

The Contribution of Oral and Inhaled Glucocorticoids to Adrenal Insufficiency in Asthma



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What is already known about this topic? Adrenal insufficiency (AI) is a well-known consequence of long-term oral glucocorticoid exposure. This is well studied in patients with asthma on maintenance oral corticosteroid. AI due to inhaled corticosteroid or intermittent oral corticosteroid is not often considered.

What does this article add to our knowledge? This article highlights the prevalence of AI in patients with asthma who are not taking regular maintenance oral corticosteroid, a population of patients in whom AI may not be routinely considered.

How does this study impact current management guidelines? This study should prompt additional consideration before prescribing glucocorticoids and increase awareness of potential AI in patients with asthma in all clinical settings, especially those in which corticosteroid treatment is not standard.

BACKGROUND: Exposure to any form of glucocorticoid preparation is associated with a risk of adrenal insufficiency (AI). **OBJECTIVE:** To establish the contribution of oral corticosteroid (OCS) and inhaled corticosteroid (ICS) exposure to the risk of AI in a cohort of patients ($n = 80$) with severe, uncontrolled asthma.

METHODS: We compiled individualized cumulative OCS and ICS exposure data using a combination of health care records and electronic inhaler monitoring using an Inhaler Compliance Assessment device and estimated the risk of AI for each participant using a morning serum cortisol concentration.

RESULTS: The predicted prevalence of AI based on morning cortisol concentrations was 25% (20 of 80). Participants on maintenance OCS therapy had the highest risk of AI at 60% (6 of 10) compared with 17% (11 of 65) in those with no recent OCS exposure. Morning serum cortisol correlated negatively

with both OCS exposure (mg/kg prednisolone) ($r = -0.4$; $P < .0002$) and ICS exposure (mg/kg fluticasone propionate) ($r = -0.26$; $P = .019$). Logistic regression of risk of AI against the number of standard treatment courses of OCS demonstrated a positive relationship although this did not reach statistical significance (odds ratio, 1.41; 95% CI, 0.97–2.05; $P = .073$). Logistic regression analysis, categorizing patients as high-risk AI (cortisol <130 nmol/L) or not (cortisol >130 nmol/L), showed that cumulative ICS exposure remained a significant predictor of AI, even when exposure to OCS was controlled for (odds ratio, 2.17 per 1 mg/kg increase in cumulative fluticasone propionate exposure; 95% CI, 1.06–4.42; $P = .033$).

CONCLUSIONS: Our data suggest that AI is common among patients with asthma and highlights that the risk of AI is associated with both high-dose ICS therapy and intermittent treatment courses of OCS. © 2022 American Academy of

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This study formed part of the INCA-SUN clinical trial. This was reviewed and approved by the research ethics committees at each institution.

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Board, GlaxoSmithKline, and Cross-Border Healthcare Intervention Trials in Ireland Network; speaker fees from GlaxoSmithKline, Astra Zeneca, and Novartis; holds patents on methods to quantify adherence, methods to assess adherence, and methods to predict exacerbations; and serves as the current Education Chair of the European Respiratory Society. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

ACT- Asthma Control Test
AI- adrenal insufficiency
BMI- body mass index
FP- fluticasone propionate
HPA- hypothalamic-pituitary-adrenal
HR-AI- high-risk adrenal insufficiency
ICS- inhaled corticosteroid/glucocorticoid
INCA- Inhaler Compliance Assessment
IQR- interquartile range
IR-AI- indeterminate risk adrenal insufficiency
IRR- incidence rate ratio
LR-AI- low-risk adrenal insufficiency
mini-AQLQ- mini Asthma Quality of Life Questionnaire
OCS- oral corticosteroid/glucocorticoid
OR- odds ratio
SST- Short Synacthen Test
TAI- tertiary adrenal insufficiency

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Key words: Cortisol; Adrenal insufficiency; Oral glucocorticoids; Inhaled glucocorticoids; Corticosteroids; Synacthen

INTRODUCTION

Suppression of the hypothalamic-pituitary-adrenal (HPA) axis by excess glucocorticoid exposure, or tertiary adrenal insufficiency (TAI), is the most common cause of adrenal insufficiency (AI),^{1,2} and is often undiagnosed. Patients with asthma receive regular glucocorticoid exposure in the form of inhaled glucocorticoid (also referred to as inhaled corticosteroid, or ICS), or with intermittent oral courses of prednisolone (oral glucocorticoid or corticosteroid, OCS), both of which are associated with TAI.² Although patients with asthma are undoubtedly at increased risk of TAI, the relative contribution of ICS remains unclear. The available literature is limited by retrospective study design, and is therefore subject to selection bias, and lacks detailed cumulative glucocorticoid exposure data. Logistic factors such as inhaler adherence, technique, and the degree of airflow obstruction can influence the proportion of ICS delivered to the patient. As a result, using the prescribed ICS dose to assess the dose-response relationship between ICS and serum cortisol may be misleading; it may overestimate the ICS dose received by the patient, thereby underestimating the contribution of ICS to HPA-axis suppression.³

The consequences of systemic glucocorticoid exposure leading to AI in patients with asthma are not trivial. In addition to the adverse cardiometabolic features of iatrogenic Cushing syndrome and the increased cardiovascular morbidity/mortality in patients exposed to exogenous glucocorticoids,^{4,5} TAI carries a risk of potentially life-threatening adrenal crises.⁶⁻⁸

The primary aim of this study was to evaluate the relationship between cumulative glucocorticoid exposure (oral and inhaled) and the risk of AI in patients with asthma. We used data from an electronic inhaler monitoring device (Inhaler Compliance Assessment device [INCA device]) to investigate the relationship between ICS exposure and morning serum cortisol, a previously validated marker of AI.⁹ The INCA device

