

## Cortisol Responses to Mental Stress and Incident Hypertension in Healthy Men and Women

Mark Hamer and Andrew Steptoe

Department of Epidemiology and Public Health, University College London, London WC1E 6BT, United Kingdom

**Context:** Heightened cardiovascular responses to mental stressors are associated with future risk of hypertension. The role of cortisol, a key stress hormone produced by the hypothalamic-pituitary-adrenal axis, remains unclear.

**Objective:** Our objective was to examine the association between cortisol responses to laboratory-induced mental stress and incident hypertension.

**Design and Setting:** This was a prospective substudy of the Whitehall II cohort with 3 years follow-up of an occupational cohort.

**Participants:** Participants included 479 initially healthy men and women (mean age,  $62.7 \pm 5.6$  yr), without history or objective signs of cardiovascular disease or hypertension at study entry.

**Intervention:** At the baseline assessment, salivary cortisol was measured in response to mental stressors, consisting of a 5-min Stroop task and a 5-min mirror tracing task.

**Main Outcome Measures:** Blood pressure was measured at study entry and at 3 yr follow-up for the determination of hypertension.

**Results:** There was considerable variation in the cortisol stress response, with approximately 40% of the sample responding to the stress tasks with an increase in cortisol of at least 1 mmol/liter. Over the 3 yr follow-up, 15.9% of the sample developed hypertension. There was an association between cortisol stress reactivity (per SD) and incident hypertension (odds ratio = 1.59; 95% confidence interval = 1.17–2.17) after adjustments for age, sex, resting cortisol, blood pressure at study entry, employment grade, smoking, body mass index, glycated hemoglobin, use of statins, and blood lipids.

**Conclusion:** These data support the notion that cortisol reactivity, an index of hypothalamic-pituitary-adrenal function, is one of the possible mechanisms through which psychosocial stress may influence the risk of hypertension. (*J Clin Endocrinol Metab* 97: E29–E34, 2012)

The accumulating evidence that stress-related factors contribute to the development of cardiovascular disease (CVD) has stimulated research into the underlying pathways involved (1). Psychophysiological stress testing can be used to better understand the mechanisms underlying the association between mental stress and CVD (2). Existing work has shown associations between heightened cardiovascular reactivity to stress and risk of incident hy-

pertension and other risk factors such as markers of subclinical atherosclerosis (3). The importance of stress reactivity in other biological pathways relevant to CVD risk has gained less attention.

Abnormalities in hypothalamic-pituitary-adrenal (HPA) function have been described in several chronic inflammatory disorders and may be a possible mechanism through which psychosocial stress influences the risk of hyperten-

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Abbreviations: BMI, Body mass index; CI, confidence interval; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HPA, hypothalamic-pituitary-adrenal; OR, odds ratio.

sion (4, 5). Indeed, experimental infusion of cortisol in normotensive men has been shown to result in an increase in blood pressure (6, 7). Nevertheless, epidemiological evidence for an association between cortisol and hypertension is less clear (8–13). The epidemiological studies to date have relied on single cortisol samples usually taken in the morning. Given that cortisol has a strong diurnal pattern, this might explain the equivocal nature of this area, and single measures of cortisol might not be appropriate to capture the dynamic nature of HPA activity. In this regard, psychophysiological testing is advantageous because extrinsic factors can be tightly controlled. Participants at risk of hypertension have demonstrated heightened HPA activity in response to acute stressors (14, 15). Also, blunted cortisol response to awakening and lower negative feedback sensitivity has been shown in participants with hypertension (16). However, because these studies have been cross-sectional, it is difficult to interpret whether HPA dysfunction is the cause or consequence of hypertension. The aim of this study was therefore to examine the association between cortisol responses to laboratory-induced mental stress and incident hypertension in initially normotensive men and women.

