

Psychosocial Stress at Work Doubles the Risk of Type 2 Diabetes in Middle-Aged Women

Evidence from the Whitehall II Study

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OBJECTIVE — To investigate the effect of psychosocial stress at work on risk of type 2 diabetes, adjusting for conventional risk factors, among a sample of British, white-collar, middle-aged men and women.

RESEARCH DESIGN AND METHODS — This was a prospective analysis (1991–2004) from the Whitehall II cohort study. The current sample consists of 5,895 Caucasian middle-aged civil servants free from diabetes at baseline. Type 2 diabetes was ascertained by an oral glucose tolerance test supplemented by self-reports at baseline and four consecutive waves of data collection including two screening phases. The job strain and iso-strain models were used to assess psychosocial work stress.

RESULTS — Iso-strain in the workplace was associated with a twofold higher risk of type 2 diabetes in age-adjusted analysis in women but not in men (hazard ratio 1.94 [95% CI 1.17–3.21]). This effect remained robust to adjustment for socioeconomic position and outside work stressors and was only attenuated by 20% after adjustment for health behaviors, obesity, and other type 2 diabetes risk factors.

CONCLUSIONS — Psychosocial work stress was an independent predictor of type 2 diabetes among women after a 15-year follow-up. This association was not explained by potential confounding and mediating factors. More evidence from prospective studies using the same work stress models is needed to support the current findings and provide further information on sex differences.

Diabetes Care 32:2230–2235, 2009

As early as the 17th century, physicians had linked diabetes to “prolonged sorrow” (1). Prolonged sorrow referred, in this case, to what is today called chronic psychosocial stress. The psychiatrist George Engel first proposed the biopsychosocial model of disease as an alternative to the traditional biomedical paradigm with its clear division between mind and body (2). Building on this model, the psychosocial hypothesis is centered on the observation that the social environment has the capacity to elicit adverse psychological reac-

tions and that repeated exposure to these has cumulative physiological impact. Nowadays, psychosocial stress is not among the established risk factors for type 2 diabetes. Two lines of evidence, however, highlight the importance of investigating the role of psychosocial stress in the development of type 2 diabetes. First, psychosocial stress has been linked to increased glucose levels and worse glucose tolerance among diabetic patients (3). Second, psychosocial stress has been linked to obesity (4) and the metabolic syndrome (5), well-established type 2 di-

abetes risk factors. The hypothesized mechanisms linking psychosocial stress to type 2 diabetes include direct psychoneuroendocrine effects and indirect effects through an unhealthy lifestyle (6).

The job strain model, developed by Karasek and Theorell (7), provides a framework for assessing psychosocial stress at work and posits that individuals working in jobs that are simultaneously characterized by high demands and low control are at risk of stress-related ill health and disease. The iso-strain model is an extension of the job strain model, which hypothesizes that individuals experiencing job strain who are simultaneously socially isolated have an even higher risk for disease. Job strain and iso-strain have been associated previously with several disease outcomes including minor psychiatric disorders (8) and cognitive decline (9), heart disease (10), obesity (4), and the metabolic syndrome (5).

There is limited evidence supporting an association between psychosocial work stress and type 2 diabetes, with conflicting findings. In the Nurses Health Study II, job strain was not linked to self-reported type 2 diabetes (11). In three other studies (the Stockholm Diabetes Prevention Program, Vasterbotten Intervention Programme, and the Belstress study), job strain was associated with a higher prevalence of type 2 diabetes among women (12–14). The design of these studies was not prospective and thus did not provide evidence about risk. In addition, these studies did not assess the effect of iso-strain. Thus, our aim was to examine the association between job strain and iso-strain and risk of type 2 diabetes among a sample of British white-collar middle-aged men and women, adjusting for conventional type 2 diabetes risk factors.

