Work stress in the etiology of coronary heart disease—a meta-analysis

by Kivimäki M, Virtanen M, Elovainio M, Kouvonen A, Väänänen A, Vahtera J

Affiliation: Finnish Institute of Occupational Health, Topeliuksenkatu 41 a, FI-00250 Helsinki, Finland. mika.kivimaki@ttl.fi

This work is licensed under a Creative Commons Attribution 4.0 International License.
Work stress in the etiology of coronary heart disease—a meta-analysis

by Mika Kivimäki, PhD,1, 2 Marianna Virtanen, PhD,2 Marko Elovaainio, PhD,3 Anne Kouvonen, PhD,1 Ari Väänänen, PhD,2 Jussi Vahtera, MD2

Kivimäki M, Virtanen M, Elovaainio M, Kouvonen A, Väänänen A, Vahtera J. Work stress in the etiology of coronary heart disease—a meta-analysis. Scand J Work Environ Health 2006;32(6 special issue):431–442.

Objectives This study focused on estimating the relative risk of coronary heart disease (CHD) in association with work stress, as indicated by the job-strain model, the effort–reward imbalance model, and the organizational injustice model.

Methods A systematic review and meta-analysis of prospective cohort studies were carried out. Studies were eligible if they had published a quantitative estimate of the association between work stress and incident CHD or cardiovascular mortality by January 2006.

Results Fourteen prospective cohort studies were identified. For a total of 83,014 employees, the age- and gender-adjusted relative ratio of CHD for high versus low job strain was 1.43 [95% confidence interval (95% CI) 1.15–1.84], but the ratio decreased to 1.16 (95% CI 0.94–1.43) after adjustment for risk factors and potential mediators. The age- and gender-adjusted risk ratio for a combination of high efforts and low rewards was 1.58 (95% CI 0.84–2.97) for 11,528 employees, and no reduction in the risk ratio was seen after further adjustments. For organizational injustice, the age- and gender-adjusted, and multiple-adjusted relative risks were 1.62 (95% CI 1.24–2.13) and 1.47 (95% CI 1.12–1.95), respectively, for a population of 7,246 men and women. There was little standardization in the assessment of work stress within all three stress models, and significant heterogeneity in the effects of stress was observed between studies. Few studies were available for female samples.

Conclusions Observational data suggest an average 50% excess risk for CHD among employees with work stress. Further research is needed to confirm that a reduction in work stress will lead to a reduction in CHD risk.

Key terms cardiovascular disease; effort–reward imbalance; job strain; mortality; organizational justice; prospective cohort study; psychosocial factors; systematic review; working population.

Activation of the stress system in the hypothalamus and the brain stem helps the body to overcome the influence of short-term physical stressors. However, prolonged overactivity of these systems may cause wear and tear and play a role in coronary heart disease (CHD), infection, and accelerated aging (1). The recognition that the physiological reactions to stress cannot only protect, but also damage the body has provided a basis for epidemiologic research on work stress.

Three models for work stress and coronary heart disease

Work-stress models aim at describing factors that are likely to elicit harmful stress at work in a large proportion of employees. These factors are conceptualized at a level of generalization that allows for their identification in a wide range of occupations. The stress model most often cited and most widely tested is the two-dimensional job-strain model (2–4) (table 1). It proposes that employees who have high job demands and low control over work simultaneously are in a job-strain situation that, if prolonged, increases the risk of stress-related diseases. Job control (or decision latitude) refers to both socially predetermined control over detailed aspects of task performance (eg, pace, quantity of work, policies and procedures, time of breaks, and scheduled hours) and skill discretion (ie, control over the use of skills by the worker). An expanded version of the job...
Work stress in the etiology of coronary heart disease

strain model adds social support to the model as a third component (5). The highest risk of illness is assumed to be related to iso-strain jobs, characterized by high demands, low job control, and low social support.

