Body Mass Index Across Development and Adolescent Hair Cortisol: The Role of Persistence, Variability, and Timing of Exposure

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Abbreviations: BMI = body mass index; HPA = hypothalamic-pituitary-adrenal; HCC = hair cortisol concentration

Abstract

Background: Research suggests a putative role of the glucocorticoid stress hormone cortisol in the accumulation of adiposity. However, obesity and weight fluctuations may also wear and tear physiological systems promoting adaptation, affecting cortisol secretion. This possibility remains scarcely investigated in longitudinal research. This study tests whether trajectories of body mass index (BMI) across the first 15 years of life are associated with hair cortisol concentration (HCC) measured two years later and whether variability in BMI and timing matter.

Methods: BMI (kg/m^2) was prospectively measured at twelve occasions between age 5 months and 15 years. Hair was sampled at age 17 in 565 participants. Sex, family socioeconomic status, and BMI measured concurrently to HCC were considered as control variables.

Results: Latent class analyses identified three BMI trajectories: "low-stable" (59.2%, n=946), "moderate" (32.6%, n=507), and "high-rising" (8.2%, n=128). BMI variability was computed by dividing the standard deviation of an individual's BMI measurements by the mean of these measurements. Findings revealed linear effects, such that higher HCC was noted for participants with moderate BMI trajectories in comparison to low-stable youth (β = 0.10, p = 0.03, 95% confidence interval (CI) = [0.02 – 0.40]); however, this association was not detected in the high-rising BMI youth (β = -0.02 , p = 0.71, 95%CI = [-0.47 – 0.32]). Higher BMI variability across development predicted higher cortisol (β = 0.17, p = 0.003, 95%CI = [0.10 – 4.91]), additively to the contribution of BMI trajectories. BMI variability in childhood was responsible for that finding, possibly suggesting a timing effect.

Conclusions: This study strengthens empirical support for BMI-HCC association and suggests that more attention should be devoted to BMI fluctuations in addition to persistent trajectories of BMI.

Keywords: Hair Cortisol Concentration (HCC), Body Mass Index (BMI), Trajectories, Obesity; Variability, Longitudinal, Developmental Stages, Childhood, Adolescence.

Childhood obesity is a serious public health concern (1). A substantial amount of research has mechanistically linked the hypothalamic-pituitary-adrenal (HPA) axis, and its glucocorticoid stress hormone cortisol, as contributory factors to the onset and persistence of obesity (2,3). While these putative effects are relatively undisputed (for an exception, see (4)), the unidirectional depiction of this association may be overly simplistic. Recent suggestions propose that obesity may also bring about the wear and tear of physiological systems promoting adaptation. Persistent individual differences in BMI are thus hypothesized to induce long-lasting changes in cortisol secretion (3–5). Given the scarcity of studies that have relied on prospective and repeatedly collected BMI during childhood and adolescence, it is unclear if persistent and/or fluctuating patterns of BMI across development predict later cortisol secretion and whether these effects are uniform across development. Adopting a developmental approach of this complex association may help extend our understanding of how the stress and metabolic systems may together increase risk for physical and mental health problems in the general population, as well as among people with overweight and obesity.

Approximately 30% of Canadian (6) and 33% of American (7) children and adolescents suffer from overweight or obesity. Furthermore, people with obesity in both childhood and adolescence, rather than in just one of these developmental periods, are substantially more likely to be with obesity in adulthood (8), suggesting that sustained obesity across early development might be a significant risk factor for future health concerns. Individuals with overweight and obesity are more likely than those in the normative weight range to report a variety of physical health concerns including diabetes, metabolic syndrome, and other cardiovascular diseases (9). They are also more likely to report higher mental health problems, including depression and anxiety (9), which can also precipitate negative health consequences over time.

While multiple physiological, emotional, and behavioral factors contribute to obesity, research underlines the implication of the HPA axis in the pathophysiology of obesity. Specifically, animal models suggest that excessive exposure to glucocorticoids increases adiposity, whereas lowering glucocorticoid exposure reverses these effects (10,11). Similarly, clinical populations with hypercortisolemia (e.g., Cushing's syndrome) exhibit higher adiposity (12). Although the biological and molecular mechanisms linking cortisol and obesity in controlled environments and clinical conditions appear fairly straightforward, observational studies conducted in community samples have produced less conclusive results (13). These incongruent findings may be partly due to time-varying cofounders affecting the measurement of cortisol (e.g., HPA axis's circadian rhythm, sleep, mood), and the biospecimen used to measure cortisol (e.g., blood, saliva, urine; (14,15)). Recent technological advances now enable the measurement of cortisol from hair, which is suggested to be a reliable marker of systemic cortisol secretion over time (i.e., months) that is less affected by time-variant confounders (16). As such, hair may be used as a non-invasive measurement of cumulative cortisol secretion to test the hypothesized role of BMI on later hair cortisol concentrations (HCC).

Within the adult literature, several studies have found that higher levels of BMI, obesity, and adiposity were associated with higher levels of HCC (for a meta-analysis see (16)). Research examining concurrent cortisol-BMI associations in youth is more inconsistent, depicting either positive associations (17,18) or non-significant findings (19,20). One hypothesis is that a shift in the BMI-hair cortisol association occurs over time, possibly driven by developmental factors and/or the timing or chronicity of obesity (21,22). In contrast, prior research has mostly investigated concurrent obesity-BMI associations, thereby complicating the determination of the role that timing and variability play in the association between BMI and cortisol secretion.

Prospective longitudinal studies with multiple measurements of height and weight across childhood and adolescence provide a unique opportunity to test whether the timing, persistence, and variability of individual differences in BMI are associated with HCC.