RESEARCH DESIGN AND METHODS

The Whitehall II (WII) Study is an occupational cohort established in 1985 with the broad aim of investigating the social gradient in disease

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Received 23 January 2009 and accepted 17 August 2009. Published ahead of print at <http://care.diabetesjournals.org> on 31 August 2009. DOI: 10.2337/dc09-0132.

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outcomes. Participants aged 35–55 years were recruited in 1985–1988 (study baseline) from 20 civil service departments in London, U.K. After the initial clinical examination, further waves of data collection were performed in 1989 (phase 2), 1991–1993 (phase 3, including a clinical examination), 1995 (phase 4), 1997–1999 (phase 5, including a clinical examination), 2001 (phase 6), and 2002–2004 (phase 7, including a clinical examination). The current analysis uses phase 3 as the baseline because it is the first phase in which an oral glucose tolerance test was given. Accurate assessment and exclusion of prevalent cases of diabetes at the beginning of follow-up is pivotal in reducing bias in the results. At phase 3, 8,808 civil servants participated in the study. Ethnic minorities were excluded from analysis ($n = 532$) because of their small number and potential of confounding the association between work stress and type 2 diabetes. Participants with no information on psychosocial work stress ($n = 1,329$) and incident diabetes ($n = 861$) were also excluded. Finally, those with prevalent cases of diabetes at phase 3 were excluded ($n = 191$). The final number of participants eligible for analysis was 5,895 (4,166 men and 1,729 women). The 2,913 participants excluded were older, were more likely to be women and to come from the lowest employment grade, and had slightly higher BMI.

Diabetes ascertainment

At phase 3, an oral glucose tolerance test was administered after an overnight fast or in the afternoon after no more than a light fat-free breakfast eaten before 0800 h. After the initial venous blood sample, participants drank 389 ml of Lucosade (75 g anhydrous glucose) over 5 min. A second blood sample was taken 2 h later. Subsequent clinical assessments for type 2 diabetes took place at phases 5 and 7. Participants were asked, “Has a physician ever told you that you have diabetes?” At phases 3, 5, and 7, if the participant answered “no”, he or she underwent the glucose tolerance test. The definition of diabetes used was a 2-h glucose tolerance test finding of at least 200 mg/dl (≥ 11.1 mmol/l) or, if the 2-h post-load value was missing, a fasting glucose level of ≥ 126 mg/dl (≥ 7.0 mmol/l) or physician-diagnosed diabetes and/or use of diabetes medication.

Psychosocial work stress

The Job Strain Questionnaire was developed to provide an integrating theoretical framework for stress-related job characteristics that can be assessed for the full workforce (7). In more detail, the questionnaire assessed the aggregate of psychological stressors affecting work (job demands), the individual’s potential control over job-related decision making (decision latitude), and the individual’s opportunity to socially interact at work (work social support) (15).

In the WII Study, job demands (4 items; Cronbach’s $\alpha = 0.67$), decision latitude (15 items; Cronbach’s $\alpha = 0.84$), and work social support (6 items; Cronbach’s $\alpha = 0.79$) were measured using the main questions from the Job Strain Questionnaire (7). Some questions from the original scales were excluded because they did not apply to this specific sample of white-collar civil servants. In 18 of 20 departments, 140 personnel managers assessed each job, independently of the holder of the post, for the level of job demands and control. This external assessment could be considered a more objective measure of the work environment in that it was made independently of the participants’ perceptions of the job. There was moderate agreement between the objective and external assessments (weighted κ 0.49–0.51). The empirical association between components of the Job Strain Questionnaire and psychological strain has been demonstrated previously in relation to depression, sleeping problems, and exhaustion (7). In the WII Study, job strain explained the most variance in depression and anxiety symptoms compared with effort-reward imbalance (another self-reported model) and with hindrance/utilization (a model of observed work stress) (16).