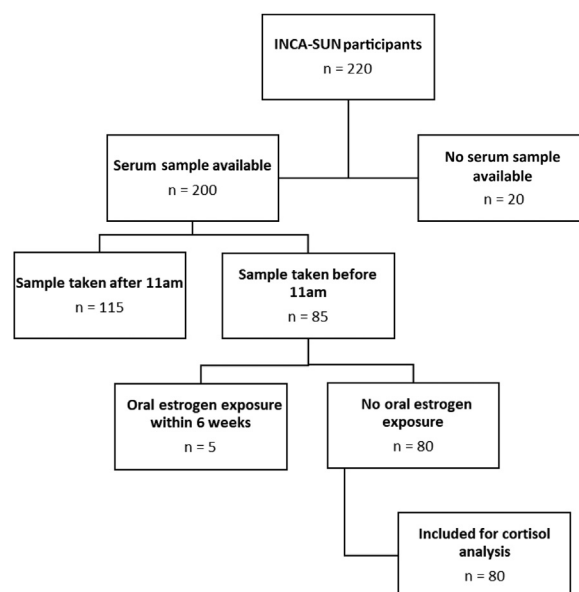


FIGURE 1. Consort diagram of study participants.

is an effective tool for the assessment of inhaler adherence, technique, and drug delivery when fitted to a Diskus inhaler device (GlaxoKlineSmith, U.K.).¹⁰⁻¹³ The detailed knowledge of each patient's cumulative ICS exposure offers a novel opportunity to accurately assess the relationship between serum cortisol concentration and cumulative OCS/ICS exposure.

Secondary aims included calculation of the prevalence of undiagnosed AI in patients with asthma, and investigation of the relationship between serum cortisol concentration and symptom burden in this cohort.

METHODS

Participant selection

Data were collected prospectively as part of the INCA-SUN study (NCT 020307669, a 32-week randomized controlled trial in which patients with severe asthma [Global Initiative for Asthma classification 4/5] had their inhaler adherence and technique electronically recorded). The INCA-SUN study protocol is described in detail by Mokoka et al.¹⁴ Participants of INCA-SUN were screened for inclusion in the study (Figure 1), and included for analysis regardless of randomization status if they met the following criteria:

1. Phlebotomy performed before 11 am at week 32.
2. Morning dose of ICS/LABA withheld before phlebotomy.
3. No known HPA-axis pathology.
4. No oral estrogen exposure within 6 weeks.

Baseline characteristics and study visit description

At enrollment to the INCA-SUN trial, baseline characteristics including age, body mass index (BMI), and medical history were recorded. At each subsequent visit, lung function, serum samples, and intercurrent OCS courses were recorded.

Glucocorticoid exposure history

Participants were prescribed inhaled salmeterol/fluticasone propionate (FP) 50/250 µg or 50/500 µg twice daily as per study

TABLE I. Participant characteristics at week 32/visit 6

Characteristic	Total cohort (n = 80)	HR-AI (n = 20)	IR-AI (n = 39)	LR-AI (n = 21)	IR/LA-AI combined (n = 60)	P value (HR-AI vs LR-AI)	P value (HR-AI vs IR/LR-AI combined)
Number (%)	80	20 (25)	39 (49)	21 (26)	60 (75)	—	—
Age (y)	49 ± 14	52 ± 12	50 ± 14	43 ± 14	48 ± 14	.06	.275
Sex: female, n (%)	46 (58)	13 (65)	20 (49)	14 (67)	33 (55)	.99	.6
AM cortisol concentration (nmol/L)	220 ± 122	65 ± 41	217 ± 50	372 ± 62	271 ± 92	<.0005	<.0005
Age at diagnosis of asthma (y)*	22.2 (6-44)	32.6 (6.1-47.9)	21.6 (3.2-38.9)	15.9 (7.0-42.9)	22 (3-43)	.32	.27
Duration of asthma (y)*	20.6 (7-32)	20.8 (5.4-32)	20.7 (11.6-40.8)	18.6 (7.0-28.2)	20 (8-36)	.69	.75
BMI (kg/m ²)*	28 (25-32)	26.2 (22.1-32.0)	29.6 (25.9-33.4)	26.9 (25.2-30.2)	28 (25-32)	.58	.23
Maintenance OCS, n (%)	10 (12.5)	6 of 20 (30)	4 of 39 (10)	0 of 21 (0)	4 (7)	.0086	.013
No exposure to OCS in study, n (%)	25 (32)	3 (15)	14 (36)	8 (40)	22 (37)	.16	.096
FEV ₁ % predicted	80% ± 25%	86% ± 26%	77% ± 24%	77% ± 25%	77% ± 24%	.28	.19
PBE count (× 10 ⁹ cells/L)*	0.27 (± 0.13-0.47)	0.23 (0.14-0.34)	0.23 (0.13-0.51)	0.38 (0.21-0.46)	0.28 (0.13-0.49)	.19	.45
FENO (ppb)*	12 (7-19)	11 (6-17)	13 (9-25)	10 (8-20)	12 (9-23)	.37	.2

AM, Morning; FENO, fractional exhaled nitric oxide; PBE, peripheral blood eosinophil; ppb, parts per billion.

All values represented as mean ± SD unless otherwise stated.

*Median (IQR).

protocol (Seretide 250 or 500 Diskus dry powder inhaler, GlaxoSmithKline).

Inhaler technique was qualitatively and quantitatively monitored with the use of an INCA device. This electronic monitoring device has been shown to be an effective tool for the measurement of adherence, technique, and drug delivery. It creates a time-stamped audio-recording of each attempted inhaler use, allowing for an accurate percentage adherence to be calculated. The recordings are interrogated and the acoustic profile generated identifies technique errors and inspiratory flow rates, thereby giving an accurate estimation of drug delivery.¹⁰⁻¹³

The INCA device was retrieved each month and interrogated. The downloaded data were used to calculate percentage adherence, and were further adjusted to account for common errors in inhaler technique.¹³ This was then multiplied by the prescribed dose of ICS to accurately estimate the received cumulative ICS dose for each month. These values were summed to calculate the cumulative ICS exposure throughout the 32 weeks of the study.

