

**ORIGINAL ARTICLE: ASTHMA**

Hair cortisol and inhaled corticosteroid use in asthmatic children

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Abstract

Background: Adrenal suppression is a side effect of long-term use of inhaled corticosteroids (ICS). Hair cortisol concentration (HCC) measurement is a non-invasive tool for measuring adrenal function that may be useful for asthmatic patients who are on long-term ICS treatment. The aim of this study was to compare HCC between children with and without asthma and to explore the association between HCC and ICS dose in asthmatic children.

Methods: A cross-sectional observational study in subjects with or without asthma ($n = 72$ and 226 , respectively, age 6–21 years). Hair samples were obtained from the posterior vertex for each subject and data on medication use were collected using questionnaires. HCC was analyzed by liquid chromatography-mass spectrometry in the most proximal 3 cm of hair.

Results: Median HCC was significantly lower in subjects with asthma than in subjects without asthma: 1.83 pg/mg and 2.39 pg/mg, respectively (P value after adjustment for age, sex, and body mass index: .036). Median HCC was 1.98 pg/mg in asthmatics using no ICS, 1.84 pg/mg in those using a low dose, 1.75 pg/mg in those on a medium dose, and 1.46 in those using a high ICS dose ($P = .54$).

Conclusion: We observed a significantly lower HCC in asthmatics than in healthy controls and a nonsignificant trend of lower HCC with increasing ICS dose. Whether HCC measurement may be used to detect individuals at risk for hypocortisolism and may be useful to monitor adrenal function in asthmatic children using ICS needs to be further investigated.

KEYWORDS

adrenal insufficiency, asthma, diagnostic techniques and procedures, drug-related side effects and adverse reactions, glucocorticoids

1 | INTRODUCTION

Inhaled corticosteroids (ICS) are the first line of maintenance therapy for asthma.¹ ICS are regarded as safe, especially in lower dosages.² However, some patients develop side effects and adrenal crisis has been documented in children using ICS.³ The percentage of adrenal suppression due to ICS use has been estimated to be around 8% and, with a high ICS dose, up to 18%.⁴ Adrenal suppression due to ICS can present with nonspecific symptoms including fatigue, anorexia, abdominal pain and weight gain or loss, and often goes unrecognized. Decreased growth can be a clinical sign of adrenal suppression, but may also occur due to poor asthma control.⁵ Further complicating the recognition of adrenal suppression is the fact that sensitivity to glucocorticosteroids varies greatly between individuals, implicating that there is no "safe dose."⁴ Genes associated with steroid sensitivity have been localized, but they cannot predict the individual risk of adrenal insufficiency.⁶ As ICS are mostly used long term, monitoring of adrenal function would seem appropriate but is not yet recommended by current asthma treatment guidelines.¹

Serum cortisol varies highly during the day and responds quickly to stress factors such as pain or anxiety. Hence random serum cortisol measurements are not suitable to assess adrenal function. Cortisol measurement without adrenal stimulation may not be sufficient to determine the dynamic adrenal response.⁷ The adrenocorticotropic hormone stimulation test is still the gold standard and evaluates the maximal response of the adrenal glands. However, this is an invasive test that only informs about the status of the hypothalamic-pituitary-adrenal axis at that specific moment.^{7,8} Hence, there is a need for a noninvasive test reflecting the effect of long-term use of ICS on adrenal function.

Hair cortisol concentration (HCC) has potential to serve this purpose.⁹ HCC measurement is painless, noninvasive, and does not require a specific timing, which makes it suitable for repeated assessments in monitoring a pediatric population. Previous literature has shown a strong intraindividual stability of HCC, especially compared with other methods of cortisol measurement.¹⁰ HCC has proven to be specific and sensitive for diagnosing clinical outcomes in hypercortisolism, for example, in patients with Cushing's disease.¹¹ There are few studies investigating the association between HCC and ICS, and these show conflicting results. However, sample sizes were small with few patients taking high dose ICS while especially these patients are at risk of adrenal insufficiency.¹²⁻¹⁴ In this cross-sectional observational study, we measured and compared HCC between asthmatic and nonasthmatic children. Additionally, the association between ICS dose and HCC was investigated.

