European Heart Journal (2008) **29**, 640–648
doi:10.1093/eurheartj/ehm584

Work stress and coronary heart disease: what are the mechanisms?

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Received 1 August 2007; revised 14 November 2007; accepted 22 November 2007; online publish-ahead-of-print 23 January 2008

See page 579 for the editorial comment on this article (doi:10.1093/eurheartj/ehm641)

Aims To determine the biological and behavioural factors linking work stress with coronary heart disease (CHD).

Methods and results A total of 10 308 London-based male and female civil servants aged 35–55 at phase 1 (1985–88) of the Whitehall II study were studied. Exposures included work stress (assessed at phases 1 and 2), and outcomes included behavioural risk factors (phase 3), the metabolic syndrome (phase 3), heart rate variability, morning rise in cortisol (phase 7), and incident CHD (phases 2–7) on the basis of CHD death, non-fatal myocardial infarction, or definite angina. Chronic work stress was associated with CHD and this association was stronger among participants aged under 50 (RR 1.68, 95% CI 1.17–2.42). There were similar associations between work stress and low physical activity, poor diet, the metabolic syndrome, its components, and lower heart rate variability. Cross-sectionally, work stress was associated with a higher morning rise in cortisol. Around 32% of the effect of work stress on CHD was attributable to its effect on health behaviours and the metabolic syndrome.

Conclusion Work stress may be an important determinant of CHD among working-age populations, which is mediated through indirect effects on health behaviours and direct effects on neuroendocrine stress pathways.

Keywords Work stress • Autonomic nervous system • Myocardial infarction • Angina • Coronary heart disease Psychosocial

Introduction

Stress at work is associated with an increased risk of coronary heart disease (CHD) but the mechanisms underlying this association remain unclear.[1] Work stress may affect CHD through direct activation of neuroendocrine responses to stressors, or more indirectly through unhealthy behaviours which increase the risk of CHD, such as smoking, lack of exercise, or excessive alcohol consumption. One of the main axes of neuroendocrine stress responses is the autonomic nervous system (ANS). Repeated activation of the ANS is characterized by lowered heart rate variability, which has been associated with work stress among men in cross-sectional studies.[2,3] Furthermore, work stress may affect dysregulation of the hypothalamic–pituitary–adrenal axis,[4] which is associated with disturbances in the circadian rhythm of cortisol and the development of the metabolic syndrome.[5,6]

Accumulation of work stress is associated with higher risks of the metabolic syndrome,[7] and incident obesity.[8] However, there are few longitudinal studies examining the effect of cumulative work stress on other intermediate mechanisms, despite evidence that chronic stress predicts cardiovascular mortality and morbidity.[9] It is important to examine cumulative exposures in order to show dose–response relations,[10] which would contribute a causal understanding of the association between work stress and CHD. In addition, there is little longitudinal evidence on the mechanisms by which work stress affects CHD. Stronger associations between work stress and CHD risk among working-age populations would also increase the specificity of this association.

This study addresses the following questions: 1 Is the accumulation of work stress associated with higher risks of incident CHD and risk factors? 2 Is this association stronger among

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working-age populations? 3 Does work stress affect CHD directly through neuroendocrine mechanisms and/or indirectly through behavioural risk factors for CHD?

Methods

Study sample and design

The Whitehall II study conducted in 1985–88 (phase 1) recruited 10 308 participants from 20 civil service departments in London. After initial participation, data collection was carried out in 1989–90 (phase 2), 1991–93 (phase 3), 1995 (phase 4), 1997–99 (phase 5), 2001 (phase 6), and 2002–04 (phase 7). Phases 2, 4, and 6 were postal questionnaires, and phases 3, 5, and 7 also included a clinical examination. Full details of the clinical examinations are reported elsewhere.[11] Ethical approval for the Whitehall II study was obtained from the University College London Medical School Committee on the ethics of human research. Informed consent was obtained from the study participants.