According to previous WII publications (17), job strain was present when the participant simultaneously scored high on the job demands questions and low on the decision latitude (job control) questions (defined as above or below the median score on the respective scales). The work social support scale was divided into tertiles, and the lowest tertile was taken as low work social support according to the first publication that investigated iso-strain (15) and in line with previous WII publications (4,5). Participants in the lowest tertile of work social support who were also identified with job strain were defined as having iso-strain. The measures of job strain (8,9,17) and

iso-strain (4,5,18) used in the current analysis have been previously linked to several disease outcomes in the WII Study.

Potential mediating and confounding factors

Participants completed a machine-readable questionnaire that was checked for completeness and validity. An interviewer elicited missing responses. Participants reported their Civil Service grade title, which was assigned to one of six grades based on salary scale. Grade 6 (clerical and office support staff) is defined as low employment grade (19). In the British civil service, employment grade is an accurate measure of status, income, and employment relations and hence socioeconomic position (19).

At study baseline, participants reported how much they were upset from a list of stressful life events from the original validated Life Event and Difficulty Schedule (20). Life events assessed included personal illness, death or illness of a close relative or friend, major financial difficulty, divorce, separation or breakup of a personal intimate relationship, other marital or family problem, and experience of a mugging, robbery, accident, or similar event. In our sample these questions loaded on to a single component in a principal components analysis of eight questions from the original scale (21). This measure was previously linked to depression in our study (21).

Clinical measurements were performed according to a standard protocol. Weight was measured by a Soehnle scale to the nearest 0.1 kg with all items of clothing removed except underwear. Height was measured to the nearest millimeter using a stadiometer with the participant standing completely erect with the head in the Frankfurt plane. BMI was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured twice in the sitting position after 5 min of rest by using a Hawksley random zero sphygmomanometer. Venous blood was taken in the fasting state or at least 5 h after a light, fat-free breakfast. Serum triglycerides were measured by automated enzymic colorimetric methods. HDL cholesterol was measured using phosphotungstate precipitation. C-reactive protein (CRP) was measured using a high-sensitivity immunonephelometric assay.

At phase 3 participants completed a validated 127-item semiquantitative food

frequency questionnaire (22). Participants reported the frequency of eating a common portion size of each item during the previous year. Dietary patterns were identified in sex-specific cluster analysis (PROC FASTCLUS; SAS Institute, Cary, NC). The four clusters identified were 1) healthy (higher-than-average consumption of wholemeal bread and fruits and vegetables; lower-than-average consumption of red meat and sweets), 2) Mediterranean-like (higher-than-average consumption of wholemeal bread, fruits and vegetables, pasta, butter, and wine; lower-than-average consumption of full-cream milk), 3) sweet (higher-than-average consumption of biscuits, cakes, white bread, and pies; average intake of fruit and vegetables), and 4) unhealthy (higher-than-average consumption of meat and sausages, white bread, fries, and full-cream milk; very low consumption of fruit and vegetables). Participants reported the number of drinks of beer, wine, or spirits they had consumed in the last 7 days. In the U.K., a standard measure of spirits, a glass of wine, and a half-pint of beer is considered to contain a unit (8 g) of alcohol. Units of alcohol consumed per week were based on the "Sensible Drinking Recommendations for Adults in the U.K." as no consumption, moderate consumption (1–28 units/week in men; 1–21 units/week in women), and heavy consumption (>28 units/week in men; >21 units/week in women). Self-reported frequency and duration of mild, moderate, and vigorous activities were reported, and hours per week of activity at the three intensity levels were calculated as MET-hours per week. Participants were asked about their smoking status. Participants who reported smoking at phase 3 were defined as current smokers. Those who reported not smoking at phase 3 (and were not identified as current or ex-smokers in previous phases) were classified as never smokers. Ex-smokers were those participants who reported past smoking at phase 3 or current or ex-smoking at previous phases.

