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ORIGINAL ARTICLE

Maternal distress in early life predicts the waist-to-hip ratio in schoolchildren

A. L. Kozyrskyj[1,2]*, Y. Zeng[1,2], I. Colman[2], K. T. HayGlass[3], E. A. C. Sellers[4], A. B. Becker[4] and B. J. MacNeil[5]

[1]*Faculty of Medicine & Dentistry, Department of Pediatrics, Women and Children's Health Research Institute, University of Alberta, Edmonton, Alberta, Canada*
[2]*School of Public Health, University of Alberta, Edmonton, Alberta, Canada*
[3]*Faculty of Medicine, Department of Immunology, University of Manitoba, Winnipeg, Manitoba, Canada*
[4]*Faculty of Medicine, Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada*
[5]*School of Medical Rehabilitation, University of Manitoba Winnipeg, Manitoba, Canada*

We report on life course stress determinants of overweight in children, using data from the longitudinal follow-up of the nested case–control arm of the SAGE (study of asthma genes and the environment) birth cohort in Manitoba, Canada. Waist and hip measurements were obtained during a clinic visit at age 9–11 years. Multiple linear regression was conducted to determine the relationship between the waist-to-hip ratio and maternal smoking during pregnancy, *postpartum* maternal distress and stress reactivity in children (cortisol, cortisol-DHEA [dihydroepiandrostrenone] ratio quartiles) following a clinic stressor at age 8–10 years. We found waist-to-hip risk at age 9–11 years to be elevated among boys and girls whose mothers had experienced distress in the postnatal period. This association varied by gender and asthma status. In healthy girls, *postpartum* distress increased waist-to-hip ratio by a factor of 0.034 ($P < 0.01$), independent of the child's stage of puberty and adrenarche, cortisol-DHEA ratio and duration of exclusive breastfeeding. Among girls with asthma, maternal smoking during pregnancy was associated with an increased waist-to-hip ratio, if the mother also experienced distress in the *postpartum* period (0.072, $P = 0.038$). Among asthmatic boys, an association between maternal distress and waist-to-hip ratio was evident at the highest cortisol-DHEA ratios. Stress-induced changes to leptin and infant over-eating pathways were proposed to explain the postnatal maternal distress effects. Drawing on the theories of evolutionary biology, our findings underscore the significance of postnatal stress in disrupting hypothalamic–pituitary–adrenal axis function in infants and increasing risk for child overweight.

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Key words: children, early puberty, overweight, *postpartum* distress, stress reactivity

Introduction

It is abundantly clear that the global trend for rising overweight and obesity among children reflects decreases in physical activity and over-consumption of energy dense foods.[1] Yet the difficulty in treating overweight highlights gaps in current understanding of what underlies the initiation and persistence of this state. Children and adults who are overweight have multiple comorbidities, including depression.[2] They also have signs of hypothalamic–pituitary–adrenal (HPA) axis perturbations and are more likely to have abnormal cortisol levels or reactivity.[3,4] For this reason, recent attention has turned to neuroendocrine processes such as cortisol secretion, to illuminate mechanisms by which psychologic processes may influence the development of overweight.[5]

Given the potential role of stress as a causal factor, a life course approach has been advocated to evaluate the temporal relationships between early life stress and the development of overweight.[6,7] Low birth weight and rapid catch-up growth during infancy have been associated with overweight in children.[8,9] Fetal stressors such as maternal smoking, result in intrauterine growth retardation and higher cortisol levels in infants and children.[10] Higher cortisol reactivity is also seen in infants of mothers with *postpartum* depression and anxiety.[11,12] Thus, programming of the HPA axis by early life environmental stressors has the potential to cause overweight in later life. This study was undertaken to determine the association between risk of overweight at age 9–11 years, and exposure to stress during fetal development, the *postpartum* period and school age. We hypothesized that maternal distress in early life had an impact on the development of overweight in children, independent of *in utero* stress and recent stress experienced by the child.

