptoms (12.1%), were victimized more often by their peers (15.3%), or had mothers who perceived the neighborhood where the family lived as dangerous (7.6%). For example, Panel A of Figure 2 shows that most children (42.1%) followed a trajectory of moderate familial SES levels, from childhood to adolescence, whereas approximately one in four were growing up in higher or lower SES families. The scores of all eight indicators of adversity were summed up into a cumulative index of adversity, which initially varied from 0 to 13 (sample mean = 4.96, (SD)= 2.35; see Figure 3). We abridged the right end of the distribution to 11 to minimise the risk that scores beyond three SDs from the mean would have a disproportionate effect in the subsequent analyses.

Developmental trajectories of social withdrawal, inattention, hyperactivity and opposition were uniquely associated with the cumulative index of adversity ($\beta_s \geq .13$, $p_s \leq .01$) and were thus included as confounders in the adjusted models. Table 2 presents the estimates drawn from the regression models that tested the association between the cumulative index of adversity and HCC, first according to a linear effect and then while including both the linear and non-linear terms, in models unadjusted and adjusted for socioemotional and behavioral potential confounders. While cumulative adversity was not associated with HCC according to a linear effect (β=-.01, p=.88), a significant quadratic effect emerged between these variables (β=.37, p=.03), which remained when the confounders were accounted for (β=.39, p=.02). Figure 4 shows that youth with lower *and* higher cumulative adversity scores had moderate-to-higher HCC (i.e. residual scores higher than the sample's mean of 0) in comparison to participants with a cumulative score of adversity more typical of this cohort who had lower HCC. Results presented in Table 2 also show that none of the single adversity indicators except for one — mother's perceptions of neighborhood dangerousness — were significantly associated with HCC on their own. Higher HCC were noted for youth who grew up in neighborhoods perceived as less *and* more dangerous (i.e. quadratic function; Table 2). This finding remained once the regression also included socioemotional and behavioral potential confounders.

We also examined whether the strength and directionality of the associations between HCC and the cumulative, as well as each adversity indicator, differed according to sex. Out of the 18 tests of sex moderation [8 indicators + 1 cumulative index = 9 indicators x 2 (linear and non-linear effects)], only two emerged as significant [hostile-reactive parenting (linear): β=-.38, p=.04; peer victimization (non-linear): β=-1.99, p=.02] (Supplementary Table 1). However, given the high number of tests conducted, we applied a Bonferroni correction for multiple testing (i.e. α

= .05/18), resulting in corrected critical *p* value of .0028. None of the two individual tests of the sex-moderated effect remain significant at this corrected *p* value.

4) Discussion

This study examined the association between HCC and a cumulative index of socioeconomic and psychosocial adversity. Each indicator was prospectively and repeatedly collected for a period up to 15 years. We found that persistent adversity was non-linearly associated with HCC at 17 years of age, whereby moderate-to-higher HCC were noted in youth exposed to lower *and* higher adversity levels, whereas lower HCC were detected at moderate levels of adversity, overall suggestive of an association following a U-shaped function.

Even though non-linear associations have been frequently theorized (Boyce and Ellis, 2005; Del Giudice et al., 2011; Miller et al., 2007), they remain rarely tested (or under-reported) in association with HPA axis activity. Our findings are nonetheless consistent with emerging evidence of non-linear associations between adversity and HCC, including O'Brien and colleagues (2013) who showed both inverted and non-inverted U-shaped functions between SES and HCC, depending on the minority status of the adult participants. Our team also previously found, in the present cohort, a U-shaped function between peer victimization and HCC in boys, while statistically controlling for other adversity indicators, including SES and hostile-reactive parenting (Ouellet-Morin et al., 2020). It is noteworthy that the same pattern of findings was found for this single indicator (peer victimization), albeit in boys only, and a cumulative adversity index capturing a broad range of socioeconomic contexts and psychosocial experiences. One explanation may be that both indexes captured long-lasting adversity, which prompts non-linear associations to emerge over time (Miller et al., 2007). Another explanation may lie in the nature of the adverse indicators targeted. As peer victimization is often unpredictable and threatens one's sense of security, these experiences may more readily activate the HPA axis.