Assessment of work stress

Self-reported work stress was measured by the job-strain questionnaire.[12] Participants report job-strain when their responses to the job demands questions are high and decision latitude (job control) questions are low (defined as being above or below the median score for the measures of job demands and decision latitude). In addition, participants are said to have iso-strain when they report job-strain and are socially isolated at work (i.e. without supportive co-workers or supervisors).[7,13,14] A cumulative measure of work stress was created by adding together the number of times the participant reported iso-strain at phases 1 and 2 (range 0–2), giving us a measure on the duration of exposure to work stress, although measured on two occasions only. Participants who lacked work stress data at either phase were assigned a missing value. The prevalence of work stress (iso-strain) was lowest in the highest civil service grade.

Follow-up measurements

CHD events included fatal CHD (ICD9 codes 410–414 or ICD10 I20–25) or incident non-fatal myocardial infarction (MI) from phases 2–7 (an average of 12 years of follow-up), with or without angina. Non-fatal MI was defined following MONICA criteria[15] based on study electrocardiograms, hospital acute ECGs, and cardiac enzymes, and excluded participants with existing MI at phase 1 or 2. Incident angina was defined on the basis of clinical records and nitrate medication use, excluding cases based solely on self-reported data without clinical verification and participants with definite angina at phase 1 or 2.

Biological risk factors for CHD included the ATPIII[16] metabolic syndrome measured at phase 3, its components (waist circumference: men $>$102 cm, women $>$88 cm; serum triglycerides: $\geq$150 mg/dL; HDL cholesterol: men $<$40 mg/dL, women $<$ 50 mg/dL; blood pressure: $\geq$130/$\geq$85 mmHg or on antihypertensive medication; fasting glucose: $\geq$110 mg/dL); morning rise in cortisol and low heart rate variability (both measured at phase 7).

For the evaluation of heart rate variability, 5 min of RR interval data were collected and analysed both in the time domain [standard deviation of all intervals between normal-to-normal sinus rhythm R waves (SDNN)] and in the frequency domains: low frequency 0.04–0.15 Hz (ms^2) and high frequency 0.15–0.4 Hz (ms^2). These measures were log-transformed to obtain a more normal distribution for the regression analyses.

For the evaluation of cortisol, participants were asked to provide samples of saliva collected at waking and 30 min after waking. Participants were asked to record time of waking. Samples were posted back and stored at $-80^{\circ}C$ for subsequent hormone analysis. Cortisol was measured as previously described.[17] Morning rise in cortisol was calculated as the difference between cortisol levels at waking and 30 min after waking.

Behavioural risk factors (at phase 3) for CHD included alcohol, smoking, activity, and diet. Alcohol consumption in the previous week was categorized into non-drinker, recommended (1–14 units for women/1–21 units for men), and unsafe (14+ units for women/21+ units for men). Cigarette smoking categories were non-smoker, ex-smoker, 1–9 cigarettes/day, 10–19 cigarettes/day, and 20+ cigarettes/day. Physical activity was measured by self-reported frequency of moderate activities (3+ times a week, at least once a week, at least once a month, never). Diet was measured by self-reported fruit or vegetable consumption (less than weekly, less than daily, and at least daily). For logistic regression analyses, these health behaviours were coded into binary variables of current vs. never/ex-smokers, unsafe drinkers vs. non/recommended limit drinkers, less than daily fruit/vegetable consumption vs. daily, and no physical activity vs. some activity.

Missing data and statistical methods

There were 10 308 civil servants who participated in the baseline (phase 1) study. By phase 7, of the 9692 participants still alive, 6484 attended the clinical examination, 71% on whom we measured heart rate variability. Of those participants who were asked to collect saliva samples, 90.1% ($n = 4609$) returned samples. Some samples were not assayed for technical reasons. Participants taking corticosteroid medication were excluded from analysis ($n = 236$). Any participants taking the first sample more than 10 min after waking were excluded from analysis ($n = 634$), this is the commonly used cut-off when investigating daytime cortisol levels, as the cortisol awakening response is already substantially under way.

A missing value on the work stress measure could indicate that the data were not available at a particular phase, the participant dropped out, or the participant was not in employment. There were 7721 participants who were still in employment at phase 2 with work stress data at phases 1 and 2. Out of these participants, 98% had follow-up data on incident CHD, 86–90% had information on health behaviours and the metabolic syndrome at phase 3, 45–49% had information on heart rate variability and cortisol at phase 7.

