Table 1 Baseline biochemistry and peak cortisol levels following insulin induced hypoglycaemia in two female adult patients taking inhaled/intranasal corticosteroids

	Patient 1	Patient 2
08.00 cortisol (200–600 nmol/l)	169/198	113/198
08.00 ACTH (<12 pmol/l)	4.5	2.8/2.9
Insulin-like growth factor-1 (0.4–1.6 U/ml)	0.54	0.89/0.79
Free thyroxine (10–21 pmol/l)	11	15.9/15.6*
Thyroid stimulating hormone (0.3–4 mIU/l)	0.77	1.77/1.95*
Prolactin (50–370 mIU/l)	224	111/87
Luteinising hormone (IU/l)†	11.3	26.4/18.4
Follicular stimulating hormone (IU/l)‡	6.5	50.1/42.7
α-subunit (IU/l)§	0.41	Not done
Anti-microsomal antibodies	Negative	Positive
Dehydrepiandrosterone (μmol/l)¶	<1.0	<1.0
Results of insulin tolerance test		
Baseline cortisol (200–600 nmol/l)	160	159
Minimum blood glucose (<2.2 mmol/l)	1.9	1.6
30 minute cortisol (nmol/l)	327	343
60 minute cortisol (nmol/l)	450	492
90 minute cortisol (nmol/l)	313	388
120 minute cortisol (nmol/l)	227	282
Peak growth hormone (>13 mU/l)	40.3	4.9

Normal ranges and units are in brackets. ''Normal'' peak cortisol level following hypoglycaemia >550 nmol/l. When more than one value is quoted, the tests were performed on different days.
*On thyroxine.
†Reference range (RR): females – premenopausal 2.5–130 IU/l, postmenopausal >15 IU/l, males 1.5–14 IU/l.
‡RR: females – premenopausal 1.6–33 IU/l, postmenopausal >16 IU/l, males 0.9–8.1 IU/l.
§RR: males and females – premenopausal 0.05–0.4 IU/l, postmenopausal 0.37–1.15 IU/l.
¶RR: females – premenopausal 2.2–9.1 μmol/l, postmenopausal 0.3–1.7 μmol/l, males 5.3–9 μmol/l.

disorders and ischaemic heart disease, the ITT is a safe test when performed in experienced centres.[3] Indeed, a review of >6500 ITTs reported that only seven patients (0.1%) experienced an adverse event, all of which reversed following intravenous glucose.[6] To our knowledge, only two studies have used the ITT to investigate the HPA axis in asthmatic children treated with inhaled fluticasone. The first reported an inadequate response to insulin-induced hypoglycaemia in three children taking 1000–2250 μg/day.[7] In the second study, nine of 18 subjects treated with 250–750 μg/day for up to 16 weeks exhibited evidence of adrenal suppression which recovered following cessation of treatment.[1]

Finally, as hypopituitarism of probable autoimmune aetiology has been reported in patients with celiac disease,[8] the possibility that autoimmune hypophysitis contributed to the patients' symptoms and pituitary deficiency cannot be definitively excluded.

In summary, this report suggests that inhaled (together with intranasal) fluticasone may suppress the HPA axis in adults and that symptomatic adrenal insufficiency may develop, particularly if dosing is variable and intermittent. These cases illustrate that clinical symptoms may alert the physician to the possibility of adrenal suppression which can then be confirmed using basal and/or stimulated tests of HPA function in selected patients. Further investigation to determine the prevalence of these effects in adult patients is warranted.

J R Greenfield, K Samaras
Department of Endocrinology, St Vincent's Hospital, and Garvan Institute of Medical Research, Sydney, Australia

Correspondence to: A/Prof K Samaras, Diabetes and Obesity Research Program, Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst 2010, Australia; K.samaras@garvan.org.au

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BTNL2 gene variant and sarcoidosis

Sarcoidosis is an inflammatory granulomatous disorder that primarily affects the lungs and lymph nodes. Other organs such as the brain, eyes, heart, and skin can also be affected. The disease is characterised by non-caseating granulomas and an exaggerated cellular immune response caused by increased inflammatory activity.[1] The course of the disease is acute and mild in approximately 20% of all patients. In most patients a chronic stage develops which can lead to lung fibrosis. Although the exact pathogenesis of sarcoidosis remains unclear, familial clustering of the disease and the increased risk of relatives to develop sarcoidosis suggest that there might be a genetic predisposition to develop the disease.[2]