Statistical analysis

Cox proportional hazards regression analysis was used to study the associations between baseline psychosocial work stress and risk of type 2 diabetes. The midpoint between the date of screening (or questionnaire completion) in which type 2 diabetes was identified and the date of the previous screening (or question-

naire) was taken as the date of occurrence of each type 2 diabetes case. Participants were censored at the time of loss to follow-up or at the end of 2004 (phase 7). Those with type 2 diabetes and the censored participants contributed their follow-up time to the overall person-years at risk for the period from 1991 to 2004. Schoenfeld residuals were plotted against follow-up time for testing the proportional hazards assumption. All *P* values were nonsignificant, confirming that the proportional hazards assumption was justified. The hazard ratios (HRs) presented in the tables represent relative risks for type 2 diabetes comparing the exposed (work stress) category to the nonexposed (no work stress) category.

Age-adjusted analysis was used to assess the association between job demands, job control, work social support, job strain and iso-strain, and incident type 2 diabetes. Multivariate-adjusted analysis was used to assess the effect of iso-strain on risk of type 2 diabetes with adjustment for other covariates. The base model was adjusted for age. A second model was adjusted for age and employment grade to account for the role of socioeconomic position. A third model was further adjusted for the extent of upset by life events to account for the role of stressors outside work. A fourth model was additionally adjusted for diet patterns, physical activity, alcohol consumption, and smoking status. Our final model was further adjusted for BMI, systolic blood pressure, triglycerides, HDL cholesterol, and CRP. Interactions were tested between the psychosocial work stress variables and sex using the likelihood ratio test.

RESULTS— After 15 years of follow-up and a mean follow-up time of 11.6 years (63,930 person-years at risk) 308 new cases of type 2 diabetes were identified. The incident rate of type 2 diabetes was 4.82 (95% CI 4.31–5.39). Compared with participants with no diabetes, participants with type 2 diabetes during follow-up were older, were more likely to come from the lower employment grade, were upset by life events at a greater extent, and had higher mean BMI, systolic blood pressure, triglyceride levels, and CRP and lower HDL cholesterol (Table 1).

In men, no association was observed between iso-strain, job strain, or any of their components and risk of type 2 diabetes. In women, high job demands, low job control, and low work social support

were not individually associated with incident type 2 diabetes. Job strain (high demands/low control) was associated with a 60% higher risk, and iso-strain with a twofold higher risk of type 2 diabetes (HR 1.94 [95% CI 1.17–3.21]). The sex differences were confirmed by a statistical test for interaction ($P_{\text{interaction}} = 0.019$) (Table 2).

In multivariate-adjusted analysis conducted among 1,225 women with data on all covariates (Table 3), the age-adjusted effect of iso-strain on incident type 2 diabetes (HR 2.33 [95% CI 1.17–3.21]) was reduced by 8% after adjustment for employment grade (2.22 [1.30–3.08]) and remained robust to further adjustment for stressful life events. Additional adjustment for health behaviors resulted in a very small decrease in effect of 3% (2.18 [1.28–3.75]). Further adjustment for BMI, blood pressure, triglyceride levels, HDL cholesterol, and CRP resulted in a further 17% decrease in effect (1.98 [1.14–3.44]).

CONCLUSIONS

Summary of findings

Women exposed to high job demands and low job control (job strain) had a higher risk of type 2 diabetes compared with those not exposed to this combination of work stressors. Women also exposed to low work social support (iso-strain) had an even higher (twofold) risk of developing type 2 diabetes. High job demands, low job control, and low work social support were not individually associated with type 2 diabetes, supporting the theory that the combination of the three is toxic to health (7). Despite the fact that the reliability of the job demands scale is not high ($\alpha = 0.67$), we are confident that psychosocial work stress was accurately assessed in our study using the iso-strain model and that the observed association with incident type 2 diabetes is a valid one.