Cox proportional hazard regression models were used to model the association between the cumulative work stress measures (from phases 1 and 2) and incident CHD events (from phases 2 to 7), adjusted for age, sex, and employment grade, smoking history, total cholesterol, and hypertension (systolic blood pressure $>$140 and diastolic blood pressure $>$90, or on antihypertensive medication). Logistic/linear regression models were then used to model the association between cumulative work stress and binary/continuous CHD risk factors. Finally, Cox proportional hazard regression models were used again to examine the reduction in the hazard ratios of cumulative work stress on CHD, adjusted for potential intermediate pathways (health behaviours and the metabolic syndrome). Heart rate variability and cortisol could not be examined as potential mediators, as they were not measured in the first few phases of data collection. All statistical significance testing used a two-sided test at the 0.05 significance level. As the main exposure (work stress) consisted of two pairwise comparisons (no report vs. one report, and

no report vs. two reports), Bonferroni corrected *P*-values (a conservative statistical adjustment to adjust for multiple comparisons) are reported to reduce the risk of type 1 errors. Some of the analyses were stratified by age-group if there was a significant interaction between age and work stress.

Results

The distribution of all the variables in the analysis is shown in *Table A1*. *Table 1* displays the hazard ratios of incident CHD by cumulative measures of work stress from phases 1 and 2. Greater reports of work stress were associated with a higher risk of CHD. This was true for both major CHD events (fatal events and MI) and definite angina. Although reporting bias may lead to a spurious association between self-reports of stress and angina pectoris,[18] the estimated risks of MI and definite angina were similar and so further analyses combined these two CHD outcomes.

There was a significant interaction between age and two reports of work stress ($P = 0.04$), so the analysis is stratified by age group. Among younger participants (aged 37–49 at phase 2), there was a clear dose–response association between greater reports of work stress and higher risks of incident CHD events. Among older participants (aged 50–60), there was little association between work stress and CHD. Stratifying by employment status at phase 5 revealed similar effects (analysis not shown).

Table 2 shows the association of work stress (measured at phases 1 and 2) with the metabolic syndrome, its components, and health behaviours (all from phase 3) among younger (aged under 50) respondents in the Whitehall II cohort. Greater reports of work stress were associated with poorer health behaviours in terms of eating less fruit and vegetables and less physical activity. In addition, work stress was associated with not drinking any alcohol (which increased the risk of CHD, *Table A2*). Work stress was also associated with the overall metabolic syndrome and four of its five components. Adjusting for health behaviours only slightly reduced the association between work stress and the overall metabolic syndrome.

Table 3 shows the association between work stress (at phases 1 and 2) and low heart rate variability (at phase 7), and morning rise in cortisol (at phase 7) for participants at all ages (there was no significant interaction between age and work stress). Greater reports of work stress were associated with lower heart rate variability in terms of lowering of the total variance and low- and high-frequency components. There was little association with morning rise in cortisol. However, additional cross-sectional analysis at phase 7 between work stress and cortisol revealed significantly elevated morning rise in cortisol among those reporting work stress ($P < 0.05$). All the analyses in *Table 3* were adjusted for age, sex, employment grade, hypertension, total cholesterol, smoking, and other health behaviours.

Table 1 Hazard ratios (95% confidence intervals) of incident coronary heart disease events (phases 2–7) by cumulative work stress (phases 1–2), age group: the Whitehall II study with an average follow-up of 12 years

Case definition and sample	Work stress			Linear trend *P*-value
	No report	One report	Two reports	
All CHD—all ages	1.00	1.23 (0.90–1.68)	1.33 (1.04–1.69)	0.01
P-value[a]		0.19	0.02	
P-value[b]		0.37	0.04	
Cases/*n*	416/6052	38/497	68/779	
CHD death or MI—all ages	1.00	1.18 (0.75–1.87)	1.56 (1.12–2.17)	0.01
P-value[a]		0.47	0.01	
P-value[b]		0.94	0.02	
Cases/*n*	242/6285	24/522	43/818	
Definite angina—all ages	1.00	1.34 (0.93–1.93)	1.43 (1.07–1.90)	0.01
P-value[a]		0.11	0.02	
P-value[b]		0.23	0.03	
Cases/*n*	337/6276	35/523	57/819	
All CHD—age 37–49 at baseline	1.00	1.40 (0.88–2.22)	1.68 (1.17–2.42)	<0.01
P-value[a]		0.16	<0.01	
P-value[b]		0.32	0.01	
Cases/*n*	174/3912	22/346	38/509	
All CHD—age 50–60 at baseline	1.00	1.09 (0.68–1.77)	1.13 (0.79–1.63)	0.47
P-value[a]		0.71	0.51	
P-value[b]		1.00	1.00	
Cases/*n*	258/2314	19/170	33/300	

