

## **ORAL AND INHALED CORTICOSTEROIDS AND ADRENAL INSUFFICIENCY: A CASE-CONTROL STUDY**

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## ABSTRACT

**Background.** Adrenal insufficiency, a well-recognised complication of treatment with oral corticosteroids, has been described in association with inhaled corticosteroid use in over 60 case reports. The risk of adrenal insufficiency in people prescribed an oral or inhaled corticosteroid in the general population is not known.

**Objective.** To quantify the association between adrenal insufficiency and oral and inhaled corticosteroid exposure.

**Methods.** Case-control study using computerised general practice data from The Health Improvement Network.

**Results.** We identified 154 cases of adrenal insufficiency and 870 controls from a cohort of 2.4 million people. There was a dose-related increased risk of adrenal insufficiency in people prescribed an oral corticosteroid with an odds ratio of 2.0 (95% CI 1.6 to 2.5) per course of treatment per year. Adrenal insufficiency was associated with a prescription for an inhaled corticosteroid within the 90 days prior to the diagnosis with an odds ratio of 3.4 (95% CI 1.9 to 5.9) and this effect was dose-related ( $p$  for trend  $< 0.001$ ). After adjusting for oral corticosteroid exposure this odds ratio was reduced to 1.6 (95% CI 0.8 to 3.2) although the dose relation remained ( $p$  for trend 0.036).

**Conclusion.** People prescribed an oral or inhaled corticosteroid are at a dose-related increased risk of adrenal insufficiency although the absolute risk is small. Our analysis suggests that the increased risk in people prescribed an inhaled corticosteroid is largely due to oral corticosteroid exposure but there may be an effect of inhaled corticosteroids when they are taken at higher doses.

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## INTRODUCTION

The association between adrenal insufficiency and treatment with oral corticosteroids has been recognized for decades<sup>1-3</sup> although the magnitude of the risk has not been determined. An association with inhaled corticosteroid use came to attention more recently with five reports in the last four years describing 60 cases of adrenal insufficiency in people taking an inhaled corticosteroid.<sup>4-8</sup> The majority of these cases were children, many of whom were taking high doses of an inhaled corticosteroid and over 80% were taking fluticasone propionate at the time. The risk of adrenal insufficiency among people in the general population prescribed an oral or inhaled corticosteroid is unknown. To quantify this we investigated the association between adrenal insufficiency and prescriptions for oral and inhaled corticosteroids in a case-control study using data from The Health Improvement Network (THIN) database.<sup>9</sup>

## METHODS

THIN is a longitudinal database derived from computerised records of diagnostic and prescription information from general practices in the United Kingdom. The database included 2.4 million people in 177 general practices when the data were extracted in 2004. A previous audit of the THIN database has confirmed a high level of completeness of clinical diagnostic and prescribing data confirming the usefulness of this dataset for medical research.<sup>9</sup>

### *Case-control set*

Cases were all people with a diagnosis of adrenal insufficiency, adrenal crisis or Addison's disease in their computerised medical records. We excluded people prescribed oral hydrocortisone because this is used almost exclusively to treat established adrenal insufficiency and we were interested in new cases. The first recorded date of adrenal insufficiency was labelled as the index date. Up to six control subjects were matched to each case by age at index date, gender and general practice and they had to be alive and contributing data on the date of the case's index date. Controls were allocated the same index date as their matched case.

### *Data extraction and processing*

Data were extracted on all recorded prescriptions for oral and inhaled corticosteroids and on smoking status, body mass index, and diagnoses of asthma and chronic obstructive pulmonary disease (COPD). We calculated the median number of courses of oral corticosteroids per year (defined as the number of separate prescriptions issued for an oral corticosteroid) for cases and controls and the mean daily dose of inhaled corticosteroid for each person in the 90 days prior to the index date.

### *Analysis*

Conditional logistic regression was used to quantify the association between adrenal insufficiency and at least one prescription for an oral or inhaled corticosteroid. The association between adrenal insufficiency and the number of courses of oral corticosteroids was also estimated and compared to those never prescribed an oral corticosteroid. The risk of adrenal insufficiency was estimated in those prescribed an inhaled corticosteroid within 90 days and more than 90 days prior to the index date compared to those never prescribed an

inhaled corticosteroid for all drugs and for beclometasone dipropionate, budesonide, fluticasone propionate and mometasone furoate separately. We chose 90 days to represent current or recent exposure. In addition we examined the impact of mean daily dose of inhaled corticosteroid exposure within 90 days of the index date, grouping daily doses as follows: 1 to 600 µg, 601 to 1200 µg, greater than 1201 µg. We assessed the impact of potential confounding by smoking, body mass index, and oral or inhaled corticosteroids as appropriate, using multivariate analyses and retaining variables that led to a change in the odds ratio (OR) of 10% or more. The analysis was carried out using Stata SE8 statistical software (StataCorp. 2003. Stata Statistical Software: Release 8.0. College Station, TX: Stata Corporation).