## Subjects and Methods

### Participants

A sample of participants was drawn from the Whitehall II epidemiological cohort (17) for psychophysiological testing during 2006–2008 (baseline) and were followed up 3 yr later for further clinical assessments. The criteria for entry into the study included no history or objective signs of CVD and no previous diagnosis or treatment for hypertension, inflammatory diseases, or allergies. This information was confirmed by a telephone interview and verified from clinical data collected from the previous seven phases of the main Whitehall II study. Volunteers were of white European origin, aged 53–76 yr, and 56.5% were in full-time employment. Selection was stratified by grade of employment (current or most recent) to include higher and lower socioeconomic status participants. Participants were prohibited from using any antihistamine or antiinflammatory medication 7 d before testing and were rescheduled if they reported illness and/or infections on the day of testing. Participants gave full informed consent to participate in the study, and ethical approval was obtained from the UCLH committee on the Ethics of Human Research.

### Psychophysiological testing at baseline

Testing was performed in either the morning or afternoon in a light- and temperature-controlled laboratory, as previously described (18). Participants were instructed to refrain from drinking caffeinated beverages or smoking for at least 2 h before the study and not to have performed vigorous physical activity or consumed alcohol the previous evening. After a 30-min rest period, baseline blood pressure was taken twice (using an automated UA-779 digital monitor) together with a resting saliva

sample. Two behavioral tasks, designed to induce mental stress, were then administered in a random order. The tasks were a computerized version of the Stroop task and mirror tracing, both of which have been used extensively in psychophysiological research (19). The tasks each lasted for 5 min. Cardiovascular measurements were continuously assessed during tasks and will be presented elsewhere. Participants then rested for 75 min. Saliva samples were collected immediately after the tasks and then at 20, 45, and 75 min after stress for the assessment of salivary cortisol. The samples were collected using Salivettes (Sarsted, Leicester, UK), which were stored at  $-30^{\circ}\text{C}$  until analysis. Levels of cortisol were assessed using a time-resolved immunoassay with fluorescence detection at the University of Dresden. The intra- and interassay coefficients of variation were less than 8%. Peak responses in cortisol tended to occur immediately after the mental stress; thus, for the purposes of the present study, samples at resting baseline and immediately after the stressor period were used to calculate a stress response change score [ $\text{Cort}_{\text{change}} = \text{Cort}_{\text{poststress}} - \text{Cort}_{\text{baseline}}$ ]. In addition, area under the curve with respect to increase was calculated (20).

### Covariates

At study entry, participants reported current smoking habit (categorized as smoker or nonsmoker). Height and weight were recorded in light clothing for the calculation of body mass index (BMI). Fasting blood samples were taken for the analysis of total and high-density lipoprotein cholesterol, and triglycerides, which was measured within 72 h in serum stored at  $4^{\circ}\text{C}$  using enzymatic colorimetric methods. Low-density lipoprotein cholesterol was derived using the Friedewald equation. Glucose homeostasis was assessed from glycated hemoglobin (HbA1c) concentration (21), assayed using boronate affinity chromatography, a combination of boronate affinity and liquid chromatography.

### Clinical assessment at follow-up

Participants returned for a standard clinic assessment (average follow-up period = 2.98 yr, ranging from 1.75–3.55 yr) that included a measure of blood pressure. After a 30-min rest period, blood pressure was taken three times (using an automated UA-779 digital monitor), and the mean value from the second and third reading was used. Hypertension was defined using standard criteria based on systolic and diastolic blood pressure of 140/90 mm Hg and above (22).

### Statistical analysis

We used  $\chi^2$  tests and one-way ANOVA to examine differences in baseline characteristics across the normotensive and hypertensive groups. We used multivariate logistic regression to compute odds ratios (OR) with accompanying 95% confidence intervals (CI) for the association between cortisol stress response (per sd) and risk of incident hypertension. Models were adjusted for age, sex, resting cortisol, systolic and diastolic blood pressure at study entry, employment grade, smoking, BMI, HbA1c, use of statins, and blood lipids. All analyses were conducted using SPSS version 15.

