Adrenocortical, Autonomic, and Inflammatory Causes of the Metabolic Syndrome
Nested Case-Control Study

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Background—The causes of metabolic syndrome (MS), which may be a precursor of coronary disease, are uncertain. We hypothesize that disturbances in neuroendocrine and cardiac autonomic activity (CAA) contribute to development of MS. We examine reversibility and the power of psychosocial and behavioral factors to explain the neuroendocrine adaptations that accompany MS.

Methods and Results—This was a double-blind case-control study of working men aged 45 to 63 years drawn from the Whitehall II cohort. MS cases (n=30) were compared with healthy controls (n=153). Cortisol secretion, sensitivity, and 24-hour cortisol metabolite and catecholamine output were measured over 2 days. CAA was obtained from power spectral analysis of heart rate variability (HRV) recordings. Twenty-four-hour cortisol metabolite and normetanephrine (3-methoxynorepinephrine) outputs were higher among cases than controls (+0.49, +0.45 SD, respectively). HRV and total power were lower among cases (both -0.72 SD). Serum interleukin-6, plasma C-reactive protein, and viscosity were higher among cases (+0.89, +0.51, and +0.72 SD). Lower HRV was associated with higher normetanephrine output (r=-0.19; P=0.03). Among former cases (MS 5 years previously, n=23), cortisol output, heart rate, and interleukin-6 were at the level of controls. Psychosocial factors accounted for 37% of the link between MS and normetanephrine output, and 7% to 19% for CAA. Health-related behaviors accounted for 5% to 18% of neuroendocrine differences.

Conclusions—Neuroendocrine stress axes are activated in MS. There is relative cardiac sympathetic predominance. The neuroendocrine changes may be reversible. This case-control study provides the first evidence that chronic stress may be a cause of MS. Confirmatory prospective studies are required. (Circulation. 2002;106:2659-2665.)

Key Words: norepinephrine ■ coronary disease ■ stress ■ metabolism ■ heart rate

There is a widespread and strong inverse association between socioeconomic position and risk of coronary heart disease (CHD).1 The Whitehall II study is investigating reasons for this phenomenon2,3 and has shown that there is a close relationship between lower social position and increased probability of having the metabolic syndrome and raised levels of associated inflammatory variables.3,4 There may be a psychosocial explanation for these findings.5-7 Consistent with such mechanisms, there have been reports of links between components of the metabolic syndrome and aspects of autonomic and neuroendocrine function.5-13 We therefore set out to test systematically the hypothesis that altered autonomic and neuroendocrine function is a feature of the metabolic syndrome in a population-based sample.

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We conducted a nested case-control study of the metabolic syndrome. Its aims are to examine (1) the strength of associations of prevalent metabolic syndrome caseness with measures of hypothalamic-pituitary-adrenocortical (HPA), sympa-tho-adrenal medullary and cardiac autonomic activity, inflammatory and hemostatic markers, and adrenal androgen output; (2) reversibility of the biologic changes associated with the syndrome; and (3) psychosocial and behavioral explanations for the neuroendocrine and other disturbances associated with metabolic syndrome caseness.
Catecholamine output

<table>
<thead>
<tr>
<th>HPA function</th>
<th>No. of Controls-Cases</th>
<th>Controls</th>
<th>Quintile Definition</th>
<th>Metabolic Syndrome Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary cortisol metabolites, mg/d^†</td>
<td>135:26</td>
<td>6.31 (5.2, 7.7)</td>
<td>8.90 (6.6, 12.0)</td>
<td>0.03 9.43 (7.0, 12.7)</td>
</tr>
<tr>
<td>Salivary cortisol 1630 h, nmol/L§</td>
<td>137:27</td>
<td>2.83 (2.5, 3.2)</td>
<td>3.00 (2.5, 3.6)</td>
<td>0.54 3.06 (2.6, 3.7)</td>
</tr>
<tr>
<td>Salivary cortisol 2200 h, nmol/L§</td>
<td>138:27</td>
<td>1.53 (1.3, 1.8)</td>
<td>1.60 (1.3, 2.0)</td>
<td>0.71 1.66 (1.3, 2.1)</td>
</tr>
<tr>
<td>Skin vasoconstrictor assay</td>
<td>149:29</td>
<td>11.9 (11.2, 12.6)</td>
<td>12.1 (11.1, 13.1)</td>
<td>0.74 12.4 (11.3, 13.5)</td>
</tr>
</tbody>
</table>

