

Original article

Lower cortisol levels in children with asthma exposed to recurrent maternal distress from birth

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Background: Existing evidence supports associations between exposure to maternal distress and the development of childhood asthma, between exposure to maternal distress and an increased cortisol response in children, and between childhood asthma and an attenuated cortisol response.

Objective: To investigate the association between children's cortisol levels and the combined predictors of exposure to maternal distress and childhood asthma.

Methods: Serum cortisol levels were examined at age 7 to 10 years in relation to asthma status and exposure to maternal distress in a representative sample of children (n = 503) born in 1995. Data from health care and prescription databases were linked with additional data collected in this longitudinal study. Maternal distress was defined as a physician diagnosis of a depressive or anxiety disorder or a prescription history of related medications as reported in the mothers' health care records. Children's asthma status was determined via examination by 2 pediatric allergists.

Results: A multiple linear regression analysis revealed that exposure to maternal distress restricted to the first year of life predicted elevated cortisol levels in children, regardless of asthma status (>40% increase). A significant interaction was discovered in the group of children exposed to maternal distress extending beyond the postnatal period such that no asthma predicted a 25.9% increase in cortisol and a diagnosis of asthma predicted a 5.2% decrease in cortisol. Cortisol levels were further lowered in atopic and bronchial hyperresponsive asthma.

Conclusion: Among children exposed to recurrent maternal distress, an elevation in cortisol levels occurs in response to an acute stressor when there is no accompanying diagnosis of

asthma, whereas, in comparison, children with asthma tend to exhibit lower cortisol levels. (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: Asthma, child, cortisol, maternal distress, stress response

Both genetic and environmental factors are believed to converge to create the asthma phenotype. Of the many environmental variables that may confer increased susceptibility toward atopic disease, psychological distress is emerging as an independent risk factor. Maternal distress during early developmental periods predicts childhood wheezing¹ and childhood asthma² in genetically at-risk populations. Recently, we have shown that exposure to persistent maternal distress is associated with the development of childhood asthma in a population-based cohort.³

The glucocorticoid hormone, cortisol, is released in response to both physical and psychological stress.⁴ Children exposed to maternal distress in early life exhibit significantly higher cortisol levels than children with no previous exposure.⁵ Chronic stress may induce hyporesponsiveness of the hypothalamic-pituitary-adrenal (HPA) axis, reducing cortisol secretion.⁶ Both exaggerated and blunted cortisol responses may contribute to the development and morbidity of asthma and atopic disease.⁷ Children with established disease have lower cortisol levels throughout the entire diurnal cycle and show an attenuated cortisol response to an acute stressor.^{8,9} What is not understood is whether the effect of exposure to maternal distress during early development on children's cortisol levels differs for children with and without asthma. Further, it is not known whether dysregulation of the HPA axis is clearly associated with the relationship between exposure to maternal distress and later expression of asthma.

We hypothesized that children without asthma experience an increase in cortisol levels in response to an acute stressor and that this relationship would intensify with increasing exposure to maternal distress. We also hypothesized that children with asthma would have blunted cortisol levels in response to an acute stressor and that this effect would be more pronounced in children with asthma exposed to maternal distress. To test these hypotheses, we investigated whether the functioning of children's stress response systems was related to the combined effects of early-life exposure to maternal distress and asthma status.

METHODS

Participants

This was a study of a sample of Manitoba children born in 1995 who were selected for a nested case-control study in the project Study of Asthma, Genes,

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Abbreviations used

BHR: Bronchial hyperresponsiveness
 HPA: Hypothalamic-pituitary-adrenal
 SAGE: Study of Asthma, Genes, and the Environment
 SES: Socioeconomic status
 TSST: Trier Social Stress Test

and the Environment (SAGE). The SAGE study design is described elsewhere.¹⁰ Plasma aliquots for cortisol level determinations were available for 507 of the 723 blood samples obtained from SAGE children at age 7 to 10 years. Informed consent and child assent was obtained from all participating families, including permission to access provincial health care database records. This study was approved by the Health Research Ethics Board at the University of Manitoba and the Health Information Privacy Committee.