Similarly, youths who cumulate several indicators of socioeconomic and psychosocial adversity, such as low family SES, single motherhood, maternal depression and alcohol use, may have been disproportionally exposed to unpredictable and chaotic familial environments, which may be more likely to trigger cortisol secretion. Interestingly, two indicators of unpredictability in the familial environment — food insecurity and neighborhood risk — were also associated with HCC in early childhood, albeit according to a linear function (Tarullo et al., 2020). U-shaped associations with HCC were also reported with regards to social recognition and work overload in parents of small children (Braig et al., 2019) and with perceived stress according to an inverted U-shaped function (Well et al., 2014). Notably, the association between income-to-need ratio and HCC was stronger in magnitude among the most impoverished parents of school-aged children, suggesting of a J-shaped non-linear association, while the children's HCC was linearly related to parental education (Ursache et al., 2017). The reports of inverted and non-inverted U-shaped, as well as J-shaped functions in the HCC literature is puzzling. Because non-linear findings are almost exclusively reported at the end of adolescence or in adulthood, we speculate that these associations may emerge following chronic adversity or over time. Consistent with this hypothesis, Mayer and colleagues (2018) have shown that young adults who initially had higher HCC in association with internship stress later showed lower HCC as their internship continued, suggesting a non-linear function unfolding over time. Notably, our finding points to a non-linear function emerging with increasing adversity while maintaining duration and timing of exposure constant. More research is needed in age-homogenous samples to untangle the putative effects of timing of onset, duration, and severity of adversity on HCC.

More generally, our findings demonstrated that the association between adversity and HCC varies in strength and direction according to increasingly severe adversity. We argue that multiple processes may underline these distinct patterns of secretion across the distribution of the severity

of adversity. Firstly, youths who grew up in environments characterized by the presence of lower (or no) adversity and who displayed moderate-to-higher HCC may have been subjected to less toxic stress threatening their physical well-being (e.g., food insecurity, physical maltreatment, and housing problems), but could have, nonetheless, been disproportionally exposed to other forms of unmeasured social stressors, including higher expectations from parents to perform at school or to pursue postsecondary education (Stull, 2013). Future studies measuring a wider range of stressors beyond the traditional adverse childhood experience indicators may help to understand why moderate-to-higher HCC are noted in youths exposed to lower levels of adversity. It would be important for these studies, however, to keep in mind that higher HCC may not necessarily signal risk for health, but rather indicate enhanced sensitivity to the resources and support offered in these environments (Boyce and Ellis, 2005).

Secondly, our study uncovered lower, not higher, HCC in youths with moderate levels of adversity. This finding is consistent with prior examples of stress inoculation effects reported in young monkeys exposed to stressors early in life (i.e., novel environments and maternal separation) followed by lower behavioral and neuroendocrine signs of anxiety in stressful contexts (Parker et al., 2004; Parker et al., 2019). These findings parallel another study reporting that lifetime experiences of negative events (e.g., serious financial difficulties, violence, and parental divorce) were non-linearly associated with indicators of well-being in adulthood, for which the most positive outcomes were noted at moderate levels of adversity (i.e., 2 to 6 negative life events; Seery et al., 2010). The idea that stressors present in the children's environment, but that were less severe or abundant, may offer opportunities to learn cognitively and emotionally to cope with stress, leading to improved personal agency to adapt to changing environments, and lower HPA axis response to future stressors needs to be tested according to prospective research designs with cortisol measured at several time points (Rutter, 2013; McLaughlin and Sheridan,

2016). These studies would thus be ideally positioned to test whether lower HCC noted at moderate levels of adversity co-occurs with (and mediates) resilient functioning.

Thirdly, our finding also depicted a notable a shift in HCC at higher levels of cumulative adversity. Consistent with previous studies (Parker et al., 2019; Ouellet-Morin, 2020), we propose that youths exposed to higher levels of adversity may perceive it would be very difficult (or impossible) to successfully end or manage these stressors. In this context, higher HCC may signal the overwhelming weight of cumulative adversity with regards to coping with chronic stress of higher severity, which could be accompanied by hypervigilance and enhanced neurophysiological responses to future stressors (Del Giudice et al., 2011). This would be coherent with HCC reverting to moderate-to-higher levels of secretion in youths exposed to more adversity in our study sample. This apparent point of inflection in the direction of the adversity-HCC association calls for future research to examine what are the inherited or environmentally-mediated mechanisms underlying individual differences in the level of severity required to trigger this shift toward higher HCC.

More generally, our hypothesis was that a cumulative index of persistent adversity would better predict later HCC than any single indicator. This expectation was informed by prior research showing that distinct forms of childhood adversity tend to aggregate in some families and cumulatively offer the best predictions for health problems later in life (Anda et al., 2006). In our study, just one indicator of adversity — neighborhood dangerousness — was significantly associated with HCC. While the specific association was consistent with prior findings (Ziliolo et al., 2017; Vliegenthart et al., 2016), the overall lack of robust patterns of association across the indicators echoed what Bryson et al. (2018) described in their own cohort; only three out of 17 indicators of adversity correlated with HCC (housing tenure, living in a safe place and higher maternal stress). This lack of consistent associations with HCC across independent adversity

indicators was also noted across distinct domains of chronic stress in new parents (Braig et al., 2019). Based on available evidence, it is possible that the magnitude of association between each form of adversity may be too small to detect a reliable signal years after exposure.