## RESULTS

We identified 289 patients with a recorded diagnosis of adrenal insufficiency but excluded 135 who had a previous prescription for oral hydrocortisone. There were therefore 154 cases and 870 controls, contributing a median of 4.9 (IQR 2.5 to 8.5) and 5.3 (IQR 2.6 to 8.5) years of data prior to the index date. The mean age of cases was 53 years (standard deviation (SD) 21) and 64 (42%) were male. Patients with adrenal insufficiency were more likely than controls to have asthma or COPD but were of similar body mass index and smoking status (Table 1).

Of the cases and controls 58 (38%) and 59 (7%) had been prescribed an oral corticosteroid, 31 (20%) and 78 (9%) had been prescribed an inhaled corticosteroid and 92 (60%) and 764 (88%) had no recorded prescriptions for either an inhaled or oral corticosteroid. Of the people prescribed an oral corticosteroid, cases and controls received a median of 2 (IQR 0.4 to 5.5) and 0.5 (IQR 0.2 to 1.2) courses of oral corticosteroid per year respectively. Of the people prescribed an inhaled corticosteroid within 90 days of the index date (22 cases and 40 controls) the mean (SD) daily dose was 1054 (774) µg for cases and 667 (367) µg for controls (data missing for one control) in the 90 days prior to the index date. The mean (SD) daily dose of beclometasone dipropionate, budesonide and fluticasone propionate for cases was 1116 (885) µg, 444 µg (based on one case) and 890 (545) µg respectively and for controls was 678 (385) µg, 467 (277) µg and 500 (192) µg respectively. There were no prescriptions for mometasone furoate.

In our univariate analyses a prescription for at least one course of oral corticosteroids was associated with an increased risk of adrenal insufficiency with an odds ratio of 8.6 (95% CI 5.5 to 13.5). Furthermore this increased risk was dose-related with an odds ratio of 2.0 (95% CI 1.6 to 2.5) per course of oral corticosteroids per year. After adjusting for the mean daily dose of inhaled corticosteroid prescribed in the past 90 days this odds ratio was almost unchanged at 1.9 (95% CI 1.5 to 2.4).

In our univariate analyses at least one prescription for an inhaled corticosteroid was associated with adrenal insufficiency with an odds ratio of 2.5 (95% CI 1.6 to 4.0). After adjusting for the number of courses of oral corticosteroids prescribed per year as a continuous variable, this odds ratio was reduced to 1.3 (95% CI 0.8 to 2.3). Before adjusting for the impact of oral corticosteroids a prescription for an inhaled corticosteroid within 90 days of the index date was associated with an increase in the risk of adrenal insufficiency with an odds ratio of 3.4 (95% CI 1.9 to 5.9) while a prescription for an inhaled corticosteroid prior to this time point was not associated with an increased risk (OR 1.6, 95% CI 0.7 to 3.4). After

adjusting for the number of courses of oral corticosteroids prescribed per year the equivalent odds ratios were 1.6 (95% CI 0.8 to 3.2) and 1.0 (95% CI 0.4 to 2.3) respectively (Table 2).

The increased risk of adrenal insufficiency in people taking an inhaled corticosteroid was dose-related (Table 3, *p* for trend < 0.001) and although this relationship was attenuated it remained significant at the 5% level after adjusting for courses of oral corticosteroids (*p* for trend = 0.036).

The increase in risk of adrenal insufficiency differed between inhaled corticosteroids although the confidence intervals were wide and overlapped. The odds ratios for a prescription within 90 days of the index date for beclometasone dipropionate and fluticasone propionate after adjusting for oral corticosteroid exposure were 1.1 (95% CI 0.5 to 2.7) and 4.6 (95% CI 1.3 to 17.0) respectively; there were insufficient data for budesonide (Table 2).

