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# Cortisol and the metabolic syndrome in South Asians

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## Summary

**OBJECTIVE—**The cardiovascular risk factors which comprise the metabolic syndrome are associated with increased hypothalamic–pituitary–adrenal axis (HPAA) activity in some Caucasian populations. South Asians have high rates of cardiovascular disease and its risk factors. We have investigated the relationships between HPAA activity, adiposity and the metabolic syndrome in a South Asian population.

**DESIGN—**Cross-sectional cohort study.

**PARTICIPANTS—**A total of 509 men and women born at the Holdsworth Memorial Hospital, Mysore, South India between 1934 and 1954 and still living in the area.

**MEASUREMENTS—**Fasting 09·00 h cortisol and corticosteroid-binding globulin. The cohort had previously been investigated for features of the metabolic syndrome.

**RESULTS—**At 09·00 h, cortisol concentration was strongly associated with systolic and diastolic blood pressure ($r = 0{\cdot}25$ and $r = 0{\cdot}24$, respectively; $P < 0{\cdot}001$), fasting glucose concentration ($r = 0{\cdot}26$; $P < 0{\cdot}001$), insulin resistance ($r = 0{\cdot}20$; $P < 0{\cdot}001$) and fasting triglyceride concentration ($r = 0{\cdot}17$; $P < 0{\cdot}001$). In general, higher cortisol concentrations added to the effect of adiposity in increasing cardiovascular risk factors, but there was evidence of an interaction between cortisol and adiposity in determining fasting glucose concentration ($P = 0{\cdot}045$) and insulin resistance ($P = 0{\cdot}006$).

**CONCLUSIONS—**Associations between 09·00 h cortisol concentration and cardiovascular risk factors in this South Asian cohort were stronger than those previously shown in Caucasian populations, despite similar mean cortisol concentrations, and were amplified by adiposity. This suggests that increased glucocorticoid action may contribute to ethnic differences in the prevalence of the metabolic syndrome, particularly among men and women with a higher body mass index.

The metabolic syndrome, a cluster of abnormalities including glucose intolerance, hypertension and dyslipidaemia (Reaven, 1988), has many similarities with Cushing's syndrome which has led to the suggestion that a milder degree of hypothalamic–pituitary–adrenal (HPA) axis dysregulation may underlie this phenotype. This is supported by cross-sectional studies which show that individuals with raised blood pressure, glucose intolerance or other features of the metabolic syndrome have raised fasting plasma cortisol



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concentrations and increased reactivity of the HPA axis (Filipovsky *et al.*, 1996; Phillips *et al.*, 1998; Lee *et al.*, 1999).

The interplay between obesity and the HPA axis is complex. Tissue steroid metabolism, principally reactivation of cortisol by 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in the liver, is altered in obese individuals leading to increased metabolic clearance of cortisol (Andrew *et al.*, 1998; Stewart *et al.*, 1999; Rask *et al.*, 2001, 2002). As a result, although cortisol secretion is enhanced somewhat, circulating cortisol concentrations are generally normal or low in obese subjects. However, some studies suggest that a subset of individuals who maintain raised plasma cortisol concentrations in the face of obesity have a high prevalence of the metabolic syndrome. In these subjects, increased plasma cortisol concentrations or HPA reactivity add to the effect of adiposity in determining the risk of glucose intolerance, raised blood pressure and the metabolic syndrome (Phillips *et al.*, 2000; Walker *et al.*, 2000; Reynolds *et al.*, 2001).

South Asians have a high morbidity and mortality from coronary heart disease and the cardiovascular risk factors which comprise the metabolic syndrome are prevalent. Although South Asians have a relatively high proportion of fat, particularly visceral fat, across the body mass index (BMI) range compared with Caucasian populations, the increase in adiposity does not fully explain the high prevalence of the metabolic syndrome (McKeigue *et al.*, 1991; Shelgikar *et al.*, 1991; Banerji *et al.*, 1999). A greater understanding of the mechanisms underlying this increased cardiovascular risk may allow new therapies to be developed. The role of glucocorticoids has not previously been investigated in this ethnic group.