A significant association was recently reported in Germany between sarcoidosis and a frequent single nucleotide polymorphism (SNP) in the *BTNL2* gene, rs2076530.[3] *BTNL2* is a member of the immunoglobulin gene family and is related to *CD80* and *CD86* co-stimulatory receptors, although its exact function is unknown.[4] *BTNL2* is located on chromosome 6p21.3 in close proximity to the *HLA* gene cluster. rs2076530 is located at position 1 of the donor splice site in intron 5 and the associated A allele causes the usage of an alternative donor site leading to a 4 bp deletion at the mRNA level, frameshift, and premature truncation at the protein level.[3] The rs2076530 SNP alone was also associated with sarcoidosis in a case-control study of white American subjects.[4] No replication of the *BTNL2* rs2076530 susceptibility to sarcoidosis has yet been studied in an independent German case-control study. We therefore performed a case-control association study in 210 patients with sarcoidosis and 202 controls. Written informed consent was given by each participant and the study was approved by the ethics committee of Bonn University School of Medicine.

The diagnosis of sarcoidosis was based on evidence of non-caseating epitheloid cell granuloma in biopsy specimens and chest radiographic abnormalities. Different stages were defined as previously described.[5] A chronic course was defined as disease over at least 2 years or at least two episodes in a lifetime. Acute sarcoidosis was defined as one episode of acute sarcoidosis which had totally resolved at the date of the examination. None of the individuals in the control group (healthy white German subjects of mean age 38.32 (15.53) years) had a history of lung disease or showed any symptoms of lung or other disease by chest radiography or laboratory blood tests. Genotyping of rs207653 was performed using the Taqman technique with a commercially available assay (Applied Biosystems, Germany). SPSS Version 12 was used for statistical analysis. The genotype distributions in the cohort were in accordance with the Hardy-Weinberg equilibrium.

The A allele frequency of rs2076530 was significantly increased in sarcoidosis patients compared with controls (A = 0.6929, G = 0.3071 in cases; A = 0.6188, G = 0.3812 in controls). It was significantly associated with an increased risk of sarcoidosis in co-dominant and dominant models (OR 2.31 (95% CI 1.27 to 4.23); $p<0.006$, table 1), but not in a recessive model ($p = 0.276$). The calculated population attributable risk (PAR) for AA homozygotes and AG heterozygotes was 34.6%. Our results were in accordance with the reported association between *BTNL2* and sarcoidosis and replicated the finding that A allele carriers of rs2076530 have a more than twofold increased risk of developing sarcoidosis compared with GG homozygotes in the German population.

We also examined whether this increased risk is present in both chronic and acute forms of sarcoidosis. Interestingly, we found that the chronic form—but not the acute form—was significantly associated with the A allele in co-dominant and dominant models (OR 2.87

Table 1 Statistical analysis of the case-control study

	Co-dominant				Dominant (AA/AG *v* GG)				Recessive (AA *v* AG/GG)			
	AA	AG	GG	p value	AA/AG	GG	OR (95% CI)	p value	AA	GG/AG	OR (95% CI)	p value
Controls	84 (41%)	82 (41%)	36 (18%)		166	36			84	116		
Cases	99 (47%)	93 (44%)	18 (9%)	**0.021**	192	18	**2.31 (1.27 to 4.23)**	**0.006**	99	111	1.25 (0.85 to 1.85)	0.276
Acute	30 (42%)	32 (45%)	9 (13%)	0.576	62	9	1.49 (0.68 to 3.28)	0.358	30	41	0.99 (0.57 to 1.71)	0.97
Chronic	59 (52%)	47 (41%)	8 (7%)	**0.021**	106	8	**2.87 (1.29 to 6.42)**	**0.007**	59	55	0.67 (0.43 to 1.07)	0.095

Significant associations are shown in bold.

(95% CI 1.29 to 6.42), p<0.0069; table 1) with a PAR for AA homozygotes and AG heterozygotes of 50%.

This study underlines the importance of the association of *BTNL2* rs2076530 variant with the susceptibility to develop sarcoidosis in a German population. Furthermore, our data suggest that susceptibility is preferentially towards the chronic form of the disease.