More recent developments in conceptualizations of work stress have broadened the view from proximal work characteristics to cover aspects of the person and the labor market context. A promising example is the effort–reward imbalance (ERI) model (6, 7) (table 1). This model maintains that an experienced imbalance between high effort spent at work and low reward received is particularly stressful, as this imbalance violates core expectations about reciprocity and adequate exchange at work. Not only high demands and challenges at work, but also overcommitment and heavy obligations in private life (eg, heavy debts) may contribute to a high expenditure of effort. Low rewards can be related to insufficient financial compensation from work, low esteem (eg, lack of help or acceptance by supervisors and colleagues), and poor career opportunities (no promotion prospects, job insecurity, and status inconsistency).

While effort–reward imbalance defines disproportionate costs for an employee in terms of gains received (ie, a distributive injustice condition) the latest research on work stress has also focused on the two remaining aspects of justice (8–10). Procedural justice indicates whether decision-making procedures include input from affected parties, are consistently applied, suppress bias, are accurate, are correctable, and are ethical (11). Relational justice refers to the treatment of workers with fairness, politeness, and consideration by supervisors (11). As justice is a fundamental value in social interaction and the organization of society (12–14), enduring problems with procedural and relational justice have been hypothesized to form an important source of stress at work, the organizational injustice model (8, 9, 15) (table 1).

**Challenge of testing the models**

Several plausible mechanisms have been suggested through which long-term work stress may have an impact on the risk of CHD (16) (figure 1, part 1). They include prolonged overactivation and dysregulation of the autonomic nervous system and the hypothalamus-pituitary-adrenal cortex (HPA) axis; both are assumed to increase disease risk, to disrupt existing disease processes, to act as triggers of acute events, such as heart attack, and to worsen prognosis. Stress is also assumed to drive susceptible persons towards the metabolic syndrome, characterized by insulin resistance, lipoprotein disturbances, reduced fibrolis, and central obesity and to accelerate cellular aging (17–19). In addition to these and other direct biological effects, work stress may influence CHD risk indirectly through increased health risk behavior (20–23), lowered help-seeking behavior, and poor compliance with medical treatment (16).

**Table 1. Sample items from scales assessing the three work-stress models.**

| Conceptual model                             | Sample Item                                                                 |
|----------------------------------------------|------------------------------------------------------------------------------|
| Job-strain model (iso-strain model)          | “Do you have to work very fast?” “I have a good deal of say in decisions about work” (reversed). “When you are having difficulties at work, how often do you get help and support from your colleagues?” |
| Effort–reward imbalance (ERI) model          | “I am often pressured to work overtime.” “Considering all my efforts and achievements, I receive the respect and prestige I deserve at work” (reversed). |
| Organizational injustice model               | “Procedures are designed to hear the concerns of all those affected by the decision” (reversed). “Decisions are made with consistency (the rules are the same for every employee)” (reversed). “My supervisor treats me fairly” (reversed). |

**Figure 1. Hypothesized pathways from work stress to coronary heart disease and alternative explanations for this association. (LDL = low-density lipoprotein)**
However, demonstrating a causal relationship between work stress and CHD is not a simple task due to the possibilities for confounding, reversed causality, bias, and the difficulties with measurements (figure 1, part 2). Randomized controlled trials in this field of research are often impractical and unfeasible. CHD takes decades to develop, and it is associated with a large variety of risk factors in adulthood and from the preemployment period in childhood and adolescence. The possibility of type I error (false positive) arises when these risk factors are additionally associated with work stress. Reversed causality (eg, if early manifestations of CHD bias perceptions of stress) and publication bias would also increase the likelihood of such an error (24). In contrast, potential sources of false null findings (type II error) include a lack of an accurate quantification of long-term stress exposure (in particular if work stress was assessed at one point in time only) (25), insufficient statistical power to detect small or moderate effects, and the operation of the healthy worker effect (a selection bias in which healthier workers remain in stressful jobs and those with health problems drop out).

The present review
At least four narrative reviews on the job-strain model and the ERI model in the etiology of CHD have recently been published (26–29). We performed a systematic review and meta-analysis on updated evidence of these models and the injustice model. Compared with narrative reviews, systematic reviews with meta-analyses are strong in that the method of summarizing the data is transparent and reproducible, and it provides a quantitative estimate of the magnitude of the risk (30). However, as narrative reviews, meta-analyses are open to bias due to validity problems in the studies included. To decrease biases from confounding and reversed causality in the observed work stress–CHD relationships, we focused exclusively on prospective etiological cohort studies (ie, observational data with the strongest internal validity).