We have investigated the relationship between fasting 09·00 h cortisol concentration and cardiovascular risk factors in 509 adults from Mysore, South India to investigate the hypothesis that the high prevalence of the metabolic syndrome in South Asians is mediated by HPA axis hyperactivity.

## Subjects and methods

### Participants and data collection

In 1993, 517 adults born between 1934 and 1954 at the Holdsworth Memorial Hospital, Mysore, South India and still living in Mysore were traced and attended a clinic as part of a study assessing the influence of size at birth on cardiovascular risk factors (Stein *et al.*, 1996; Fall *et al.*, 1998). Detailed information on the subjects' medical and social history was collected and they had standardized anthropometric measurements, including skinfold thickness at four sites, and blood pressure and electrocardiogram (ECG) recordings. Blood samples, taken between 08·00 and 09·30 h after a 12-h fast, were previously analysed for lipids and paired glucose, and insulin concentrations were available from 0, 30 and 120 min during a standard 75 g oral glucose tolerance test.

For the current study, stored fasting sera from 509 of these subjects were analysed for cortisol and corticosteroid-binding globulin (CBG) in the Regional Endocrine Laboratory at Southampton General Hospital. Subjects without a stored sample ($n = 2$) and subjects on oral glucocorticoid therapy ($n = 6$) were excluded. The study was approved by the local ethics committee and the subjects gave informed consent at the time of the original study.

### Laboratory assays

Cortisol was measured using an in-house radioimmunoassay (RIA), interassay coefficient of variation (CV) 7·4–10·3%. CBG was assayed with a commercial assay (Medgenix Diagnostics, Fleurus, Belgium), intra-assay CV 3·3–7·7%, interassay CV 4·5–5·0%. Plasma

glucose, insulin, total cholesterol, high-density lipoprotein (HDL)-cholesterol and triglyceride were measured as described previously (Stein *et al.*, 1996; Fall *et al.*, 1998).

### Data analysis

Generalized obesity was defined as a BMI greater than 25 kg/m$^2$ and central obesity as a waist–hip ratio (WHR) of 0·9 in men and 0·85 in women. These cut-offs have previously been defined for urban Indian populations (Ramachandran *et al.*, 2001). Total body fat (%) was calculated from the skinfolds according to the equations of Durnin & Womersley (1974). Free cortisol index represents a ratio of cortisol to CBG. Insulin resistance and insulin secretion were estimated using the homeostasis model assessment (HOMA; Matthews *et al.*, 1985). Glucose, insulin and triglyceride concentrations and HOMA variables had skewed distributions and were transformed to normality using logarithms. The metabolic syndrome was identified in those subjects with a systolic blood pressure ≥ 150 mmHg, a 2-h glucose ≥ 7·8 mmol/l and a triglyceride concentration above the median value (≥ 1·8 mmol/l in men or ≥ 1·4 mmol/l in women; Fall *et al.*, 1998).

The relationships between cortisol, CBG and free cortisol index and the components of the metabolic syndrome were examined using partial correlation coefficients and multiple linear and logistic regression, correcting for age, sex, adiposity and adult lifestyle factors (smoking and alcohol intake). Outcomes and predictors were used as continuous variables where possible. Statistical analyses were performed using SPSS statistical software version 10·0 (Chicago, IL, USA). A *P*-value of less than 0·05 was considered to be statistically significant.