## DISCUSSION

This is the first study to quantify the increased risk of adrenal insufficiency in people prescribed oral and inhaled corticosteroids in the general population. We found a strong dose-response relationship between oral corticosteroid exposure and the risk of adrenal insufficiency. We also found that a prescription for an inhaled corticosteroid within 90 days of the diagnosis was associated with an increased risk of adrenal insufficiency, although this association was reduced after adjusting for oral corticosteroid exposure. This suggests that the increased risk of adrenal insufficiency associated with inhaled corticosteroid exposure was largely explained by exposure to oral corticosteroids, although we found some evidence of a persistent increase in risk with higher doses of inhaled corticosteroids and with current exposure to fluticasone propionate after adjusting for oral corticosteroid exposure.

No previous studies have assessed the effect of oral or inhaled corticosteroid use in the general population on adrenal insufficiency. By using computerized general practice data we were able to assemble enough cases of adrenal insufficiency with detailed prescription data to perform a case-control study of the impact of oral and inhaled corticosteroids on the risk of adrenal insufficiency. By matching cases to control subjects individually we have minimized confounding by age, sex and local clinical and community factors. The validity of a diagnosis of adrenal insufficiency has not been tested in computerized datasets although the validity of other clinical outcomes is known to be high<sup>10</sup>. Although our case definition was based on a diagnosis of adrenal insufficiency, adrenal crisis or Addison's disease in a patient's computerised records and not on specific biochemical criteria, general practitioners are unlikely to record a diagnosis of adrenal insufficiency without good supportive evidence and therefore the specificity of the diagnosis should be high. We did not have data on lifetime exposure to oral corticosteroids and so may not have adjusted our inhaled corticosteroid analyses fully for this confounding exposure, in which case our final estimates for the association between inhaled corticosteroid use and risk of adrenal insufficiency may be too high. Finally, since our data relate to prescriptions rather than actual treatment, we cannot be certain of the time-scale over which treatment was actually taken; it is possible that some prescribed treatments, particularly courses of oral corticosteroids for use during an exacerbation, were never taken with the effect that exposure to such treatments was over-estimated in our analysis.

Adrenal suppression as a consequence of oral corticosteroid use was recognized in the 1950s and 1960s<sup>1-3</sup> and became apparent when patients with asthma were weaned from oral to

inhaled corticosteroids in the 1970s<sup>11-14</sup>. The magnitude of the risk of adrenal insufficiency in people taking an oral corticosteroid is poorly characterized however. Our study has quantified the magnitude of the risk and shown a dose-response relationship with a doubling of the risk per course of oral corticosteroid prescribed per year. To what extent the recent use of oral corticosteroids is responsible for the increased risk or a marker of previous use of corticosteroids is uncertain.

The evidence that inhaled corticosteroids are associated with adrenal insufficiency comes mainly from case reports and case series<sup>4-8,15-23</sup>. The extent to which adrenal insufficiency relates to the use of oral or inhaled corticosteroids in these reports is difficult to disentangle, however, since reporting of oral corticosteroid intake is limited and may be underestimated. The survey by Todd et al<sup>4</sup> provides some evidence that inhaled corticosteroids can be responsible for adrenal insufficiency since all but one of 33 cases had had less than 21 days treatment with oral corticosteroids in the year prior to presentation and several including many of the children were taking particularly high doses of inhaled corticosteroids.

An additional finding of Todd's survey was that most cases were associated with the use of fluticasone propionate<sup>4</sup>. The largest increase in risk in our study occurred in association with a recent prescription for fluticasone propionate although the numbers were small. The mean daily dose of fluticasone propionate in our cases was relatively high, 890 µg, considering that fluticasone propionate is roughly twice as potent as beclometasone dipropionate and budesonide<sup>24</sup>. We cannot say whether high doses of fluticasone propionate were given inappropriately, because its greater potency was not appreciated, or whether it was given to people with more severe asthma, in which case the increased risk of adrenal insufficiency may be due to greater exposure to oral corticosteroids in the past. The absorption of fluticasone propionate varies considerably with lung function and this could increase the risk of systemic adverse effects in patients with good lung function<sup>25</sup>.

The main clinical message from our study is that people prescribed an oral or inhaled corticosteroid are at a dose-related increased risk of adrenal insufficiency although in absolute terms this increase is small. Our analysis suggests that exposure to oral rather than inhaled corticosteroids is the major factor explaining the association with inhaled corticosteroids but we cannot exclude an impact of inhaled corticosteroids, particularly at higher doses, or of current exposure to fluticasone propionate. Since adrenal insufficiency is rare in the general population and may present in a non-specific way, the diagnosis needs to be considered in people with suspicious symptoms who are taking an inhaled corticosteroid, particularly when taken at higher doses, and when oral corticosteroids are taken intermittently.

