Hypertension Is Not the Link Between Job Strain and Coronary Heart Disease in the Whitehall II Study

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Background: Hypertension is assumed to be one of the mechanisms through which job strain (a combination of high work demands and low job control) increases coronary heart-disease risk. However, direct tests of this hypothesis are lacking.

Methods: We examined whether hypertension mediated the association between job strain and coronary heart disease among 5630 men and 2456 women free of coronary heart disease at study entry. Job strain was assessed at phase 1 (1985 to 1988); hypertension and systolic and diastolic blood pressure (BP) were assessed at phases 1, 3 (1992 to 1993), and 5 (1997 to 1999); and incident coronary heart disease was assessed from the end of phase 1 to phase 7 (2003 to 2004) (698 events; median follow-up, 16.1 years).

Results: After adjustment for age, sex, ethnicity, and employment grade, job strain was associated with an increased incidence of coronary heart disease. Further adjustments, for hypertension, systolic BP, and diastolic BP at phase 1 and across phases 1, 3, and 5, and the slope of hypertension and BP over time, had little effect on this association, although measures of hypertension and BP were strongly related to incident coronary heart disease.

Conclusions: Data, including repeated casual measurements of hypertension and BP, suggest that the development of chronic hypertension is not a key mechanism linking job strain and coronary heart disease. Further research on ambulatory measurements is needed to determine whether episodic BP elevations have a role in this association. Am J Hypertens 2007;20:1146–1153 © 2007 American Journal of Hypertension, Ltd.

Key Words: Hypertension, myocardial ischemia, occupational health, epidemiology.
Data from the Whitehall II Study of British civil servants, an ongoing, large-scale, prospective, occupational cohort study, enabled us to examine the contribution of hypertension and BP to associations between job strain and CHD. A unique feature of this study involves the opportunity to determine the development of hypertension with repeated measurements after the assessment of job strain, and to link this information to data on the incidence of CHD over a long period of time. If chronic hypertension represents a key mechanism through which job strain increases CHD risk, as has been suggested, then adjustment for hypertension and BP at baseline and follow-up should substantially reduce the strength of the association between job strain and incident CHD among employees free of CHD at study entry.

**Methods**

**Study Population**

In 1985, all nonindustrial civil servants aged between 35 and 55 years, in 20 departments in Central London, were invited to a cardiovascular medical examination. All major departments were included, and were mainly departmental headquarters, responsible for setting up and administering policies, but two were district offices that implemented policy and provided services to the public. Most of the invitees were office-based, administrative employees, ranging from top civil servants to messengers. With 73% participation, the baseline cohort included 6895 men and 3413 women, all of whom gave signed, informed consent.

In this study, we included participants with no history of CHD at phase 1; no missing data on job strain, BP, hypertension, or demographic characteristics at phase 1; and at least one measurement of hypertension and BP at phases 3 or 5, for a total of 5630 men and 2456 women (Fig. 1). These participants were slightly younger (44.3 vs 44.9 years, \( P < .0001 \)), more likely to be men (70% vs 55%, \( P < .0001 \)) and white (88% vs 82%, \( P < .0001 \)), and less likely to be from lower-grade occupations (19% vs 37%, \( P < .0001 \)) than the 2014 excluded subjects free of CHD. Similar differences in age and proportion of lower-grade workers were seen between participants and those excluded with prevalent CHD at phase 1 (age, 49.0 years; 33% clerical; \( P = .03 \)). However, the proportion of men was greater in those with CHD (79%, \( P = .008 \)), and there were no ethnic difference between groups. The study protocols and processes for obtaining informed consent were approved by the University College London Medical School Committee on the Ethics of Human Research.

**Study Design**

The baseline and odd-numbered phases of the Whitehall II Study involve a clinical screening and self-administered questionnaire, while the even-numbered phases are questionnaire only. In this study, job strain was measured at phase 1 (1985 to 1988), and hypertension and BP were measured at phase 1, phase 3 (1992 to 1993), and phase 5 (1997 to 1999) (Table 1). Follow-up for incident CHD was from the end of phase 1 to phase 7 (2003 to 2004).