## Results

The characteristics of the cohort have previously been described in detail and are summarized in Table 1 (Stein *et al.*, 1996). In this relatively young population (mean age 47 years) the prevalence of obesity was high; 29·5% of men and 48·6% of women had a BMI greater than 25 kg/m$^2$, a cut-off that has been used in previous studies in urban Indian populations. Both men and women had high waist-to-hip ratios (WHR above 0·9 in 66·3% of men and above 0·85 in 45·4% of women). Overall, 14·5% of the subjects had type 2 diabetes (mean BMI 25·3 kg/m$^2$) and 8·6% were identified as having the metabolic syndrome (mean BMI 26·1 kg/m$^2$). It is noteworthy that only 43 of the 509 subjects (8·4%) had a BMI > 30 kg/m$^2$, the WHO definition of obesity, despite the high prevalence of type 2 diabetes.

Fasting 09·00 h cortisol concentration ranged from 76 to 780 nmol/l (mean 311, SD 111), CBG ranged from 0·25 to 1·90 μmol/l (mean 0·69, SD 0·18) and free cortisol index ranged from 0·11 to 1·77 (mean 0·48, SD 0·20). Fasting cortisol concentration and free cortisol index were inversely related to BMI [cortisol fell by 2·5 (95% CI 0·4-4·6) nmol/l per unit rise in BMI; $P = 0·02$], but there were no significant relationships with WHR, subscapular-to-triceps skinfold ratio, total body fat (%) or age. Mean cortisol concentration and free cortisol index were higher in those subjects who smoked (cortisol concentration 329 *vs.* 305 nmol/l, $P = 0·04$) and consumed alcohol (cortisol concentration 363 *vs.* 304 nmol/l, $P < 0·001$), but there were no gender differences and no associations with social class as measured by the Kuppuswamy (1962) score, a standardized questionnaire method for Urban Indian populations.

There were strong associations between fasting cortisol concentration and cardiovascular risk factors. The partial correlation coefficients (corrected for age, sex and BMI) were significant for systolic blood pressure ($r = 0·25$, $P < 0·001$), diastolic blood pressure ($r = 0·24$, $P < 0·001$), fasting glucose ($r = 0·26$, $P < 0·001$), insulin resistance ($r = 0·20$, $P <$

0·001) and fasting triglyceride ($r = 0·17$, $P < 0·001$). There was a similar, though weaker, trend for fasting insulin concentration ($r = 0·12$, $P = 0·08$). High cortisol concentrations were also associated with reduced insulin secretion ($r = −0·14$, $P = 0·03$). These associpations were seen in both sexes but were generally stronger in women (data not shown) and were also observed with the free cortisol index. Table 2 shows the mean value of each risk factor in fasting cortisol quintiles. The prevalence of type 2 diabetes and the metabolic syndrome was increased in those subjects with the highest 09·00 h cortisol concentration (Table 3).

We found that the associations between fasting cortisol concentration and cardiovascular risk factors were particularly evident in men and women with higher BMI (Fig. 1). In multiple regression analyses, the effects of cortisol and BMI on systolic blood pressure and triglycerides were additive. A standard deviation increase in cortisol raised systolic blood pressure by 4·4 mmHg ($P < 0·001$), while the effect of a standard deviation increase in BMI was 3·9 mmHg ($P < 0·001$). However, a significant interaction between fasting cortisol concentration and adiposity (whether assessed by BMI or percentage total body fat) was observed for fasting plasma glucose ($P = 0·057$ and $P = 0·045$, respectively) and insulin resistance ($P = 0·045$ and $P = 0·006$, respectively). Thus, for example, the correlation between fasting cortisol and insulin resistance increased across BMI tertiles: BMI < 21·8 $r = 0·07$ ($P = 0·4$), BMI 21·8–25·5 $r = 0·22$ ($P = 0·004$) and BMI > 25·5 $r = 0·25$ ($P = 0·001$).