OCS exposure for the preceding year was recorded at enrollment and again at each study visit, including duration, cumulative dose, and timing relative to phlebotomy, and was further confirmed using hospital and community pharmacy records. All oral glucocorticoid exposure is expressed as prednisolone, where 5 mg prednisolone is equivalent to 20 mg hydrocortisone and 0.75 mg dexamethasone.¹⁵

Total cumulative glucocorticoid exposure was calculated to combine both inhaled and oral glucocorticoid exposure and expressed as milligram prednisolone equivalent. Inhaled FP is a potent glucocorticoid and has a relative receptor affinity for the glucocorticoid receptor of approximately 1800, significantly higher

than that of endogenous cortisol (relative receptor affinity 10).^{16,17} Inhaled FP is reported to exert a similar suppressive effect on the HPA axis as prednisolone, on a 1 mg FP:8.5 to 10 mg prednisolone basis.¹⁸⁻²⁰ In this study, we have used the more conservative estimate of 1 mg FP:8.5 mg prednisolone to convert ICS exposure to milligram prednisolone equivalent.

Prescription of all other glucocorticoid preparations (including intranasal preparations) was recorded at enrollment and again at each study visit.

Assessment of adrenal function

Serum samples taken at week 32 were analyzed using the Elecsys II Cortisol immunoassay (Roche Diagnostics, Mannheim, Germany), a second-generation cortisol immunoassay with a coefficient of variation of 1.8% to 2.1% and cross-reactivity with prednisolone of 7.9%.

Morning serum cortisol concentration is an effective screening tool for AI and can reduce the need for Short Synacthen Test (SST) by 40%.^{9,21-23} Our research group has previously reported that a morning cortisol concentration of more than 315 nmol/L predicts a normal SST response with 100% specificity, and a cortisol concentration of less than 69 nmol/L predicts SST failure with 99% sensitivity using the Siemens Immulite 2500 (Siemens Healthcare GmbH, Erlangen, Germany) and Roche Modular E170 (Roche Diagnostics, Mannheim, Germany) analyzers.²¹ Further local studies of SST data using the Roche Elecsys II immunoassay have shown that a morning serum cortisol concentration of less than 130 nmol/L predicts SST failure (100% specificity, 95% CI, 83%-100%; 38% sensitivity, 95% CI, 26%-53%), and that a morning serum cortisol value of 294 nmol/L

TABLE II. Cumulative total, oral, inhaled, and intranasal glucocorticoid exposure

Exposure	Total cohort (n = 80)	HR-AI (n = 20)	IR-AI (n = 39)	LR-AI (n = 21)	IR/LR-AI combined (n = 60)	P value (HR- vs LR- AI)	P value (HR-AI vs IR/LR-AI combined)
Total glucocorticoid exposure							
Combined OCS/ICS in study (mg prednisolone equivalent)*	1426 (823-1835)	1866 (1358-3445)	1354 (738-1737)	997(863-1559)	1274(803-1619)	.007	.0029
Oral glucocorticoids							
OCS courses previous year*	3(2-5)	5 (2-7.5)	3 (2-5)	3 (2-5)	3 (2-5)	.07	.028
OCS courses in study*	1 (0-2)	1.5 (0-2.5)	1 (0-1)	1 (0-1)	1 (0-1)	.15	.05
OCS in study (mg)*	202.5 (0-650)	470 (172.5-1965)	162.5 (0-275)	62.5 (0-210)	165 (0-365)	.0017	.0016
OCS in study (mg/kg)*	2.4 (0-8.3)	7.5 (2.6-27)	1.7 (0-5.8)	1.6 (0-6.4)	1.7 (0-5.7)	.0066	.0011
OCS in study (mg) excluding maintenance steroids*	187.5(0-350)	277.5 (195-690)	125 (0-280)	180 (0-330)	133 (0-280)	.15	.07
OCS in study (mg/kg) excluding maintenance steroids*	1.73 (0-3.25)	3.14 (0.71-7.55)	1.35 (0-3.14)	0.66 (0-2.5)	1.65 (0-4.05)	.066	.039
Inhaled glucocorticoids							
High-dose ICS, n (%)	50 (63)	17 of 20 (85)	21 of 39 (54)	12 of 21 (57)	33 (55)	.089	.0179
ICS adherence (%)*	85% (64%-91%)	89% (IQR, 82- 94)	85% (IQR, 58- 92)	68% (IQR, 63-88)	81 (61-90)	.009	.029
ICS exposure in study (mg FP)*	175.5(113.4-215)	212.5 (173.3- 220.4)	158.4 (111.3- 211.3)	163.3 (137.1- 188.4)	160.9 (111.4-207.5)	.01	.003
ICS exposure (mg/kg FP)*	2.08 (1.47-2.79)	2.56 (1.98-3.24)	1.88 (1.30- 2.55)	1.93 (1.61- 2.80)	1.91 (1.34-2.57)	.047	.004
Intranasal glucocorticoids							
Intranasal glucocorticoid prescription, n (%)	54 (68)	13 (65)	30 (79)	11 (52)	41 (68)	.5	.7

AE, Adverse event; AI, adrenal insufficiency, prednisolone equivalent calculated where 1 mg FP is equivalent to 8.5 mg prednisolone; OCS, oral glucocorticoid (prednisolone).

*Median (IQR).