Methods and measurement

To examine the association between maternal distress and presence of childhood asthma in relation to children's stress response functioning, provincial health care and prescription database records were linked with data collected during a clinic assessment with the SAGE children 7 to 10 years old. The assessment included a detailed parent questionnaire, asthma status assessment by 2 pediatric allergists, pulmonary function testing (methacholine challenge), skin prick testing of 16 common allergens, and the collection of blood samples by venous puncture. Cortisol levels were measured in a laboratory at the University of Manitoba, where plasma samples were diluted 1:240 and assayed by using a commercially available ELISA kit (Cayman Chemical, Ann Arbor, Mich). Assayed values were measured in nanograms per milliliter. Assay sensitivity was 70 pg/mL, with an interassay variance of 14.8% and an intra-assay variance of 7.8%.

Because of the constraints of a previous research protocol for the SAGE cohort, this study was not designed specifically to assess the stress response in children with and without asthma. However, several features of the blood collection process strengthen our findings from a single cortisol level determination. The majority of blood samples (66%) were obtained during a 4-hour midday period (10:00–14:00 h), with a range of 08:08 to 18:52. Midday is the recommended time to administer stress tests because of the minimal fluctuation in cortisol levels during this time in school children.^{11–13} Time of sample collection also was tested in models to control for diurnal changes in cortisol release. Venous puncture was performed at the end of the clinic assessment, after skin prick and pulmonary function testing. The use of needles for blood collection or vaccination has been documented to induce activation of the HPA axis in children.^{14,15} Aside from the physical stressors involved, anticipation of the clinical examination by children has been shown to function as a stressor.¹² In our study, a topical anesthetic (eutectic mixture of local anesthetic patch) was applied to each child before or at the beginning of the clinic visit to minimize discomfort from venipuncture, so children were aware of the upcoming venipuncture at least 2 hours in advance. At the time of recruitment, families also were made aware of the study procedures, including the blood draw. Collectively, the venipuncture and the children's anticipation of the study procedures were identified as acute stressors that could provide an indication of the children's cortisol response.^{16,17}

Maternal distress was defined as at least 1 physician diagnosis of a depressive or anxiety disorder (International Classification of Diseases, Ninth Revision codes: 296, affective psychoses; 300, neurotic disorders; 308, acute reaction to stress; 309, adjustment reaction; and 311, depressive disorder not elsewhere classified) or at least 1 prescription for antidepressant, anxiolytic, or hypnotic medication, as recorded in Manitoba's prescription and health care databases. Maternal distress was classified as no distress, late distress (2–7 years of age), postnatal distress (first year only), or recurrent distress (first year plus 2–4 and/or 5–7 years). The intervals for the maternal distress measure were modeled after the study by Essex et al,⁵ and a similar database measure was validated in a study of the complete SAGE birth cohort.^{3,18} Although the database measure had high specificity (83%; 95% CI, 78% to 87%) and was free

from recall bias or positive response bias, the moderate sensitivity (42%; 95% CI, 21% to 66%) indicates that it may have underrepresented mothers who experienced distress but did not seek health care.³ In the study by Yallop et al,¹⁸ intensity of health care for depression or anxiety in the postpartum period was much greater among mothers with recurrent distress after the birth of their child than among mothers with distress limited to the postpartum period.

Asthma in the cohort children was defined as a diagnosis of asthma made by 2 pediatric allergists during the clinic assessment, which involved, as per the Canadian Asthma Consensus Guidelines,¹⁹ conducting a physical examination and history to determine the presence of cough and wheeze, allergic conditions, and asthma medications. Methacholine bronchoprovocation tests were performed by using the classic Cockcroft technique to define the PC₂₀.²⁰ Bronchial hyperresponsiveness (BHR) was defined as a PC₂₀ < 8 mg/mL methacholine. At the end of the clinical visit, skin prick tests to common relevant allergens were carried out (tree pollen mix, weed pollen mix, ragweed (separate), grass pollen mix, *Alternaria*, *Cladosporium*, *Penicillium*, house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), cockroach, cat, dog, feathers, and peanut). Atopic asthma was defined as pediatric allergist–diagnosed asthma in combination with a positive skin prick test result to at least 1 common allergen. Children with asthma with a negative skin prick test result were labeled nonatopic. Bronchial hyperresponsive asthma constituted allergist–diagnosed asthma in combination with BHR. Potential confounding factors considered in this study were sex, age, family history of asthma, socioeconomic status (SES), early-life exposure to environmental tobacco smoke, duration of exclusive breast-feeding, number of physician's office visits since birth, low birth weight, use of oral and inhaled corticosteroid medications in the last 12 months, and the time of blood sample collection. With some exceptions, all independent and confounding variables were derived from parent report (Table I).