## Discussion

This study has demonstrated that fasting 09·00 h cortisol concentration is strongly associated with cardiovascular risk factors in a South Asian population and that this relationship is amplified by adiposity. As has previously been shown in Asian cohorts, the prevalence of diabetes and the metabolic syndrome is high despite relatively small numbers of people who are obese in standard terms. The cross-sectional design of the study does not allow determination of whether higher cortisol concentration is the forerunner of hypertension, impaired glucose tolerance and dyslipidaemia in these individuals, but the large numbers in the study ensure that the relationship is likely to be robust. Furthermore, as a single cortisol measurement is a crude index of HPA activity, it is likely that we have underestimated the strength of the relationship between HPA activity and disease.

The mean fasting cortisol concentration in this population is similar to, although somewhat lower than, values reported in the UK (Phillips *et al.*, 1998). Likewise, the levels of CBG accord with previously published data (Heyns & Coolens, 1988). Seventeen people had fasting 09·00 h cortisol concentrations above 550 nmol/l (the upper limit of normal in Caucasian populations). Although the cause of these high cortisol concentrations is uncertain, it is likely that the combination of fasting and the novel clinical setting in which our blood samples were obtained will have acted as a significant stressor for some individuals in this population. Omitting these individuals from the analysis did not alter the relationships described, although the interaction between cortisol concentration and BMI was no longer significant.

The inverse association between 09·00 h cortisol concentration and BMI is well documented in Caucasian population studies and is thought to reflect impaired reactivation of cortisol in the liver by 11β-HSD1, together with a possible increase in peripheral metabolism by A-ring reductastes in obese individuals (Andrew *et al.*, 1998; Stewart *et al.*, 1999; Rask *et al.*, 2001, 2002). Despite increased secretion of cortisol by the HPA axis (reflected in enhanced total cortisol metabolite excretion) circulating concentrations often remain low. Future studies in this population should include urine collection to assess tissue steroid metabolism.

The associations between fasting 09·00 h cortisol concentration and risk factors for cardiovascular disease are strong and to our knowledge have not been documented previously in an South Asian population. We found similar relationships in our cohort from Hertfordshire, UK (Phillips *et al.*, 1998), but in Mysore they are even more striking and provide convincing cross-sectional evidence that glucocorticoids may be involved in the development of the metabolic syndrome. As 09·00 h cortisol concentrations were not high on average compared with Western populations, our hypothesis that hyperactivity of the HPA axis may be a determinant of cardiovascular risk in this ethnic group is not supported by the data. However, the strength of the association between circulating cortisol concentration and the metabolic variables suggests that this population may be particularly sensitive to the effects of glucocorticoids, which may in turn explain the ethnic differences in prevalence of the metabolic syndrome. Interestingly, higher concentrations of cortisol were also associated with reduced insulin secretion, which is consistent with *in vivo* and *in vitro* experiments showing that glucocorticoids regulate insulin secretion (Delaunay *et al.*, 1997).

Adiposity generally added to the effect of raised 09·00 h cortisol concentration, increasing cardiovascular risk factors, and there was evidence of an interaction between cortisol and adiposity in determining fasting glucose concentration and insulin resistance. The correlation between cortisol and insulin resistance, for example, was strongest in those subjects with the highest BMI or body fat content. This accords with observations that the correlation between cortisol and systolic blood pressure is most marked in obese subjects (Phillips *et al.*, 2000). Although the mechanism of this interaction is unclear, a recent study suggests that glucocorticoid action may be increased in skeletal muscle, an important insulin target tissue, in obese individuals (Whorwood *et al.*, 2002). The interaction could therefore be explained if elevated concentrations of cortisol together with increased tissue sensitivity to glucocorticoids resulted in a marked increase in glucocorticoid hormone action and a high prevalence of the metabolic syndrome.

Individual differences in HPA activity are only partly genetically determined (Kirschbaum *et al.*, 1992). We have previously suggested that intrauterine programming of the HPA axis could provide an alternative explanation for such differences (Phillips *et al.*, 1998). There was no association between fasting cortisol concentration and birthweight or other birth measurements in this cohort (Ward *et al.*, 2001), but some animal models provide evidence for programming of the HPA axis, for example as a result of prenatal immune challenge, without any effect on birthweight (Reul *et al.*, 1994). The Dutch famine of 1944–45 serves as a human model of maternal undernutrition during pregnancy. In this cohort, individuals exposed to famine in mid or late gestation had impaired glucose tolerance as adults, but the effect of famine was greater than that attributable to the reduction in birthweight in these individuals (9% *vs.* 2%; Ravelli *et al.*, 1998).