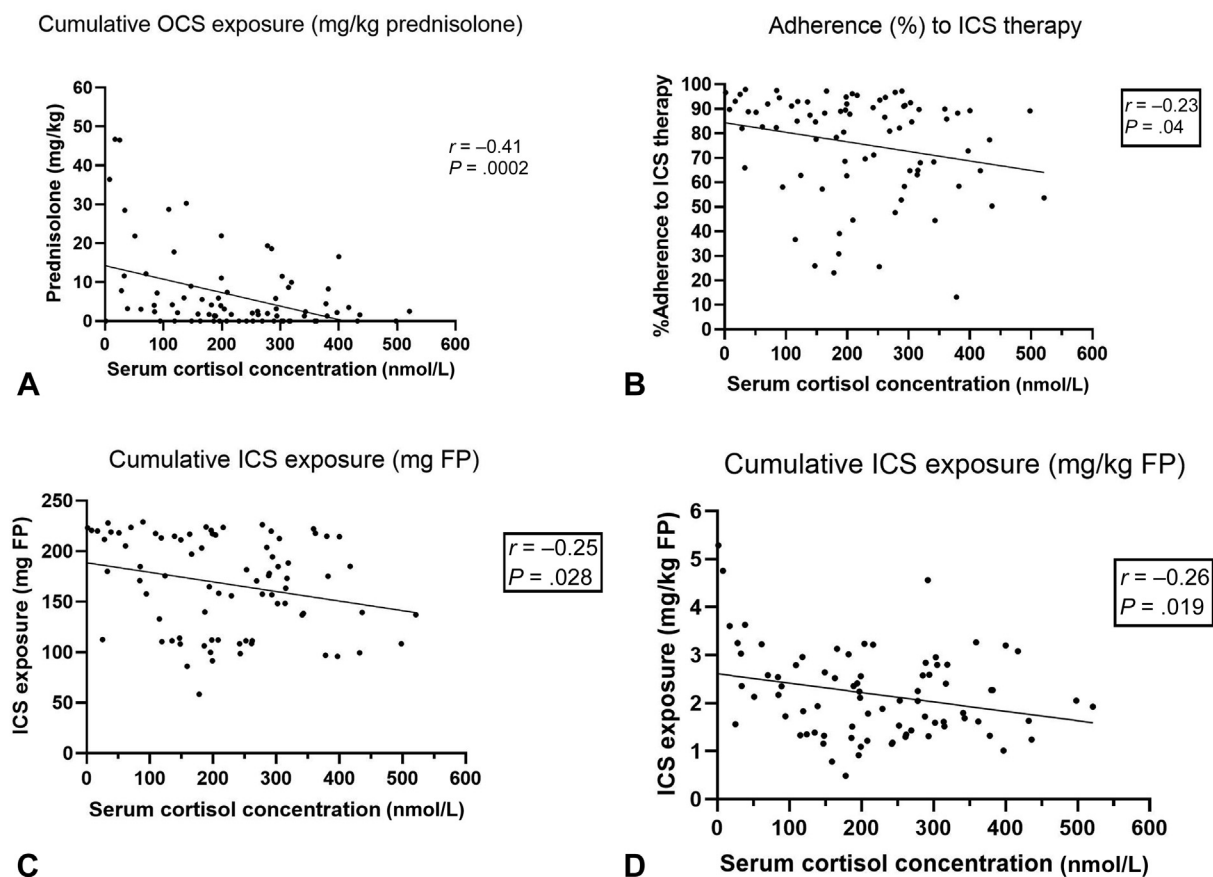


FIGURE 2. There is a negative correlation between morning serum cortisol concentration and (A) cumulative OCS exposure adjusted for weight (mg/kg prednisolone), (B) adherence (%) to inhaled glucocorticoid therapy (FP), (C) cumulative ICS exposure (mg FP), and (D) cumulative ICS exposure adjusted for participant weight (mg/kg FP).

predicts a normal SST response (100% specificity, 95% CI, 92%-100%; 67% sensitivity, 95% CI, 44%-84%), consistent with published work using the same assay.²⁴ We used these threshold cortisol values to stratify participants into 3 groups. Participants with a morning cortisol value of less than 130 nmol/L are predicted to fail an SST, and therefore are at highest risk of AI (HR-AI). Participants with a morning cortisol value of more than 294 nmol/L are likely to pass an SST, and so were classified as lower risk of AI (LR-AI). Those whose cortisol concentration fell between these thresholds were classed as having indeterminate risk of AI (IR-AI).

Asthma control and quality-of-life parameters

Patient symptoms and quality-of-life parameters were recorded at each visit using the Asthma Control Test (ACT),²⁵ the mini Asthma Quality of Life Questionnaire (mini-AQLQ),²⁶ and the Euroqol 5-dimension 3-level with Visual Analogue Scale.²⁷ The ACT is a subjective measure of asthma control over the previous month, with scores ranging from 5 to 25 and higher scores indicating better control.²⁵ The mini-AQLQ is a 15-question test, with higher scores indicating better control. The Euroqol 5-dimension 3-level is a quality-of-life questionnaire, where patients rate their health between 1 and 100, 1 being the worst imaginable and 100 being the best.

Statistical analysis

All statistical analyses were performed using Stata SE-16 (Stata Corp LLC, TX) & GraphPad Prism 9.2 (GraphPad Software Inc, La Jolla, CA). Data were expressed as counts (%) for categorical variables. For continuous valued variables, data were expressed as means with SDs unless evidence of skew was apparent, in which case medians with interquartile ranges are reported. Normality was tested for using histograms and the Shapiro-Wilk test in Stata SE-16. Between-group comparisons were performed using *t* test or Wilcoxon rank-sum tests as appropriate. Multivariate analyses were performed for analysis of glucocorticoid exposure using generalized linear models, including linear regression for continuous variables, logistic regression for binary outcomes, and Poisson regression for the analysis of count outcomes.

Provisional univariable analysis of participant groups performed by multinomial logistic regression (including age, sex, BMI, duration of asthma, lung function, measures of inflammation, OCS and ICS exposure) revealed no significant difference between the indeterminate and lower risk groups. As such, for the purposes of regression analyses and to reduce the risk of type 2 error, we compared the HR-AI group with those at lower risk (LR-AI and IR-AI combined). All other comparisons were made between the HR-AI and LR-AI groups. Age and sex have been included as covariates in all analyses in which AI is an outcome. As standard, a *P* value of less than .05 was considered as statistically significant.