Methods

This was a longitudinal follow-up of the nested case-control arm of the 1995 SAGE (study of asthma genes and the

*Address for correspondence: Dr A. L. Kozyrskyj, Faculty of Medicine & Dentistry, Department of Pediatrics, Women and Children's Health Research Institute, University of Alberta, 11402 University Avenue, Edmonton, Alberta, Canada.
(Email anitakozyrskyj@med.ualberta.ca)

environment) birth cohort in Manitoba, Canada, as described previously.[13] Children with (36%) and without asthma (64%) were recruited into the case-control study at age 8–10 years. This represented all children with asthma of parents agreeing to be contacted for study; their urban–rural distribution was similar to the whole population of Manitoba children with asthma.[13] Children in the control group were randomly sampled from households stratified by urban-rural and household income area. As part of a research objective to investigate the association between overweight in preadolescence and the onset of asthma in adolescence, waist and hip measurements were obtained during a second clinic visit at 9–11 years of age. In this paper, we report on the stress determinants of overweight in children, using the waist-to-hip ratio as our anthropometric overweight index. The waist-to-hip ratio has been found to be positively correlated with insulin resistance indices and leptin levels in children.[14]

Waist measurements were taken with the child in a standing position in centimeters. A horizontal line was drawn above the uppermost lateral border of the child's right iliac crest and then across the line to indicate the mid-axillary line of the body. Standing on the child's right side, the research nurse placed the measuring tape around the trunk in a horizontal line at the level marked on the right side of the trunk. The widest circumference over the buttocks was located for hip measurement. All measurements were performed three times and the mean was recorded.

In chronological order from pregnancy, child exposures to or markers of stressors were evaluated as: smoking during pregnancy, distress in the mother during the *postpartum* period and abnormal stress response at school age. The latter included cortisol levels and the ratio of cortisol and dihydroepiandrostrenone (DHEA) following a clinic stressor, both assayed in a plasma sample obtained in children at age 8–10 years. We have reported on cortisol levels in previous analyses on SAGE children, arguing that study procedures such as venepuncture and skin prick tests, and their anticipation functioned as acute stressors in the evaluation of a child's stress response.[15] For these analyses, we employed the cortisol/DHEA ratio that has been advocated as a more powerful measure of HPA axis integrity following a stressor than cortisol levels.[16] Cortisol and DHEA levels were measured in a laboratory at the University of Manitoba where plasma samples (diluted 1:240 and 1:6, respectively) were assayed using commercially available ELISA kits (Cayman Chemical, Diagnostic Systems Laboratories). Assayed values were measured in nanograms per milliliter. Assay sensitivity was 70 pg/ml, with an inter-assay variance of 14.8% and an intra-assay variance of 7.8%. DHEA assay sensitivity was 100 pg/ml. Its inter-assay coefficient of variation (CV) was 5.3% and the intra-assay CV was 4.4%.

Recognizing that low and high cortisol levels are markers of chronic stress, cortisol/DHEA ratios were expressed in quartile format on the basis of assay determinations in all SAGE children at age 8–10 years.[15,17] Maternal distress during the *postpartum* period was based on mother's response to a question on whether she felt down, depressed or hopeless during the year after the birth of their child, as per the following categories: not at all, several days, more than half the days and nearly every day. Values in the highest frequency category were defined as the presence of *postpartum* distress. We found this category to have the greatest agreement with maternal use of health care and prescription medications for depression or anxiety in the postnatal period.[15,18] Maternal smoking during pregnancy, birth weight and other explanatory factors such as child age and Aboriginal status (First Nations or Metis), exclusive breastfeeding >3 months, activity level (vigorous activity in the last week) and maternal education were also based on mother questionnaire. Birth weight categories included: small-for-gestational age (<10th percentile), low birth weight appropriate for gestation (gestational age <37 weeks, and birth weight between 10th and 90th percentile) and not low birth weight, according to sex-specific percentiles for Canadian children.[19] Onset of puberty was assessed in boys and girls through child self-report of the Tanner stages of puberty, based on comparison to standardized drawings for genital and breast development, respectively.[20–22] Higher Tanner scores indicated early onset puberty. A pediatric allergist examined children at age 8–10 years to diagnose the presence of asthma.