In summary, this study has revealed strong relationships between HPA activity, as indicated by a fasting 09·00 h cortisol concentration, and the components of the metabolic syndrome in a South Asian population and has demonstrated that adiposity may amplify these effects. Longitudinal studies are needed to confirm that those individuals with higher circulating cortisol concentrations or increased stress responsiveness in young adulthood go on to develop the metabolic syndrome. Further research into the mechanisms behind these observations may lead to new therapeutic approaches to reduce the prevalence of diabetes and the metabolic syndrome in this population, but controlling obesity is likely to be particularly important.

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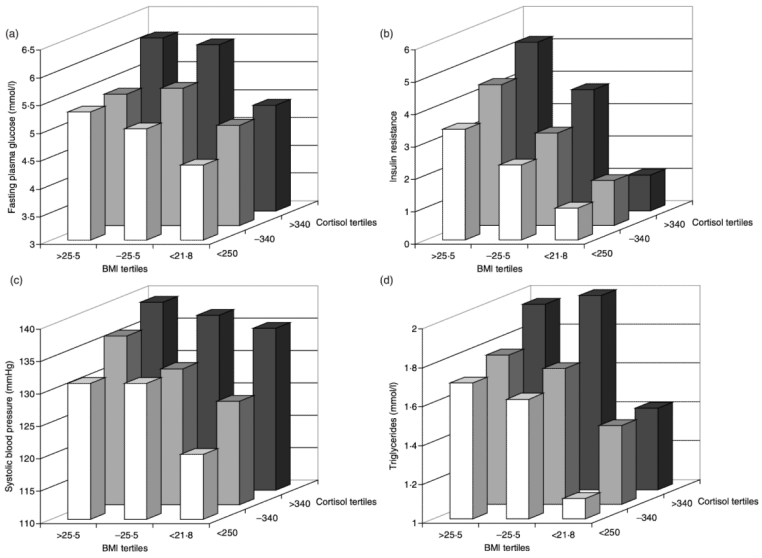


**Fig. 1.**

Histograms showing the combined effects of fasting 09·00 h cortisol concentration (nmol/l) and BMI (kg/m$^2$) on (a) fasting plasma glucose (mmol/l), (b) insulin resistance (HOMA), (c) systolic blood pressure (mmHg) and (d) fasting triglyceride concentration (mmol/l) in 509 adults from Mysore, India.





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**Table 1**

Baseline characteristics, fasting 09·00 h cortisol and CBG concentrations and free cortisol index in 509 adults from Mysore, India