Hazard ratios are adjusted for age, sex, employment grade, hypertension, total cholesterol, and smoking history.
[a]*P*-value adjusted for age, sex, employment grade, hypertension, total cholesterol, and smoking.
[b]Bonferroni corrected *P*-value adjusted for age, sex, employment grade, hypertension, total cholesterol, and smoking.

Table 2 Odds ratios (95% confidence intervals) of health behaviours (phase 3) and metabolic syndrome (phase 3), by cumulative work stress (phases 1–2): Whitehall II respondents aged under 50 at phase 2

	Model 1	Model 2	Cases/*n*
Health behaviours			
Less than monthly fruit/vegetable			
No report of work stress	1.00		42/3575
One report	1.10 (0.43–2.84)		5/316
Two reports	2.12 (1.07–4.18)		11/461
No alcohol consumption			
No report of work stress	1.00		558/3581
One report	1.24 (0.92–1.67)		66/316
Two reports	1.42 (1.11–1.82)		101/461
No physical activity			
No report of work stress	1.00		377/3581
One report	1.07 (0.74–1.55)		37/316
Two reports	1.33 (1.00–1.78)		66/460
Current smoker			
No report of work stress	1.00		464/3580
One report	1.27 (0.93–1.73)		56/316
Two reports	1.11 (0.84–1.47)		68/460
Metabolic syndrome			
High waist			
No report of work stress	1.00	1.00	231/3292
One report	1.29 (0.84–1.99)	1.24 (0.81–1.92)	26/283
Two reports	1.51 (1.08–2.13)	1.46 (1.03–2.06)	45/426
High fasting glucose			
No report of work stress	1.00	1.00	570/3201
One report	1.02 (0.74–1.42)	1.05 (0.76–1.47)	48/269
Two reports	1.40 (1.08–1.80)	1.43 (1.10–1.85)	89/410
High triglycerides			
No report of work stress	1.00	1.00	802/3308
One report	1.18 (0.89–1.57)	1.16 (0.87–1.54)	78/280
Two reports	1.33 (1.06–1.69)	1.30 (1.03–1.65)	119/425
HDL cholesterol			
No report of work stress	1.00	1.00	597/3308
One report	1.21 (0.89–1.63)	1.17 (0.86–1.59)	61/280
Two reports	1.32 (1.03–1.68)	1.26 (0.98–1.62)	95/425
Hypertension			
No report of work stress	1.00	1.00	1182/3332
One report	0.87 (0.67–1.13)	0.88 (0.67–1.14)	93/285
Two reports	1.13 (0.91–1.39)	1.13 (0.91, 1.40)	159/430
ATPIII metabolic syndrome			
No report of work stress	1.00	1.00	357/3308
One report	1.33 (0.93–1.91)	1.33 (0.93–1.91)	39/280
Two reports	1.72 (1.30–2.29)	1.69 (1.26–2.25)	69/425

Logistic regression odds ratios in model 1 are adjusted for age, sex, and employment grade; logistic regression odds ratios in model 2 are additionally adjusted for health behaviours.

Table 4 displays the hazard ratios of incident CHD for the younger respondents (aged under 50) by work adjusted for behavioural risk factors and the metabolic syndrome. There was a 16% reduction in the hazard ratios when behavioural risk factors were adjusted for, and a similar reduction when adjusting for the overall metabolic syndrome. Adjusting for both health behaviours and the metabolic syndrome reduced the work stress–CHD association by ~32%.

Discussion

Cumulative work stress is a risk factor for CHD and neuroendocrine stress responses, especially among the younger, working-age population. Around 32% of the effect of work stress on CHD can be explained by the effect of work stress on health behaviours (low physical activity and poor diet in particular) and the metabolic syndrome.