Comparison with other studies

In the Nurses' Health Study II job strain was not associated with incident type 2 diabetes (11). The discrepancy with the current results is probably due to differences in the population under study. In our sample of civil servants, working conditions differ widely among the 5,766 different jobs assessed and thus the variation in work stress is probably higher (23). In the Nurses Health Study, working overtime was associated with increased risk

Table 1—Baseline (1991–1993) characteristics of the WII participants by diabetes status during 15 years of follow-up

	Diabetes during follow-up	No diabetes
<i>n</i>	308	5,587
Women	29.9 (92)	29.3 (1,637)
Age (years)	50.5 ± 0.35	48.8 ± 0.08
Employment grade*		
High	33.9 (104)	41.5 (2,316)
Medium	50.5 (155)	44.6 (2,489)
Low	15.6 (48)	14.0 (779)
Diet pattern		
Healthy	28.4 (81)	34.1 (1,723)
Mediterranean-type	19.3 (55)	19.1 (965)
Sweet	14.4 (41)	14.2 (716)
Unhealthy	37.9 (108)	32.6 (1,648)
Alcohol consumption		
No	12.0 (37)	10.1 (565)
Moderate	18.2 (56)	15.8 (882)
Heavy	69.8 (215)	74.1 (4,140)
Smoking status		
Never smoker	46.7 (143)	50.5 (2,770)
Ex-smoker	35.6 (109)	36.5 (2,006)
Current smoker	17.7 (54)	13.0 (714)
Physical activity (MET-h/day)	3.17 ± 0.16	3.57 ± 0.04
Upset by life events score†	2.80 ± 0.04	3.24 ± 0.19
Height (cm)†	172.6 ± 0.12	171.1 ± 0.53
BMI (kg/m ²)†	27.7 ± 4.7	25.1 ± 3.5
Systolic blood pressure (mmHg)†	124.6 (0.84)	120.1 (0.18)
Triglycerides (mmol/l)†	2.03 ± 0.09	1.42 ± 0.01
HDL cholesterol (mmol/l)†	1.28 ± 0.02	1.44 ± 0.01
CRP (mg/l)†	3.04 ± 0.32	1.78 ± 1.05

Data are means ± SEM or *n* (%). **P* < 0.05. †*P* < 0.01.

for type 2 diabetes, although the mechanisms underlying this relationship are unclear. In two case-control studies in Sweden and one cross-sectional study in Belgium, job strain was associated with higher odds of type 2 diabetes in women (12–14,24).

Potential pathways

A potential noncausal explanation for the observed effect is that early life adversity

affected both response to stress and type 2 diabetes. The WII Study concentrates on adult life, and thus data on childhood factors are limited. We further adjusted our final model for leg length and birth weight (indicators of early life adversity), which are risk factors for type 2 diabetes in our study, but no decrease in the risk estimates was observed (data not shown), indicating that the association between psychosocial work stress and incident

type 2 diabetes was not confounded by early life conditions.

The observed association could also be confounded by the general psychopathology of affected participants as psychological traits have been previously linked to type 2 diabetes. In our study a series of psychological traits (such as anger and hostility) and minor psychiatric morbidity (General Health Questionnaire) were investigated in relation to incident type 2 diabetes, but no associations were found.

Psychosocial work stress can increase the risk of type 2 diabetes directly by chronic activation of psychoneuroendocrine pathways with the release of catecholamines such as adrenaline and norepinephrine and glucocorticoids such as cortisol, resulting in increased hepatic glucose output, decreased insulin secretion and sensitivity, central accumulation of body fat, hypertension, and an adverse lipid profile. Indirect pathways can operate through lack of adherence to healthy lifestyle behaviors. We provide evidence that health behaviors have no effect as mediating factors in explaining the psychosocial work stress-incident type 2 diabetes association, whereas obesity and other biological risk factors account for 20% of the effect. We can conclude therefore that the majority of the effect of psychosocial work stress on type 2 diabetes is beyond an unhealthy lifestyle and changes in body weight, blood pressure, blood lipids, and systemic inflammation. We speculate that cortisol levels, which are chronically elevated under chronic psychosocial stress, may play a key role in explaining this association. Cortisol can interfere in the normal regulation of blood glucose by altering the body's release and sensitivity to insulin (6). Even though data on salivary cortisol were obtained in the WII Study, this was at phase 5 and for a limited number of participants, so the