Data analysis

All statistical analyses were conducted by using Statistical Package for the Social Sciences version 15.0 for windows (SPSS Inc, Chicago, Ill). Cortisol levels were not normally distributed (positively skewed), making it necessary to log-transform the values. Transformed data were used for all major analyses, but actual means are reported to facilitate data interpretation. As others have done,^{21–23} 4 outliers with cortisol values above or below 3 SDs from the mean were removed, leaving data for 503 children for further analyses.

A multiple linear regression analysis was conducted in a stepwise fashion, retaining variables at $P < .05$. Goodness of model fit was assessed by the percent of variation explained by included variables (R^2). Model results are reported as standardized β regression coefficients and as percent increases or decreases in cortisol levels, derived by adding the unstandardized regression coefficients for the respective variables.

RESULTS

The final sample consisted of 503 children, 315 with no asthma and 188 with an asthma diagnosis. Of the children without asthma, 170 (54 %) were boys, and the mean age was 8.59 years (SD, .59). In the group of children with asthma, 113 (60.1%) were boys, and the average age was 8.27 years (SD, .60). The distribution of all variables included in the study can be seen in Table II. Children with asthma had significantly more physician visits since birth and a higher percentage of corticosteroid medication use. Neither of these 2 factors was significantly related to cortisol levels. Oral corticosteroids (which treat other inflammatory conditions such as allergic reactions to drugs) were used by a similar proportion of the children without and with asthma (1.9% vs 4.8%, respectively; $P = .07$). Inhaled corticosteroid medications were used predominantly in children with asthma, not those without (38.8% vs 3.5%, respectively; $P < .0001$), but the inhaled route of administration has been reported to have inconsistent systemic effects in children.^{24,25} Important to our analysis, the percentage use of

TABLE I. Independent, dependent, and control variables for multiple linear regression analysis

Variable type	Name	Definition	Measure
Dependent variable	Cortisol level	Plasma cortisol level	Continuous measure of plasma cortisol in ng/mL
Independent variables	Maternal distress	Database record of a physician diagnosis of depression or anxiety (specified ICD-9 codes) or a prescription for depression or anxiety-related medications during the first year of life, age 2-4 y, and age 5-7 y	0 = no distress 1 = late episodes only (age 2-7 y) 2 = first year only (first year) 3 = recurrent (first year plus age 2-4 y and/or 5-7 y)
	Asthma	Pediatric allergist diagnosis at age 7-10 y	0 = no asthma 1 = asthma
Confounding variables	Sex	Reported male or female sex	0 = male 1 = female
	Age	Reported age of 7, 8, 9, or 10 y	0 = 7; 1 = 8; 2 = 9; 3 = 10
	Family history	Reported history of parental asthma	0 = no asthma 1 = one parent 2 = both parents
	SES	Reported level of income	0 = low (<\$20 K) 1 = moderate (\$20 K-\$80 K) 2 = high (>\$80 K)
	ETS	Reported history of maternal smoking during first year of life	0 = mother did not smoke 1 = mother smoked
	Low birth weight	Database record of weight at birth, low birth weight is <2.5 kg	0 = low (<2.5 kg) 1 = not low (>2.5 kg)
	Exclusive breast-feeding	Reported duration of exclusive breast-feeding, defined as time from birth until introduction of formula or cow's milk	0 = <12 wk 1 = >12 wk
	GC medication	Reported use oral and/or inhaled corticosteroid medication	0 = no 1 = yes
	Sample time	Time of blood sample collection	Continuous (24-h clock)
	Physician visits	Calculated total number of physician office visits	Continuous

ETS, Environmental tobacco smoke; GC, glucocorticoid; ICD-9, International Classification of Diseases, Ninth Revision; SES, socioeconomic status.

corticosteroid medication did not vary by maternal distress category within children with asthma ($P = .72$). Finally, although cortisol levels were available in 507 of the 723 SAGE children, these children did not differ from the overall case-control study in terms of the percentage of children who had asthma¹⁰; the distribution of maternal distress categories also was similar to that for the complete birth cohort of 14,000 children.³