2 | MATERIALS AND METHODS

2.1 | Study population

Asthmatic children treated with ICS were selected from the Integrated Primary Care Information (IPCI) database, which contains general practitioner (GP) records of around 1.7 million patients in 2017.¹⁵

Asthmatic patients were eligible if they were between 6 and 18 years old, had doctor-diagnosed asthma, were treated with ICS, and did not use hydrocortisone therapy at the time of HCC measurement (other oral corticosteroids were allowed). The GPs of eligible patients were asked to recruit selected patients in the study. Healthy controls were part of a cohort from a previous study on hair cortisol.¹⁶ Subjects for this cohort were recruited from primary and secondary schools in the Netherlands and among siblings of children attending a pediatric outpatient clinic. They were eligible for inclusion if they were between 6 and 18 years old, did not use glucocorticoids or other medication influencing glucocorticoid metabolism at the time of HCC measurement or in the previous 3 months, and did not have a chronic disease. These children were invited to take part in the study and received oral and written information.

2.2 | Hair sample collection and analysis

Approximately 100 to 150 hairs were cut from the posterior vertex of the scalp as close to the scalp as possible. The hair sample was taped to a piece of paper and stored at room temperature. The samples were sent to the Department of Clinical Chemistry, Erasmus MC, Rotterdam, The Netherlands. The samples were processed and analyzed as described previously.^{13,17} The proximal 3 cm of hair were used for analyses. As hair grows on average about 1 cm per month, 3 cm relates to the cortisol production during the 3 months before hair sample collection.¹⁸ The hair samples were weighed, cut into 1-cm pieces and washed in LC-MS grade isopropanol for 2 minutes. After solid phase extraction, hair cortisol was quantified per milligram of hair by liquid chromatography-tandem mass spectrometry (LCMS) using a Xevo TQ-S system (Waters Chromatography, Milford, MA).

2.3 | Clinical data including ICS use

Information on patient characteristics such as age, sex, asthma control, comorbidities, medication use in the previous 3 months and systemic corticosteroid use at any time was obtained from questionnaires that were completed by all subjects on the same day as the hair sample collection (the index date). As there were up to 2 years between patient selection and hair sampling, some patients had turned older than 18 years at the time of hair collection.

If information on ICS dose was missing, prescription data from the IPCI database for the same period was used to complete dosage information.

2.4 | Statistical analyses

ICS exposure was analyzed in two ways. Firstly, ICS dosage was converted to budesonide equivalent doses (125 µg fluticasone = 200 µg budesonide, 200 µg beclomethasone = 200 µg budesonide, 80 µg ciclesonide = 200 µg budesonide, and 100 µg beclomethasone extra-fine = 200 µg budesonide).¹⁹ Secondly, dosages were categorized as "high," "medium," and "low": low dose was defined as a daily budesonide equivalent dose of less than 400 µg, medium dose as 400 to 800 µg and high dose as more than 800 µg, irrespective of age.¹⁹

Statistical analyses were performed using RStudio version 1.1.442. Body mass index (BMI) z scores adjusted for age and sex were calculated based on the 1997 Dutch nationwide growth study and height z scores were calculated according to the 2010 Dutch reference values, using Growth Analyser (Growth Analyser BV; Rotterdam, the Netherlands).^{20,21} Missing data on height and/or weight was imputed using multiple imputations. Asthma was categorized as uncontrolled for a score of less than or equal to 19 in the Asthma Control Test (children ≥ 12 years old) or childhood Asthma Control Test (children < 12 years old).^{22,23} HCC was log-transformed to achieve normality. The influence of asthma and ICS dose on HCC was investigated using a linear regression model with and without adjustment for age, sex, and BMI z score, with the significance level set at greater than .05. Differences in anthropometric measures were tested using the Wilcoxon signed-rank test. To rule out the effect of oral corticosteroids, analyses were repeated with exclusions of asthmatics using oral corticosteroids in the 3 months before hair sample collection.