Y Li, B Wollnik
Center for Molecular Medicine Cologne (CMMC) and Institute of Human Genetics, University of Cologne, Germany

S Pabst, M Lennarz
Medizinische Universitäts-Poliklinik, Rheinische-Friedrich-Wilhelms Universität Bonn, Germany

E Rohmann
Center for Molecular Medicine Cologne (CMMC) and Institute of Human Genetics, University of Cologne, Germany

A Gillissen
Städtisches Klinikum St Georg, Leipzig, Germany

H Vetter, C Grohé
Medizinische Universitäts-Poliklinik, Rheinische-Friedrich-Wilhelms Universität Bonn, Germany

Correspondence to: Professor Dr med C Grohé, Medizinische Universitäts-Poliklinik, Wilhelmstr, 35-37, D-53111 Bonn, Germany; c.grohe@uni-bonn.de

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Asthma and allergies in Germany

We read the study by Zöllner and colleagues published recently in *Thorax* about the levelling off of asthma and allergies among children in Germany between 1992 and 2001.[1] We have published a study looking at the same issue and using a similar protocol (ISAAC)[2] to assess the symptoms, diagnosis, and severity of asthma and allergies in more than 15 000 children aged 6–7 and 13–14 years between 1995 and 2000 in Münster, Germany.[3] We found a tendency towards an increase in current symptoms of asthma and allergies in both age groups, but more so among girls.[3]

Indices of diagnosis either remained the same or increased in parallel with the increase in symptoms, arguing against a change in diagnostic behaviour as an explanation for our results. Indices of severity also showed a homogenous increase in the 5 year study period, pointing towards an increase in the overall burden of asthma and allergies within the society.[3]

Regrettably, these results, coming from Germany, were not considered in either the discussion of Zöllner's report or in the affirmative title that no increase in asthma and allergies occurred in Germany in the 1990s. Even more regrettable is the fact that when our study was alluded to in the discussion and conclusion of the paper by Zöllner *et al*, it was cited—contrary to our results—as one of the studies showing a decrease or levelling off of asthma and allergies among children.[1]

W Maziak, U Keil
Institute of Epidemiology and Social Medicine, University Clinic of Muenster, Muenster, Germany; maziak@net.sy

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Authors' reply

Unfortunately, the paper by Maziak *et al*[1] published in *Allergy* was listed as reference number 18 instead of number 21 in the reference list of our paper.[2] We apologise for any misunderstanding which may have arisen from this error. A correction is published below.

In the paper by Maziak *et al*[1] the prevalences in 1994/5 and 1999/2000 are compared. As we know from our own studies, trend analyses based on (only) two time points may be difficult and should be interpreted with caution. Indeed, in their investigation Maziak *et al* did not find a significant increase in the lifetime prevalence of asthma and hay fever, except in one subgroup. The effect found in 13–14 year old girls could also be due to a former underdiagnosis of asthma in girls, as discussed in their paper.

Since our results are based on six cross sectional surveys, we consider the title and the conclusion—that we did not see an increase in asthma and allergies from 1992 to 2001—to be appropriate.

I Zöllner
Department of Epidemiology and Health Reporting, Baden-Wuerttemberg State Health Office, Wiederholdstr 15, D-70174 Stuttgart, Germany; Iris.Zoellner@rps.bwl.de

Reference

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CORRECTIONS

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In the paper entitled ''No increase in the prevalence of asthma, allergies, and atopic sensitisation among children in Germany: 1992–2001'' by I K Zöllner *et al* which appeared in the July 2005 issue of *Thorax* (2005;**60**:545–8), the authors apologise for a mistake which occurred in the reference list. Reference number 18 should be number 21 and references 19–21 should be listed as 18–20.

doi: 10.1136/thx.2005.040444corr1

The paper entitled ''Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis'' by G J Rodrigo and J A Castro-Rodriguez (10.1136/thx.2005.040444) has been published previously on 17 June 2005 as a *Thorax* Online First article but under the incorrect DOI (10.1136/thx.2005.047803). The publishers apologise for this error. The definitive version of the article can be found at the following citation: *Thorax* 2005;**60**:740–6.

doi: 10.1136/thx.2005.040881corr1

In the paper entitled ''Hormone replacement therapy, body mass index and asthma in perimenopausal women: a cross sectional survey'' by F Gómez Real *et al* published in the January 2006 issue of *Thorax* (2006;**61**:34–40), the fourth author should be **K A Franklin**, not K Franklin.