**Baseline Characteristics**

Demographic characteristics included sex, age, ethnicity (white versus other), and employment grade (high, intermediate, or low) at baseline. The following coronary risk factors were assessed at phase 1: body mass

**Table 1.** Measurements by Study Phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age, Sex, Ethnicity, Employment grade, Job strain, Hypertension, Systolic BP, Diastolic BP, Antihypertensive medication, Body mass index, Total cholesterol, Smoking, Alcohol consumption, Prevalent CHD</td>
</tr>
<tr>
<td>3,5</td>
<td>Hypertension, Systolic BP, Diastolic BP, Antihypertensive medication</td>
</tr>
<tr>
<td>After 1 to 7</td>
<td>Follow-up of Incident CHD</td>
</tr>
</tbody>
</table>

BP = blood pressure, CHD = coronary heart disease.
index (mean = 24.5 kg/m², SD = 3.4, n = 8078), serum cholesterol concentration (mean = 5.9 mmol/L, SD = 1.1, n = 8041), smoking (current smoker, n = 1275; ex-smoker, n = 2652; never-smoker, n = 4098), and heavy drinking (average consumption > 21 units of alcohol per week, n = 1128; ≤21 units, n = 6898; one unit refers to a half pint of beer, small glass of wine, or one shot of spirits).

Job Strain
Participants were asked four questions assessing job demands (Cronbach alpha = 0.67) and 15 questions on job control (alpha = 0.84), and were instructed to respond on a scale from 1 to 4. Overall scores for each scale were calculated using the sum of items. As recommended by Karasek,19 scores for the two scales were dichotomized at the median and combined into four groups: (1) high demands and low job control (“high strain”); (2) high demands and high job control (“active”); (3) low demands and low job control (“passive”); and (4) low demands and high job control (“low strain”). When dichotomizing the job-demand and job-control scores, the sexes were analyzed together.

Hypertension and Blood Pressure
At phases 1, 3, and 5, systolic BP (SBP) and diastolic BP (DBP) were measured twice in a sitting position after a 5-min rest with the Hawksley random-zero sphygmomanometer.21 The average of these two readings was taken to be the measured SBP and DBP. For each participant, either of two cuff sizes (adult and adult large) was chosen to cover two thirds of the upper arm for measurement. Systolic was defined as the pressure at which the Korotkoff sound was first heard clearly, and diastolic was defined as the pressure at which the sound disappeared. Participants were asked whether they were taking antihypertensive medication. In keeping with the standard definitions, subjects with SBP ≥140 mm Hg and DBP ≥90 mm Hg, or on antihypertensive treatment, were considered hypertensive.

Coronary Heart Disease
Prevalent CHD involved a history of nonfatal myocardial infarction or definite angina at phase 1, and incident CHD involved CHD death, a first nonfatal myocardial infarction, or definite angina during follow-up. For the assessment of fatal CHD, participants were flagged at the National Health Service Central Registry, which provided information on the date and cause of death (of the 10,308 participants in the Whitehall II Study, 10,301 were successfully flagged). Fatal CHD was defined according to the International Classification of Diseases, Ninth Revision (ICD 9 codes 410 through 414 as underlying causes of death). Potential prevalent and new cases of nonfatal myocardial infarction were ascertained by questionnaire items concerning chest pain and a physician’s diagnosis of heart attack. Confirmation of myocardial infarction according to Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) criteria23 was based on electrocardiographic findings, markers of myocardial necrosis, and a history of chest pain in the medical records. The assessment of angina was based on the participant’s reports of symptoms, with corroboration via medical records or abnormalities in a resting electrocardiogram (ECG), an exercise ECG, or a coronary angiogram.

Statistical Methods
We used SAS statistical software, version 9.1 (SAS Institute, Cary, NC). Analysis of variance was used for comparing means, and the chi-square test was used for assessing frequencies in different job-strain groups. Age-, sex-, ethnicity- and employment grade-adjusted means by job-strain group were calculated for hypertension, SBP, and DBP at phase 1, for estimated mean hypertension prevalence and BP levels over time, and for estimated change in these measures over time. Estimates of mean hypertension and BP, and changes in hypertension and BP over time, were obtained from multilevel models with measurement occasion (ie, study phase) nested within individuals using the PROC MIXED maximum likelihood procedure. Mean exposure for each individual was estimated from the mean of predicted values. To obtain estimates of change over time, models with a random intercept and slope were fitted with systolic BP, diastolic BP, and hypertension as the dependent variables, and phase of measurement as a covariate. An unstructured covariance matrix was used to specify a random intercept-slope model with different variances for the intercept and slope, and a covariance between them. The use of multilevel models to estimate means and change allowed the inclusion of participants with missing data at either phase 3 or 5.