Cardiac autonomic activity

| Urinary normetanephrine, µg/d                  | 152:28                | 177 (151, 207)  | 233 (185, 293)     | 0.02 231 (182, 293)    | 0.04  |
| Urinary metanephrine, µg/d                    | 152:28                | 116 (96, 139)   | 123 (94, 161)      | 0.66 109 (83, 143)     | 0.44  |

Inflammatory and hemostatic factors

| Serum interleukin-6, pg/mL                     | 138:29                | 1.10 (0.9, 1.3) | 1.90 (1.5, 2.4)    | <0.001 1.93 (1.5, 2.5) | <0.001 |
| Plasma C-reactive protein, mg/L                | 148:29                | 1.49 (1.2, 1.9) | 2.37 (1.6, 3.4)    | 0.02 2.60 (1.8, 3.8)   | 0.007 |
| Plasma fibrinogen, g/L                         | 148:30                | 3.05 (2.9, 3.2)| 3.18 (3.0, 3.4)    | 0.25 3.14 (2.9, 3.4)   | 0.59  |
| Plasma D-dimer, ng/mL                          | 153:30                | 40.1 (33, 49)   | 40.2 (30, 53)      | 0.98 46.0 (35, 61)     | 0.22  |
| Plasma viscosity, mPa/s                        | 149:30                | 1.23 (1.2, 1.25)| 1.27 (1.25, 1.29)  | <0.001 1.28 (1.25, 1.30)| <0.001 |
| Plasma von Willebrand factor, IU/dL            | 153:30                | 11.3 (10, 13)   | 13.6 (12, 16)      | 0.02 13.3 (11, 15)     | 0.07  |
| Plasma fibrinogen, g/L (mean of 2 working days) | 153:30                | 103.3 (93, 114)| 97.0 (82, 112)     | 0.41 100.5 (85, 116)   | 0.67  |
| BMI, kg/m^2                                    | 142:29                | 26.2 (25, 27)   | 31.5 (30, 33)      | <0.001 32.2 (31, 34)   | <0.001 |

Values are age-adjusted means and 95% confidence intervals. Maximum sample size: 30 cases, 153 controls for quintile definition; 30 cases, 166 controls for ATPIII definition.

*Adverse quintile definition (see Methods).
†NCEP Adult Treatment Panel 3rd report definition.
‡Urinary cortisol metabolites = SUM(α- and β-tetrahydrocortisol, cortols, cortolones, 5β-tetrahydrocortisone).
§Mean of 2 working days.
| Total adrenal androgens = SUM(epiandrosterone, androsterone, etiocholanolone) |

### Methods

We conducted a case-control study nested within the Whitehall II cohort, with double-blind assessment of neuroendocrine variables, restricted to men for reasons of economy. CHD risk factor and cardiac measures were collected at phase 5 (third clinic examination, 1997 to 1998). Neuroendocrine measurements were collected at later workplace visits. The University College London research ethics committee approved the study protocol, and participants gave informed consent.

### Case Definition

Cases of metabolic syndrome were participants with 3 or more of the following 5 risk factors in the adverse quintile at phase 5: 2-hour glucose (>7.25 mmol/L [131 mg/dL]), systolic blood pressure (>136 mm Hg), fasting triglycerides (>1.90 mmol/L [168 mg/dL]), HDL cholesterol (<1.10 mmol/L [43.6 mg/dL]), and waist to hip ratio (>0.977). Diabetics and those on hypotensive medication were assigned to the top glucose and blood pressure quintiles, respectively. For comparison, a case-control analysis using the later-defined ATPIII definition of metabolic syndrome is shown (Table 1).