The association between work stress and CHD was stronger among employees younger than 50 and those still in employment. This is in agreement with previous age group analyses of work stress[19] and is consistent with the fact that more robust work stress–CHD associations have been found in studies employing younger[20,21] than older cohorts.[22,23] Among older employees, the impact of work stress might be attenuated because of a healthy worker survivor bias. Retirement during the follow-up removes work stress and this exposure misclassification may also reduce the effect of work stress. Furthermore, an increasing number of other age-related causes of CVD may eclipse the effect of work stress as these other causes figure into both the numerator and the denominator of the ratio.

An important case–control study (INTERHEART[24]) of 11 119 patients with a first MI and 13 648 age- and sex-matched controls in 52 countries found that 'permanent' stress at work was associated with over twice the odds of MI compared with those reporting no stress at work. However, few studies have been able to move from demonstrating associations to causality. This article builds on the INTERHEART and other studies by advancing a causal understanding of this association in terms of dose–response associations, establishing the plausibility of this association in terms of underlying biological and behavioural

Table 3 Regression coefficients (95% confidence intervals) of heart rate variability (phase 7) and morning rise in cortisol (phase 7), by cumulative work stress (phases 1–2): Whitehall II respondents, all ages

	All ages	*n*
Log of low frequency power		
No report of work stress	0.00	2769
One report	−0.09 (−0.23 to 0.04)	211
Two reports	−0.14 (−0.25 to −0.02)	310
P-value for linear trend	<0.01	
Log of high frequency power		
No report of work stress	0.00	2769
One report	−0.05 (−0.21 to 0.11)	211
Two reports	−0.14 (−0.27 to 0.00)	310
P-value for linear trend	<0.05	
Log of SD of NN intervals		
No report of work stress	0.00	2769
One report	−0.05 (−0.12 to 0.01)	211
Two reports	−0.05 (−0.10 to 0.00)	310
P-value for linear trend	<0.05	
Morning rise in cortisol		
No report of work stress	0.0	2368
One report	0.00 (−1.85 to 1.85)	169
Two reports	−0.60 (−2.11 to 0.91)	274
P-value for linear trend	0.45	

All models are adjusted for age, sex, employment grade (phase 1), total cholesterol (phase 1), hypertension (phase 1), smoking history (phase 1), and other health behaviours (phase 3). In addition, morning rise in cortisol is adjusted for waking up time.

mechanisms, and demonstrating the specificity of this association among working-age populations.

There are relatively few studies which have found associations between work stress and (un)healthy behaviours. Work stress is associated with smoking and exercise,[25] whereas fatty food intake increases under stressful conditions.[26] Work stress has also been linked with problem drinking, although in this cohort, non-drinkers had the highest risk of CHD (and were more likely to report work stress).

Previous cross-sectional analysis from the Whitehall II study has shown low control at work is associated with poor autonomic function,[2] and neuroendocrine activation during the working day.[4] Longitudinal analyses from the study have shown that work stress is related to CHD,[14] the metabolic syndrome,[7] and predicts weight gain and incident obesity.[8] This study adds to the literature by showing a linear association between work stress and CHD events, the components of the metabolic syndrome, and lower heart variability. In addition, ∼16% of the effect of work stress on CHD can be explained by the effect of work stress on the metabolic syndrome. As there was little reduction in the association between work stress and the metabolic syndrome after adjusting for health behaviours, work stress may directly affect neuroendocrine stress mechanisms independently of health behaviours, resulting in increased risks of the metabolic syndrome. Direct biological stress-effects are additionally possible through acute work-related stressors triggering MI in susceptible individuals,[27] a possibility which is consistent with the relatively small effect attenuation after adjustment for metabolic components and the fact that the association between work stress and CHD diluted in individuals who stopped work during follow-up. Heart rate variability and cortisol were not measured in the early phases of the study, so their role as a potential mediator of the work stress–CHD association could not be examined. However, adjusting for health behaviours did not change the association between work stress and (low) heart rate variability, suggesting a direct effect on the ANS and neuroendocrine function, rather than indirect effects through health behaviours. The association between work stress and the heart rate variability components suggests that work stress leads to vagal withdrawal and sympathetic saturation indicating a prevalence of sympathetic mechanisms leading to cardiac electrical instability.[28]

Cumulative work stress did not predict a greater cortisol awakening response. However, there was a cross-sectional association between work stress and greater cortisol awakening response. A lag period of around 12 years between exposure (work stress) and disturbances in the circadian rhythm of cortisol may not be optimal for the detection of the hypothesized neuroendocrine effect.