Multiple linear regression was conducted to determine the relationship between the waist-to-hip ratio and: *postpartum* maternal distress, maternal smoking during pregnancy and recent stress markers in children (cortisol-DHEA ratio quartiles). The second lowest quartile was set as the reference category in order to determine associations with low and high cortisol/DHEA ratios. All models were tested for age, Tanner stage of puberty, adrenarche stage (DHEA levels), exclusive breastfeeding >3 months, physician activity level, ethnicity, maternal education level and small-for-gestational-age. Interactions terms were also tested. Data were analyzed using SAS statistical software package Version 9.2 (SAS Institute, Inc.). Appropriate institutional ethics committee clearance and participants' informed consent were obtained. Results are reported as regression coefficients at the 95% level of confidence, separately for girls and boys, and for boys and girls stratified by asthma status to account for overrepresentation by asthma status in the case-control design. To simplify reporting of two-way interactions with cortisol-DHEA ratios, these models are presented as β-coefficients of the other factor for each quartile of the cortisol-DHEA ratio. Our threshold for significance was lowered from 0.05 to 0.0125 (0.05/4 quartiles) for interaction effects to adjust for multiple comparisons and keep the overall cut-off of $\alpha = 0.05$.

Results

A total of 556 children in the nested case-control SAGE study had cortisol and DHEA levels measured at age 8–10 years. A complete data set with these stress hormones, maternal

postpartum distress and other survey measures, and waist and hip measurements at age 9–11 years (mean age = 10.7 years) was available for 393 children (see Table 1). At this age, 50% of children had a waist-to-hip ratio of 0.83 and in 10%, the ratio was 0.92 and higher. The median waist-to-hip ratio was higher in boys (0.84) than girls (0.82). A greater percentage of boys had waist-to-hip ratios in the highest quartile (24% *v.* 18% in girls). At age 8–10 years, more boys, especially boys with asthma, had cortisol-DHEA ratios in the highest quartile range. Boys with asthma were most likely to have mothers

Table 1. *Sociodemographics, maternal characteristics and waist-to-hip ratios of study children and their stress hormone levels*