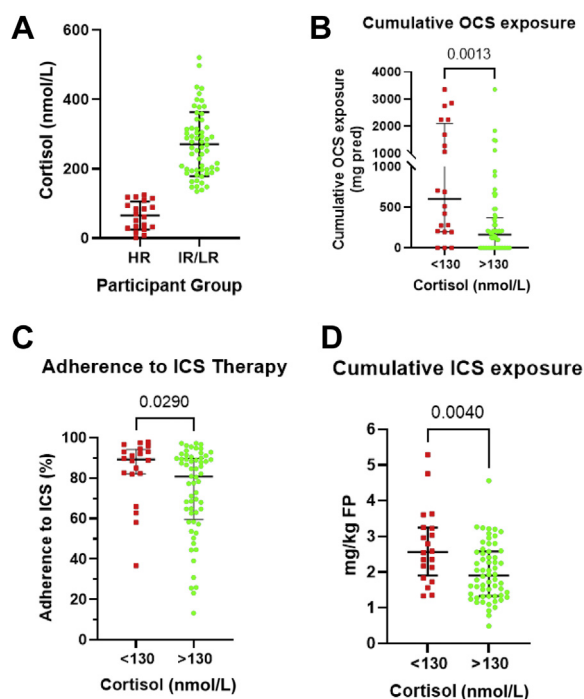


FIGURE 3. Comparison of (A) morning serum cortisol concentration (mean $\pm$ SD), (B) cumulative oral prednisolone exposure (median, IQR), (C) adherence to ICS therapy (median, IQR), and (D) cumulative ICS exposure adjusted for weight (median, IQR) between participants at highest risk of AI (cortisol <130 nmol/L) and those at indeterminate or lower risk of AI (>130 nmol/L). *mg pred*, Milligram prednisolone.

RESULTS

Participant characteristics

Eighty patients were included in the study (Table I). There was a female preponderance (58%), with a mean age of 48.8 ± 14 years and median BMI 28 kg/m^2 (interquartile range [IQR], 25–32 kg/m^2). The mean FEV₁ was $80\% \pm 25\%$, and the median ACT score was 20 (IQR, 16–22). Fifty patients (63%) were on high-dose FP (500 μg twice a day) and 30 (37%) were prescribed 250 μg twice a day. Fifty-five patients (68%) received at least 1 treatment course of oral steroids during the study. The median number of OCS courses prescribed was 1 (IQR, 0–2).

In this cohort, 20 of 80 (25%) were HR-AI (morning serum cortisol concentration <130 nmol/L). Of these, 6 of 20 (30%) were on maintenance OCS and 3 of 20 (15%) had received a course of OCS within the previous week. Excluding all participants exposed to OCS within the last week ($n = 15$), 11 of 65 (17%) were classified as HR-AI. Of these patients, the mean duration since last OCS exposure was 98 ± 47 days. Twenty-one participants (26%) were LR-AI (morning serum cortisol >294 nmol/L), none of whom were prescribed maintenance OCS therapy. Thirty-nine participants (49%) had indeterminate risk of adrenal insufficiency (IR-AI; cortisol concentration, 130–294 nmol/L).

There was no statistically significant difference between the HR-AI or LR-AI group in age, age at diagnosis of asthma, BMI, or duration of disease (P value .055, .32, .58, and .69, respectively) (Table I). The HR-AI group had a higher mean FEV₁

($86\% \pm 26\%$) compared with the LR-AI group ($77\% \pm 25\%$) but this did not reach significance ($P = .28$).

Morning cortisol and OCS exposure

The participants at HR-AI had greater cumulative OCS exposure (milligram prednisolone) than the LR-AI participants (470 mg prednisolone [IQR, 173–1965] vs 62.5 mg prednisolone [IQR, 0–210]; $P = .0017$). When participants on maintenance OCS therapy were excluded, the participants at HR-AI still had a greater absolute exposure to prednisolone than those at LR-AI; however, the statistical significance of this finding was reduced (278 mg prednisolone [195–690] vs 180 mg prednisolone [0–330]; $P = .07$) (Table II).

Morning serum cortisol concentration exhibited a negative correlation with both cumulative OCS exposure (milligram prednisolone) ($r = -0.4$; $P = .0002$) and weight-based OCS exposure (mg/kg prednisolone) ($r = -0.41$; $P < .0002$) (Figure 2). If we consider a standard pulse of OCS therapy as a 5-day course of 40 mg prednisolone/d, the risk of AI increased with each OCS course (odds ratio [OR], 1.41; 95% CI, 0.97–2.05; $P = .073$). When adjusted for ICS exposure, the risk of AI associated with a pulse course of OCS therapy was no longer significant (OR, 1.29; 95% CI, 0.86–1.94; $P = .220$).

The median number of pulse steroid courses prescribed in the year preceding the study period was 3 (IQR, 2–5) (Table II). Using Poisson regression analysis, we observed that the HR-AI group had a higher incidence rate ratio (IRR) of OCS prescription in the previous year than the LR-AI and IR-AI groups combined (IRR, 1.51; 95% CI, 1.2–1.9; $P = .0005$) (unadjusted for ICS exposure). Throughout the study, there were fewer pulse courses of steroids prescribed overall (median, 1 course; IQR, 1–2) but, again, the HR-AI group had a significantly higher IRR of OCS prescription (IRR, 1.84; 95% CI, 1.2–2.8; $P = .004$, unadjusted for ICS exposure) during the study.

Ten participants (13%) were receiving maintenance OCS as well as ICS, with a median daily dose of 10 mg prednisolone (IQR, 5–10). These patients had a significantly higher cumulative OCS exposure (median, 2240 mg prednisolone, IQR, 1690–2850 mg vs 187.5 mg prednisolone, IQR, 0–350 mg; $P < .00005$), a significantly lower morning cortisol (mean, 92 ± 74 nmol/L vs 238 ± 116 nmol/L; $P = .0002$; 95% CI, 71–222), and were more likely to be at HR-AI than patients not on maintenance OCS (60% vs 19%; $P = .005$).