The Whitehall II cohort is a sample of primarily office-based white-collar workers. There were few manual workers in the cohort. It is possible that the mechanisms underlying the association of work stress with CHD may differ in manual workers, although there is little evidence for this hypothesis.[29] Previous research has suggested that the effect of work stress on cardiovascular is less consistent among women.[30] The Whitehall II cohort is predominantly male (67%), although gender-stratified analysis revealed similar estimates of work stress on CHD among younger men and women. Missing data is a common problem all cohort studies face. Non-responders at the later clinical examinations were more likely to report work stress, consume less alcohol, have poor diets and high cholesterol, come from lower employment grades, be smokers, physically inactive, and obese, resulting in an underestimation of these effects in the analyses. The results on the heart rate variability and cortisol are less robust compared with the other outcomes due to the greater non-response at phase 7. The metabolic syndrome has been criticized as a purely artificial construct,[31] not contributing any further information over its component risk factors, although recent results suggest otherwise.[32] This article acknowledges this debate on the metabolic syndrome and presents results on the syndrome itself as well as its components. There may be unmeasured confounders which may 'cause' the association between work stress and CHD, such as other sources of stress and personality type.

This study adds to the evidence that the work stress–CHD association is causal in nature.[10] We demonstrate, within a population of office staff largely unexposed to physical occupational hazards, a prospective dose–response relation between psychosocial stress at work and CHD over 12 years of follow-up. We confirm, during the same exposure period, the plausibility of the proposed pathways involving behavioural mechanisms,

Table 4 Hazard ratios of incident all coronary heart disease events (phases 3–7) by cumulative work stress (phases 1–2) adjusted for health behaviours (phase 3) and metabolic syndrome (phase 3): Whitehall II respondents aged under 50 at phase 2

	Model 1	+All health behaviours	
No report	1.00	1.00	140/3408
One report	1.52 (0.93–2.48)	1.43 (0.87–2.34)	18/292
Two reports	1.56 (1.02–2.37)	1.47 (0.97–2.25)	26/434
P-value for linear trend	0.02	0.04	
		+Metabolic syndrome	
No report	1.00	1.00	144/3419
One report	1.48 (0.90–2.41)	1.44 (0.88–2.36)	18/294
Two reports	1.61 (1.06–2.43)	1.51 (1.00–2.29)	27/439
P-value for linear trend	0.01	0.03	
		+Health behaviours and metabolic syndrome	
No report	1.00	1.00	136/3265
One report	1.41 (0.84–2.37)	1.27 (0.75–2.15)	16/275
Two reports	1.56 (1.02–2.39)	1.38 (0.90–2.13)	25/416
P-value for linear trend	0.03	0.11	

Model 1 is adjusted for age, sex, and employment grade.

neuroendocrine and autonomic activation, and development of risk factor clustering, represented by the metabolic syndrome.[1,2,6,7] Further, those who are older (and are more likely to be retired and less exposed to work stress) are less susceptible to the work psychosocial effect, presenting a coherent pattern in our findings. This study demonstrates that stress at work can lead to CHD through direct activation of neuroendocrine stress pathways and indirectly through health behaviours.

Acknowledgements

We thank all participating civil service departments and their welfare, personnel, and establishment officers; the Occupational Health and Safety Agency; the Council of Civil Service Unions; all participating civil servants in the Whitehall II study; and all members of the Whitehall II study team.

Conflict of interest: none declared.

Funding

The Whitehall II study has been supported by grants from the Medical Research Council; Economic and Social Research Council; British Heart Foundation; Health and Safety Executive; Department of Health; National Heart Lung and Blood Institute (HL36310), US, NIH; National Institute on Aging (AG13196), US, NIH; Agency for Health Care Policy Research (HS06516); and the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socio-economic Status and Health. M.M. is supported by an MRC Research Professorship, H.H. by a public health career scientist award from the Department of Health, and M.K. by the Academy of Finland (grant 117 604).