## Results

At baseline, 509 participants had complete data on cortisol and all covariates. Thirty participants did not com-

**TABLE 1.** Characteristics of the study population at baseline in relation to development of hypertension at follow up (n = 479)

Baseline characteristic	Normotensive at follow-up (n = 403)	Hypertensive at follow-up (n = 76)	P value
Age (yr)	62.8 ± 5.6 (54.0–76.0)	62.7 ± 5.6 (53.0–76.0)	0.99
Men [n (%)]	211 (52.4)	46 (60.5)	0.19
Highest work grade [n (%)]	163 (40.4)	27 (35.5)	0.25
Current smokers [n (%)]	22 (5.5)	4 (5.3)	0.95
Resting systolic BP (mm Hg)	120.6 ± 15.0 (65.5–185.5)	137.9 ± 15.0 (99.0–189.5)	<0.001
Resting diastolic BP (mm Hg)	74.9 ± 8.7 (47.0–105.5)	86.8 ± 7.9 (73.0–109.5)	<0.001
HDL cholesterol (mmol/liter)	1.70 ± 0.47 (0.80–3.50)	1.67 ± 0.47 (0.90–3.40)	0.64
LDL cholesterol (mmol/liter)	3.89 ± 0.96 (1.34–7.22)	3.97 ± 0.86 (2.08–6.14)	0.52
Body mass index (kg/m <sup>2</sup> )	25.7 ± 4.1 (15.0–43.9)	26.7 ± 3.3 (20.9–36.6)	0.02
HbA1c (%)	5.47 ± 0.38 (4.30–7.90)	5.40 ± 0.41 (4.20–6.50)	0.15
Resting cortisol (mmol/liter)	6.61 ± 4.60 (0.44–39.55)	6.14 ± 3.65 (1.04–24.25)	0.39
Statins use [n (%)]	32 (7.9)	11 (14.5)	0.07
Mean follow-up (d)	1087 ± 81 (639–1294)	1099 ± 64 (920–1224)	0.24

For continuous data, the values are means ± SD, and the range is shown in parentheses. BP, Blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

plete follow-up (three deceased, seven lost to follow-up, 20 declined); thus, the analytic sample comprised 479 participants (mean age, 62.7 ± 5.6 yr; range, 53–76 yr). Participants that did not complete follow-up were slightly older than those that remained in the study (65.3 vs. 62.7 yr,  $P = 0.01$ ), and on average they recorded higher systolic blood pressure at study entry (130.9 vs. 123.5 mm Hg,  $P = 0.01$ ).

Seventy-six participants (15.9% of sample) developed hypertension through follow-up. Participants with incident hypertension were more likely to be taking statins and have higher blood pressure and BMI at study entry compared with participants who remained normotensive (Table 1).

There was considerable variation in the cortisol stress response, with approximately 40% of the sample responding to the stress tasks with an increase in cortisol of at least 1 mmol/liter (18). In analysis adjusted for age, the cortisol stress response (per SD increase) was associated with incident hypertension (OR = 1.62; 95% CI = 1.26–2.07; Wald = 14.57;  $P < 0.001$ ). In additional models, the association remained largely unchanged (OR = 1.59; 95% CI = 1.17–2.17; Wald = 8.66;  $P = 0.003$ ) after additional

adjustments for sex, follow-up time, resting cortisol, blood pressure at study entry, employment grade, smoking, BMI, HbA1c, use of statins, and blood lipids (Table 2). In further stratified analysis, the association was slightly stronger in women and among leaner participants with BMI in the normal range (Table 2). There was also an association between area under the curve with respect to increase (per SD increase) and risk of hypertension (fully adjusted OR = 1.33; 95% CI = 1.04–1.71; Wald = 4.26;  $P = 0.039$ ), and this can be seen in Fig. 1, which displays the cortisol response profile in relation to incident hypertensive status.