In univariate regression analyses, only low birth weight ($\beta = .110$; $P < .013$) and age ($\beta = .116$; $P < .009$) predicted children's cortisol levels. Of particular importance for this study, time of blood sample collection, number of physician visits since birth, and corticosteroid use in the past 12 months were not predictive of cortisol levels. Additional factors that were not predictive of cortisol levels included sex, family history of asthma, SES, maternal smoking during the first year of life, and duration of exclusive breast-feeding. In a multivariate regression of all potential confounding variables, only low birth weight and age were significantly predictive of cortisol levels and were entered as covariates in further models.

Mean cortisol levels trended lower, but were not statistically different, in children with asthma (mean, 47.45; SD, 26.47) than in children with no asthma (mean, 51.71; SD, 32.68). In contrast, maternal distress significantly predicted cortisol levels. The highest mean values were found in children exposed to maternal distress during the first year of life only (mean, 73.52; SD, 38.76), followed by those exposed to recurrent maternal distress (mean, 52.64; SD, 30.55). Lower mean cortisol levels were found in children who were never exposed to maternal distress (mean,

46.48; SD, 27.97) and in those who were exposed to maternal distress commencing after their first year of life (mean, 50.78; SD, 31.34). Mean values, adjusted for low birth weight and age, for children with and without asthma in each category of maternal distress are shown in Fig 1.

Results for the multiple linear regression analyses are shown in Table III. Maternal distress during the first year of life was found to predict cortisol levels significantly ($\beta = .138$; $P = .003$), whereas asthma diagnosis did not ($\beta = -.021$; $P = .643$). Although not statistically significant, the latter result was in the anticipated direction of lower cortisol levels in children with asthma. Independent of low birth weight and age, postnatal maternal distress (restricted to the first year of life) retained its significant predictability of cortisol, whereas recurrent maternal distress emerged as an additional significant predictor. In this model, the interaction between asthma diagnosis and maternal distress also was found to be a significant predictor of children's cortisol levels, such that exposure to recurrent maternal distress from the first year of life predicted significantly lower cortisol levels ($\beta = -.157$; $P = .012$) in children with asthma.

Models that tested the phenotypes atopic asthma and bronchial hyperresponsive asthma produced results similar to models for any asthma. The regression coefficient for the interaction term between atopic asthma and recurrent maternal distress cortisol was -0.39 ($P = .03$), indicating an even greater effect on cortisol levels. Similarly, the regression coefficient for the interaction term between bronchial hyperresponsive asthma and recurrent maternal distress cortisol was -0.34 ($P = .05$). There were no

TABLE II. Distribution of population characteristics

		No asthma	Asthma	P value
Total participants		315	188	
Sex	Male, n (%)	170 (54.0)	113 (60.1)	.18
	Female, n (%)	145 (46.0)	75 (39.9)	
Age (y)	7, n (%)	7 (2.2)	13 (6.9)	<.001
	8, n (%)	124 (39.4)	114 (60.6)	
	9, n (%)	174 (55.2)	59 (31.4)	
	10, n (%)	10 (3.2)	2 (1.1)	
	Mean $\pm$ SD	8.59 $\pm$.59	8.27 $\pm$.60	
Maternal distress	None, n (%)	127 (40.3)	70 (37.2)	.87
	Late only, n (%)	134 (42.5)	87 (46.3)	
	First year only, n (%)	11 (3.5)	6 (3.2)	
	Recurrent, n (%)	43 (13.7)	25 (13.3)	
Low birth weight (<2.5 kg)	Yes, n (%)	15 (4.8)	13 (6.9)	.31
	No, n (%)	300 (95.2)	175 (93.1)	
Time of blood sample	Mean $\pm$ SD	12:26 $\pm$ 2:16	11:41 $\pm$ 1:54	.43
Corticosteroid medication	Yes, n (%)	17 (5.4)	76 (40.4)	<.001
	No, n (%)	298 (94.6)	112 (59.6)	
Family history of asthma	None, n (%)	247 (78.4)	130 (69.1)	.07
	One parent, n (%)	61 (19.4)	52 (27.7)	
	Both parents, n (%)	7 (2.2)	6 (3.2)	
Socioeconomic status	Low, n (%)	9 (2.9)	10 (5.3)	.65
	Middle, n (%)	192 (61.0)	106 (56.4)	
	High, n (%)	88 (27.9)	63 (33.5)	
	Missing, n (%)	26 (8.3)	9 (4.8)	
Exclusively breast-fed	Yes, n (%)	110 (34.9)	88 (46.8)	.01
	No, n (%)	194 (61.6)	93 (49.5)	
	Missing, n (%)	11 (3.5)	7 (3.7)	
Maternal smoking (first year)	Yes, n (%)	39 (12.4)	43 (22.9)	<.01
	No, n (%)	269 (85.4)	142 (75.5)	
	Missing, n (%)	7 (2.2)	3 (1.6)	
Number of physician visits	Mean $\pm$ SD	56.51 $\pm$ 29.26	71.45 $\pm$ 28.80	.05