Appendix 1

Table A1 Distribution of the variables in the analysis

Sex	
Men	3413
Women	6895
Age group (phase 1)	
35–39	2811
40–44	2663
45–49	2107
50–56	2727
Cigarette smoking (phase 1)	
Never smoker	5062
Ex-smoker	3274
0–9 cigarettes/day	540
10–19 cigarettes/day	774
20 or more cigarettes/day	418
Missing	240
Moderate exercise (phase 3)	
Three times/week or more	1284
One to two times/week	3695
One to three times/month	2290
Never/hardly	1042
Missing	2000
Current smoker (phase 3)	
Non-smoker	7168
Smoker	1145
Missing	1995

Continued

Table A1 *Continued*

Fruit/vegetable consumption (phase 3)	
Less than daily	8198
Daily or more	112
Missing	1998
High waist (phase 3)	
Normal	7258
Male >102 cm or female >88 cm	737
Missing	2313
High waist (phase 3)	
Normal	7258
Male >102 cm or female >88 cm	737
Missing	2313
High glucose (phase 3)	
Normal	6006
≥110 mg/dL	1603
Missing	2699
High blood pressure (phase 3)	
Normal	4823
High BP[a]	3351
Missing	2134
Employment grade (phase 1)	
High	3028
Middle	4943
Low	2337
Total cholesterol (phase 1)	
<5.2 mmol/L	2510
5.2–6.2 mmol/L	4006
>6.2 mmol/L	3718
Missing	74
Hypertension (phase 1)	
Normotensive	9461
Systolic BP >140 mmHg/diastolic BP[a] >90 mmHg	832
Missing	15
ISO-strain (phase 1–2)	
No report	6363
One report	529
Two reports	829
Missing	2587
Alcohol consumption (phase 3)	
Low	1625
Moderate	5399
High	1288
Missing	1996
High triglycerides (phase 3)	
Normal	5770
≥150 mg/dL	2252
Missing	2286
Low HDL (phase 3)	
Normal	6477
Male <40 mg/dL, female <50 mg/dL	1542
Missing	2289

Continued

Table A1 *Continued*

Metabolic syndrome (phase 3)	
No syndrome	6897
Metabolic syndrome	1125
Missing	2286
Heart rate variability (phase 7)	$n = 4095$
Morning rise in cortisol (phase 7)	$n = 3490$

[a]Includes those on antihypertensive medications.

Appendix 2

Table A2 Hazard ratios of incident all coronary heart disease events (phases 3–7): Whitehall II respondents aged under 50 at phase 2

Employment grade	
High	1.00
Middle	1.14 (0.84–1.56)
Low	1.65 (1.04–2.60)
Work stress	
No reports of work stress	1.00
One report	1.55 (0.97–2.46)
Two reports	1.62 (1.10–2.40)
Waist circumference	
Normal	1.00
High waist	2.04 (1.35–3.09)
Triglycerides normal	1.00
High triglycerides	1.93 (1.44–2.59)
Glucose tolerance normal	1.00
Glucose intolerance	1.35 (0.96–1.89)
HDL cholesterol	
Normal	1.00
Low	2.03 (1.50–2.74)
Blood pressure	
Normal	1.00
High blood pressure/antihypertensive medication	2.16 (1.63–2.87)
Overall metabolic syndrome	
No syndrome	1.00
Three or more MS components	2.52 (1.82–3.49)
Reported fruit/vegetable consumption	
Daily or more	1.00
Less than daily	2.38 (1.12–5.06)
Physical activity	
Three times/week or more	1.00
One to two times/week	1.51 (0.93–2.46)
One to three times/month	1.91 (1.15–3.16)
Never	2.16 (1.20–3.90)

Continued

Table A2 ***Continued***

Alcohol consumption in the last week	
Non-drinker	1.00
Safe alcohol limits	0.62 (0.43–0.88)
Unsafe alcohol limits	0.71 (0.46–1.11)
Cigarette smoker	
Non-smoker	1.00
Ex-smoker	1.04 (0.75–1.44)
1–9 cigarettes/day	2.15 (1.24–3.72)
10–19 cigarettes/day	1.39 (0.74–2.60)
20+ cigarettes/day	3.06 (1.71–5.49)

Hazard ratios are adjusted for age and sex.