We fitted Cox proportional-hazard models to study associations between these variables and incident CHD. Hazard ratios for incident CHD were adjusted for age, sex, ethnicity, and employment grade. The fully adjusted model for job strain and CHD included additional adjustments for all measures of hypertension and BP (baseline measure, mean exposure, and slope over time). These models were rerun for employees who were normotensive at phase 1, to eliminate prevalent hypertension at baseline as a source of bias.

If the effect of an exposure on an outcome is partly or wholly mediated through another variable, observational data should show an association between exposure and outcome which will be attenuated after adjustment for the mediator variable. The greater the attenuation, the larger the mediated effect. Applied to our hypothesis, this would mean (1) that there would be an association between job strain (exposure) and BP or hypertension (possible mediator); (2) that BP and hypertension (possible mediator) would predict incident CHD (outcome); (3) that job strain (exposure) would predict incident CHD (outcome); and
that this association would attenuate after adjustment for BP and hypertension (possible mediator). Failure to meet all four criteria would suggest that the effects of BP and hypertension may not explain the association between job strain and incident CHD.

Results

Sample characteristics are shown in Table 2. Women, nonwhite employees, and those in lower grades were more likely to have passive jobs, while men, white employees, and high grades were more likely to have active jobs. Differences in proportions with high-strain jobs were not large. Participants with active or high strain jobs were also slightly younger.

Association of Job Strain With Hypertension and BP

Table 3 shows the prevalence of hypertension at phase 1, mean estimated hypertension prevalence across phases 1 to 5, estimated increase in hypertension prevalence over time, and corresponding measures for BP by category of job strain. After adjustment for age, sex, ethnicity, and grade, no association was found between job strain and measures of hypertension or BP. The only exception was mean systolic BP, which was marginally higher among employees with low strain compared to employees with passive, active, or high-strain jobs.

Association of Hypertension and BP With Incident CHD

We identified 698 incident CHD events (519 in men, 179 in women) during a mean follow-up of 16.1 years, with an incidence rate of 53.6 per 10,000 person-years. As shown in Table 4, hypertension at phase 1 and estimated high or increasing hypertension risk across phases 1 to 5 were all associated with elevated incidence of CHD. Other predictors of CHD were high SBP and DBP at phase 1, and a high mean level of these measures across phases 1 to 5. No association was found between change in BP over time and incident CHD.

Contribution of Hypertension and BP to Association Between Job Strain and CHD

There was no evidence for any large age, sex, or employment-grade differences in the associations between job strain and CHD (all interaction terms, \( P \geq .25 \)). However, job strain was a stronger predictor of CHD among white than nonwhite employees (\( P \) for interaction = .03). The age-, sex-, and employment grade-adjusted hazard ratio for high versus low strain was 1.50 (95% confidence interval [CI], 1.15 to 1.95) in white employees, and 0.82 (95% CI, 0.47 to 1.47) in nonwhite employees.

In the total cohort, high strain was associated with a 1.4 times higher CHD risk than low strain in a model adjusted for age, sex, ethnicity, and employment grade (Table 5, model A). Additional adjustments for hypertension, SBP, and DBP at phase 1 (Table 5, model B), as well as the means and slopes of these measures over time (Table 5, models C and D), had little or no effect on this association. Further adjustment for coronary risk factors at phase 1, ie, body mass index, cholesterol, smoking, and alcohol consumption, did not attenuate the hazard ratio (1.41; 95% CI, 1.10 to 1.80). We repeated this analysis with the 7440 employees who were normotensive and free of CHD at phase 1. Analyses of these data replicated the findings (Table 5). We repeated this analysis among white employees, and again found no attenuation in the hazard ratio for high versus low strain 1.54 (95% CI, 1.18 to 2.00) after adjustment for age, sex, employment grade, and measures of hypertension and BP.