2.5 | Ethical considerations

The protocol of this study was approved by the scientific review committee of IPCI. The Medical Ethics Review Committee from the Erasmus MC stated that the study did not fall within the remit of the Medical Research Involving Human Subjects Act (WMO) (MEC-2011-474). Written informed consent was obtained from all subjects and/or parents or legal guardians.

3 | RESULTS

In total, 73 asthmatic and 226 nonasthmatic subjects were included in the study. Median age was 13.2 years for asthmatics and 11.4 years for nonasthmatics. In both cohorts more boys than girls were included (Table 1). The height z score was smaller in children with asthma than in the healthy controls (median z score -0.3 vs 0.2 , respectively, $P < .001$). Of all asthmatic children, 20 (28%) had uncontrolled asthma based on the (childhood) Asthma Control Test. One asthmatic child had an abnormally high HCC (62 pg/mg). This patient was excluded from analysis as the HCC was probably caused by inference due to the use of hydrocortisone ointment. The HCC range completely overlapped between asthmatic and nonasthmatic subjects. Median HCC was lower in asthmatic subjects (1.83 pg/mg; interquartile range [IQR], 1.21-3.04) than in nonasthmatic subjects (2.39 pg/mg; IQR, 1.48-3.78; $P = .18$). After adjustment for age, sex, and BMI z score this difference was significant ($P = .036$). HCC increased significantly with age ($P < .0001$), with and without adjustment (Table 2).

In the 3 months before hair collection, 17 asthmatic subjects did not use any ICS and 55 subjects used ICS in a median daily budesonide equivalent dose of 500 μg . Of the subjects using ICS, 29 used a low dose, 22 a medium dose, and 4 a high dose.

With and without adjustment for age, sex, and BMI, budesonide equivalent dose was not significantly associated with HCC in subjects using ICS (regression coefficient [β] $-.40$ per mg budesonide; $P = .26$) (Figure 1, Table 2). When categorizing ICS dose, median HCC was

1.98 pg/mg in the group using no ICS, 1.84 pg/mg in those using a low ICS dose, 1.75 pg/mg in those on a medium dose, and 1.46 pg/mg in those using a high ICS dose, but these differences were not significant (β for increasing ICS dose category: -0.06 ; unadjusted $P = .58$; adjusted for BMI z score, age, and sex: $P = .54$) (Figure 2). Median HCC was higher in asthmatics not using ICS than in healthy controls, this difference was not significant (P value after adjustment for age, sex, and BMI z score: $.15$).

When analyzing HCC with the exclusion of asthmatics using oral corticosteroids, results remained similar. After adjustment for age, sex, and BMI, asthma was significantly associated with lower HCC. HCC tended to decrease with increasing budesonide dose (β after adjustment for age, sex, and BMI: $-.41$; $P = .32$). But there was no correlation with increasing ICS dose category (β , -0.06 ; $P = .56$). Median HCC was 1.98 pg/mg in asthmatics using no ICS, 1.83 pg/mg in those using a low dose, 1.77 pg/mg in those on a medium dose, and 1.46 pg/mg in those using a high ICS dose (Table 3).

4 | DISCUSSION

In this study, we showed that children with asthma have a significantly lower HCC than children without asthma after adjustment for age, sex, and BMI, but the HCC range completely overlapped between asthmatic and nonasthmatic subjects. In addition, we observed a nonsignificant trend of decreasing HCC with higher dosages of ICS.

TABLE 1 Demographics of study cohort at index date

	Patients with asthma (n = 72)	Healthy controls (n = 226)
Median age, y (IQR)	13.2 (10.5; 17.9)	12.6 (8.8; 14.8)
Females, n (%)	24 (33.3)	112 (49.6%)
Median height z score (IQR)	-0.3 (1.2)	0.2 (1.2)
Missing, n	1 (0)	0 (0%)
Median BMI, z score (IQR)	-0.5 (-1.0; 0.5)	-0.1 (-0.6; 0.6)
Missing, n (%)	3 (4.2)	0 (0%)
Uncontrolled asthma ^a , n (%)	20 (28)	-
Medication use 3 mo before hair collection:		
ICS use, n (%)	55 (76)	-
Low dose ^b	29 (40)	-
Medium dose ^b	22 (31)	-
High dose ^b	4 (6)	-
Budesonide equivalent use ($\mu\text{g}/\text{d}$) (IQR)	500 (400; 1000)	-
Oral corticosteroids use (prednisone), n (%)	2 (2.8)	-
Oral corticosteroids use 3-6 mo before hair collection, n	1 (0)	-

Abbreviations: BMI, body mass index; ICS, inhaled corticosteroids; IQR, interquartile range.