The present study tested whether developmental trajectories of BMI, ascertained from infancy to adolescence, were associated with later HCC, collected at age 17, in a community sample followed prospectively from 5 months of age. We further investigated whether variability in BMI also predicted HCC, as repeated fluctuations in BMI may act as a stressor on the organism, a possibility that remains largely unexplored in previous cross-sectional research. Given the dearth of developmentally informed research examining the association between longitudinal timing patterns (i.e., persistent trajectories, variability) of BMI and cortisol levels, we remain agnostic as to whether we should expect a positive or negative association between the longitudinal measures of BMI and HCC. Finally, we investigated whether increased BMI or BMI fluctuations may be more strongly associated with HCC at specific developmental periods. Using a different study, Ruttle and colleagues (23) examined cortisol levels from early to late adolescence and age 18 BMI and found that the strength of association between diurnal salivary cortisol levels and BMI depended on the age at which cortisol was measured. However, considering the lack of previous developmentally sensitive research examining BMI-cortisol associations from infancy to adolescence, we take an exploratory approach without *a priori* hypothesis.

Methods

Participants. Using birth registries from the province of Quebec, families with a child born between October 1997 and July 1998 (N=2940) were contacted to take part in the Quebec Longitudinal Study of Child Development. Approximately 7.7% were unable to be contacted, refused to participate, or were screened out based on exclusion criteria, yielding a sample of

N=2120 individuals. Specifically, babies were included only if the mother's pregnancy had lasted between 24 and 42 weeks (i.e., 99.9% of all registered births) and if the mothers could speak French or English (for more information, see 24). Participants were included in the current study if they had at least half of the 12 BMI measurements taken between the ages of 5 months and 15 years (n=1581, 74.6%) so that we can reliably estimate the BMI trajectories. At age 17, 1150 youth who still participated in the study were contacted to collect hair for cortisol measurement if they still lived in the province of Quebec and could be reached. A total of 565 participants provided hair samples; however, twenty-two participants did not provide BMI at age 17, leading to a final sample of 543 participants (225 males). A total of 565 participants provided hair samples; however, twenty-two participants did not provide BMI at age 17, leading to a final sample of 543 participants (225 males). Descriptive analyses revealed that compared to the initial cohort (*N*=2120; 5 months of age), adolescents who participated in the hair cortisol sampling were more likely to be female ($\chi^2 = 17.56$, $p < .001$), White ($\chi^2 = 6.35$, $p < .01$), and from higher SES families ($r_{pb}=.09$, $p < .001$). Statistical analyses accounted for this selective attrition by including inverse-probability weights in analyses.

Ethics approval and consent to participate

All methods in this manuscript were performed in accordance with relevant guidelines and regulations. Parents gave informed written consent and child assent (at later ages) were obtained. The project was approved by the Institutional Review Boards of the Institut de la Statistique du Québec and the University of Montreal (CERAS-2014-15-136-P).

Measures

Body Mass Index (BMI). From ages 5 months to 5 years, measures of height and weight were obtained through maternal report, whereas between 6 and 13 years, height and weight were

measured by a trained researcher during home visits without shoes and only lightweight clothing on. Weight was measured to the nearest 0.1 kg using a calibrated spring scale and height to the nearest 0.1 cm using standard measuring tape. Both weight and height were measured twice and averaged. If the initial two readings differed by more than 0.2 kg for weight or 0.5 cm for height, a third measurement was taken. The average of the closest two readings was then used (25). At ages 15 and 17, participants reported their own weight. Consistent with other studies of community samples (23,26,27), BMI was calculated by dividing body weight in kilograms by the square of height in meters (kg/m^2). Based on best-practice (28), we used BMI rather than BMI z-scores to derive group-based trajectories to ease the interpretability of the data and preserve the variability within the sample to identify groups with different developmental trajectories (also see (29)). All BMI outliers were winsorized to within 3 SD of the mean at each assessment (*n* range: min=7; max=23 outliers).

Hair Cortisol. Materials and instructions to collect hair samples were mailed when participants were 17 years old (30). Using curved scissors and hair clamps, participants were instructed to cut 3 cm of hair strand (~ 25 mg) from the posterior vertex area of the scalp. Participants also self-reported information concerning their hair (e.g., hair colour/curvature, frequency of washing, treatments, etc.) and health (e.g., medication, smoking status, alcohol and drug use, sleep, chronic diseases). Hair samples were mailed back to researchers. The first 3cms of hair was washed and processed following protocols established by Kirschbaum and colleagues (31) and assayed in duplicate using a commercially available luminescence immunoassay (detection range: 0.005-4.0 µg/dl; intra-assay coefficient of variation=5.39%; see (32) for additional information). All hair cortisol outliers (*n*= 6) were winsorized to within 3 SD of the mean (M= 16.19pg/mg, SD=14.84). Following this, HCC values were log10-transformed to normalize the distribution.

Control Variables

BMI at age 17. Following the instructions and computation of BMI outlined above, BMI was concurrently measured with HCC.

Family Socioeconomic Status. Information on maternal and paternal education and occupational prestige, single parenthood, and family income was collected at several occasions between 5 months and 15 years of age and aggregated into an index of family SES (see (32) for additional information).

Statistical analyses

Preliminary analyses revealed that, of the possible confounding variables, four were uniquely related to HCC: smoking status, month of hair collection, washed 24 hours or less before sampling, natural hair colour. Fifteen participants were missing partial (*n*=9) or all (*n*=6) information on these variables and were given a value equal to the sample's mean. A standardized residual was created by regressing out the effects of all hair-related confounders. Age 17 BMI was also related to HCC and included in the subsequent analytical models as an independent predictor of hair cortisol to better tease apart whether the longitudinal trajectories of BMI provided different information than concurrent BMI.

Group-based developmental trajectories were derived using Mplus (version 7.0; (33)). We estimated models including 1-to-4 groups to capture homogenous patterns of BMI from 5 months to 15 years of age using growth mixture models. We then repeated these analyses specifically for the three developmental epochs, that is, infancy: 5 months to 5 years; childhood: 6 to 10 years; adolescence: 12–15 years. The best-fitting model for BMI trajectories was selected according to the Bayesian Information Criterion (BIC), LoMendell-Rubin likelihood ratio test (LMR-LRT), entropy estimate and clinical pertinence. BMI variability from 5 months to 15 years was computed

for everyone by dividing the standard deviation of an individual's BMI measurements by the mean of their BMI measurements. The higher the coefficient of variation, the higher the standard deviation of an individual relative to their mean, indicating more variability. It is important to measure fluctuations in relation to the mean as an individual's mean BMI may influence how much variation can be expected. Similar measures were computed according to each developmental epoch.