Morning cortisol and ICS exposure

In HR-AI participants, 85% were prescribed high-dose FP (1000 $\mu\text{g}/\text{d}$), with the remainder prescribed 500 $\mu\text{g}/\text{d}$. Median adherence to ICS therapy in the HR-AI group was 89.3%, giving a median cumulative FP exposure of 213 mg FP (IQR, 173–220), or 2.56 mg/kg FP (1.98–3.24) (Table II). Within the LR-AI group, 57% were prescribed high-dose FP (mean prescribed dose, 786 $\mu\text{g}/\text{d}$). The median adherence rate to ICS therapy was 68.4%. Using data from the INCA device, we found that LR-AI participants received a median cumulative ICS exposure of 163.3 mg (IQR, 137–188.4), or 1.93 mg/kg FP (1.61–2.8). Comparing the HR-AI group to the LR-AI group, we found that there was a significant difference in both adherence to ICS therapy (89% [IQR, 82%–94%] vs 68.4% [IQR, 63%–88%]; $P = .029$) and cumulative ICS

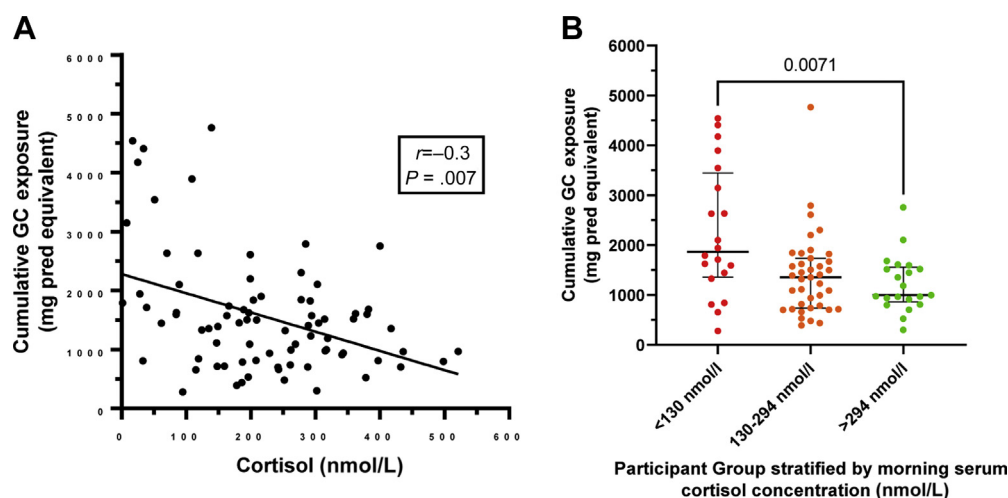


FIGURE 4. Relationship between total cumulative GC exposure (mg prednisolone equivalent) and serum cortisol concentration. **(A)** There is a negative correlation between total cumulative GC exposure and serum cortisol concentration. **(B)** Participants at highest risk of TAI received the greatest total cumulative GC exposure (oral and inhaled GC exposure combined) during the 32-week study period compared with those at indeterminate and lower risk. GC, Glucocorticoid; mg pred, milligram prednisolone. Prednisolone equivalent calculated where 1 mg FP is equivalent to 8.5 mg prednisolone.

exposure (212.5 mg FP [IQR, 173-220] vs 163 mg FP [IQR, 137-188]; $P = .003$) (Table II and Figure 3).

Prescription of high-dose FP (1000 μ g/d) increased the risk of AI (OR, 4.57; $P = .023$; 95% CI, 1.3-18.2, unadjusted for OCS exposure) compared with 500 μ g/d FP. If OCS exposure is adjusted for, the risk of AI associated with prescription of high-dose FP was no longer statistically significant (OR, 3.49; 95% CI, 0.86-14.14; $P = .080$). There was a negative correlation between morning cortisol concentration and ICS exposure expressed as either mg FP ($r = -0.25$; $P = .0283$) or mg/kg FP ($r = -0.26$; $P = .019$) (Figure 2). A multivariate logistic regression analysis, accounting for cumulative glucocorticoid exposure, sex, and age, showed objectively measured cumulative ICS exposure to be a significant predictor of AI, independent of OCS exposure (OR, 2.17 per 1 mg/kg increase in FP exposure; 95% CI, 1.06-4.42; $P = .033$). Using predicted ICS exposure based on prescribed dosing yielded similar results although they did not reach statistical significance (OR, 2.09 per 1 mg/kg increase in predicted FP exposure; 95% CI, 0.99-4.41; $P = .054$).

Morning cortisol and intranasal glucocorticoid use

Overall, 54 participants (68%) were also prescribed intranasal glucocorticoid preparations. There was no difference in intranasal glucocorticoid use between any participant group (Table II).

Morning cortisol and total cumulative glucocorticoid exposure

Overall, the median total cumulative glucocorticoid exposure (oral/inhaled combined) over the 32-week study period was 1426 mg prednisolone equivalent (IQR, 823-1835). Participants at highest risk of AI had the greatest total exposure (1866 mg prednisolone equivalent; IQR, 1358-3345), followed by the IR-AI group (1354 mg prednisolone equivalent; IQR, 738-1737). Participants at LR-AI had the lowest total glucocorticoid exposure (997 mg prednisolone equivalent; IQR, 863-1559) (Table II and Figure 4). There was a negative correlation between morning

serum cortisol concentration and total cumulative glucocorticoid exposure ($r = -0.3$; $P = .007$) (Figure 4).

Morning cortisol and objective markers of asthma activity

There was no significant correlation between serum cortisol and FEV₁ ($r = -0.09$; $P = .4$) at week 32, or in measures of type 2 inflammation such as fractional exhaled nitric oxide ($r = 0.1$; $P = .37$) or peripheral blood eosinophil count ($r = 0.06$; $P = .5814$). There was no significant difference between FEV₁, fractional exhaled nitric oxide, or peripheral blood eosinophil count between any of the participant groups.

Morning cortisol and subjective markers of asthma activity

Morning serum cortisol exhibited a positive correlation with ACT score ($r = 0.252$; $P = .02$) (Figure 5). Logistic regression analysis accounting for age and sex, comparing HR-AI patients (cortisol <130 nmol/L) with the rest of the cohort (cortisol >130 nmol/L), shows that each unit increase in ACT score is associated with a decreased odds of AI (10%; OR, 0.9 per unit change in ACT score; 95% CI, 0.80-1.00; $P = .040$). The median ACT score at week 32 was 20 (IQR, 15-22), consistent with well-controlled asthma; however, the HR-AI group reported a lower median final ACT score of 17 (IQR, 12-21) compared with 20 (IQR, 16-22) for those who were not predicted to be at high risk of AI (cortisol >130 nmol/L) (Table III). Final ACT score did not correlate with final FEV₁ ($r = 0.04$; $P = .7$) (Figure 5).