### Study Sample

Because of the low prevalence of the metabolic syndrome (~12%), the study was designed to have 3 controls per case. For 90% power to detect a mean case-control difference of 0.5 SD in outcome variables at a significance level of 0.05, the sample size required was 224. Men working in London civil service offices at phase 5 were selected from the cohort according to presence or absence of metabolic syndrome at phase 3 (second clinic examination, 1991 to 1993). A research nurse, blinded to case-control status, recruited participants at the phase 5 clinic. Participants were excluded if they...
had used inhaled or oral steroids within the past 3 months. Of the 283 men invited to participate, 63 refused, giving a response rate of 77.7% (n=220). To avoid dilution of case-control differences, participants who were metabolic syndrome cases at phase 3 but not at phase 5 (n=23) were defined as ex-cases and excluded from the control group. Caseness at phase 5 could not be defined for 14 participants because of incomplete data, yielding 30 cases and 153 controls. Of the 30 cases, 23 had had the metabolic syndrome at phase 3. This final sample gave a power of 62% to detect a 0.5 SD difference between cases and controls.

Urinary Catecholamines, Cortisol, and Androgens

A research nurse visited each participant 3 times at his workplace on consecutive days. At visit one, the participant was given a calibrated urine bottle (2500 mL) containing preservative (10 mL 150 g/L ascorbic acid) for timed 24-hour urine collection. At visit 2 (the next day), the nurse collected a 20 mL sample that was frozen (−80°C) on the same day. Urine was analyzed for cortisol and adrenal androgen metabolites using GC-MS and metanephrine and normetanephrine using radioimmunoaassay.

Salivary Cortisol and Skin Vasoconstrictor Sensitivity to Glucocorticoids

Participants collected saliva at 4.30 PM on 10 PM on 2 consecutive working days in a Salivette (Sarstedt). Participants recorded potential acute influences on cortisol level, such as difficult tasks or conversations or consumption of cigarettes or food in the hour before sampling. Salivary cortisol was measured by fluoroimmunoaassay using rabbit anti-cortisol antiserum.15 The intra-assay coefficient of variation was 8.8% at 0.3 nmol/L and 6.6% at 4.7 nmol/L. The skin vasoconstriction assay was carried out as a measure of glucocorticoid sensitivity.16

Biomedical Examination

Clinic examination included resting blood pressure, ECG, weight, height, and waist and hip circumference. Venous blood was taken in the fasting state or at least 5 hours after a light, fat-free breakfast before undergoing a 2-hour 75-g oral glucose tolerance test. Blood was anticoagulated with EDTA (viscosity) or citrate (hemostatic markers). Plain serum and plasma were stored at −80°C until analysis. Plasma viscosity was measured at 37°C in a Coulter capillary viscometer. Plasma fibrinogen (Clauss method), von Willebrand factor, fibrin D-dimer, and tissue plasminogen activator (t-PA) antigen were measured as previously described.17 Serum interleukin-6 (IL-6) was assayed using a high-sensitivity two-site ELISA kit. Plasma C-reactive protein (CRP) was determined using automated turbidimetry. Serum amyloid A (SAA) was measured by latex nephelometry. Serum cholesterol and triglycerides were measured by automated enzymic colorimetric methods. HDL cholesterol was measured using phosphotungstic acid precipitation. Glucose was measured in fluoride plasma by an electrochemical glucose oxidase method.

Heart Rate Variability

After 5 minutes of rest in a quiet room, a digitized recording (5 minutes) was made of supine beat-to-beat heart rate (R waves).18 Computerized QRS detection and ectopic beat identification were used. In comparison with cardiologist review, the algorithm had high sensitivity (92%) and specificity (95%) for the detection of supraventricular ectopic beats with normal QRS complexes. Time domain measures derived from these data were heart rate and heart rate variability (SD of RR intervals). Frequency domain measures (Blackman-Tukey method) included total power (0.04 to 0.4 Hz) and low-frequency (LF, 0.04 to 0.15Hz) and high-frequency (HF, 0.15 to 0.4Hz) power. HRV data are missing for 37 (17%) subjects.