Alike previous studies, regression analyses with the concurrent BMI and HCC variables were first examined. Following this, the BMI trajectories were coded into binary variables and included in the regression models, followed by the inclusion of the BMI variability variable. Similar regression analyses were also conducted at each developmental stage to investigate the possibility that timing of exposure may yield distinct patterns of association.

Results

The 4-group solution showed a somewhat better fit than the 3-group model, with a lower BIC and nonsignificant LMR-LRT test (1-group: BIC=74862.94, entropy=not applicable, LMR-LRT=not applicable; 2-groups: BIC=70188.72, entropy=.93, LMR-LRT=4670.10, $p<0.001$; 3-groups: BIC= 68165.50, entropy=.91, LMR-LRT=2005.59, $p<0.01$; 4-groups: BIC= 66938.92, entropy=.87, LMR-LRT=1230.01, $p>0.05$). Despite this, the 3-group solution, representing distinct, homogeneous, and clinically relevant BMI patterns with at least 5% of participants in each group, was selected: "low-stable" (n=946; 59.2%), "moderate" (n=507; 32.6%) and "high-rising" (n=128; 8.2%; see Figure 1). Although the proportion of males and females differed in the BMI trajectories, the same pattern of trajectories emerged for boys and girls separately, thus BMI trajectories were estimated for the entire group and sex was included as a confounder in subsequent analyses. A 3-group solution was also selected for the BMI data at each developmental stage (see Supplemental

Table 1 for model fit information). The BMI trajectories were categorized into binary variables, using the low-stable group as the reference category for subsequent analyses.

Descriptive statistics are provided in Table 1. Bivariate associations among the main study variables revealed that BMI at age 17 and SES were both significantly associated with the BMI trajectories and variability indices (see Table 2). Multiple regression results replicated prior findings identifying a positive concurrent association between age 17 BMI and HCC (Table 3, Model 1). Upon including the binary BMI trajectory variables in the model, additional significant effects were also identified, suggesting that youth with moderate BMI trajectory had higher HCC than those in the low-stable group. However, this association did not persist for youth belonging to the high-rising trajectory when compared to the low-stable group (Table 3, Model 2; Figure 2). Notably, the observed association for the moderate BMI trajectory was identified over and above the effects of sex, SES, BMI at age 17 years, and adjusted for non-random attrition. Next, we examined whether similar patterns of findings emerged at each developmental epoch by repeating the analyses according to BMI trajectories estimated during infancy (5 months to 5 years), childhood (6 to 10 years), and adolescence (12 to 15 years), respectively. Results revealed no significant associations with BMI trajectories in infancy, childhood, or adolescence (Table 4a).

Using multiple hierarchical linear regressions, we then tested whether BMI variability between 5 months and 15 years, reflecting the degree of BMI fluctuation over this period, was uniquely associated with HCC at age 17. Results revealed a significant positive linear association between BMI variability and HCC over and above the BMI trajectories and other confounders (Table 3, Model 3). When rerunning the analyses according to each developmental period, only BMI variability in childhood was significantly associated with HCC at age 17 (Table 4b).

Discussion

This study examined associations between developmental trajectories of BMI, from infancy to adolescence, and HCC two years later, at 17 years of age. Results revealed that individuals in the moderate BMI group, but not those in the high-rising group, had higher HCC than those in the low-stable group. Additionally, higher variability in BMI from infancy to adolescence predicted higher HCC, over and above the contribution of the BMI trajectories. Subsequent analyses revealed that only BMI variability in childhood, and not infancy nor adolescence, sustained this finding. The present study extends prior cross-sectional investigations of BMI and cortisol associations by ascertaining the putative impact of timing, persistence, and variation in BMI profiles over the first 15 years of life on age 17 HCC, providing additional targets for future mechanistic investigations.

In line with previous studies conducted in adulthood, we found a positive concurrent association between age 17 BMI and HCC. While inconsistent findings have been reported, the vast majority of prior research has reported a positive concurrent association between BMI, obesity, adiposity and HCC in adults (for a meta-analysis, see (16)). Additional studies have also detected a positive BMI-HCC association in children (17,18), but the magnitude and direction of this association is more tenuous (19,20). The present study extends this work by examining this association longitudinally in youth for whom the measures of height and weight have been collected at 12 occasions between the age of 5 months and 15 years. This enabled us to not only replicate previous cross-sectional associations, but also to test the prospective BMI-HCC associations according to persistent individual differences in BMI. Additionally, these repeated measurements made possible to examine this association specifically for each developmental period and to explore the role of BMI variability over time. Higher HCC were noted for youth belonging to the moderate BMI trajectory, from infancy to adolescence, compared to the low-

stable group, but this association was not present for the high-increasing group. This finding echoes a nonlinear pattern of association, which was also reported in the Whitehall II study for the association between BMI classifications assessed once and short-term salivary diurnal cortisol in adults. While individuals in both the lower and highest BMI groups had the flattest cortisol slopes during the day, individuals in the "in-between" overweight categories showed the steepest cortisol diurnal decrease (34). As research inconsistently tests for non-linear associations, some may be missed due to the intertwined effects of maturation, timing of initial exposure, chronicity and time since the exposure ended (35). Indeed, Ruttle and colleagues (36) have shown that stressors measured more proximally in time are associated with increased levels of morning salivary cortisol, whereas chronic stressors were related to lower levels of morning cortisol. Future research should explore whether *persistent* stressors of sufficient intensity, such as higher BMI levels, may instigate HPA axis down-regulation over time, requiring measuring both BMI and HCC on multiple occasions over an extended period. Such a study could help ascertain whether higher HCC are indeed observed initially, before a second pattern of influence in the opposite direction may become superimposed, leading to a nonlinear pattern of associations emerging between BMI and HCC.