statistically significant associations between cortisol levels and positive skin test reactivity, BHR, nonatopic asthma, or nonbronchial hyperresponsive asthma, on their own or in interaction with maternal distress.

Regardless of asthma status, plasma cortisol was at least 40% higher in children exposed to postnatal distress during infancy than in children without asthma whose mothers had never experienced distress (Table IV). When first exposure to maternal distress occurred after the first year of life, no significant changes in cortisol were predicted. In comparison with children with no asthma or maternal distress exposure, recurrent maternal distress predicted a 25% increase in cortisol levels for children without asthma and, in contrast, a 5% decrease for children with asthma. When the reference category was children with asthma and no exposure to maternal distress, a 13% reduction in cortisol levels was seen in children with asthma exposed to recurrent maternal distress.

DISCUSSION

In our population-based study of 503 schoolchildren, children exposed to maternal distress restricted to their first year of life responded to an acute stressor with elevated cortisol levels, regardless of their asthma status. In those exposed to recurrent maternal distress since birth, having no asthma predicted a 26% elevation in cortisol levels. Children with asthma exhibited a lower cortisol response to the acute stressor, seen as a 5.2%

decrease in plasma cortisol. Cortisol levels were 13% lower after exposure to recurrent maternal distress when comparisons were made within children with asthma. These associations were independent of 2 important confounding factors, age and low birth weight,^{14,26,27} and were not present in children exposed to maternal distress beginning after the age of 1 year. They also were stronger for the asthma phenotypes, atopic asthma, and bronchial hyperresponsive asthma. Others also have documented elevated cortisol levels in healthy children after early-life exposure to maternal distress.^{5,28,29} This study extends our previous finding of an increased risk of childhood asthma from exposure to persistent maternal distress³ and appears to be the first to find an association between children's cortisol levels and their asthma status that varies according to their exposure to maternal distress from birth.

Our findings support a growing body of literature showing attenuated activity of the HPA axis in atopic disease^{8,30} and suggest that early-life exposure to maternal distress may play a role in this association. Early exposure to maternal distress may sensitize children to subsequent stress exposure, but chronic activation of the HPA axis may lead to protective adaptations; numerous studies have found chronic stress to be associated with flat diurnal cortisol patterns.^{6,31} High chronic home life stress was discovered to be associated with higher afternoon cortisol levels and a flattened cortisol rhythm throughout the day in healthy children, but no differences were found in children with asthma.³² A blunted HPA axis response in children with asthma may be the outcome of