Questionnaire

The phase 5 health questionnaire included questions on civil service employment grade, work characteristics (decision latitude, job demands, social support at work), estimated value of household assets (house, contents, car, savings [less debt]), dietary pattern (usual kind of bread and milk, frequency of eating fresh fruit and vegetables), physical activity (moderate activity quartile and vigorous activity category based on recall of past 4 weeks’ activities), smoking habit (current, past, or never smoker), and alcohol consumption (quantiles based on units consumed in previous week). The 3 job strain scale scores were obtained by summing item scores from the Karasek-Theorell questionnaire.

Statistical Methods

Table 1 presents the case-control analysis (see Case Definition above). ANOVA was used to test for case-control differences. Outcome variables with skewness ≥1 were log transformed. Means were adjusted for age by stratifying into 5-year age groups. Table 2 tests the reversibility of the case-control differences in outcome variables by comparing these differences, where statistically significant, for cases as in Table 1 and the group of ex-cases (see Study Sample above). Outcome variables have been standardized to have mean score of 0 and SD of 1, so that differences can be compared on the same scale. Tables 3 and 4 examine statistical explanations for the observed case-control differences using multiple linear regression. Prespecified variables or factors were added to the age-adjusted model, first singly and then in combination. The resulting percentage change (generally a reduction) in the case-control difference estimates how much the explanatory factors account for the observed difference. Participants with incomplete data were excluded from analyses. Table 3 analyzes the ability of psychosocial factors to explain the autonomic and other differences related to the metabolic syndrome, whereas Table 4 does the same with behavioral factors.

Multiple imputation (Norm software)19 of variables used to define caseness was used to assess potential selection bias attributable to the exclusion from analysis of 14 participants with incomplete data. There were trivial differences (<2%) between multiple-imputation results and those based on excluding the subjects with unknown caseness.

Results

Demographic characteristics of the 63 nonparticipants were compared with the 220 men who accepted (mean age, 51.8 years). Refusers were 1.6 years older and in lower employment grades (both P<0.05). The percentages married (participants 78%, refusers 83%) and with metabolic syndrome at phase 5 (participants 15%, refusers 17%) were similar.

The quintile and ATPIII definitions of metabolic syndrome produced an identical pattern of case-control differences (Table 1). Means for the two overlapping groups of controls were similar, and only data for the control group based on the quintile definition are shown. Urinary cortisol metabolite and normetanephrine outputs were higher in metabolic syndrome cases than in controls. Other measures of HPA function were similar. Resting heart rate was higher, and all HRV measures except LF/HF ratio were lower in cases than controls. Total urinary adrenal androgen output did not differ by caseness, but epiandrosterone tended to be lower among cases. Plasma tPA antigen, viscosity, IL-6, and CRP were higher in cases than controls, but D-dimer, fibrinogen, von Willebrand factor, and SAA were similar in the 2 groups. Cases were more obese than controls (mean body mass index [BMI] difference, 5.3 kg/m² on quintile definition, 6.0 kg/m² on ATPIII definition).

Employment grade was correlated (lower value indicating lower grade) with HRV and total power of HRV (both r=−0.20, P<0.02). Serum IL-6 was inversely correlated with HRV (r=−0.20, P<0.02).
Table 2 compares differences from controls in mean levels of outcome variables in 2 groups: phase 5 cases, as Table 1, and ex-cases, who had metabolic syndrome at phase 3 but not at phase 5. There was no evidence of regression to the mean among outcome variables in these two groups using a graphical method, and therefore variables not differing significantly by caseness were dropped from Table 2. Between phases 3 and 5, mean BMI increased 1.0 kg/m² in controls, among outcome variables in these two groups using a graphical method, and therefore variables not differing significantly by caseness were dropped from Table 2. Between phases 3 and 5, mean BMI increased 1.0 kg/m² in controls,

### TABLE 2. Phase 5 Metabolic Syndrome Cases and Ex-Cases: Standardized Differences From Controls in Neuroendocrine, Hemostatic, and Inflammatory Measures

<table>
<thead>
<tr>
<th>Neuroendocrine measures</th>
<th>No. of Controls:Ex-Cases:Cases</th>
<th>Ex-Cases</th>
<th>Phase 5 MS Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cortisol metabolites</td>
<td>135:21:26</td>
<td>0.07 (−0.39, 0.53)</td>
<td>0.49 (0.06, 0.93)*</td>
</tr>
<tr>
<td>Urinary normetanephrine</td>
<td>152:22:28</td>
<td>0.58 (0.14, 1.03)*</td>
<td>0.45 (0.04, 0.86)*</td>
</tr>
</tbody>
</table>