In addition to the effect of BMI trajectories over time, we found that higher variability in BMI over time—that is, higher levels of fluctuation in BMI from one measurement to the next—uniquely predicted higher HCC at age 17 years. While theoretical models of stress and development suggest that repeated activation of the stress response system may eventually lead to down-regulation of the HPA axis and lower levels of cortisol (37,38); however, this theory does not seem to apply to BMI variability-HCC associations. This may be because many developmentally normative processes, from infancy to adolescence, could co-occur with unhealthy

changes in BMI. For example, both a growth spurt without accompanying weight gain and a dramatic loss in weight due to food restriction would result in reducing BMI (and higher variability); however, these two processes may be differentially related to HPA axis functioning. Gaining a better understanding of the driving mechanisms and contexts behind shifts in BMI might help elucidate the BMI variability-cortisol association. Thus, similar studies conducted in adulthood, a time when changes in BMI are less developmentally driven and more specific to weight gain/loss and health behaviors, could help to further shed light on this association independent of average BMI.

Developmentally sensitive analyses revealed that higher variability in BMI during the childhood period to be associated with HCC at age 17, while it was not the case during infancy and mid-adolescence. Although it should be noted that measurements of BMI during the childhood period were obtained by researchers at home visits rather than mother reports (infancy) or self-reports (ages 15 and 17), therefore lowering possible measurement errors (and slightly increase statistical power), developmental driven explanations for this finding may be proposed. Fluctuations in BMI could be developmentally more normative when occurring during infancy and adolescence due to normative changes in activity level (i.e., non-mobile infants progressing to crawling and walking), periods of rapid growth, and the accumulation of fat during puberty. In contrast, BMI fluctuations during childhood is less expected as a steadier and more moderate rate of growth is noted. That is, higher BMI variability during childhood may be more closely related to atypical patterns of weight gain and loss and thus more strongly associated with high levels of HCC.

In summary, the current study contributed to the literature by showing that persistently moderate BMI over time and higher variability in BMI may be associated with cortisol secretion.

Furthermore, we uncovered specific developmental epochs during which the effect of BMI fluctuations was the most salient, possibly elucidating previously incongruent BMI-cortisol associations, and raising more questions for future investigations. Collectively, these findings suggest that persistently moderate BMI across development and higher BMI variability during childhood may bring forth the wear and tear of the HPA axis, leading to higher chronic cortisol secretion in adolescence. Over time, such prolonged and excessive activity of the HPA axis may compromise later development, increasing the risk for physical and mental health problems (39,40). This hypothesis remains to be tested in longitudinal studies featuring repeated measures of BMI. Additionally, the larger standard errors noted for the high-rising trajectories in Figure 2 may point to co-occurring divergent patterns of association with HCC, whereby some participants may exhibit higher HCC whereas other have lower HCC. Further investigations over a longer period and in adulthood may help to shed more light on these findings.

While the longitudinal nature of this project allowed us to examine temporal associations between BMI and hair cortisol, it is important to acknowledge several limitations. First, the measurement of BMI involved maternal reports during infancy and self-reports during adolescence, which may have introduced reporting biases (41,42). Further studies should attempt to replicate our findings using longitudinal and direct assessments of BMI. Second, the nonsignificant findings for the association between the high-rising group and HCC might be attributed to the smaller number of participants in this group compared to the moderate trajectory, leading to lower statistical power to detect an effect. As well, the large error bar in Figure 2 for the high-rising vs. moderate trajectories suggests that other processes may be at play, such as BMI variability. Third, our sample predominantly consisted of White adolescents from middle-to-upper socioeconomic backgrounds, which limit the generalizability of our results to more diverse and

socioeconomically varied populations. Future studies involving more frequent BMI measurements across a broader demographic will be crucial to understanding the patterns of these associations in different groups. Fourth, HCC was assessed only once, preventing from examining how the BMI-HCC association unfolds or shift across early development. Future studies should also investigate the psychological and social mechanisms that may be intricately linked to BMI and cortisol, including body image perception, self-esteem, mood disorders and peer victimization, to which the current investigation is blind to. While additional research is necessary, this study provides a developmentally informed investigation of the complex association between BMI and cortisol and provides evidence for examining the mechanisms through which obesity relates to health and well-being.

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Author Contributions:

- CYC: Responsible for data analyses, interpretation and the writing of the paper
- PLR: Responsible for study design, data analyses and interpretation, and wrote a first draft of the paper.
- SMC: Data collection and provided feedback on the report.
- SJL: Data collection and provided feedback on the report.
- MCG: Provided feedback on the report.
- MB: Provided feedback on the report.
- RT: Data collection and provided feedback on the report.
- MB: Data collection and provided feedback on the report.
- IOM: Responsible for study design, data collection, data analyses, writing the paper, interpretation, and provided feedback on the report.

Competing Interests:

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Data Availability Statement:

The datasets generated during and/or analyzed during the current study were obtained from a third party, the Institut de la statistique du Québec, and are not publicly available due to the privacy legislation in the province of Québec, Canada. Requests to access these data can be directed to the

Institut de la statistique du Québec's Research Data Access Services - Home (www.quebec.ca). For more information, contact Marc-Antoine Côté-Marcil (marc-antoine.cote-marcil@stat.gouv.qc.ca).

References

1. Daniels SR, Arnett DK, Eckel RH, Gidding SS, Hayman LL, Kumanyika S, et al. AHA scientific statement: Overweight in children and adolescents: Pathophysiology, consequences, prevention, and treatment. Circulation. 2005;111(15):1999–2012.

2. Rebuffé-Scrive M, Walsh UA, McEwen B, Rodin J. Effect of chronic stress and exogenous glucocorticoids on regional fat distribution and metabolism. Physiology & Behavior. 1992 Sep 1;52(3):583–90.