Out of 18 tests of sex-moderation effects between HCC and the cumulative index, and each indicator of adversity, only two were detected: with hostile-reactive parenting and peer victimization, for which significant associations emerged only for boys. However, these findings did not survive the correction for multiple testing. Our findings contrast with a previous study including 215 teenagers aged between 12 and 17 years who retrospectively reported person- (e.g., violence, severe illness) and environment-related (e.g., death of a parent, family member moved) negative life events (van Dammen et al., 2020). Boys confronted with more person-related adversity had higher HCC, whereas no association with HCC was detected for girls. If boys' HPA axis respond differently to person- versus environment-related negative life events, the adversity indicators selected in the present study may not have allowed the detection of these distinct patterns of association.

The present study has notable strengths, including the scope and repeated measurement of multiple indicators of socioeconomic and psychosocial adversity over 15 years. Nonetheless, we did not examine whether the adversity-HCC association varied according to the timing of exposure, as was previously suggested (Lupien et al., 2009; Trickett et al., 2010). Moreover, while we relied on indicators collected repeatedly to derive our index of cumulative adversity, we measured HCC only once, at 17 years of age. We could thus not assess the developmental changes in HCC that may emerge over time. Future longitudinal cohorts should measure HCC levels at multiple occasions in the first two decades of life to clarify the temporal sequence of events. Also, because our cohort initially included mostly infants growing up with both of their parents, of White European descent, aged in their late twenties or early thirties, for whom the

majority of parents had a high school diploma and a family income surpassing the national cut-off point indicating poverty, the current findings may not generalize to at-risk and ethnically diverse samples. Nonetheless, adverse childhood experiences were prevalent in our cohort and aggregated within some families, which supports the relevance of examining these questions in population-based samples as well. Finally, we did not control for either inherited sources of influence or other negative life events that may have occurred during the three month period preceding the hair sample collection (e.g., death or imprisonment of a parent), which may have affected the magnitude of the adversity and HCC associations.

Our study suggests that the investigation of the association between childhood adversity and HCC should rely on a wide range of adversity indicators collected repeatedly over longer periods of time to derive robust cumulative indexes of persistent adversity. The present findings also question the assumption of linearity and offer additional support to a handful of studies that have already reported U-shaped, inverted U-shaped and J-shaped associations between HCC and adversity. The possibility that non-linear associations may best capture the adversity-HCC association should be tested systematically.

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Table 1. Summary of the estimated developmental trajectories for each adversity risk factor

		Fit and parsimony indices			
	Classes	LL	BIC	Entropy	LMR-LTR
SES (5 months-15 years)	1	-22 924.02	45 952.59	---	---
	2	-17 308.54	34 751.50	.93	10 867.17***
	3	**-14 827.62**	**29 819.54**	**.93**	**4801.11***
	4	-13 485.59	27 165.35	.93	2597.12
Maternal alcohol use (5 months-13 years)	1	-22 590.79	45 248.80	---	---
	2	**-20 911.21**	**41 919.51**	**.94**	**3250.35*** **
	3	-20 419.98	40 966.91	.89	950.64
Maternal hostile-reactive behavior (29 months-15 years)	1	-22 324.21	44 745.47	---	---
	2	-20 776.59	41 680.09	.80	2994.95***
	3	**-20 328.97**	**40 814.72**	**.77**	**866.22*** **
	4	-20 176.82	40 540.28	.74	304.30*
	5	-20 058.40	40 383.50	.74	228.98
Maternal depression (5 months-13 years)	1	-16 878.42	33 831.53	---	---
	2	-16 007.34	32 119.23	.82	1685.74***
	3	**-15828.56**	**31 791.55**	**.67**	**345.97** **
	4	-15 727.53	31 619.35	.71	195.53*
	5	-15 672.40	31 538.96	.71	106.69
Peer victimization (6-15 years)	1	-20 025.89	40 126.45	---	---
	2	-19 400.86	38 906.28	.61	1209.56***
	3	**-19 271.95**	**38 678.33**	**.61**	**249.47*** **
	4	-19 199.99	38 564.27	.53	139.26
Neighborhood dangerousness (5 months-15 years)	1	-11 365.13	22 812.39	---	---
	2	-10 306.50	20 725.01	.73	2047.63***
	3	-10 011.67	20 165.23	.76	570.55***
	4	**-9880.87**	**19 933.49**	**.70**	**254.13*** **
	5	-9822.67	19 846.96	.68	112.63