Table 2—Age-adjusted HRs (95% CI) for the effect of job strain, iso-strain, and their components on incident type 2 diabetes among middle-aged men and women after 15 years of follow-up in the WII Study

	Men		Women		Men and women		<i>P</i> for sex interaction
	No. of cases/total	HR (95% CI)	No. of cases/total	HR (95% CI)	No. of cases/total	HR (95% CI)	
Job demands	106/2,222	0.82 (0.63–1.07)	40/756	1.06 (0.70–1.62)	146/2,978	0.88 (0.70–1.10)	0.38
Job control	84/1,846	0.86 (0.66–1.13)	63/1,171	1.09 (0.70–1.69)	147/3,017	0.94 (0.75–1.18)	0.36
Work social support	69/1,377	1.00 (0.75–1.33)	31/585	1.08 (0.70–1.67)	100/1,962	1.02 (0.81–1.30)	0.79
Job strain	43/987	0.82 (0.59–1.15)	35/512	1.59 (1.03–2.45)	78/1,499	1.04 (0.80–1.34)	0.019
Iso-strain	25/475	1.07 (0.71–1.63)	20/241	1.94 (1.17–3.21)	45/716	1.33 (0.97–1.83)	0.083

Table 3—Multivariate-adjusted HRs (95% CI) from complete-case analysis among 1,225 women showing the effect of iso-strain on incident type 2 diabetes after 15 years of follow-up in the WII Study

	HR (95% CI)
Age-adjusted	2.33 (1.37–3.95)
Age + employment grade	2.22 (1.30–3.80)
Age + employment grade + life events	2.22 (1.30–3.79)
Age + employment grade + life events + health behaviors*	2.18 (1.28–3.75)
Age + employment grade + life events + health behaviors + biological factors†	1.98 (1.14–3.44)

No. of cases/total = 70/1,225. *Diet patterns, physical activity, alcohol consumption, smoking status. †BMI, height, systolic blood pressure, triglycerides, HDL cholesterol; CRP.

information could not be used in the current analysis.

Sex differences

A null finding for the effect of psychosocial work stress and type 2 diabetes among men was observed in all three studies that have investigated this association in both men and women (12–14). Even though investigation of sex differences was not among the aims of the current study, potential explanations for this observation will be discussed briefly. One explanation is that men misreport their working conditions to a greater extent than women, resulting in information bias. This explanation, however, is excluded as a potential explanation because psychosocial work stress was previously linked to cardiometabolic disease among men in our study (5,17) and elsewhere (25). Because there is a greater concentration of women in the lower employment grades, we also tested whether the observed sex interaction was due to an interaction between stress and employment grade. From sensitivity analysis, we found that there was an effect of iso-strain on incident type 2 diabetes among the men in low employment grades. These data are not presented because of the small number of low-employment-grade men in the analysis (n = 229) but provide a suggestion that any effect of work stress on type 2 diabetes is higher among the low-employment-grade participants, and this could partially explain the sex differences in effect. The proportion of women in the low employment grade in the current analysis was 35% compared with 5% for men.

To our knowledge this is the first study to investigate the prospective effect of psychosocial stress at work on incident type 2 diabetes assessed by an oral glucose

tolerance test. We suggest that future investigations of the effect of psychosocial work stress on type 2 diabetes are performed with stratification by sex and socioeconomic position.

Acknowledgments— The WII Study was supported by grants from the Medical Research Council, Economic and Social Research Council, British Heart Foundation, Health and Safety Executive, Department of Health, National Institutes of Health National Heart Lung and Blood Institute (HL36310) and National Institute on Aging (AG13196), Agency for Health Care Policy Research (HS06516), and the John D. and Catherine T. MacArthur Foundation Research Networks on Successful Midlife Development and Socioeconomic Status and Health.

No potential conflicts of interest relevant to this article were reported.

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 WII Study, and all members of the WII Study team.

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