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CLINICAL VIGNETTE

doi:10.1093/eurheartj/ehm436
Online publish-ahead-of-print 16 October 2007

Pulmonary thromboembolism and 'temporary' patent foramen ovalis: ischaemic stroke due to paradox embolism

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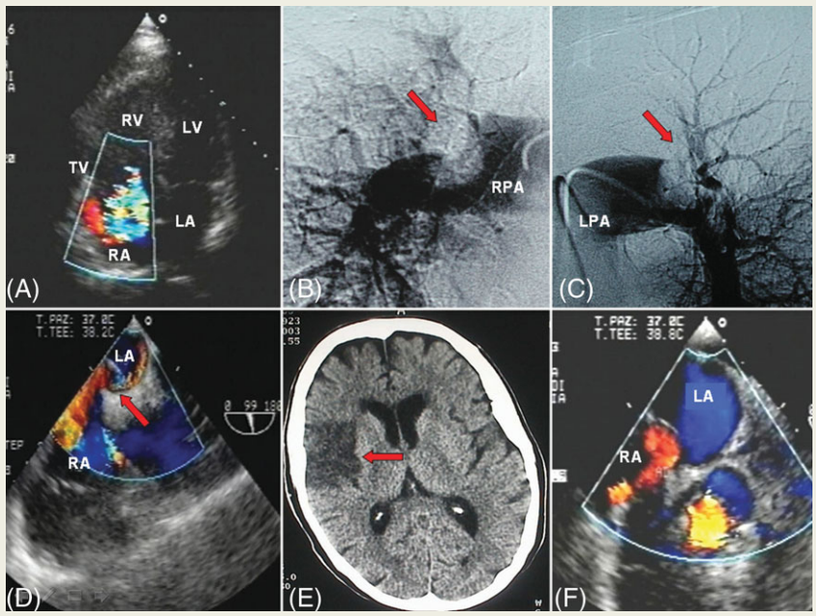

An 80-year-old woman was admitted to the orthopaedic department of our hospital for elective right hip prosthesis implantation after recent fracture of the right femore. The first day after surgery, the patient became symptomatic for dyspnoea. Haemo-gas analysis showed hypoxia with hypocapnia. Slight elevation of D-dimer (14.5 mcg/mL) and normal ECG was found out. An echocardiogram revealed right ventricle (RV) dilatation with free wall hypokinesis and massive tricuspidal valve regurgitation secondary to pulmonary hypertension (Panel A). A floppy interatrial septum was also evidenced. Lower limb echo-Doppler showed left iliac vein thrombosis. Based on this evidence, pulmonary angiography was performed and bilateral thromboembolism diagnosed (Panels B and C). Loco-regional pulmonary thrombolysis and low molecular weight heparin at full dosage were started. During the second day, the patient became symptomatic for left-side emiparesis and afasia. Sovra-aortic trunks duplex scan, colour flow Doppler, and CT brain scan were negative. Transoesophageal echocardiography revealed a floppy aneurismatic interatrial septum (Type C), patent foramen ovalis with right to left shunt in basal conditions and positive micro bubble test (Panel D). Forty-eight hours later, the patient repeated the CT brain scan, showing major ischaemic stroke in right temporal lobe (Panel E). Subsequently, a caval filter was placed. One month later, a transoesophageal echocardiogram revealed aneurismatic floppy interatrial septum without right to left shunt even after Valsalva manoeuvre, and normal pulmonary pressure (Panel F). It seems plausible that the unexpected increase of pulmonary pressure secondary to pulmonary thromboembolism opened the foramen ovalis permitting right to left embolism.

Panel A. Transthoracic echocardiogram showing severe tricuspidal insufficiency. LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle; TV, tricuspidal valve.

Panel B. The red arrow points to massive embolism of the right pulmonary artery (RPA).

Panel C. The red arrow points to massive embolism of left pulmonary artery (LPA).

Panel D. Transoesophageal echocardiogram showing patent foramen ovalis with right-to-left shunting (red arrow).

Panel E. CT brain scan showing ischaemic area in the right temporal lobe (red arrow).

Panel F. Transoesophageal echocardiogram showing floppy interatrial septum without evidence of right-to-left shunting after Valsalva manoeuvre.