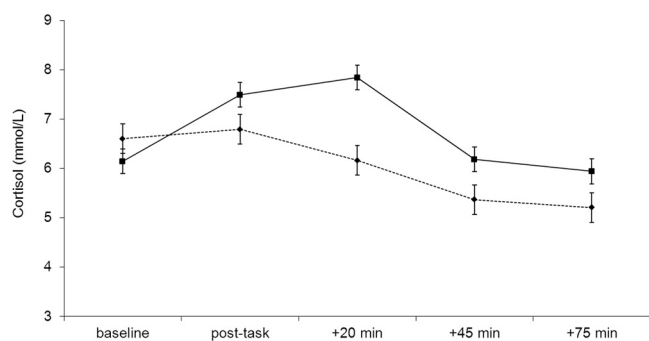
### Sensitivity analyses

Although participants entering this study had no previous diagnosis or treatment for hypertension, we excluded 27 participants identified as hypertensive from their baseline blood pressure readings. This did not, however, change the association between cortisol reactivity and risk of hypertension (fully adjusted OR per SD = 1.58; 95% CI = 1.13–2.21; Wald = 7.10;  $P = 0.008$ ). In further analysis, we used linear regression to model blood pressure as a continuous variable, and cortisol reactivity re-

**TABLE 2.** Association between cortisol stress response (per SD increase) and incident hypertension

	Model 1 odds ratio (95% CI)	Model 2 odds ratio (95% CI)	Model 3 odds ratio (95% CI)
Whole sample (n = 479, 76 cases)	1.62 (1.26–2.07)	1.59 (1.17–2.15)	1.59 (1.17–2.17)
Men (n = 257, 46 cases)	1.56 (1.15–2.10)	1.44 (0.97–2.12)	1.44 (0.97–2.12)
Women (n = 222, 30 cases)	1.73 (1.13–2.66)	1.94 (1.16–3.25)	2.05 (1.16–3.63)
BMI < 25 kg/m <sup>2</sup> (n = 215, 27 cases)	1.67 (1.12–2.48)	1.82 (1.13–2.92)	1.86 (1.10–3.14)
BMI ≥ 25 kg/m <sup>2</sup> (n = 264, 49 cases)	1.62 (1.17–2.25)	1.43 (0.96–2.14)	1.43 (0.94–2.17)

Model 1 is adjusted for age. Model 2 is adjusted for age, systolic and diastolic blood pressure at study entry, and resting cortisol. Model 3 is adjusted for age, sex, systolic and diastolic blood pressure at study entry, resting cortisol, employment grade, smoking, BMI, HbA1c, use of statins, and blood lipids.



**FIG. 1.** The cortisol stress response profile in relation to hypertensive status at follow-up. *Solid line* represents participants developing hypertension. Data are mean  $\pm$  SEM adjusted for age.

mained a significant predictor of mean arterial pressure at follow-up [age-adjusted beta coefficient (B) = 1.26; 95% CI = 0.25–2.26;  $P = 0.015$ ]. The youngest woman in the study was aged 55 yr, and all women reported postmenopausal status. Thirty-nine women reported taking hormone replacement therapy, although removal of these women did not appreciably alter the results (fully adjusted OR = 1.45; 95% CI = 1.04–2.01; Wald = 4.86;  $P = 0.028$ ). There was individual variability in the dynamics of the cortisol stress response. We therefore additionally calculated a peak cortisol response variable, based on the peak value from the saliva sample taken either immediately or 20 min after stress. Using peak cortisol reactivity did not, however, have an impact on the results (fully adjusted OR = 1.50; 95% CI = 1.16–1.93; Wald = 9.84;  $P = 0.002$ ).

## Discussion

Previous data have shown associations between heightened cardiovascular reactivity and future risk of hypertension and CVD. The aim of this study was to investigate the association between cortisol stress reactivity and incident hypertension in initially normotensive men and women. We observed an association between cortisol reactivity and incident hypertension, with a 59% increase in the odds of hypertension per SD change in cortisol reactivity. These associations were largely independent of conventional risk factors, including blood pressure at study entry. Indeed, it appeared that the moderate stressor used in the present study was sensitive enough to induce HPA axis reactivity in hypertensive-prone participants but not in normotensives.