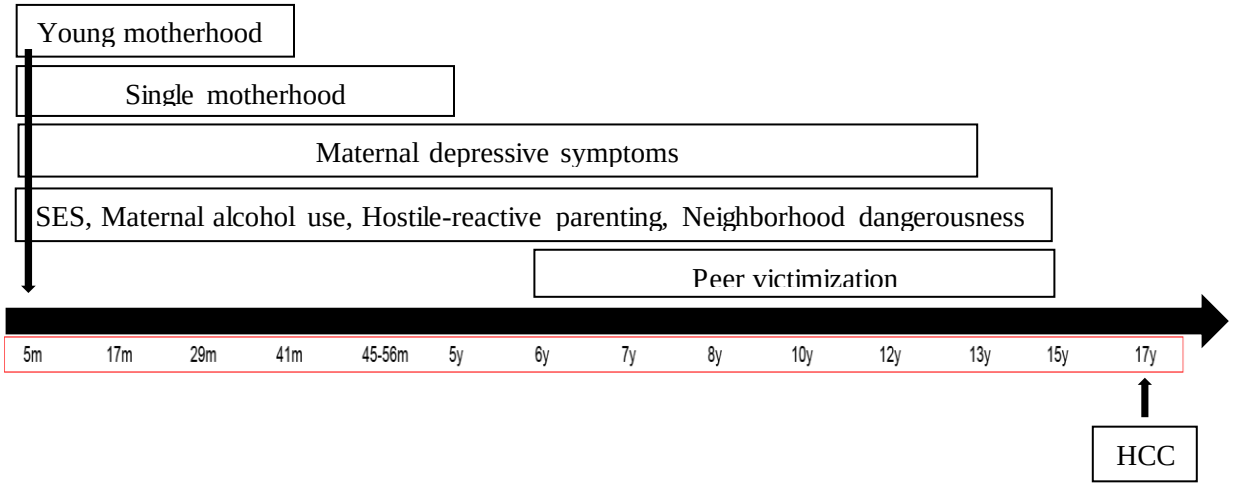
Notes. All the analyses are based on maximum available *n* value. The models in bold are the selected models. LL = Log-Likelihood; BIC: Bayesian information criteria; LMR-LTR : Lo-Mendell-Rubin likelihood ratio test; SES = socioeconomic status. *** = $p < .001$; ** = $p < .01$; * = $p < .05$. Data compiled from the final master file of the Quebec Longitudinal Study of Child Development (1998–2018), ©Gouvernement du Québec, Institut de la statistique du Québec.

Table 2. Associations between HCC and the cumulative and each indicator of adversity, according to linear and non-linear models unadjusted and adjusted for individual confounders

Risk factors	Unadjusted Models		Adjusted Model	
	Linear effects B (SE)	Non-linear effects B (SE)	Linear effects B (SE)	Non-linear effects B (SE)
Cumulative index	-.003 (.10)	.01 (.01)*	-.16 (.07)*	.02 (.01)*
Each adversity indicator				
Young motherhood	-.12 (.14	---	-.10 (.12)	---
Single motherhood	.04 (.15)	---	.08 (.15)	---
SES	-.08 (.06)	-.02 (.09)	-.04 (.36)	-.01 (.09)
Maternal alcohol use	.03 (.05)	---	.00 (.05)	---
Hostile-reactive parenting	.03 (.07)	.06 (.10)	-.21 (.36)	.07 (.10)
Maternal depressive symptoms	.07 (.06)	.04 (.10)	-.03 (.38)	.03 (.10)
Peer victimization	-.04 (.07)	-.29 (.35)	-.33 (.36)	.08 (.10)
Neighborhood dangerousness	.09 (.10)	.23 (.11)*	-.74 (.43)	.23 (.11)*

Notes. HCC = Hair cortisol concentration; B = Unstandardized Beta; SE = Standard Error; SES = Socioeconomic status. * = $p < .05$. Data compiled from the final master file of the Quebec Longitudinal Study of Child Development (1998–2018), ©Gouvernement du Québec, Institut de la statistique du Québec.

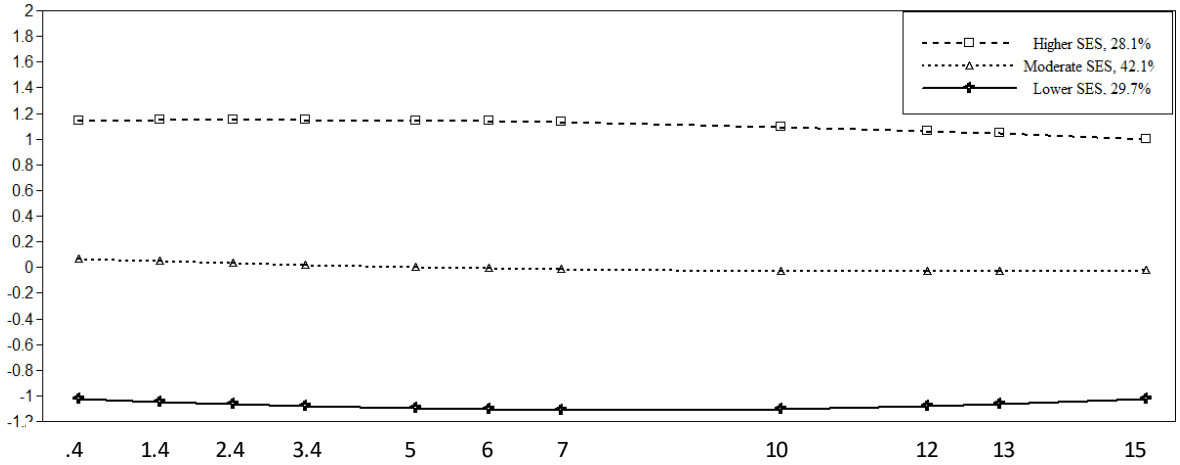
Figure 1. Overview of the timeline for the main study variables.