Methods
Search strategy
We identified potentially relevant studies through Medline (1979, the year the first work-stress model was published, to January 2006) using a combined text word and medical subheading (MeSH) search strategy. We entered a script, (job strain OR effort-reward OR justice) AND cardiovascular diseases [MeSH] AND prospective. We replicated this literature search with additional terms, such as “job control”, “work stress”, “job stress”, and “psychosocial factors” to examine whether it would add to the identification of relevant studies. We continued searching for potentially suitable studies by using cross-references from original articles and reviews and by interviewing experts in the field (31). We screened titles, key words, and abstracts of the citations identified by the searches and obtained full copies of potentially suitable studies for further assessment.

Criteria for inclusion
We included prospective cohort studies if they had reported quantitative estimates and confidence intervals (or standard errors) of the relative risk (RR) for coronary heart disease or cardiovascular mortality associated with work stress. We excluded studies with no original data (eg, reviews), those lacking relevant measurement of the exposure or outcome, those that were not genuine prospective cohort studies, as well as overlapping papers reporting duplicate data for a same stress model. Among the excluded studies were also those analyzing the components of job strain (demands and control) separately but not the combination of the two, as the job-strain model explicitly states that “cardiovascular risk results not from a single factor, but from the joint effects of the psychological demands of the work situation and the range of decision-making freedom with respect to task organization and skill usage . . . [p 910]” (32). In cases of duplicate reports, we selected the one with a more valid assessment of the exposure or outcome or, if there was no difference in this respect, the paper first published.

Study selection
Two authors (MK, JV) independently assessed the studies identified by the search strategy to identify suitable cohort studies according to the aforementioned criteria. Details about each exclusion criterion were obtained independently and cross-checked for accuracy. All disagreements were resolved by consensus.

Data analysis
We used statistical software provided by Stata version 8 for a standard meta-analysis of observational studies (33, 34). We calculated summary estimates of relative risk for employees high versus low on work stress across the studies by means of a random effects method using inverse variance weighting. The random effects model assumes that the underlying effect of work stress may vary around some overall central effect and is not
necessarily fixed across studies. This approach provides more conservative summary estimates than a fixed effects model assuming that the differences between study results are solely due to chance.

Separate summary estimates were obtained for each of the three stress models, for age- and gender-adjusted data, and for multiple-adjusted data. For the studies of the job-strain model, we made a forest plot in which the contribution of each study to the summary estimate was represented by the area of the box whose center was at the relative risk estimate for job strain from that study. The summary estimate was shown by the middle of a diamond (left and right extremes showing the corresponding 95% confidence intervals). A corresponding summary estimate was reported for the ERI and organizational justice models without forest plots due to the small number of studies. For each summary estimate, we assessed heterogeneity between the studies. We used meta-regression to assess the difference in combined relative risk estimates of CHD for work stress between men and women (34, 35).

To study the presence of publication bias, we evaluated and tested funnel plot asymmetry (available from the first author upon request), as suggested by Begg & Mazumdar (36). Publication bias arises from the possibility that statistically significant findings are more likely to get published than nonsignificant results. Thus publication bias is assumed to be present if larger studies (in which smaller effects can be significant) report smaller effects than small studies (larger effects are needed for significant findings with these data).

**Results**

Our search strategy yielded 58 articles (51 from the electronic search, 5 from cross-references, and 2 from experts), of which 14 included independent primary data on both work stress, as an exposure variable, and CHD, as an outcome, and were prospective cohort studies (figure 2). Replication of the PubMed search with additional terms identified 202 other articles, but none of them met the inclusion criteria.