Finally, we calculated the means and slopes for hypertension, SBP, and DBP, based on pre-event data (\( n =

<table>
<thead>
<tr>
<th>Phase 1 characteristic</th>
<th>Total sample</th>
<th>Job strain category</th>
<th>( P ) for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low-strain</td>
<td>Passive</td>
</tr>
<tr>
<td>Sex, ( n ) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>5630 (69.6)*</td>
<td>1403 (24.9)†</td>
<td>1467 (26.1)</td>
</tr>
<tr>
<td>Women</td>
<td>2456 (30.4)</td>
<td>384 (15.6)</td>
<td>1205 (49.1)</td>
</tr>
<tr>
<td>Age (y) (SE)</td>
<td>44.3 (0.1)</td>
<td>44.4 (0.1)</td>
<td>44.6 (0.1)</td>
</tr>
<tr>
<td>Ethnicity, ( n ) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7153 (88.5)</td>
<td>1635 (22.9)</td>
<td>2220 (31.0)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>933 (11.5)</td>
<td>152 (16.3)</td>
<td>452 (48.4)</td>
</tr>
<tr>
<td>Employment grade, ( n ) (%)</td>
<td></td>
<td>Low (18.7)</td>
<td>112 (7.4)</td>
</tr>
</tbody>
</table>

* Column percentages.
† Row percentages.
The age-, sex-, ethnicity-, and employment grade-adjusted hazard ratio for high strain was 1.36 (95% CI, 1.03 to 1.78), and the fully adjusted hazard ratio was 1.37 (95% CI, 1.04 to 1.81).

Discussion

The development of hypertension has been assumed to be one of the reasons why employees exposed to job strain are at increased risk of CHD. To our knowledge, this study represents the first large-scale investigation to test this hypothesis with measurements of job strain, subsequent hypertension, and BP, and a follow-up of CHD in a working population with no prevalent CHD at baseline. These data provide no support for the hypertension hypothesis. Although both job strain and hypertension predicted incident CHD, they were not related to each other as hypothesized. Adjustment for hypertension and BP had little effect on the association between job strain and CHD.

Similar results were obtained among white employees and employees who were normotensive at study entry. Our findings are in accordance with several prospective cohort studies that showed no substantial change in the association between job strain and CHD after adjustment for baseline risk factors, including hypertension and BP.16–18 Because the assessment of baseline hypertension does not cover the development of hypertension after

Table 3. Adjusted* means of hypertension and BP measures by job strain categories (n = 8086)

<table>
<thead>
<tr>
<th>Category</th>
<th>Hypertension (%)</th>
<th>Mean†</th>
<th>Slope‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low strain</td>
<td>9.4 (0.7)</td>
<td>123 (0.4)</td>
<td>0.05 (0.01)</td>
</tr>
<tr>
<td>Passive</td>
<td>8.6 (0.6)</td>
<td>128 (0.4)</td>
<td>0.04 (0.01)</td>
</tr>
<tr>
<td>High strain</td>
<td>7.7 (0.8)</td>
<td>124 (0.4)</td>
<td>0.04 (0.01)</td>
</tr>
<tr>
<td>Active</td>
<td>13.6 (0.5)</td>
<td>123 (0.4)</td>
<td>0.04 (0.01)</td>
</tr>
<tr>
<td>For heterogeneity</td>
<td>.16</td>
<td>.32</td>
<td>.04</td>
</tr>
</tbody>
</table>

Table 4. Associations of hypertension, systolic BP, and diastolic BP with incident CHD (n = 8086, 698 events)

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Hazard ratio*</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (hypertensive versus normotensive)</td>
<td>2.17</td>
<td>1.78 to 2.64</td>
<td></td>
</tr>
<tr>
<td>Mean†</td>
<td>1.46</td>
<td>1.39 to 1.55</td>
<td></td>
</tr>
<tr>
<td>Slope‡</td>
<td>1.48</td>
<td>1.40 to 1.58</td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.24</td>
<td>1.19 to 1.30</td>
<td></td>
</tr>
<tr>
<td>Baseline (per 10 mm Hg)</td>
<td>1.35</td>
<td>1.25 to 1.45</td>
<td></td>
</tr>
<tr>
<td>Mean†</td>
<td>1.01</td>
<td>0.94 to 1.08</td>
<td></td>
</tr>
<tr>
<td>Slope‡</td>
<td>1.38</td>
<td>1.29 to 1.49</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>1.41</td>
<td>1.32 to 1.51</td>
<td></td>
</tr>
<tr>
<td>Baseline (per 10 mm Hg)</td>
<td>0.98</td>
<td>0.91 to 1.06</td>
<td></td>
</tr>
</tbody>
</table>

BP = blood pressure; CHD = coronary heart disease; CI = confidence interval.