| | Men *n* = 258 | Women *n* = 251 | All *n* = 509 |
|---|---|---|---|
| Age (years) | 47·0 (4·7) | 47·0 (4·7) | 47·0 (4·7) |
| BMI (kg/m$^2$) | 22·9 (4·1) | 24·8 (4·9) | 23·8 (4·6) |
| WHR | 0·91 (0·06) | 0·83 (0·06) | 0·87 (0·07) |
| Total body fat (%) | 23·1 (6·7) | 35·7 (5·6) | 29·2 (8·8) |
| Generalized obesity (*n*,%) * | 76 (29·5) | 12 (48·6) | 198 (38·9) |
| Central obesity (n,%) * | 171 (66·3) | 114 (45·4) | 285 (56·0) |
| Systolic BP (mmHg) | 131 (17) | 132 (18) | 132 (18) |
| Diastolic BP (mmHg) | 80 (11) | 77 (11) | 79 (11) |
| FPG (mmol/l) † | 5·2 (1·3) | 5·3 (1·3) | 5·2 (1·3) |
| 2 h Glucose (mmol/l) † | 6·5 (1·4) | 6·9 (1·4) | 6·7 (1·4) |
| Insulin resistance ‡, † | 2·28 (2·79) | 2·57 (2·52) | 2·42 (2·66) |
| Insulin secretion ‡, † | 142 (2·52) | 133 (2·26) | 137 (2·39) |
| Triglyceride (mmol/l) † | 1·8 (1·7) | 1·5 (1·7) | 1·6 (1·7) |
| HDL cholesterol (mmol/l) | 0·92 (0·22) | 1·01 (0·24) | 0·96 (0·23) |
| Total cholesterol (mmol/l) | 5·0 (1·0) | 4·9 (0·9) | 4·9 (1·0) |
| Type 2 diabetes (*n*,%) | 34 (13·2) | 40 (15·9) | 74 (14·5) |
| Metabolic syndrome (*n*,%) | 17 (6·6) | 27 (10·8) | 44 (8·6) |
| Ischaemic heart disease (*n*,%) | 24 (9·3) | 27 (10·8) | 51 (10·0) |
| Cortisol (nmol/l) | 312 (107) | 309 (115) | 311 (111) |
| CBG (umol/l) | 0·65 (0·16) | 0·73 (0·19) | 0·69 (0·18) |
| Free cortisol index | 0·50 (0·20) | 0·45 (0·19) | 0·48 (0·20) |

Data are mean (SD) unless otherwise indicated. BMI, body mass index; WHR, waist–hip ratio; BP, blood pressure; FPG, fasting plasma glucose.

* Generalized obesity: BMI > 25 kg/m$^2$, central obesity: WHR > 0·9 (men), > 0·85 (women) (Ramachandran *et al.*, 2001).

† Geometric mean (SD).

‡ Estimated using the homeostasis model assessment (HOMA; Matthews *et al.*, 1985).

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**Table 2**

Mean values of cardiovascular risk factors according to fasting 09·00 h cortisol concentration in 509 adults from Mysore, India

| Cortisol (mmol /l) | No. | Systolic BP (mmHg) | Diastolic BP (mmHg) | Fasting glucose (mmol/l) | Insulin resistance† | Insulin secretion† | Triglyceride (mmol/l) |
|---|---|---|---|---|---|---|---|
| < 215 | 100 | 126 | 76 | 4·9 | 2·1 | 152 | 1·4 |
| − 270 | 104 | 129 | 76 | 5·0 | 2·3 | 151 | 1·6 |
| − 320 | 100 | 132 | 77 | 5·3 | 2·6 | 151 | 1·7 |
| − 400 | 102 | 136 | 82 | 5·1 | 2·3 | 137 | 1·7 |
| > 400 | 103 | 136 | 82 | 5·8 | 2·8 | 103 | 1·8 |
| All | 509 | 132 | 79 | 5·2 | 2·4 | 137 | 1·6 |
| *P*-value* | | < 0·001 | < 0·001 | < 0·001 | < 0·001 | 0·001 | < 0·001 |

**P*-value for trend corrected for age, sex, BMI, smoking and alcohol status;

†estimated using the homeostasis model assessment (HOMA; Matthews *et al.*, 1985).

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## Table 3

Proportion of subjects (%) with type 2 diabetes and the metabolic syndrome in tertiles of fasting 09·00 h cortisol in 509 adults from Mysore, India

| Cortisol (nmol/ l) | No. | Type 2 diabetes (%) | Metabolic syndrome (%) |
|---|---|---|---|
| < 250 | 164 | 9·4 | 6·1 |
| −340 | 174 | 12·3 | 6·3 |
| > 340 | 171 | 22·5 | 13·5 |
| All | 509 | 14·5 | 8·6 |
| *P*-value for trend * | | < 0·001 | 0·001 |

* *P*-value corrected for age, sex, BMI.