The 14 included studies comprised a total population of 83,014 employees for the test of the job-strain model, 11,528 employees for the test of the ERI model, and 7,246 employees for the test of the organizational injustice model (table 2). Of the combined study population, 52% were men and 48% were women. The ages ranged between 17 and 65 years, except for the NHANES I study (37), the nurses’ health study (38), and the Framingham offspring study (39), which also included older participants up to the ages of 74, 71, and 77 years, respectively. Seven studies were from European countries (the United Kingdom, Sweden, Finland, Belgium, Germany, Denmark), five came from the United States, and one was from Japan. While the studies on job strain were from Europe, the United States and Japan, only European studies were available for the ERI and injustice models.

**Assessment of exposure**

A large variety of measurement instruments was used to assess work stressors in studies of the theoretical stress models. Typically the studies assessed work stress at one point in time only. Eleven independent studies tested the job-strain model (37–46). While the measure of job strain in all of these studies was generated by cross-tabulating the dichotomized or trichotomized scales of job demands and job control, the items included in these scales varied between the studies. Seven studies analyzed individual scores, but, in four studies, occupation-wise job-strain scores were imputed to the data (table 2).

In the four studies examining the ERI model, individual scores for effort–reward imbalance were constructed with two different approaches, first, by calculating the ratio of the effort and reward scales and then dividing this ratio into thirds or quartiles (43, 47) and, second, by cross-tabulating the dichotomized scales (6, 48). Also regarding the ERI model, the item content of the scales varied between the studies. Seven studies analyzed individual scores, but, in four studies, occupation-wise job-strain scores were imputed to the data (table 2).
独立的研究被进行以评估ERI，一个包括Bosma et al但不包括Kuper et al，另一个包括Kuper et al但不包括Bosma et al。

两项研究评估了组织不公与CHD之间的关联。其中一项研究，长期暴露于不公评估通过3年重复测量的一个5项量表，平均值用于分析（8）。第二项研究在一个单一时间点评估了公平（15）。