	Girls ($n = 175$)	Boys ($n = 218$)	Non-asthma girls ($n = 116$)	Asthma girls ($n = 59$)	Non-asthma boys ($n = 130$)	Asthma boys ($n = 88$)
Study age (mean years)	10.68	10.63	10.74	10.55	10.66	10.60
Aboriginal status (%)						
Yes	17.7	10.6	16.4	20.3	8.5	13.6
Tanner stage (breast/genital; %)						
Stage 1	39.9	66.7	39.5	40.7	67.5	65.5
Stage 2	47.4	33.3	47.4	47.5	32.5	34.5
Stage 3	12.7	0.0	13.2	11.9	0.0	0.0
Asthma (%)						
Yes	33.7	40.4	0.0	100.0	0.0	100.0
Physical activity (vigorous; %)						
<2 days per week	25.1	16.1	24.1	27.1	18.5	12.5
Mother not completed high school (%)						
Yes	7.1	8.7	7.9	5.5	9.5	7.3
Mother smoked during pregnancy (%)						
Yes	12.6	16.5	11.2	15.3	15.4	18.2
Birth weight (%)						
SGA	12.2	6.8	10.9	14.6	6.3	7.6
LBW-AGA	0.0	3.4	0.0	0.0	3.2	3.8
Not SGA LBW-AGA	87.8	89.8	89.1	85.5	90.6	88.6
Exclusive breastfeeding (%)						
≤3 months	40.6	44.0	40.5	40.7	37.7	53.4
>3 months	59.4	56.0	59.5	59.3	62.3	46.6
Maternal distress *postpartum* (%)						
Yes	24.6	24.8	23.3	27.1	28.5	19.3
DHEA level quartiles (range; %)						
<5.7	21.1	28.9	20.7	22.0	27.7	30.7
5.7–8.0	25.1	25.2	22.4	30.5	24.6	26.1
8.0–11.5	25.7	23.4	25.9	25.4	25.4	20.5
>11.5	28.0	22.5	31.0	22.0	22.3	22.7
Cortisol-DHEA level quartiles (range; %)						
<9.85	25.7	20.2	24.1	28.8	18.5	22.7
9.85–15.35	30.3	23.4	30.2	30.5	23.9	22.7
15.35–22.97	23.4	27.1	23.3	23.7	30.0	22.7
>22.97	20.6	29.4	22.4	17.0	27.7	31.8
Waist-to-hip ratio at study age (mean)	0.83	0.85	0.83	0.82	0.84	0.85
Waist-to-hip ratio quartiles (range; %)	35.4	19.3	32.8	40.7	22.3	14.8
0.79						
0.79–0.83	25.7	28.0	28.5	20.3	26.9	29.6
0.83–0.88	21.1	28.4	19.8	23.7	29.2	27.3
>0.88	17.7	24.3	19.0	15.3	21.5	28.4

SGA, small forgestational age; LBW-AGA, low birth weight appropriate for gestational age; DHEA, dihydroepiandrostrenone.

Table 2. *Sociodemographics, maternal characteristics and stress hormone levels of study children and children lost to follow-up*

	Study sample ($n = 393$)	Lost to follow-up ($n = 163$)	*P*-value
Study age (mean years)	10.65	10.52	0.08
Gender (%)			
Boys	55.5	57.7	0.63
Aboriginal status (%)			
Yes	13.7	30.6	<0.01
Asthma (%)			
Yes	37.4	31.9	0.22
Physical activity (vigorous; %)			
<2 days/week	20.1	28.8	0.03
Mother not completed high school (%)			
Yes	8.0	22.8	<0.01
Mother smoked during pregnancy (%)			
Yes	14.8	27.0	<0.01
Birth weight (%)			
SGA	9.1	10.3	0.33
LBW-AGA	1.4	4.3	
not SGA, LBW-AGA	89.0	85.3	
Exclusive breastfeeding (%)			
⩽3 months	42.5	50.6	0.08
>3 months	57.5	49.4	
Maternal distress *postpartum* (%)			
Yes	24.7	13.2	<0.01
DHEA level quartiles (range; %)			
<5.7	25.5	23.9	0.98
5.7–8.0	25.2	25.8	
8.0–11.5	24.4	25.8	
>11.5	24.9	24.5	
Cortisol-DHEA level quartiles (range; %)			
<9.85	22.7	30.7	0.23
9.85–15.35	26.5	21.5	
15.35–22.97	25.5	23.9	
>22.97	25.5	23.9	

SGA, small forgestational age; LBW-AGA, low birth weight appropriate for gestational age; DHEA, dihydroepiandrostrenone.

who smoked during pregnancy and breastfed exclusively for <3 months. Girls, however, were more likely to have early-onset puberty (highest percent with Tanner 2 and 3 scores at age 9–11 years) and early adrenarche (highest DHEA levels at age 8–10 years), and to be of Aboriginal (First Nations or Metis) origin. Girls with asthma were the most likely to be born small-for-gestational age and to have cortisol-DHEA ratios in the lowest quartile range. *Postpartum* distress was more common in mothers of girls with asthma or of boys without asthma. Children lost to follow-up or with missing data ($n = 163$) were more likely to be of Aboriginal status, and have mothers with a lower level of education and higher rates of smoking during pregnancy (Table 2). The majority of these mothers were Aboriginal, 55% and 64% respectively. *Postpartum* distress was less common in the lost to follow-up group and found in 7% of Aboriginal mothers.