3. van der Valk ES, Savas M van Rossum E. Stress and Obesity: Are There More Susceptible Individuals? Curr Obes Rep. 2018;7(2):193–203.

4. Travison TG, O'Donnell AB, Araujo AB, Matsumoto AM, McKinlay JB. Cortisol levels and measures of body composition in middle-aged and older men. Clinical Endocrinology. 2007;67(1):71–7.

5. Van Rossum EFC. Obesity and cortisol: New perspectives on an old theme: Obesity and Cortisol. Obesity. 2017 Mar;25(3):500–1.

6. Rao DP, Kropac E, Do MT, Roberts KC, Jayaraman GC. Childhood overweight and obesity trends in Canada. Health Promot Chronic Dis Prev Can. 2016 Sep;36(9):194–8.

7. Skinner AC, Ravanbakht SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of Obesity and Severe Obesity in US Children, 1999–2016. Pediatrics. 2018 Mar 1;141(3):e20173459.

8. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obesity Reviews. 2016;17(2):95–107.

9. Pulgarón ER. Childhood Obesity: A Review of Increased Risk for Physical and Psychological Comorbidities. Clinical Therapeutics. 2013 Jan 1;35(1):A18–32.

10. Cunningham JJ, Calles-Escandon J, Garrido F, Carr DB, Bode HH. Hypercorticosteronuria and Diminished Pituitary Responsiveness to Corticotropin-Releasing Factor in Obese Zucker Rats*. Endocrinology. 1986 Jan 1;118(1):98–101.

11. Naeser P. Effects of adrenalectomy on the obese-hyperglycemic syndrome in mice (gene symbolob). Diabetologia. 1973 Oct 1;9(5):376–9.

12. Shibli-Rahhal A, Van Beek M, Schlechte JA. Cushing's syndrome. Clinics in Dermatology. 2006 Jul 1;24(4):260–5.

13. Bose M, Oliván B, Laferrère B. Stress and obesity: the role of the hypothalamic–pituitary–adrenal axis in metabolic disease. Curr Opin Endocrinol Diabetes Obes. 2009 Oct;16(5):340–6.

14. Klimes–Dougan B, Hastings PD, Granger DA, Usher BA, Zahn–Waxler C. Adrenocortical activity in at-risk and normally developing adolescents: Individual differences in salivary cortisol basal levels, diurnal variation, and responses to social challenges. Development and Psychopathology. 2001 Sep;13(3):695–719.

15. El-Farhan N, Rees DA, Evans C. Measuring cortisol in serum, urine and saliva – are our assays good enough? Ann Clin Biochem. 2017 May 1;54(3):308–22.

16. Stalder T, Steudte-Schmiedgen S, Alexander N, Klucken T, Vater A, Wichmann S, et al. Stress-related and basic determinants of hair cortisol in humans: A meta-analysis. Psychoneuroendocrinology. 2017 Mar 1;77:261–74.

17. Veldhorst MAB, Noppe G, Jongejan MHTM, Kok CBM, Mekic S, Koper JW, et al. Increased Scalp Hair Cortisol Concentrations in Obese Children. The Journal of Clinical Endocrinology & Metabolism. 2014 Jan 1;99(1):285–90.

18. Noppe G, van den Akker ELT, de Rijke YB, Koper JW, Jaddoe VW, van Rossum EFC. Long-term glucocorticoid concentrations as a risk factor for childhood obesity and adverse body-fat distribution. Int J Obes. 2016 Oct;40(10):1503–9.

19. Larsen SC, Fahrenkrug J, Olsen NJ, Heitmann BL. Association between Hair Cortisol Concentration and Adiposity Measures among Children and Parents from the "Healthy Start" Study. PLOS ONE. 2016 Sep 23;11(9):e0163639.

20. Olstad DL, Ball K, Wright C, Abbott G, Brown E, Turner AI. Hair cortisol levels, perceived stress and body mass index in women and children living in socioeconomically disadvantaged neighborhoods: the READI study. Stress. 2016 Mar 3;19(2):158–67.

21. Del Giudice M, Ellis BJ, Shirtcliff EA. The Adaptive Calibration Model of stress responsivity. Neuroscience & Biobehavioral Reviews. 2011 Jun 1;35(7):1562–92.

22. Trickett PK, Noll JG, Susman EJ, Shenk CE, Putnam FW. Attenuation of cortisol across development for victims of sexual abuse. Development and psychopathology. 2010;22(01):165–75.

23. Ruttle PL, Javaras KN, Klein MH, Armstrong JM, Burk LR, Essex MJ. Concurrent and Longitudinal Associations Between Diurnal Cortisol and Body Mass Index Across Adolescence. Journal of Adolescent Health. 2013 Jun 1;52(6):731–7.

24. Orri M, Boivin M, Chen C, Ahun MN, Geoffroy MC, Ouellet-Morin I, et al. Cohort Profile: Quebec Longitudinal Study of Child Development (QLSCD). Soc Psychiatry Psychiatr Epidemiol. 2021 May 1;56(5):883–94.

25. Van Hulst A, Wills-Ibarra N, Nikiéma B, Kakinami L, Pratt KJ, Ball GDC. Associations between family functioning during early to mid-childhood and weight status in childhood and adolescence: findings from a Quebec birth cohort. Int J Obes. 2022 May;46(5):986–91.

26. Oskis A, Loveday C, Hucklebridge F, Thorn L, Clow A. Diurnal patterns of salivary cortisol across the adolescent period in healthy females. Psychoneuroendocrinology. 2009 Apr 1;34(3):307–16.

27. Netherton C, Goodyer I, Tamplin A, Herbert J. Salivary cortisol and dehydroepiandrosterone in relation to puberty and gender. Psychoneuroendocrinology. 2004 Feb 1;29(2):125–40.