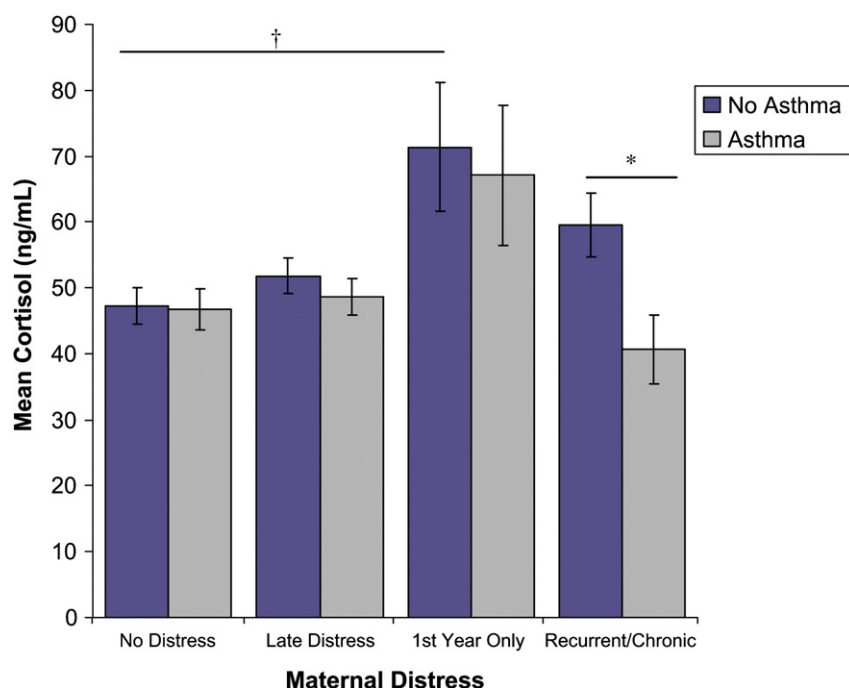


FIG 1. Cortisol levels, adjusted for age and low birth weight (adjusted mean $\pm$ SEM), in response to an acute stressor for children with and without asthma (7-10 years old) exposed to different levels of maternal distress throughout childhood. *Difference from no-asthma group with recurrent exposure, significant at $P < .05$. †Difference from no-asthma group with no exposure, significant at $P < .05$.

diminished steroid receptor sensitivity subsequent to chronic stress, as proposed in a recent editorial and supported by Miller et al.^{33,34} In the cross-sectional analyses by Miller et al,³³ the blood cells of preadolescents with asthma who perceived low parental support (ie, had greater stress) had lower cytokine expression (IL-5 and IFN- γ) and activation of eosinophils in response to the administration of a corticosteroid than children reporting higher parental support. These *in vitro* effects were not evident in healthy control children.

Maternal distress in early life affects the stress response of offspring^{5,17,29,30} and has been linked to the development of atopic disease in children.^{1-3,35,36} Infants at risk for allergic disease have a diminished morning surge of cortisol,³⁷ and those exposed to caregiver stress have higher levels of TNF- α ,³⁵ a cytokine that reduces cortisol synthesis.³⁸ Rather than being caused by asthma, an altered stress response subsequent to recurrent maternal distress that originates during the first year of life when the immune system is maturing³⁹ may play a role in its development. This hypothesis is strengthened by our finding that all children exposed to maternal distress after the age of 1 year responded to an acute stressor with cortisol levels similar to those children who had never been exposed to maternal distress. This observation is consistent with the general principle of fetal programming and of a critical window for the origins of health occurring in the prenatal to early postnatal period.^{40,41}

Our study improved on previous research in 3 main ways. First, although our database measure likely missed less severe maternal distress, it was less susceptible to response and recall biases than maternal self-report.³ The database measure also permitted assessment of recurrent distress in relation to children's cortisol. Second, we also were able to test associations with various asthma phenotypes at age 7 to 10 years, enabling us to obtain a more valid

measure of persistent asthma than previous studies with younger children.^{1,42} Indeed, our findings were stronger for atopic and bronchial hyperresponsive asthma. Last, our analyses controlled for the use of exogenous steroids. No association between corticosteroid medication use and cortisol levels was found, likely due to the predominance of inhaled formulations, which do not consistently lower cortisol levels in children.^{24,25} More importantly, corticosteroid use among children with asthma did not vary significantly by maternal distress. Despite this similarity of use, lower cortisol levels were found in children with asthma exposed to recurrent maternal distress, even when they were compared with other children with asthma.