In girls without asthma, pregnancy smoking and *postpartum* maternal distress were positively correlated with the waist-to-hip ratio ($r = 0.24$, $P = 0.009$ and $r = 0.29$, $P = 0.0016$, respectively). DHEA levels were inversely correlated with birth weight category ($r = -0.34$, $P = 0.010$) in girls with asthma. In boys without asthma, waist-to-hip ratio was correlated with DHEA levels ($r = 0.21$, $P = 0.017$) and to a lesser extent with birth weight category ($r = -0.16$, $P = 0.068$). Maternal smoking during pregnancy was negatively correlated with birth weight category (with the lowest rank for small-for-gestational age as, $r = -0.27$, $P = 0.018$) in boys with asthma. Aside from a modest correlation between maternal distress and child cortisol-DHEA ratios in boys without asthma ($r = 0.18$, $P = 0.042$), there were no other correlations between the stress indicators of maternal smoking during pregnancy, maternal *postpartum* distress and child cortisol-DHEA ratios.

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Table 3. *Maternal postpartumdistress and other predictors of the waist-to-hip ratio in children at age 9–11 years by quartile of the cortisol-DHEA ratio*

		Cortisol/DHEA ratio quartile level							
		First quartile		Second quartile		Third quartile		Fourth quartile	
Study group	Variable	β-coefficient	*P*-value	β-coefficient	*P*-value	β-coefficient	*P*-value	β-coefficient	*P*-value
Girls[a]	Tanner stage[e]	−0.006	NS	−0.004	NS	0.055	<0.01*	−0.017	NS
	Smoked during pregnancy[e]	0.038	NS	−0.012	NS	−0.053	NS	0.059	0.02
	Postpartum maternal distress[e]	−0.319	NS	0.022	NS	0.056	<0.01*	0.031	NS
	Aboriginal status	0.040	<0.01*	0.040	<0.01*	0.040	<0.01*	0.040	<0.01*
	Exclusive breastfeeding >3 months	−0.021	0.02*	−0.021	0.02*	−0.021	0.02*	−0.021	0.02*
Girls without asthma[b]	Tanner stage[e]	−0.012	NS	−0.004	NS	0.043	<0.01*	−0.017	NS
	Postpartum maternal distress	0.034	<0.01*	0.034	<0.01*	0.034	<0.01*	0.034	<0.01*
	Exclusive breastfeeding >3 months	−0.024	0.03 *	−0.024	0.03*	−0.024	0.03*	−0.024	0.03*
	Aboriginal status	0.045	<0.01*	0.045	<0.01*	0.045	<0.01*	0.045	<0.01*
Boys[c]	*Postpartum* maternal distress[e]	−0.013	NS	−0.020	NS	−0.001	NS	0.49	<0.01*
	Aboriginal status	0.036	<0.01*	0.036	<0.01*	0.036	<0.01*	0.036	<0.01*
Boys with asthma[d]	*Postpartum* maternal distress[e]	−0.053	NS	−0.008	NS	0.020	NS	0.054	0.05

DHEA, dihydroepiandrostrenone; NS, not significant.

[a] The model is also adjusted for DHEA level and asthma status.

[b] The model is also adjusted for DHEA level.

[c] The model is also adjusted for DHEA level.

[d] The model is also adjusted for DHEA level, Aboriginal status and birth weight.

[e] Effect depending on cortisol/DHEA ratio quartile level.

*Statistically significant at $P < 0.05$ level for independent effects, and $P < 0.0125$ level for dependent effects.