The mini Asthma Quality of Life Questionnaire (mini-AQLQ) correlated positively with serum cortisol concentration ($r = 0.31$; $P = .0055$), where higher mini-AQLQ score indicated better self-rated quality-of-life scores. Logistic regression evaluating the relationship between suppressed cortisol (<130 nmol/L) and mini-AQLQ, accounting for age and sex, showed a similar signal but did not reach statistical significance ($P = .073$; 95%

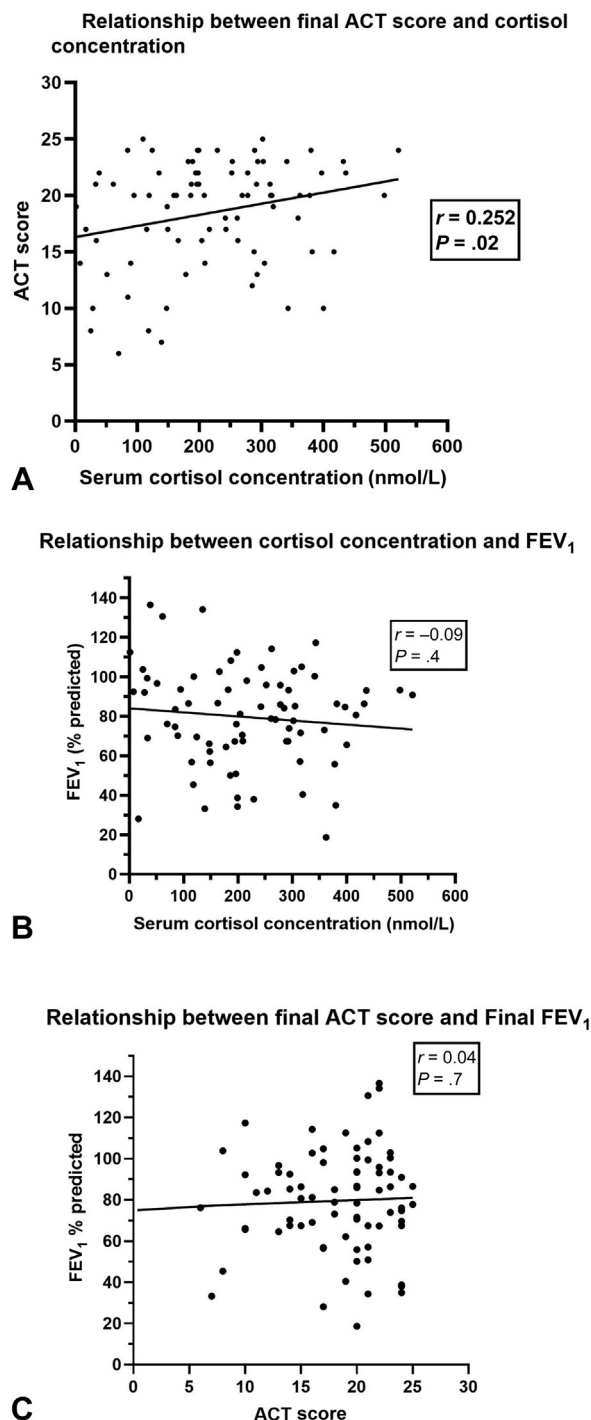


FIGURE 5. There is a (A) positive correlation between morning serum cortisol concentration and final ACT score; however, there is no correlation (B) between final FEV₁ % predicted value and morning serum cortisol, or (C) between final ACT score and final FEV₁ % predicted value. This is suggestive that although patients with lower serum cortisol concentration have poorer subjective asthma symptoms, this is not accompanied by worse objective markers of asthma control. We hypothesize that one possible explanation for the discrepancy between subjective symptoms and objective markers of asthma control in patients with low morning serum cortisol is the contribution of undiagnosed AI to subjective symptoms.

CI, 0.48-1.03). There was no significant between-group difference between the HR-AI group and the LR-AI or LR-AI/IR-AI groups combined for Euroqol 5-dimension 3-level or Euroqol Visual Analogue Scale scores.

DISCUSSION

The prevalence of AI based on morning cortisol concentrations observed in our study population was 25%, reducing to 17% when patients with recent (<7 days) OCS exposure were excluded. Although our data are comparable with existing literature on patients with asthma receiving high-dose/long-term ICS,^{2,9} to our knowledge this is the first study to use an electronic monitoring device to collect individual cumulative ICS exposure data. With cumulative OCS exposure data, this allows for a more nuanced analysis of the relationship between glucocorticoid exposure and cortisol, while avoiding the selection bias inherent in retrospective reviews of synacthen testing.

It is likely that the true prevalence of TAI in our cohort is higher than the rates we have reported. Our locally validated cortisol threshold value, which is used to identify those at highest risk of AI (<130 nmol/L), has 100% specificity to predict SST failure, but a sensitivity of only 38%. It is therefore reasonable to expect that a proportion of the participants in the IR group may fail an SST.

The high prevalence of undiagnosed AI in this cohort is concerning. All patients with AI are at risk of adrenal crisis and identification of at-risk patients is key in reducing this, because steroid sick-day rule knowledge in patients on glucocorticoids in nonendocrine settings is typically poor.²⁸ Equally concerning for this patient group are the cardiometabolic complications of glucocorticoid excess. The development of TAI infers sufficient glucocorticoid exposure to cause HPA-axis suppression; therefore, TAI can be considered a marker of iatrogenic Cushing's syndrome and vice versa.²⁹ Exposure to exogenous glucocorticoids is associated with a dose-dependent increase in cardiovascular morbidity and mortality, even after adjusting for underlying disease severity,^{4,5} which is higher again in patients with iatrogenic Cushing syndrome or TAI.⁴