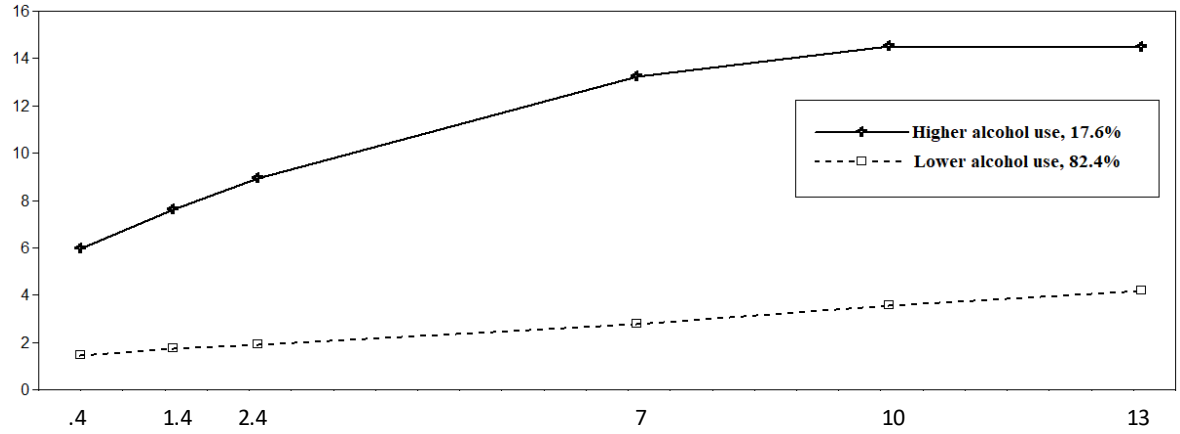
Notes. SES = Socioeconomic status; HCC = Hair cortisol concentration.

Figures 2. Developmental trajectories of each adversity indicator

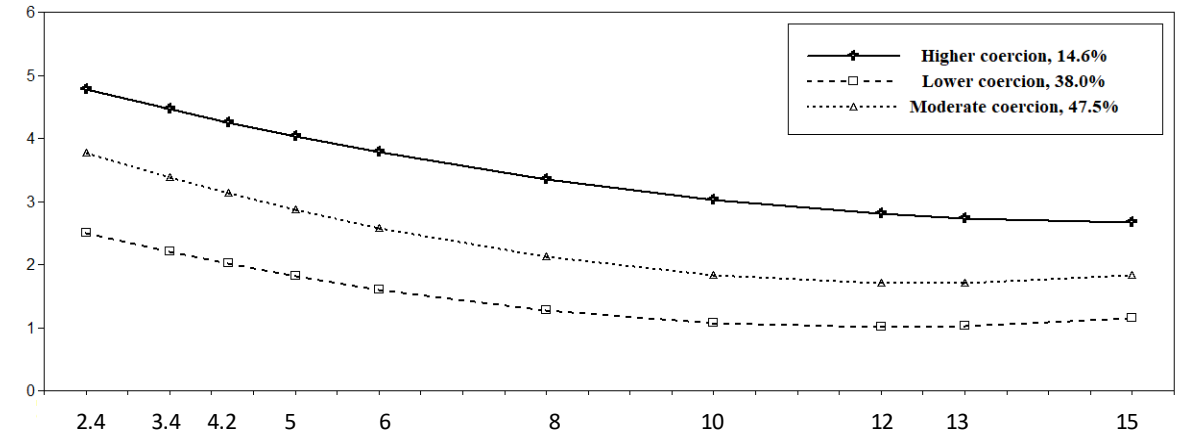
Panel A. Family socioeconomic status (SES), from 5 months to 15 years