At age 9–11 years, the waist-to-hip ratio in girls was associated with maternal *postpartum* distress only in the presence of higher stress response levels at age 8–10 years (Table 3). This interaction was such that exposure to maternal distress in the *postpartum* period predicted an increase of 0.056 in waist-to-hip ratio when cortisol-DHEA ratios fell into the third highest quartile. The Tanner score predicted a 0.055 increase in the waist-to-hip ratio of girls with cortisol-DHEA ratios in the third quartile as well. At the highest cortisol-DHEA quartile range, maternal smoking during pregnancy predicted waist-to-hip ratio by an increase of 0.059. DHEA levels were not related to the waist-to-hip ratio in girls. All of these associations were independent of asthma and Aboriginal status, and an inverse association with duration of exclusive breastfeeding. In boys, the waist-to-hip ratio was also related to an interaction between maternal *postpartum* distress and the cortisol-DHEA ratio, but by a factor of 0.049 in the highest cortisol-DHEA ratio quartile (Table 3). Aboriginal status was also positively correlated with the waist-to-hip ratio. Aside from a borderline relationship between DHEA levels and waist-to-hip ratio ($P = 0.06$), no other associations were found in boys.

Asthma status altered the association between maternal distress and the waist-to-hip ratio. In non-asthmatic girls (Table 3), maternal distress was related to waist-to-hip ratio, independent of other factors (β-coefficient = 0.034). The β-coefficient for maternal distress was 0.036 prior to the addition of the breastfeeding variable to the model. As for the all girls model, Tanner score continued to be associated with waist-to-hip ratio at the third quartile of the cortisol-DHEA ratio. Maternal pregnancy smoking was predictive of waist-to-hip ratio but not after the addition of the interaction term for Tanner score and cortisol-DHEA ratio. A 34.5% of the variation in waist-to-hip ratio in non-asthmatic girls was explained by these factors. Among non-asthmatic boys, neither pregnancy smoking, nor *postpartum* distress or cortisol-DHEA levels were associated with the waist-to-hip ratio. Instead, the best predictors of waist-to-hip ratio were DHEA levels, and the interaction between physical activity and Aboriginal status. Aboriginal status increased the waist-to-hip ratio by 0.084 ($P = 0.01$) among less active boys, but was not a predictor in boys with vigorous physical activity. DHEA levels significantly increased the waist-to-hip ratio by 0.0023 ($P = 0.047$). Physical activity, aboriginal status, their interaction and DHEA explained 12.5% of the waist-to-hip ratio variation in boys without asthma.

In girls with asthma, there was a significant interaction between *postpartum* distress and maternal smoking during pregnancy. Smoking during pregnancy increased waist-to-hip ratio by a factor of 0.072 ($P = 0.038$) among girls whose mothers had *postpartum* distress. It was not associated with the waist-to-hip ratio in the absence of postnatal distress. Aboriginal status also increased risk for overweight (β-coefficient = 0.05, $P = 0.01$). No other associations were found in girls with asthma. These factors explained 21% of variation in waist-to-hip ratio for girls with asthma. In boys with asthma (Table 3), the waist-to-hip ratio was higher by 0.056, if exposure to maternal distress *postpartum* was followed by high cortisol-DHEA ratios at age 8–10 years. This association was independent of low birth weight status (small or appropriate for gestational age) but it was not significant after adjustment for multiple comparisons. A total of 19% of the variation in waist-to-hip ratio was explained by these factors in asthmatic boys. Low birth weight was not related to the waist-to-hip ratio in multivariate models in boys or girls.