To our knowledge, this is the first study to show a prospective association between cortisol stress reactivity and incident hypertension. The link between mental stress, cortisol reactivity, and hypertension risk is plausible (23) because cortisol can directly influence the central nervous

system, affecting areas of the brain that are involved in the control of blood pressure (hypothalamus, limbic system, *etc.*). In addition to the brain, glucocorticoid receptors are present in the heart and in the vascular smooth muscle of the resistance vessels as well as in the kidney and therefore directly affect blood pressure (23). A previous study in healthy participants demonstrated that mental stress-induced endothelial dysfunction and baroreflex impairment was prevented by blocking cortisol production with metyrapone (24). In several other studies, participants at risk of hypertension have demonstrated heightened HPA activity in response to acute stressors (14, 15). Also, blunted cortisol response to awakening and lower negative feedback sensitivity has been shown in participants with hypertension (16). However, because these studies have been cross-sectional, it is difficult to interpret whether HPA dysfunction is the cause or consequence of hypertension. Epidemiological evidence for an association between cortisol and hypertension has been inconsistent (8–13), but this might be largely explained by inadequate assessment of HPA activity, because most previous studies have relied on single samples of cortisol that can be influenced by a strong diurnal variation. In addition, most of the previous studies have been cross-sectional, which makes interpretation difficult. The present study therefore adds to the current literature by first using a stronger assessment of HPA activity and second by demonstrating a prospective association between cortisol and hypertension.

Several studies have linked raised cortisol levels with metabolic risk factors, including fasting glucose, lipids, and obesity (25, 26). In addition, other data have shown that the association between cortisol and blood pressure becomes weaker with increasing levels of BMI (8). In the present study, we observed an association between cortisol stress responses and BMI in linear regression analysis [beta coefficient (B) = 0.023; 95% CI = 0.00–0.045], although the association between cortisol and incident hypertension was independent of BMI, albeit slightly stronger in leaner participants.

The present study has a number of strengths and limitations. The major strength is the prospective design of the study that allows greater confidence in interpreting the directionality of the observed relationships. It should be noted that there was a large amount of variability in individual responses to the stressors, and only 40% of participants in this study were defined as cortisol responders, which is consistent with our previous findings from another sample tested with the same behavioral tasks (27). Cortisol responses to stress tend to be greater when participants are confronted by social-evaluative challenges rather than psychomotor and problem-solving tasks of the type used here (28). Cortisol stress responses were mea-

sured on a single occasion, and there may be adaptation on repeated testing, although we have previously demonstrated strong reproducibility of these responses over two repeated stress sessions (29). Participants that dropped out of the study had higher blood pressure at study entry and thus would have been more likely to develop hypertension. Our results are therefore reflective of the healthiest participants from this sample and might not be representative of the general older population. We cannot rule out the role of unmeasured confounding risk factors or genetic influences that might account for cortisol and hypertension risk. For example, higher cortisol concentrations have been observed in young normotensive participants with a family history of hypertension (30). Nevertheless, given that the present sample comprised older adults, one might speculate that individuals with a genetic propensity to hypertension would have developed the disease earlier in life and therefore would have been excluded from entry into this study. Although hypertensive status cannot be confirmed from clinic blood pressure readings taken on one occasion, the subjects in the present sample have undergone regular clinical assessments over the last 25 yr as part of the Whitehall II study. Therefore, issues such as the white-coat effect are unlikely to have biased our results.

In conclusion, we have demonstrated a prospective association between cortisol responses to laboratory-induced mental stress and incident hypertension. These findings provide support for the hypothesis that hyperactivity of the HPA axis is one of the mechanisms through which psychosocial stress may influence the risk of hypertension and CVD.

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Address all correspondence and requests for reprints to: Mark Hamer, Ph.D., Department of Epidemiology and Public Health, 1–19 Torrington Place, University College London, London WC1E 6BT United Kingdom. E-mail: m.hamer@ucl.ac.uk.

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