^aBased on the (childhood) Asthma Control Test.

^bLow dose: less than 400 μg , medium dose: 400-800 μg , high dose: greater than 800 μg .

TABLE 2 Results of linear regression analysis on log-transformed hair cortisol concentration

Subjects	Variable	Univariate analyses, β (95% CI)	P value	Multivariable analyses, β (95% CI)	P value
All subjects	Asthma: yes	-.15 (-0.37; 0.07)	.18	-.24 (-0.46; -0.01)	.04
	Female sex	-.11 (-0.30; 0.07)	.23	-.15 (-0.33; 0.04)	.12
	Age, y	.05 (0.03; 0.07)	<.001	.05 (0.02; 0.07)	<.001
	BMI z score	.13 (0.04; 0.22)	.01	.08 (-0.01; 0.18)	.09
Asthmatics using ICS	Budesonide equivalent dose, mg	-.29 (-0.95; 0.36)	.58	-.40 (-1.09; 0.29)	.26
	Female sex	.18 (-0.26; 0.62)	.43	.07 (-0.41; 0.54)	.79
	Age, y	.03 (-0.03; 0.08)	.32	.03 (-0.03; 0.09)	.31
	BMI z score	-.06 (-0.26; 0.14)	.24	.09 (-0.10; 0.28)	.34
All asthmatics	Increasing ICS dose category ^a	-.06 (-0.26; 0.14)	.58	-.06 (-0.27; 0.14)	.54
	Female sex	.07 (-0.30; 0.44)	.71	-.00 (-0.38; 0.38)	.99
	Age, y	.03 (-0.01; 0.07)	.18	.03 (-0.02; 0.07)	.26
	BMI z score	.11 (-0.05; 0.27)	.19	.09 (-0.07; 0.26)	.28

Abbreviations: BMI, body mass index; CI, confidence interval; ICS, inhaled corticosteroids.

Bold values indicate $P < .05$.

^aNo ICS, low dose ICS, medium dose ICS, high dose ICS.

Our data are consistent with a smaller prior study on HCC in 20 subjects which also observed a lower HCC in asthmatic children than in nonasthmatic children. Medication was not analyzed in this study.¹⁴ Smy et al observed an HCC reduction of about 50% after ICS initiation in 18 asthmatic children. In a later study these authors reported similar HCC in 407 asthmatic and 53 nonasthmatic children 0 to 18 years old.^{12,24} A difference between their and our study was that Smy et al used an immunoassay to measure hair cortisol, and did not adjust for confounders. Adjusting is important as we found that HCC increased significantly with age. Other research groups have shown that sex and BMI also influence HCC and as they are associated with asthma, should be controlled for.²⁵⁻²⁷

In estimating the relationship between ICS use and HCC, the duration of ICS use is an important aspect. Improvement of adrenal function 6 and 12 months after initiation of ICS therapy has been documented.²⁸ However the actual risk of adrenal suppression is highest after years of corticosteroid use.⁴ We measured the association between ICS and HCC in chronic ICS users who had been using ICS for a period of at least 2 years. Like in our study, Smit et al¹³ investigated the effect of ICS dose on HCC in a cross-sectional design including 80 asthmatic children, and also did not see a significant dose effect. We observed that the median HCC