Conclusions

We found risk for overweight at age 9–11 years to be elevated among Canadian boys and girls whose mothers had experienced distress in the postnatal period. This risk varied by gender and asthma status. In healthy girls, the association between maternal *postpartum* distress and the waist-to-hip ratio was independent of child stage of puberty and adrenarche, and stress reactivity, as measured by cortisol-DHEA responses to a clinic stressor 2 years before. Among girls with asthma, maternal smoking during pregnancy was associated with an increased waist-to-hip ratio, if the mother also experienced distress in the *postpartum* period. Among boys with asthma, an association between maternal distress and waist-to-hip ratio was evident at the highest ratios of the cortisol-DHEA response to the clinic stressor. Independently, *postpartum* distress increased the waist-to-hip ratio by a factor of 0.034 in healthy girls and by 0.072 in girls with asthma, if their mother smoked during pregnancy. In comparison, intrauterine growth retardation has been reported to increase the waist-to-hip ratio in young women by a factor 0.016 following moderate restriction in growth and by 0.025 with severe growth restriction.[23]

Our findings contribute to the growing body of evidence for the role of maternal and family stress in the development of overweight in children and young adults.[24,25] The 'developmental origins of health and disease (DOHaD)' or 'adaptive developmental plasticity' theory offers a framework for potential pathways. This theory posits that the fetus adjusts its metabolic processes for growth, reproduction and maintenance to be appropriate for the environment in which it predicts it will live; this prediction is based on its *in utero* environment.[26,27] Poor prenatal nutrition compromises fetal growth; change to an improved postnatal nutrition triggers rapid growth.[28] When this mismatch in environments occurs, the risk of overweight, insulin resistance and cardiovascular disease is increased.[8,9] A mismatched environment can also result in physiologic changes intended to accelerate reproduction. Higher rates of premature puberty and adrenarche (higher DHEA levels) are seen in children, who are born low birth weight and experience rapid weight gain.[29–32] In our study, early onset puberty increased the waist-to-hip ratio in girls and 'explained away' the correlation of waist-to-hip with pregnancy smoking. The puberty association was evident only

at higher ratios for cortisol-DHEA, both markers of an adverse *in utero* environment.[10] We also found that DHEA levels were inversely correlated with birth weight in asthmatic girls and positively related to the waist-to-hip ratio in healthy boys. However, the association between maternal *postpartum* distress and the waist-to-hip ratio was independent of DHEA levels and Tanner stage of puberty in girls. *Postpartum* distress was also not correlated with maternal smoking during pregnancy.

The window of developmental plasticity has been proposed to extend to the *postpartum* period, either independent of or interdependent with *in utero* development.[26] Animal models of maternal care show that low levels of maternal grooming can produce offspring with higher levels of abdominal fat, elevated blood glucose levels and reduced insulin sensitivity.[33] In humans, maternal psychopathology in the *postpartum* period has been associated with earlier onset of puberty, which is also accelerated by rapid infant weight gain.[28,34] Lessened sensitivity to infant cues and overfeeding have been identified as causes of rapid weight gain in infants.[35] This type of feeding is more common in mothers with *postpartum* depression.[36] Rapid weight gain and future overweight are observed less often in infants who are breast-fed.[37] We also found a protective effect for breastfeeding on overweight in healthy girls. The association between postnatal distress and waist hip diminished but only slightly following adjustment for breastfeeding. Thus, we propose an additional pathway to infant overfeeding, one that involves the HPA axis.[38] Reduced maternal–infant interaction in women with *postpartum* depression can evoke cortisol reactivity in the infant.[11,12,39] Stress-induced stimulation of cortisol is accompanied by reductions in leptin in adults, a hormone which regulates appetite.[40] Postnatal administration of leptin has prevented rapid weight gain in low birth rat pups fed a high fat diet; weight gain occurred in pups not receiving leptin.[41] Leptin levels are lower in small-for-gestational age than normal weight newborns.[42] This *in utero* programming of leptin levels could explain the interaction we found between maternal distress and pregnancy smoking in girls with asthma.