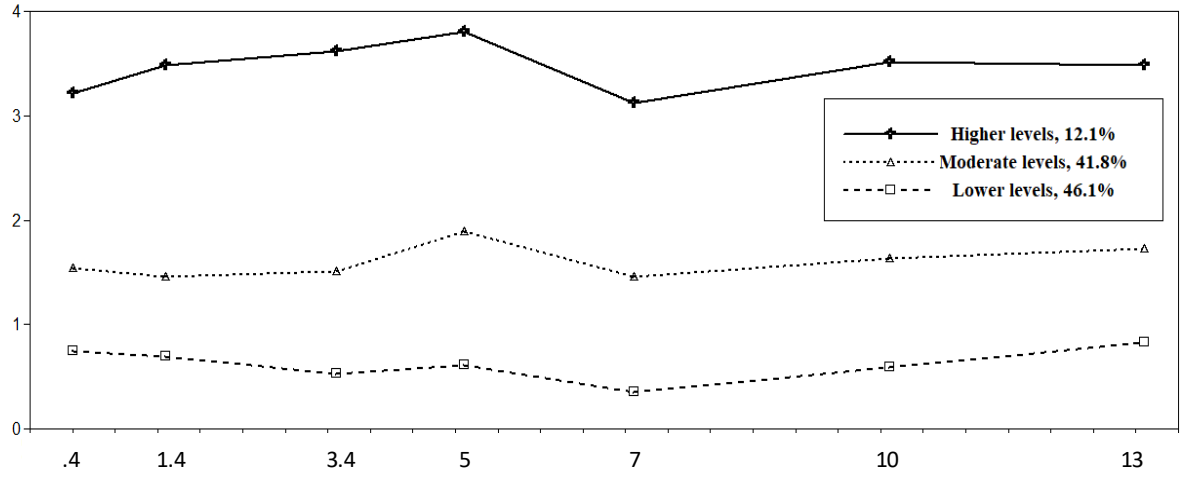
Panel B. Maternal alcohol use, from 5 months to 13 years



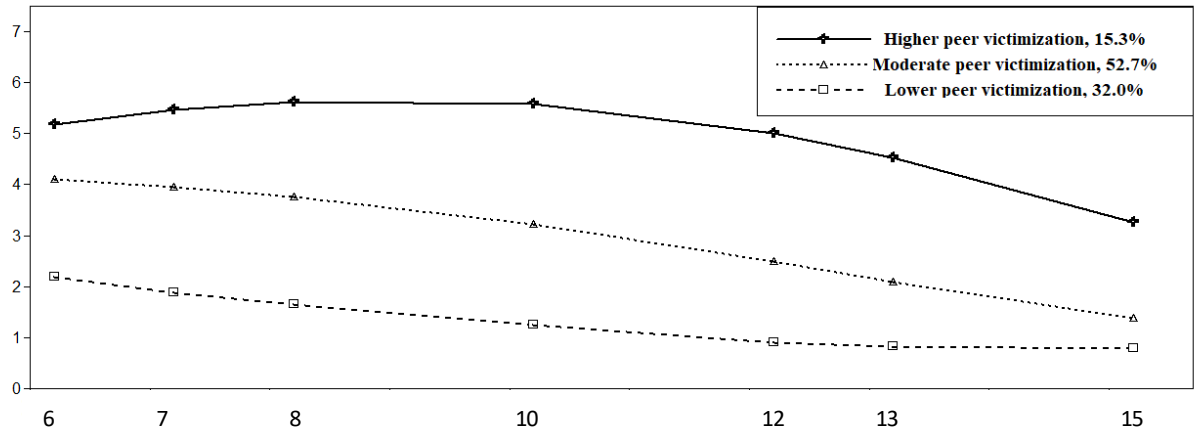
Panel C. Maternal hostile-reactive behavior, from 29 months to 15 years



Panel D. Maternal depressive symptoms, from 5 months to 13 years



Panel E. Peer victimization, from 6 to 15 years



Panel F. Neighborhood dangerousness, from 5 months to 15 years

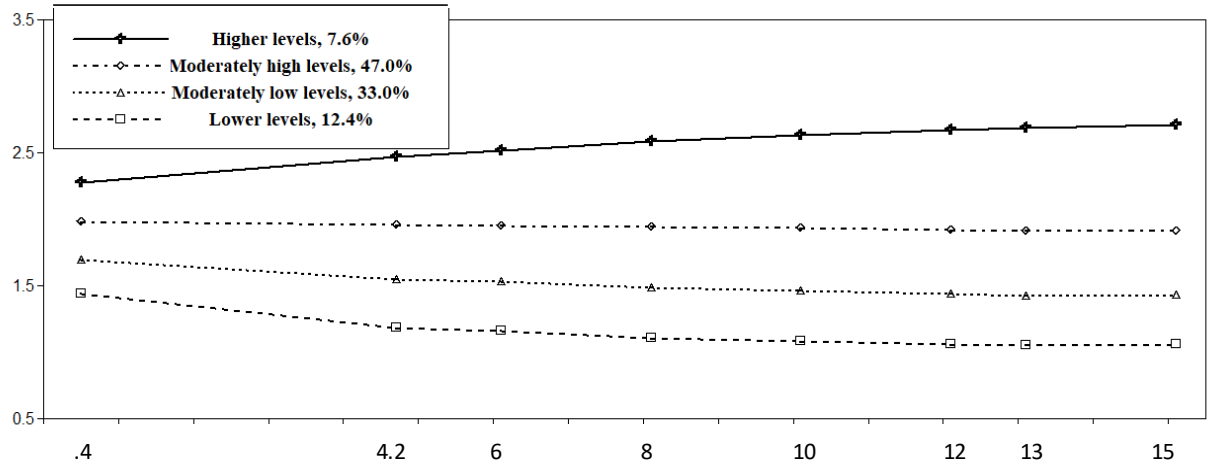


Figure 3. Distribution of the cumulative index of adversity, from infancy to adolescence