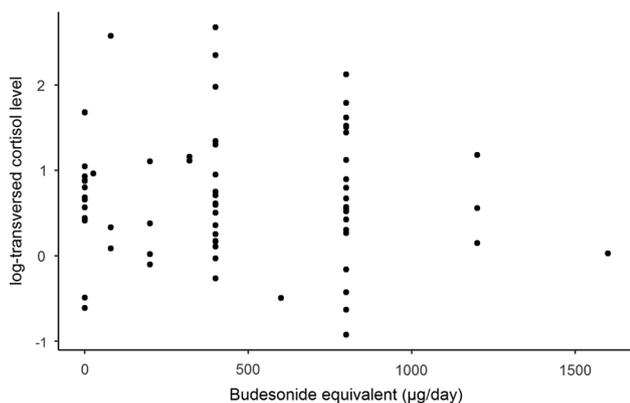
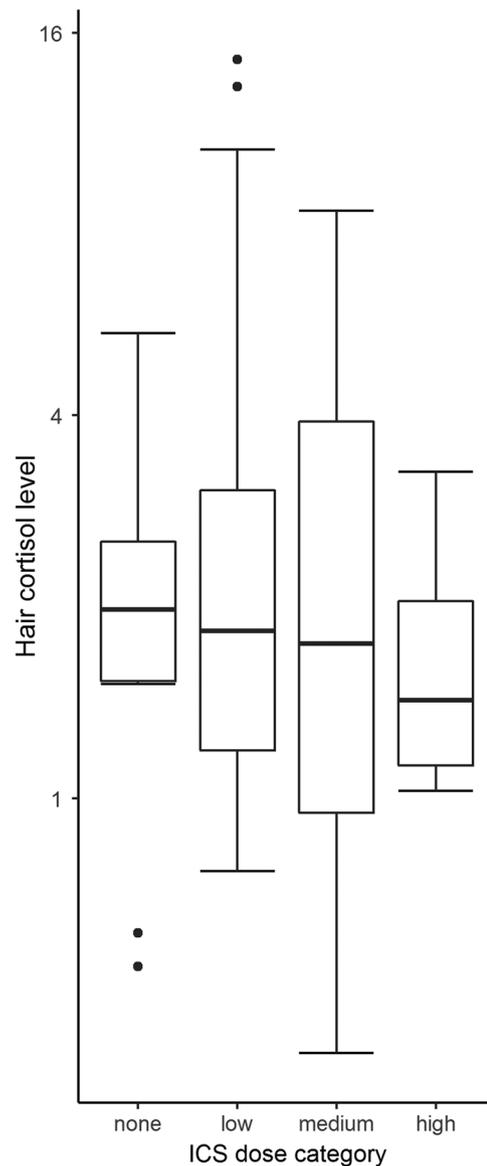
**FIGURE 1** Scatterplot of hair cortisol concentration by budesonide equivalent dose in asthmatic subjects**FIGURE 2** Hair cortisol concentrations in ICS equivalent dose categories dose in asthmatic subjects. ICS, inhaled corticosteroids

TABLE 3 Results of linear regression analysis on log-transformed hair cortisol concentration after exclusion of patients using oral corticosteroids

Subjects	Variable	Univariate analyses, β (95% CI)	P value	Multivariable analyses, β (95% CI)	P value
All subjects	Asthma: yes	-.15 (-0.37; 0.07)	.19	-.23 (-0.45; -0.01)	.04
	Female sex	-.13 (-0.31; 0.05)	.16	-.15 (-0.33; 0.04)	.13
	Age, y	.05 (0.03; 0.07)	<.0001	.05 (0.02; 0.07)	<.001
	BMI z score	.13 (0.04; 0.22)	.01	.08 (-0.01; 0.18)	.10
Asthmatics using ICS	Budesonide equivalent dose, mg	-.29 (-0.97; 0.37)	.40	-.41 (-1.1; 0.29)	.32
	Female sex	.21 (-0.26; 0.67)	.39	.01 (-0.38; 0.41)	.96
	Age, y	.03 (-0.02; 0.09)	.29	.03 (-0.02; 0.08)	.21
	BMI z score	.11 (-0.07; 0.30)	.25	.09 (-0.08; 0.26)	.31
All asthmatics	Increasing ICS dose category ^a	-.06 (-0.26; 0.15)	.60	-.06 (-0.27; 0.15)	.56
	Female sex	.08 (-0.30; 0.47)	.68	.01 (-0.38; 0.41)	.95
	Age, y	.03 (-0.01; 0.07)	.16	.03 (-0.02; 0.07)	.25
	BMI z score	.11 (-0.05; 0.27)	.19	.09 (-0.87; 0.26)	.30

Abbreviations: BMI, body mass index; CI, confidence interval; ICS; inhaled corticosteroids.