### Cardiac autonomic activity

| Heart rate | 127:21:25 | 0.31 (−0.14, 0.77) | 0.61 (0.18, 1.04)† |
| Heart rate variability (SDRR) | 127:21:25 | −0.64 (−1.08, −0.21)† | −0.72 (−1.15, −0.28)‡ |
| Total power | 127:21:25 | −0.66 (−1.10, −0.22)† | −0.72 (−1.13, −0.30)‡ |
| Low-frequency power | 127:21:25 | −0.59 (−1.02, −0.16)† | −0.71 (−1.12, −0.30)‡ |
| High-frequency power | 127:21:25 | −0.52 (−0.96, −0.08)* | −0.63 (−1.05, −0.22)† |

### Inflammatory and hemostatic factors

| Serum interleukin-6 | 138:21:29 | 0.42 (−0.01, 0.85)§ | 0.89 (0.51, 1.27)‡ |
| Plasma C-reactive protein | 148:22:29 | 0.29 (−0.14, 0.72) | 0.51 (0.12, 0.90)* |
| Plasma viscosity | 149:23:30 | 0.43 (0.01, 0.86)* | 0.72 (0.33, 1.10)‡ |
| Plasma tPA antigen | 150:23:30 | 0.44 (0.01, 0.88)* | 0.58 (0.18, 0.98)† |

Standardized age-adjusted differences (95% CI).
Ex-cases: Phase 3 (1991–1993) cases not classified as cases at phase 5 (1997–98); n=23.
Differences are proportions of 1 SD. All variables were standardized to mean = 0, SD = 1.
Difference from control group *P<0.05, †P<0.01, ‡P<0.001.
§Ex-case—phase 5 MS case difference P=0.08.

Table 3 compares differences from controls in mean levels of outcome variables in 2 groups: phase 5 cases, as Table 1, and ex-cases, who had metabolic syndrome at phase 3 but not at phase 5. There was no evidence of regression to the mean among outcome variables in these two groups using a graphical method, and therefore variables not differing significantly by caseness were dropped from Table 2. Between phases 3 and 5, mean BMI increased 1.0 kg/m² in controls,

### TABLE 3. Change Due to Adjustment for Psychosocial and Material Factors in Case-Control Differences in Neuroendocrine, Autonomic, Inflammatory, and Hemostatic Measures

<table>
<thead>
<tr>
<th>Neuroendocrine measures</th>
<th>n</th>
<th>Case-Control Difference*</th>
<th>Employment Grade</th>
<th>Assets</th>
<th>Job</th>
<th>Strain</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cortisol metabolites</td>
<td>154</td>
<td>0.328</td>
<td>2</td>
<td>27</td>
<td>−9</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Urinary normetanephrine</td>
<td>173</td>
<td>0.269</td>
<td>−20</td>
<td>−7</td>
<td>−9</td>
<td>−37</td>
<td></td>
</tr>
</tbody>
</table>

### Cardiac autonomic activity

| Heart rate | 146 | 9.12 | −4 | −7 | −3 | −13 |
| Heart rate variability (SDRR) | 146 | −11.48 | −1 | −14 | 3 | −14 |
| Total power | 146 | −0.723 | 2 | −9 | 3 | −7 |
| Low-frequency power | 146 | −0.756 | −3 | −14 | 2 | −19 |
| High-frequency power | 146 | −0.831 | −3 | −11 | 2 | −14 |

### Inflammatory and hemostatic factors

| Serum interleukin-6 | 160 | 0.540 | 3 | 1 | 2 | 10 |
| Plasma C-reactive protein | 170 | 0.436 | 13 | −1 | 3 | 15 |
| Plasma viscosity | 173 | 0.0371 | 7 | 8 | 1 | 16 |
| Plasma tPA antigen | 176 | 0.247 | 6 | −15 | −3 | −9 |