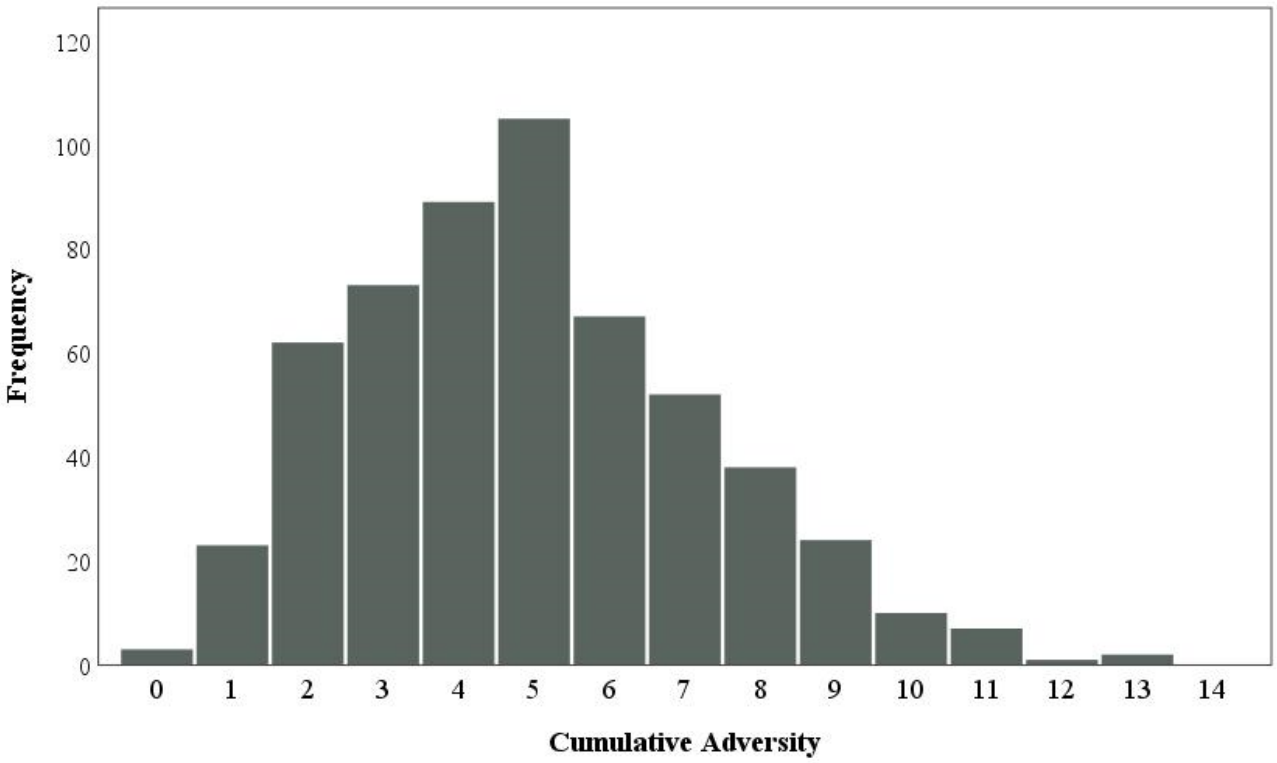
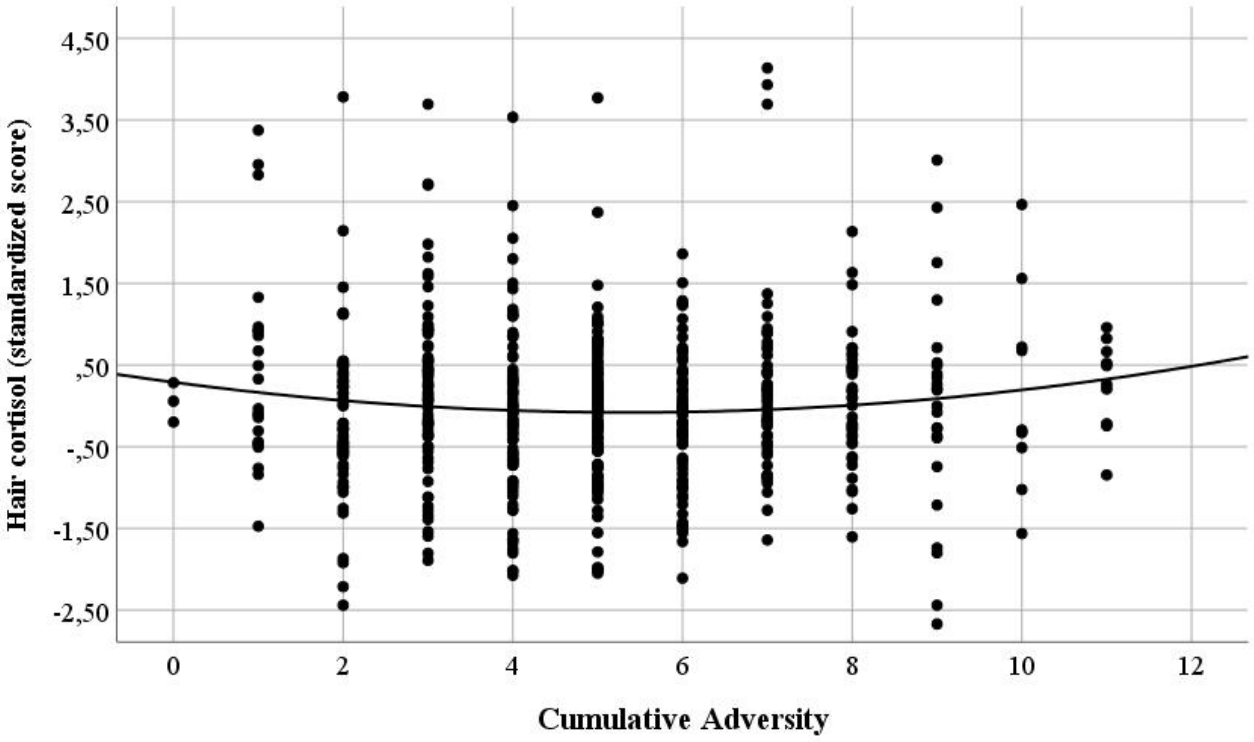