Bold values indicate $P < .05$.

^aNo ICS, low dose ICS, medium dose ICS, high dose ICS.

was lower by increasing ICS dose categories (low, medium, and high) but this difference in median HCC did not reach statistical significance probably because of low numbers, especially of patients using high dose ICS, and the variety in sensitivity to glucocorticosteroids. The median HCC was even higher in asthmatic subjects not using ICS than in subjects without asthma, though this difference was not significant.

ICS reaches the systemic circulation through two paths: absorption from the lungs and absorption of swallowed drug. The part of the dose that is absorbed through the gastrointestinal system will be considerably reduced by hepatic first-pass inactivation, probably resulting in smaller systemic availability with poor inhalation technique.²⁹ Systemic absorption of ICS is also age dependent. Studies have shown that the same ICS dose in young children and adults, despite large differences in the dose per kilogram bodyweight, leads to similar plasma concentrations.^{30,31} Global Initiative for Asthma guidelines use different dose categories for children 6 to 12 years and from 12 years onward. In real life, the dose is tailored to treatment response aiming for a balance between optimal asthma control and minimal side effects. The Dutch asthma guidelines recommend a starting dose of 200 μ g budesonide twice daily, irrespective of age.¹⁹ Therefore we used similar dose categories for all children.

Also, genes associated with an increased risk of adrenal suppression in children using glucocorticosteroids have been localized.^{6,32} Genotyping might further clarify the relation between corticosteroids and adrenal function. However adrenal function tests will still be needed when suspecting a case of adrenal insufficiency.

Our study has some limitations. Firstly, the number of patients using ICS was limited. This affected power and precluded stratifying for type of ICS and exploring the full dose range. Stratification would have been interesting as different types of ICS might have a different effect on the HPA axis.³³ Because there was time between selection of ICS users in the IPCI database and actual hair sample collection, some subjects with asthma had stopped use ICS at the time of hair sampling. Furthermore, medication use was based on questionnaire data, which is prone to an overestimation of adherence.³⁴ A strength

of our study is that we were able to adjust for sex, age, and BMI z score as we know that they are associated with HCC levels.²⁵ Another strength is that we used the LCMS method to measure HCC, in contrast to an immunoassay which is more prone to interference with synthetic corticosteroids. Immunoassays such as enzyme-linked immunosorbent assay are also known to be less sensitive and specific for low cortisol concentrations than LCMS.³⁵ And, importantly, we investigated ICS doses as a continuous variable as well as categorical, which made it possible to further characterize the effect of ICS. The group with high dose ICS had the lowest median HCC, which is in line with the fact that children taking a high dose ICS are most at risk for adrenal insufficiency. This highlights again that they need to be monitored regularly to screen for symptoms of systemic effects.

What is the clinical relevance of our findings? We have shown that on a population level asthma is associated with a lower HCC when adjusting for age, sex, and BMI. However, HCC values of asthmatic patients overlapped with those of healthy controls, suggesting that they were still within a normal range. Still, there was a tendency, although not significant, for the HCC to decrease with increasing ICS dose. So especially with high doses, it is important to be aware of possible insufficient adrenal function. HCC measurement is a feasible, patient-friendly tool with potential to identify ICS-treated individuals that are at risk for adrenal insufficiency. We propose that future studies in children with asthma on high dose ICS should include HCC as adrenal function tests to see if hair cortisol measurement is a useful monitoring tool of adrenal insufficiency on an individual level. There is a need to develop reference ranges for HCC measured by LCMS in children aged 0 to 18 years, and the predictive value of different HCC cut-off values for developing adrenal insufficiency needs to be established.

To conclude, in this study we demonstrated that children with asthma have lower HCC than children without asthma, possibly due to adrenal suppression caused by ICS use. Whether HCC can be used as a monitoring tool to predict the risk of hypocortisolism in children with asthma needs to be further explored.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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