28. Cole TJ, Faith MS, Pietrobelli A, Heo M. What is the best measure of adiposity change in growing children: BMI, BMI %, BMI z-score or BMI centile? Eur J Clin Nutr. 2005 Mar;59(3):419–25.

29. Pryor LE, Brendgen M, Tremblay RE, Pingault JB, Liu X, Dubois L, et al. Early Risk Factors of Overweight Developmental Trajectories during Middle Childhood. PLOS ONE. 2015 Jun 29;10(6):e0131231.

30. Ouellet-Morin I, Laurin M, Robitaille MP, Brendgen M, Lupien SJ, Boivin M, et al. Validation of an adapted procedure to collect hair for cortisol determination in adolescents. Psychoneuroendocrinology. 2016 Aug 1;70:58–62.

31. Kirschbaum C, Tietze A, Skoluda N, Dettenborn L. Hair as a retrospective calendar of cortisol production—Increased cortisol incorporation into hair in the third trimester of pregnancy. Psychoneuroendocrinology. 2009 Jan 1;34(1):32–7.

32. Ouellet-Morin I, Cantave C, Paquin S, Geoffroy MC, Brendgen M, Vitaro F, et al. Associations between developmental trajectories of peer victimization, hair cortisol, and depressive symptoms: a longitudinal study. J Child Psychol Psychiatry. 2021 Jan;62(1):19–27.

33. Muthén LK, Muthén BO. Mplus statistical modeling software: Release 7.0. Los Angeles, CA: Muthén & Muthén. 2012;

34. Kumari M, Chandola T, Brunner E, Kivimaki M. A Nonlinear Relationship of Generalized and Central Obesity with Diurnal Cortisol Secretion in the Whitehall II Study. The Journal of Clinical Endocrinology & Metabolism. 2010 Sep 1;95(9):4415–23.

35. Miller GE, Chen E, Zhou ES. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychological bulletin. 2007;133(1):25.

538 36. Ruttle PL, Shirtcliff EA, Serbin LA, Ben-Dat Fisher D, Stack DM, Schwartzman AE.
539 Disentangling psychobiological mechanisms underlying internalizing and externalizing
540 behaviors in youth: Longitudinal and concurrent associations with cortisol. Hormones and
541 Behavior. 2011 Jan;59(1):123–32.

542 37. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism.
543 Psychoneuroendocrinology. 2005;30(10):1010–6.

544 38. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. Hormones
545 and Behavior. 2003 Jan 1;43(1):2–15.

546 39. McEwen BS, Stellar E. Stress and the individual: mechanisms leading to disease. Archives
547 of internal medicine. 1993;153(18):2093–101.

548 40. Shonkoff JP. Building a new biodevelopmental framework to guide the future of early
549 childhood policy. Child development. 2010;81(1):357–67.

550 41. Huybrechts I, Himes JH, Ottevaere C, De Vriendt T, De Keyzer W, Cox B, et al. Validity of
551 parent-reported weight and height of preschool children measured at home or estimated
552 without home measurement: a validation study. BMC Pediatr. 2011 Jul 7;11(1):63.

553 42. Sherry B, Jefferds ME, Grummer-Strawn LM. Accuracy of Adolescent Self-report of Height
554 and Weight in Assessing Overweight Status: A Literature Review. Archives of Pediatrics &
555 Adolescent Medicine. 2007 Dec 1;161(12):1154–61.

556

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Figure Legends

Figure 1. Body mass index (BMI) trajectory groups.

Notes. 1-group: BIC=74862.94, entropy=not applicable, LMR-LRT=not applicable; 2-groups: BIC=70188.72, entropy=.93, LMR-LRT=4670.10, $p<0.001$; 3-groups: BIC= 68165.50, entropy=.91, LMR-LRT=2005.59, $p<0.01$; 4-groups: BIC= 66938.92, entropy=.87, LMR-LRT=1230.01, $p>0.05$. Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec.

Figure 2. Mean level of hair cortisol (log-transformed standardized residual) as a function of BMI trajectory class.

Note: ** = $p < 0.01$; n.s. = nonsignificant. The one-way ANOVA test revealed significant mean differences in HCC [F (2, 540) = 5.72, p = 0.003]. A Tukey post-hoc test indicated that when compared to those in the low-stable BMI trajectory group (Mean = -.13; SD = .93), participants in the moderate BMI trajectory had significantly higher HCC (Mean = .17; SD = .97), but there were no significant mean differences detected between the low-stable group and the high-rising BMI group (Mean = .01; SD = 1.04), suggesting the possibility of a curvilinear effect. Of note, the variances of HCC were similar between each group, as indicated by a nonsignificant Levene Statistic [(2 ,540) = .44, p = .64]. The error bars represent standard errors. Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec.

Table 1. Individual characteristics of the total sample and according to BMI trajectories

	Total sample (%)	Low stable trajectory (*n*=326)	Moderate trajectory (*n*=179)	High-rising trajectory (*n*=38)	χ^2
Sociodemographic characteristics					
Child female sex	58.6	57	61	60.5	0.77
Low maternal education (no high school diploma)	7.7	7.7	6.7	13.5	8.23
Low paternal education (no high school diploma)	10.7	8.9	11.2	23.7	13.70*
Insufficient family income	13.6	13.8	13.4	13.2	0.01
Single parent/blended family	28.7	25.8	32	37	4.34
Race (White)	71.3	93.9	89.9	97.4	3.61
Hair characteristics					
Curly hair	31.1	30.4	30.2	42.1	1.96
Frequency of washing (once a day or more)	43.8	44.2	43	44.7	10.62
Hair coloration and bleaching	16.9	13.8	19.6	31.6	8.31*
Hair straightening treatment	4.1	4	3.9	5.3	0.13
Other hair treatments	1.7	0.06	3.4	2.6	5.40
Medication use in the past 3 months					
Glucocorticoids	12.9	12.6	13.4	13.2	0.05
Antihistamine	15.1	14.4	16.2	15.8	0.24