We found a strong association between total cumulative glucocorticoid exposure and risk of AI in asthma. Our data also demonstrate a clear association with OCS exposure and AI in patients with severe asthma. As expected, taking maintenance OCS conveyed the highest risk (60%). Intermittent OCS courses in patients treated with high-dose ICS were associated with a significant risk of AI (OR, 1.41 per treatment course). Interestingly, when the effect of ICS exposure is controlled for, the risk of AI with each OCS course was no longer significant. In addition, participants who had AI without recent OCS exposure had a mean duration of 98 days since last OCS exposure. This is beyond the time frame for acute suppression of the HPA axis due to exogenous glucocorticoid exposure, and suggests that the ongoing exposure to high-potency ICS therapy impairs the usually brisk recovery of the HPA axis from an OCS course. These patients, who may have inadequate steroid replacement between OCS courses, are particularly vulnerable to reduced quality of life,³⁰ adrenal crises, and potentially increased mortality.^{1,31,32}

In our study, ICS exposure was demonstrably associated with AI, even after controlling for OCS exposure. The risk of AI doubled with every additional 1 mg/kg cumulative FP exposure,

TABLE III. Patient-reported symptom burden and quality of life

Questionnaire	Total cohort	HR-AI	IR-AI	LR-AI	IR/LR-AI combined	P value (HR- vs LR-AI)	P value (HR- vs IR/LR- AI combined)
ACT*	20 (15.5-22)	17 (12-21)	20 (16-22)	20 (15-23)	20 (17-22)	.1028	.08
mAQLQ*	5.3 (4.2-6.3)	4.3 (2.3-5.9)	5 (4.3-6.1)	5.8 (4.5-6.5)	5.4 (4.5-6.3)	.1185	.08
EQ-5D-3L*	6 (5-7)	6 (5-7)	6 (5-7)	5 (5-6)	6 (5-7)	.15	.35
EQ-VAS*	80 (70-85)	77.5 (56-82.5)	80 (72-85)	75 (70-85)	80 (70-85)	.24	.075

EQ-5D-3L, Euroqol 5-dimension 3-level questionnaire; EQ-VAS, Euroqol Visual Analogue Scale.

ACT lower score, poorer subjective asthma control; EQ-5D lower score, better self-reported quality of life; EQ-VAS lower score, poorer self-reported quality of life; mAQLQ lower score, poorer self-reported quality of life.

*Median (IQR).

independent of OCS (OR, 2.17 per 1 mg/kg increase in FP exposure; 95% CI, 1.06-4.42; $P = .033$). Although there was an apparent statistically significant difference between the risk of AI based on predicted ICS exposure (calculated using prescribed dose) and actual ICS exposure (calculated using the INCA device data), this was smaller than we might have expected, likely due to the high level of ICS adherence observed in our study cohort (median, 85%). We hypothesize that in a clinical setting, where adherence to ICS therapy is closer to 50%,³³ the difference in risk of AI between expected and actual ICS exposure would be even more pronounced.

These data highlight the importance of recent guidance from the Society for Endocrinology who suggest that, in addition to patients on maintenance OCS treatment, patients on more than 500 µg/d FP should be issued with a steroid card, advised regarding sick-day rules, and receive empiric stress dose hydrocortisone when undergoing endoscopy/surgical procedures,³⁴⁻³⁶ or during nonrespiratory illness where systemic glucocorticoids may not be part of routine treatment.

Although our data show a linear relationship with adherence and cortisol suppression, it is worth noting that the rates of adherence in this study are significantly higher than those seen in real-world practice.³³ It is not surprising that the highest adherence, and therefore highest received dose of ICS, is seen in the HR-AI group but the relationship between adherence and cortisol suppression is likely to be more nuanced than this. In clinical practice, poorly adherent patients suffer more frequent exacerbations and are subject to more pulse courses of OCS. It is also plausible that the higher rates of adherence in patients with undiagnosed TAI may be driven by a symptomatic benefit from glucocorticoid replacement, but we cannot definitively conclude this from our data.

There is no significant correlation between serum cortisol concentration and objective markers of asthma activity (FEV₁, fractional exhaled nitric oxide, and peripheral blood eosinophil count), nor were there any significant between-group differences in these parameters. However, there was a significant positive correlation between cortisol and both ACT score and mini-AQLQ score. Although the difference in ACT score and mini-AQLQ score between those at HR-AI and the rest of the cohort did not meet statistical significance ($P = .08$ and $.08$, respectively), the numerical difference met the minimal clinically important difference for both (3 points and 0.5 points, respectively).³⁷ This suggests that, despite similar lung function between the HR-AI group and the rest of the cohort and an absence of evident type 2 inflammation, there is an increased symptom burden reported by patients with concomitant AI. It

is accepted that AI is associated with poorer quality of life, even when adequately treated.¹⁵ One possible explanation for this discrepancy between objective markers of asthma activity and the more subjective ACT score is that, due to the nonspecificity of the ACT, the worse quality of life associated with AI may be misattributed to asthma. However, any such association should be interpreted with caution due to the strong confounding between symptoms, oral steroid prescription, and cortisol suppression. The reciprocal relationship between patient-reported symptoms, high-dose ICS/OCS prescription, and resulting adrenal suppression cannot be fully investigated in an observational study such as this, particularly with such a limited sample size. Ideally, this relationship should be further investigated in a larger study using structured equation models or similar methods to identify possible confounding or mediating effects; however, our relatively small data set makes this approach nonviable.

Study limitations

The relatively small sample size included in our analysis potentially increases the chance of type 2 error occurring. Because of the INCA-SUN trial design, we observed above-average adherence to ICS exposure in this cohort, and therefore it is not possible to comment definitively on the relationship between poor ICS adherence and the risk of AI. Because the INCA-SUN study included only patients with severe asthma, there is a potential for selection bias in our analysis. Although this analysis relates to the dose-response relationship between cumulative glucocorticoid exposure and serum cortisol concentration, which we would expect to be applicable across a broader spectrum of patients, we do not have data relating to patients with mild to moderate asthma to confirm this.

Conclusions

To our knowledge, this is the first study to use an electronic monitoring device to objectively record inhaler usage, allowing for detailed analysis of the relationship between ICS exposure and morning serum cortisol concentration. Although cumulative exposure to OCS therapy appears to have a greater influence on the risk of AI, we have shown that cumulative ICS exposure is independently associated with AI risk. There is a suggestion that patients with concomitant AI experience a greater symptom burden than those with intact adrenal function, which may be, in part, explained by the presence of AI; however, further studies are required to delineate this association.

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