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## **CONFLICTS OF INTEREST**

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**Table 1. Demographic details of cases and controls**

	<b>Cases (n=154)</b>		<b>Controls (n=870)</b>		<b>Odds Ratio (95% CI)</b>	
	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>		
<b>Male</b>	64	41.6	359	41.3	Matching variable	
<b>Age at adrenal crisis</b>					Matching variable	
<15	10	6.5	58	6.7	" "	
15-24.9	6	3.9	47	5.4	" "	
25-34.9	18	11.7	103	11.8	" "	
35-44.9	24	15.6	133	15.3	" "	
45-54.9	25	16.2	140	16.1	" "	
55-64.9	19	12.3	106	12.2	" "	
65-74.9	30	19.5	169	19.4	" "	
≥75	22	14.3	114	13.1	" "	
<b>Smoking status</b>					Reference	
Non smoker	64	41.6	282	32.4	Reference	
Ex-smoker	7	4.5	31	3.6	0.9	(0.4 - 2.3)
Current smoker	41	26.6	225	25.9	0.8	(0.5 - 1.2)
Missing	42	27.3	332	38.2	0.4	(0.2 - 0.7)
<b>Body Mass Index (Kg/m<sup>2</sup>)</b>					Reference	
Underweight (<18.5)	5	3.2	12	1.4	2.1	(0.7 - 6.3)
Normal (18.5-24.9)	52	33.8	233	26.8	Reference	
Overweight (25.0-29.9)	25	16.2	156	17.9	0.7	(0.4 - 1.2)
Obese (>30)	7	4.5	51	5.9	0.6	(0.3 - 1.4)
Missing	65	42.2	418	48.0	0.6	(0.4 - 1.0)
<b>Diagnosis of asthma or COPD</b>					Reference	
Asthma	32	20.8	90	10.3	2.4	(1.5 - 3.8)
COPD	10	6.5	27	3.1	2.2	(1.0 - 4.7)
Asthma and COPD	5	3.2	17	2.0	1.8	(0.6 - 5.2)

**Table 2. Association between individual inhaled corticosteroids and adrenal insufficiency**

Inhaled corticosteroid exposure before adrenal crisis*	Cases (n=154)		Controls (n=870)		Odds Ratio (95% CI)		Odds Ratio adjusted for OCS (95% CI) ***	
	No.	%	No.	%				
<b>Any inhaled corticosteroid</b>								
Never**	123	79.9	792	91.0	Reference		Reference	
greater than 90 days	9	5.8	38	4.4	1.6	(0.7 - 3.4)	1.0	(0.4 - 2.3)
within 90 days	22	14.3	40	4.6	3.4	(1.9 - 5.9)	1.6	(0.8 - 3.2)
<b>Fluticasone propionate</b>								
greater than 90 days	1	0.6	3	0.3	2.1	(0.2 - 20.6)	2.6	(0.2 - 28.8)
within 90 days	8	5.2	4	0.5	10.4	(3.1 - 35.3)	4.6	(1.3 - 17.0)
<b>Budesonide</b>								
greater than 90 days	4	2.6	14	1.6	2.0	(0.6 - 6.4)	1.4	(0.4 - 4.7)
within 90 days	1	0.6	5	0.6	1.3	(0.2 - 11.5)	Insufficient data	
<b>Beclometasone dipropionate</b>								
greater than 90 days	12	7.8	36	4.1	2.2	(1.1 - 4.3)	1.1	(0.4 - 2.6)
within 90 days	14	9.1	33	3.8	2.7	(1.4 - 5.3)	1.1	(0.5 - 2.7)

\* at least one prescription

\*\* never exposed to any inhaled corticosteroid - reference for all risk estimates

\*\*\* adjusted for number of courses of oral corticosteroids per year

**Table 3. Association between mean daily dose of inhaled corticosteroid and adrenal insufficiency**

Mean daily dose of inhaled corticosteroid (mcg)	Cases (n=154)		Controls (n=870) *		Odds Ratio (95% CI)	Odds Ratio adjusted for OCS (95% CI) **
	No.	%	No.	%		
0	132	85.7	830	95.4	Reference	Reference
< 600	6	3.9	21	2.4	1.6 (0.6 - 4.1)	0.6 (0.2 - 2.3)
600.1 to 1200	10	6.5	15	1.7	4.6 (1.9 - 10.2)	2.5 (1.0 - 6.2)
> 1200.1	6	3.9	3	0.3	13.3 (13.3 - 53.9)	3.7 (0.7 - 19.2)
p value for trend					<0.001	0.036

\* one missing data point

\*\* adjusted for number of courses of oral corticosteroids per year

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