Hyperactivity/Inattention	11.2	12.0	10.6	7.9	0.74
Anti-inflammatory	27.4	27.9	26.3	28.9	0.23
Anti-depressant	3.5	2.8	5.6	—	4.16
Anxiolytics	0.06	0.06	0.06	—	0.24
Other medications	18.2	17.2	20.7	15.8	1.39
Health problems					
Cardiovascular problems	2.0	2.1	2.2	—	0.86
Epilepsy	0.02	0.03	—	—	0.67
Diabetes	0.09	0.03	1.7	2.6	3.63
Cholesterol	0.07	0.09	0.06	—	0.52
Glaucoma	0.02	—	0.06	—	2.03
Kidney problems	1.1	0.09	1.7	0.06	1.05
Asthma or respiratory diseases	7.9	6.4	11.2	5.3	3.89
Thyroid problems	0.06	0.06	0.06	—	0.24
Health behaviors in the past 3 months					
10 minutes or less physical activity per week	63.5	61	68.2	63.2	1.74
Smoking	18.8	16.6	21.2	26.3	2.84

Notes: Maternal and paternal education were measured when the child was age 15. All other variables were measured at age 17. Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec .

Table 2. Bivariate Pearson Correlations

	1.	2.	3.	4.	5.	6.
1. Sex	--	0.047	0.010	-0.034	-0.093*	.032
2. SES		--	-0.151**	-0.117*	-0.213**	.033
3. Age 17 BMI			--	0.598**	0.559**	.131**
4. BMI Trajectories				--	0.575**	.112**
5. BMI Variability					--	.165**
6. Age 17 HCC						--

Notes: The sex variable is coded 1 = female, 2 = male. SES= Socioeconomic Status; BMI = Body Mass Index; HCC= Hair cortisol concentration. BMI trajectories is coded 1= low-stable, 2=moderate, 3=high-rising; * $p < 0.05$, ** $p < 0.01$. Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec .

Table 3. Associations Between the Developmental Trajectories of BMI and Hair Cortisol Concentrations at Age 17

	Model 1			Model 2			Model 3		
Predictors	*β*	*t*	*p*	*β*	*t*	*p*	*β*	*t*	*p*
Control Variables									
Sex	0.023	0.546	0.585	0.028	0.653	0.514	0.040	0.944	0.346
SES	0.056	1.302	0.193	0.047	1.095	0.274	0.066	1.522	0.128
BMI at age 17	**0.134**	**3.095**	**0.002**	**0.112**	**2.073**	**0.039**	0.060	1.069	0.285
BMI Variables									
Moderate BMI Trajectory				**0.103**	**2.137**	**0.033**	0.066	1.326	0.185
High-Rising BMI Trajectory				-0.019	-0.370	0.711	-0.077	-1.389	0.165
BMI Variability							**0.165**	**2.962**	**0.003**
	***R* = .139 (*p* < .05)**			***R* = .175 (*p* <.05)**			***R* = .215 (*p* < .001)**		

Notes: Analyses are weighted for non-random attrition. The sex variable is coded 1 = female, 2 = male. *β* =standardized coefficients; SES= Socioeconomic Status; BMI = Body Mass Index; Moderate BMI Trajectory is coded 0= low stable/ high-rising, 1= moderate; High-Rising BMI Trajectory is coded 0= low stable/ moderate, 1= high-rising. Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec.

Table 4a. Associations Between the Developmental Trajectories of BMI at Various Life Stages and Hair Cortisol Concentrations at Age 17

	Infancy (5 months-5 years)			Childhood (6-10 years)			Adolescence (12-15 years)		
Predictors	*β*	*t*	*p*	*β*	*t*	*p*	*β*	*t*	*p*
Sex	0.025	0.579	0.563	0.023	0.541	0.588	0.029	0.684	0.494
SES	0.055	1.264	0.207	0.050	1.144	0.253	0.061	1.418	0.157
BMI at age 17	0.141	3.159	0.002	0.166	3.220	0.001	0.074	1.328	0.185
Moderate Trajectory	-0.005	-0.115	0.908	-0.009	-0.180	0.857	0.066	1.315	0.189
High Increasing Trajectory	-0.036	-0.805	0.421	-0.076	-1.511	0.131	0.080	1.497	0.135

Table 4b. Associations Between the Variability of BMI Across Various Life Stages and Hair Cortisol Concentrations at Age 17

	Infancy (5 months-5 years)			Childhood (6-10 years)			Adolescence (12-15 years)		
Predictors	*β*	*t*	*p*	*β*	*t*	*p*	*β*	*t*	*p*
Sex	0.024	0.559	0.576	0.015	0.338	0.735	0.030	0.691	0.490
SES	0.058	1.336	0.182	0.067	1.476	0.141	0.047	1.042	0.298
BMI at age 17	0.141	3.146	0.002	0.096	1.967	0.050	0.133	2.991	0.003
BMI Variability	0.046	1.072	0.284	**0.104**	**2.129**	**0.034**	0.059	1.334	0.183

Notes: Analyses are weighted for non-random attrition. The sex variable is coded 1 = female, 2 = male. *β* =standardized coefficients; SES= Socioeconomic Status; BMI = Body Mass Index. Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec

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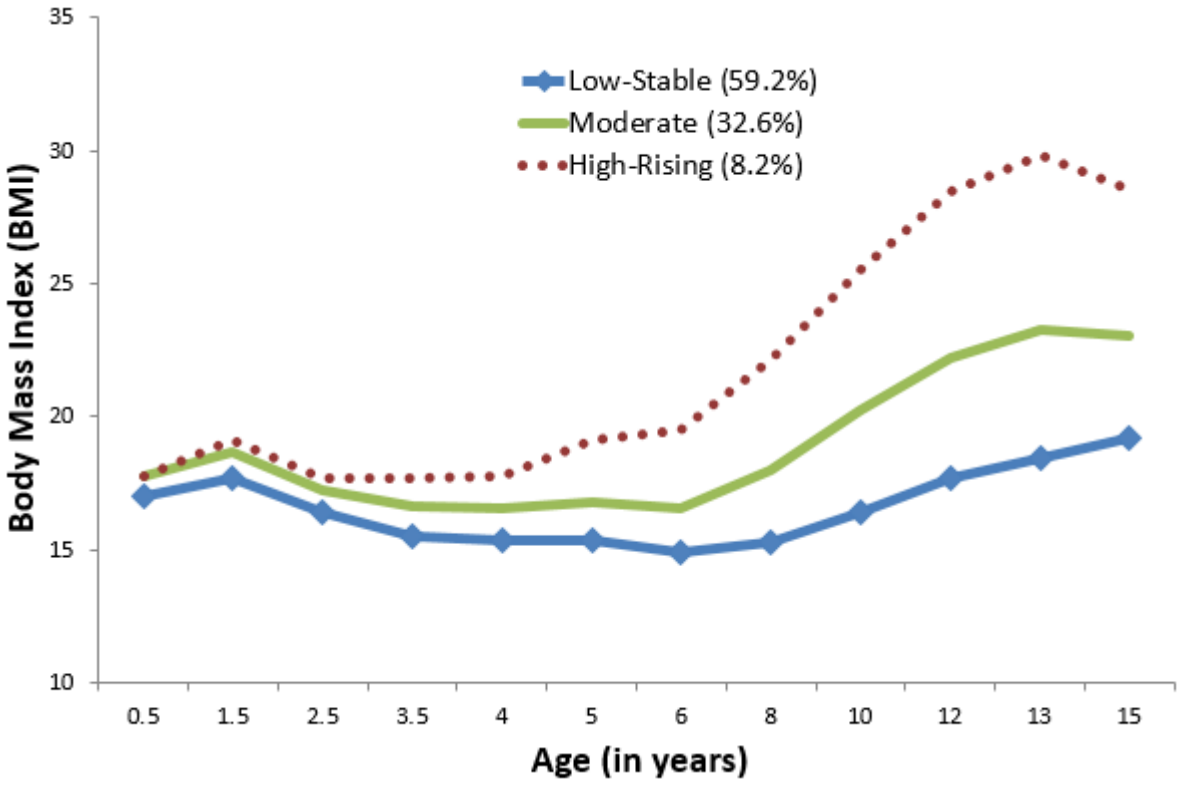
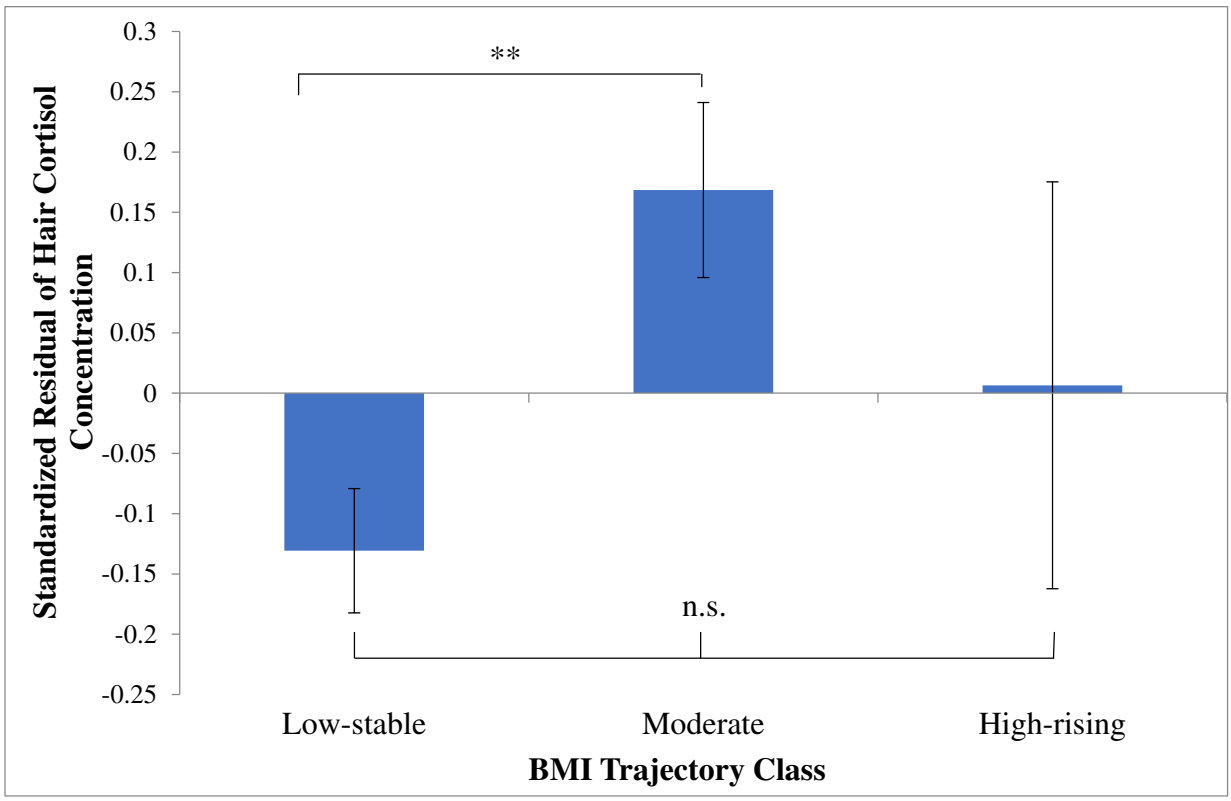

Low-Stable (59.2%)
Moderate (32.6%)
High-Rising (8.2%)
Body Mass Index (BMI)
35
30
25
20
15
10
0.5
1.5
2.5
3.5
4
5
6
8
10
12
13
15
Age (in years)


Standardized Residual of Hair Cortisol Concentration
0.3
0.25
0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
-0.2
-0.25
**
n.s.
Low-stable
Moderate
High-rising
BMI Trajectory Class