* Based on Cox proportional hazard models adjusted for age, sex, ethnicity, and employment grade. Hazard ratios for hypertension and BP slopes are additionally adjusted for their baseline values.

† Estimated mean hypertension risk or mean level of BP across phases 1, 3 and 5. Hazard ratios for mean values are per 1 SD increase in standardized predictor.

‡ Estimated increase in hypertension risk or BP level between phase 1 and phase 5. Hazard ratios for slope are per 1 SD increase in standardized predictor.
baseline, these previous studies comprised an incomplete test for the hypertension hypothesis. In contrast, we measured hypertension and BP at two follow-ups, and constructed estimates of long-term exposure to BP and change in exposure to hypertension over time. These exposures were powerful predictors of CHD. The use of these data, as well as information on BP levels and changes, made our mediator test more sensitive than those in previous investigations. Exclusion of participants with prevalent hypertension at baseline reduced the likelihood of bias due to reversed causality.

Although our findings failed to support the hypertension hypothesis, they do not exclude the possibility that strain-related, episodic elevations in BP could act as a trigger for coronary events among employees with prevalent CHD (the trigger hypothesis). Triggering of acute events is thought to take place when atherosclerotic plaque disruption occurs within a proinflammatory and prothrombotic milieu. Shear stress, induced by acute emotional stress, may contribute to plaque ruptures, and work-related stressful events were associated with the triggering of myocardial infarction in case-crossover analyses. Furthermore, chronic BP elevations at work might increase the risk for CHD.

If BP elevations at work explained the effect of job strain on CHD, then the association between job strain and CHD would attenuate as a consequence of adjustment for work-time BP, but not necessarily after adjustment for casual clinic BP measured outside the worksite. There is some evidence that the effect of job strain on worksite BP levels does not necessarily spill into private life. This is because positive findings on the job strain-BP relation are usually based on ambulatory BP or BP assessed at the workplace, whereas null findings were repeatedly reported for casual clinic BP. Importantly, Ducher et al found no global relationship between job strain and BP levels, but revealed a significant association between job strain and worksite BP in a subgroup of newly diagnosed hypertensive subjects.

### Study Strengths and Limitations

Several strengths of this study reduce the possibility of a false-negative conclusion (type II error). Our study addressed all the elements of the hypertension hypothesis, and the observational evidence was based on a large, well-characterized cohort, a 16-year follow-up period, and repeated measurements of the potential mediators, ie, hypertension and BP. Furthermore, all components of outcomes (CHD deaths, first nonfatal myocardial infarctions, and definite angina) were confirmed by clinical records. However, three limitations are noteworthy.

First, selection bias is possible, because 21% of the baseline cohort was excluded due to missing data on job strain or hypertension (or BP). Although selective loss to follow-up may have resulted in a slight underestimation of the association between job strain and CHD, it is unlikely...
to have completely masked the role of hypertension in this relationship.

Second, studies suggest that ambulatory BP measures may be superior to casual measures as predictors of cardiovascular morbidity and mortality. Although the observed strong associations of hypertension measures with incident CHD suggest that our assessments tapped the risk factor accurately, it would be beneficial to repeat the current assessments with portable BP monitors and multiple readings, to test directly whether greater transient elevations in BP at work underlie the effects of job strain on CHD.

Third, findings from a cohort aged 35 to 55 years in 1985 to 1988, and almost exclusively white collar, may not apply to wider populations, eg, we observed that there was no effect of high versus low strain among nonwhite employees. Future research with larger, more diverse samples, including a larger variety of ethnic groups and populations from developing countries, is needed to confirm the generalizability of our findings, and to explore potential sex differences.

Conclusions

Our strong study design demonstrated that although both job strain and hypertension were important predictors of CHD, hypertension did not mediate the association between job strain and CHD. This suggests that the development of hypertension is not the primary cause of increased CHD risk among employees with job strain. Future research should concentrate on other mechanisms, such as the increased likelihood of BP elevations that act upon preexisting disease (the trigger hypothesis, or chronic worksite BP elevations), the development of metabolic syndrome, and disturbances in coagulation and inflammatory and immune responses. In addition, the pathway from job strain to CHD could be indirect, eg, via increased adverse health-related behaviors.

References