Negative percentages are the reductions (attenuations), and positive percentages are the increases in the age-adjusted case-control difference due to addition of the stated variable(s) to the regression model.
*Age-adjusted mean case-control difference. All outcome variables were log transformed, except heart rate, SDRR, and plasma viscosity (skew<1.0). For the log-transformed variables, the exponential of the case-control difference gives the ratio of the case to the control values. All: Model adjusts for employment grade, household assets, and 3 job strain variables.
1.9 kg/m² in cases, and 0.5 kg/m² in ex-cases (difference from controls, \(P<0.01, 0.27\), respectively). Standardized case-control differences (see Statistical Methods) allow meaningful comparisons across outcomes. Mean levels of all variables except urinary normetanephrine tended to be more favorable in ex-cases than cases. Total cortisol metabolites were 0.5 SD higher in cases than controls but less than 0.1 SD higher in ex-cases. The contrast for IL-6 approached significance.

Psychosocial and material factors partially attenuated the association of metabolic syndrome with catecholamine output and cardiac autonomic function (Table 3). Job strain had a modest explanatory effect for corticosteroid output. Except for t-PA antigen, psychosocial and material factors did not account for the case-control differences in hemostatic and inflammatory variables.

Among the health-related behaviors, smoking and diet had comparatively consistent explanatory effects for HRV and inflammatory variables but not for corticosteroid or normetanephrine output. Physical activity adjustment attenuated case-control differences in t-PA antigen and IL-6. Other attenuations were small. Alcohol intake was not an important determinant, except for corticosteroid output and heart rate. Adjustment for all health behaviors attenuated neuroendocrine differences modestly (change \(\approx -7\%\)), whereas heart rate and inflammatory marker differences were attenuated by approximately one fifth. Differences in BMI accounted statistically for one third to two thirds of the case-control differences in outcome variables, except urinary normetanephrine (\(-23\%\)). BMI is closely associated with waist to hip ratio \((r=0.7)\), one of the five variables used to define metabolic syndrome. Taken together, degree of obesity and health behaviors accounted for 44% to 94% of the case-control differences in the outcome variables, with the exception of urinary normetanephrine (\(-29\%\)).

**Discussion**

Metabolic syndrome was associated with raised 24-hour cortisol metabolite and normetanephrine output and even more strongly with cardiac autonomic activity. The study demonstrates that function of both major neuroendocrine axes is altered in an important precursor state of CHD. Differences in cortisol output and cardiac autonomic activity associated with metabolic syndrome were reduced in ex-cases, indicating that the changes are at least partially reversible. Psychosocial factors explained a substantial part of the increased normetanephrine output associated with metabolic syndrome. Adverse cardiac autonomic function related to the syndrome was attributable both to psychosocial factors and degree of obesity. The direction of causality cannot be inferred from case-control studies; however, the findings are consistent with our hypothesis that an adverse psychosocial environment contributes to development of metabolic syndrome.

The results add to prospective data from the full Whitehall II cohort\(^{20}\) and elsewhere\(^{21}\) that adverse psychosocial conditions in adulthood are associated with an increased risk of CHD. Thus, metabolic syndrome may be an intermediate on the pathway between long-term psychosocial stress and coronary disease.

<table>
<thead>
<tr>
<th>TABLE 4. Change Due to Adjustment for Health-Related Behaviors in Case-Control Differences in Neuroendocrine, Autonomic, Hemostatic, and Inflammatory Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors Used in Adjustment</strong></td>
</tr>
<tr>
<td><strong>(%) Change in Case-Control Difference</strong></td>
</tr>
<tr>
<td><em><strong>n</strong></em></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>Neuroendocrine measures</strong></td>
</tr>
<tr>
<td>Total cortisol metabolites</td>
</tr>
<tr>
<td>Urinary normetanephrine</td>
</tr>
<tr>
<td><strong>Cardiac autonomic activity</strong></td>
</tr>
<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>Heart rate variability (SDRR)</td>
</tr>
<tr>
<td>Total power</td>
</tr>
<tr>
<td>Low-frequency power</td>
</tr>
<tr>
<td>High-frequency power</td>
</tr>
<tr>
<td><strong>Inflammatory and hemostatic factors</strong></td>
</tr>
<tr>
<td>Serum interleukin-6</td>
</tr>
<tr>
<td>Plasma C-reactive protein</td>
</tr>
<tr>
<td>Plasma viscosity</td>
</tr>
<tr>
<td>Plasma tPA antigen</td>
</tr>
</tbody>
</table>