Although we took great care in ensuring the validity of our data, we were constrained by the original objectives of the SAGE project. Several factors known to affect cortisol levels were included in the study (eg, age, sex, time of blood sample collection, corticosteroid medications, and low birth weight), whereas others, such as maternal prenatal distress, baseline cortisol levels, and sleep, diet, and activity patterns in children, were not.⁴³⁻⁴⁵ Cortisol measurements in children during early development also would have verified whether a blunted stress response was present before the diagnosis of asthma.^{8,9,36} Notwithstanding our inability to measure these factors, the obtained results are considered to represent a true population effect because of the large sample size⁴⁶ and the statistical control of several important confounding variables.⁴⁷

A second, related limitation was the absence of a standard measure for the stress response, such as the Trier Social Stress Test (TSST), and the measurement of precortisol and postcortisol levels after the TSST.^{44,48} However, elevated cortisol levels in schoolchildren have been documented at the beginning of a clinic appointment prior to the administration of the TSST.¹² The

TABLE III. Summary of multiple linear regression analysis for variables predicting cortisol levels in children age 7 to 10 years (N = 503)

Variable	R ²	F(df)	B*	β†	95% CI for β	P value
Model 1	.026	6.779 (2, 500)				.001
Age			.106	.119	.029 to .182	.007
Low birth weight			.269	.114	.064 to .474	.010
Model 2	.047	4.080 (4, 498)				.001
Age			.095	.107	.015 to .174	.019
Low birth weight			.225	.095	.019 to .432	.032
Asthma diagnosis			-.024	-.021	-.124 to .076	.643
Maternal distress						
Late only			.069	.063	-.034 to .172	.189
Postnatal only			.413	.138	.145 to .681	.003
Recurrent			.116	.073	-.031 to .264	.122
Model 3	.059	3.444 (5, 497)				.000
Age			.097	.110	.018 to .176	.016
Low birth weight			.228	.096	.022 to .434	.030
Asthma diagnosis			.080	.071	-.079 to .238	.325
Maternal distress						
Late only			.105	.096	-.024 to .234	.112
Postnatal only			.455	.152	.124 to .787	.007
Recurrent			.259	.163	.074 to .443	.006
Interaction: asthma × maternal distress						
Asthma × late only			.102	.071	-.314 to .110	.345
Asthma × postnatal			.122	-.024	-.674 to .431	.666
Asthma × recurrent			-.391	-.157	-.696 to -.086	.012

*Unstandardized coefficient.

†Standardized coefficient.

TABLE IV. Predicted change in cortisol values using nonstandardized regression coefficients

Measure	Predicted change (%)
Reference category:	
Children with no asthma and no distress exposure	
No asthma × late distress only	10.5
No asthma × postnatal distress only	45.5*
No asthma × recurrent distress	25.9*
Asthma × late distress only	8.3
Asthma × postnatal distress only	41.3*
Asthma × recurrent distress	-5.2*
Reference category:	
Children with asthma and no distress exposure	
Asthma × late distress only	0.3
Asthma × postnatal distress only	33.3*
Asthma × recurrent distress	-13.2*

*Significant at $P < .05$.

perceived stressfulness of the SAGE clinic assessment may have differed among children, with children with asthma potentially being more accustomed to medical appointments. Adjustment for the number of physician office visits did not alter the results. Finally, due to the lack of a standardized stress test and the small number of children in some of the maternal distress groups, we would have anticipated null findings subsequent to a type II error. This was not the case, and lower cortisol levels were found only among children with asthma exposed to recurrent maternal distress, indicating a true interaction.

In conclusion, we found that exposure to maternal distress in early life was associated with a cortisol response to an acute

stressor in school children that differed according to the presence of asthma. An elevated cortisol response occurred in healthy children exposed to recurrent maternal distress, whereas children with asthma responded with lower cortisol levels. Despite limitations to the measurement of the stress response in our study, these findings provide hypothesis-generating evidence on how maternal distress and the social environment of families may contribute to asthma development in children.

Some data were accessed from the Population Health Research Data Repository at the Manitoba Center for Health Policy. The results and conclusions are those of the authors, and no official endorsement by Manitoba Health was intended or should be inferred. We acknowledge the computer analysis support of Shamima Huq, as well as the research support provided by Rishma Chooniedass, Miriam Clement, Donna Everette, Brenda Gerwing, Saif Huq, Joel Liem, Marilyn Lilley, Tanya Lilley-Chan, Ingrid Loewen, Melissa Moyon, Jennifer Protudjer, Michelle Tillett, John Weselake, and Lauren Yallop in the collection of data for the nested case-control study used to validate the asthma and maternal depression definitions.

Clinical implications: These findings point to the dysregulation of stress response systems in children with asthma exposed to recurrent maternal distress, supporting the practice of screening for symptoms of distress in new mothers.

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