Gender and asthma differences in predictors of the waist-to-hip ratio warrant further comment. Independent effects for maternal distress and puberty-stress reactivity in healthy girls indicate distinct postnatal and *in utero* pathways for overweight. As low birth weight was not found to be a predictor, we propose that the puberty-stress pathway in healthy girls is not through fetal growth retardation. In contrast, since low birth weight and DHEA levels were associated with the waist-to-hip ratio in healthy boys, a low birth weight and premature adrenarche pathway to overweight may be prominent in boys who do not develop asthma. This hypothesis is consistent with findings that impaired fetal growth affects central fat distribution in boys but not girls, and that postnatal growth is a larger risk factor for central adiposity in women.[43,44] Maternal *postpartum* distress was related to the waist-to-hip ratio in both girls and boys with asthma, pointing to a postnatal stress pathway for overweight in asthma. We previously reported increased risk for childhood asthma following early life exposure to maternal distress in the SAGE population.[18] Since leptin is a putative factor for adolescent asthma, it is a plausible mediator in the stress pathway.[45] In this analysis of SAGE children, the association between *postpartum* distress and the waist-to-hip ratio was seen in asthmatic boys with a heightened cortisol response after a clinic stressor. This interaction explained more of the variation in waist-to-hip for boys than did the maternal distress-smoking model in girls. Leptin levels are known to be higher in overweight children but elevated levels have also been found in adults with longstanding posttraumatic stress.[45,46] Thus, stress-induced lowering of leptin levels postnatally and elevation in later childhood, may both be required for overweight to develop in boys with asthma.[41] However, stress-induced lowering of leptin levels in the postnatal period may be needed for fetal programming of leptin levels to increase risk for overweight in girls who develop asthma. Finally, children with asthma are more likely to become overweight secondary to lower physical activity.[47] Although physical activity was related to waist-to-hip in healthy boys in our study, this association was not found to be independent of early life stress exposure and Aboriginal status in children with asthma.

In addition, worthy of comment is the discrepancy in our results and the longitudinal study by Ajslev *et al.*,[48] which failed to find an association between *postpartum* distress and childhood overweight. Our study differed from this study in a number of important ways. We employed a measure of *postpartum* distress that was based on a cut-off value for the highest scores and not unit increases in a distress scale, child overweight was derived from measurement and not parent report, and our population of children was older. We also included measures of recent stress reactivity and conducted gender-specific analyses. However, we were constrained by the original objectives of the SAGE project and did not have access to factors known to affect child weight, such as maternal weight and infant growth.[49] We selected the waist-to-hip ratio but there are additional measures of fat distribution in children.[49] Our *in utero* measure of stress, pregnancy smoking, was at risk for reporting bias, although maternal under-reporting would have biased findings towards the null.[50] Maternal pregnancy smoking was our exposure of interest in place of birth weight because it is a well-known risk factor for low birth weight,[50] but can cause fetal changes in addition to fetal growth retardation.[26] We would have preferred to include a measure of maternal distress during pregnancy but it was not available. Not-withstanding our inability to measure these factors, we believe the obtained results represent a true population effect because of the large sample size and method of stratified sampling. The 30% loss to follow-up predominantly affected Aboriginal children, so study findings are less generalizable to this population of children. To adjust for the higher prevalence of childhood asthma subsequent to the case-control design, analyses were stratified by asthma status. We also implemented statistical

control of several important confounding variables, including the inclusion of DHEA levels in models to adjust the cortisol-DHEA ratio for rising DHEA levels in adrenarche.[29] Although we did not use standardized tests for stress reactivity, the cortisol-DHEA ratio which measures the extent to which elevated cortisol levels are unopposed by DHEA has been advocated as a valid measure of the stress response in a clinic setting.[16]

To summarize, we implemented a life course approach to investigate stress determinants of overweight in children. We found that maternal *postpartum* distress affected the waist-to-hip ratio to a similar extent as fetal growth restriction. The association could not be explained by maternal smoking during pregnancy or short duration of exclusive breastfeeding in healthy girls. Consequently, we propose that programming of the HPA axis in infants by early life environmental stressors has an important role to play. Our findings also suggest gender-specific and childhood asthma pathways for the development of overweight. In the end, many of our findings point to the importance of DOHaD and evolutionary biology in explaining risk for overweight.

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