Figure 4. Association between the cumulative adversity index and HCC at 17 years of age



Notes. A standardized HCC value of 0 indicates the sample's mean HCC.

HCC = Hair cortisol concentration.

Online Supplement 1

Socioemotional and behavioral potential confounders

We investigated whether emotional and behavioral individual characteristics were uniquely associated with the cumulative adversity index. This was to done to identify which ones ought to be statistically accounted for to ensure that the estimation of the magnitude between adversity and HCC levels is not affected by these factors. The following socioemotional and behavioral characteristics were investigated: hyperactivity-impulsivity (3 items; e.g., *could not sit still*), physical aggression (3 items; e.g., *got into a fight*), anxiety (4 items; e.g., *appears fearful/nervous*), social withdrawal (3 items; e.g., *do things on his own, was rather solitary?*), inattention (4 items; e.g., *cannot concentrate*), and opposition (3 items; e.g., *was defiant or refused to comply with adults' requests or rules*). All items were rated according to a 3-point scale by different school teachers when the participating children were aged 6, 7, 8, 10 and 12 years using items derived from the Canadian National Longitudinal Study of Children and Youth (Canada, 1996), which incorporates items from the Child Behaviour Checklist (Achenbach, 1991), the Ontario Child Health Study scales (Offord, Boyle, & Racine, 1989) and the Preschool Behaviour Questionnaire (Tremblay, Desmarais-Gervais, Gagnon, & Charlebois, 1987). The data related to each behavior were summarized using growth mixture models, as done previously in this cohort (Ouellet-Morin et al., in press; Vergunst et al., 2018), for which the 3-group models fitted best the data.

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Supplementary Table 1. Sex-moderation effects of the associations between HCC and the cumulative and each indicator of adversity, according to linear and non-linear models unadjusted and adjusted for individual confounders

Risk factors	Unadjusted Models		Adjusted Model	
	Sex-moderation Linear effects B (SE)	Sex-moderation Non-linear effects B (SE)	Sex-moderation Linear effects B (SE)	Sex-moderation Non-linear effects B (SE)
Cumulative index	-03 (.04)	-.001 (.003)	-.03 (.04)	-.002 (.003)
Each adversity indicator				
Young motherhood	-.22 (.24)	---	-.24 (.24)	---
Single motherhood	.16 (.30)	---	.15 (.30)	---
SES	-.04 (.12)	.26 (.19)	-1.04 (.74)	.25 (.19)
Maternal alcohol use	.09 (.11)	--	-.08 (.11)	---
Hostile-reactive parenting	-.28 (.14)*	-.07 (.19)	-.06 (.75)	-.06 (.20)
Maternal depressive symptoms	.17 (.13)	.07 (.21)	-.10 (.78)	.07 (.21)
Peer victimization	.06 (.14)	-.46 (.19)*	1.84 (.74)*	-.47 (.19)*
Neighborhood dangerousness	-.03 (.21)	-.33 (.25)	1.33 (.93)	-.37 (.25)

Notes. HCC = Hair cortisol concentration; B = Unstandardized Beta; SE = Standard Error. * = $p < .05$. Data compiled from the final master file of the Quebec Longitudinal Study of Child Development (1998–2018), ©Gouvernement du Québec, Institut de la statistique du Québec.

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