See footnotes to Table 3. HRB indicates health-related behavior. Sample sizes differ from Table 3 because of missing values in adjustment factors.
alterations, including higher cortisol output\textsuperscript{11} and serum IL-6 level.\textsuperscript{22} The observed associations may also reflect neuroendocrine origins of metabolic syndrome. Cushing’s syndrome is one model for such a mechanism.

Heart rate variability characterizes autonomic influences on the heart, including anxiety,\textsuperscript{23,24} and low HRV is a risk factor for CHD.\textsuperscript{25} Here, power spectral analysis reveals relative sympathetic predominance (lower total and LF power) and lower vagal tone (HF power) in metabolic syndrome cases, a relation shown previously in the ARIC study.\textsuperscript{9} We extend this observation with a case definition based on a glucose tolerance test as well as lipid levels and blood pressure.

The evidence that sympathoadrenal and autonomic activity mediate the link between psychosocial exposures and metabolic syndrome was more consistent than that for HPA activity. Compared with HRV and catecholamine metabolite output,\textsuperscript{26} salivary cortisol secretion exhibits greater biological variability (intraclass correlation of 0.3 over 2 days), and this may account for our null findings. Alternatively, higher corticosteroid excretion in the metabolic syndrome may not be accompanied by increased circulating cortisol concentrations if there is raised peripheral cortisol metabolism.\textsuperscript{12}

Our study found several inflammatory and hemostatic factors to be strongly related to the metabolic syndrome, among them IL-6\textsuperscript{22} and C-reactive protein. Markers of inflammation predict weight gain,\textsuperscript{27} diabetes,\textsuperscript{28} and CHD.\textsuperscript{29} Previous studies link a low-grade inflammatory response with psychological stress.\textsuperscript{30} In Whitehall II, raised plasma fibrinogen predicts CHD and is linked with low job control and low employment status.\textsuperscript{5} Here we show the IL-6 level is related to cardiac autonomic activity in healthy controls, as well as being raised among cases.

Individuals classified as cases on two occasions (phases 3 and 5) have, as predicted, a poorer neuroendocrine profile than the ex-cases (phase 3 only). This longitudinal component of the study provides evidence for reversibility of the neuroendocrine and inflammatory alterations linked with the metabolic syndrome. Both allostatic load and physiological interpretations fit with our results. Neuroendocrine changes may precede the physiological alterations,\textsuperscript{31} or HPA and autonomic activity may follow the improvement in the risk factors defining caseness. It may be that both of these mechanisms operate.

Psychosocial measures explained some 13% of case-control differences in HRV indices and 37% of those in normetanephrine, the 3-methoxy metabolite of norepinephrine. In view of the measurement problems associated with determining psychosocial exposure, these are important explanatory effects. BMI in contrast is a more reliable measure and is closely associated with waist to hip ratio and metabolic syndrome variables, but accounted for only 23% of additional normetanephrine output in cases. Normetanephrine output, reflecting total α- and β-adrenergic activity, may rise due to increase in drive from higher centers and the number of adrenergic neurons in adipose tissue. In comparison with the explanatory power of psychosocial factors, health-related behaviors together explained a similar proportion of the metabolic syndrome effect on cardiac autonomic activity and much less of the effect on catecholamine output.

In conclusion, we provide evidence of alterations in function of both major neuroendocrine stress pathways in the metabolic syndrome. Our observation of a simultaneous and strong relation with cardiac autonomic activity invites investigation in the full Whitehall II cohort. Psychosocial factors seem to be putative causal exposures, although the evidence is weaker for the HPA axis than autonomic function. Inflammatory responses, but not adrenal androgen metabolism, seem to be implicated in this relatively early phase of coronary risk development. Additional tests of this hypothesis require studies involving women as well as men and prospective, population-based evidence for the association between psychosocial stress and the metabolic syndrome.

**Acknowledgments**

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