### 表2. 工作压力模型和冠状动脉疾病（CHD）特征的研究

| 研究          | 集合 | 参与人数 (N) | 男性 (%) | 年龄 (年) | 压力指标     | 结果          | 持续时间 (年) | 事件 (N) | 调整                  |
|---------------|------|--------------|---------|---------|--------------|--------------|--------------|---------|-----------------------|
| Reed et al, 1989 (40) | The Honolulu heart program, Hawaii | 7377 | 100 | 45–65 | 工作紧张（模拟） | 冠状动脉心脏病 | 18 | 359 | 年龄、吸烟、血压、胆固醇、体力活动、血清粘度 |
| Johnson et al, 1989 (41) | 随机样本的男性工人，瑞典 | 7219 | 100 | 25–65 | 内部紧张（模拟） | 冠状动脉心脏病 | 9 | 193 | 年龄 |
| Siegrist et al, 1990 (6) | Blue-collar men, Germany | 416 | 100 | 25–55 | ERI | 冠状动脉心脏病 | 6.5 | 21 | 年龄、血压、血清胆固醇、冠状动脉心脏病、心理健康、家庭史、教育、社会地位 |
| Alterman et al, 1994 (42) | The Chicago Western Electric study, United States | 1683 | 100 | 38–56 | 内部紧张（模拟） | 冠状动脉心脏病 | 25 | 115 | 年龄、血压、教育、身体指数、胆固醇、糖尿病、身体质量指数 |
| Steenland et al, 1997 (37) | The NHANES I study, United States | 3575 | 100 | 25–74 | ERI | 冠状动脉心脏病 | 16 | 519 | 年龄、血压、教育、身体指数、胆固醇、糖尿病、身体质量指数 |
| Bosma et al, 1998 (48) | The Whitehall II study, United Kingdom | 4393 | 67 | 35–55 | 内部紧张（模拟） | 冠状动脉心脏病 | 5.3 | 251 | 年龄、性别、负性情绪、吸烟、胆固醇、高血压、身体质量指数 |
| Kivimäki et al, 2002 (43) | Industrial employees, Finland | 812 | 67 | 17–65 | 内部紧张 | 冠状动脉心脏病 | 25.6 | 73 | 年龄、性别、职业群、吸烟、体力活动、血压、胆固醇、身体质量指数 |
| Lee et al, 2002 (38) | The nurses' health study, United States | 35038 | 0 | 46–71 | 内部紧张 | 冠状动脉心脏病 | 4 | 146 | 年龄、吸烟、饮酒、高血压、过敏、糖尿病、血清胆固醇、身体质量指数 |
| Kuper et al, 2002 (47); Kuper & Marriott, 2003 (44) | The Whitehall II study, United Kingdom | 10300 | 67 | 35–55 | 内部紧张 | 冠状动脉心脏病 | 11 | 916 | 年龄、性别、负性情绪、吸烟、血压、血清胆固醇、身体质量指数 |
| Eaker et al, 2004 (39) | The Framingham offspring study, United States | 3039 | 56 | 18–77 | 内部紧张 | 冠状动脉心脏病 | 10 | 149 | 年龄、血压、血清胆固醇、身体质量指数、吸烟、糖尿病 |
| Bacquer et al, 2005 (45) | The Belgian job stress project, Belgium | 14337 | 100 | 35–59 | 内部紧张 | 冠状动脉心脏病 | 3.2 | 87 | 年龄、教育、身体指数、吸烟、糖尿病、血压、血清胆固醇、身体质量指数、吸烟、工作 |
| Uchiyama et al, 2005 (46) | The hypertension follow-up group study, Japan | 1615 | 56 | 40–65 | 内部紧张 | 冠状动脉心脏病 | 5.6 | 47 | 年龄、血压、身体指数、肌纤维化、血压、血清胆固醇、身体质量指数 |
| Kivimäki et al, 2005 (8) | Men from the Whitehall II study, United Kingdom | 6442 | 100 | 35–55 | 公正性 | 冠状动脉心脏病 | 8.7 | 237 | 年龄、负性情绪、吸烟、血压、血清胆固醇、身体质量指数、吸烟、工作、内 积极情绪 |
| Netterström et al, 2006 (49) | Men from the MONICA II study, Denmark | 659 | 100 | 30–60 | 内部紧张 | 冠状动脉心脏病 | 13 | 47 | 年龄、社会经济状况、负性情绪、吸烟、血清胆固醇、身体质量指数、血压、血清胆固醇、身体质量指数、吸烟、工作 |
| Elovaara et al, 2006 (15) | Industrial employees, Finland | 804 | 67 | 17–65 | 公正性 | 冠状动脉心脏病 | 25.6 | 73 | 年龄、性别、职业群、吸烟、身体质量指数、血压、血清胆固醇、身体质量指数、工作 |

a) 持续时间
b) Bosma et al, 1998 (48) 和 Kuper et al, 2002 (47) 来自同一群体，前者有更全面的 ERI 评估，但后者有更客观的评估结果。因此，进行了两个meta-分析，一个包括 Bosma et al but not Kuper et al and the other including Kuper et al but not Bosma et al.

### 评估冠状动脉心脏病

在包括的研究中，持续时间从4年到26年不等。对于工作紧张模型，结果定义包括在医院或死亡记录（39, 42–45, 49）中的CHD。
Work stress in the etiology of coronary heart disease

recorded death from cardiovascular disease (CVD) in national mortality registers (41, 43). In the Whitehall II study, self-reported angina was included in the outcome in addition to medical records (45), and the outcome in the nurses’ health study was self-reported myocardial infarction confirmed by medical records (definite or probable myocardial infarction) and next-of-kin or postal-authorities-reported CHD deaths ascertained by records of the National Death Index (38). The outcome in the hypertension follow-up group study was CVD events indicated as initial cerebral hemorrhage, cerebral infarction, subarachnoidal hemorrhage, myocardial infarction, heart failure, aortic aneurysmal rupture, or sudden death (46). In the Honolulu heart program study, data for the outcome included hospitalization and mortality data combined with information from obituary notices in local newspapers, a less-convincing outcome measure (40).

The studies of the ERI model defined their outcomes as self-reported angina or self-reported physician-diagnosed ischemia (48), expert judgments on definite or probable fatal or nonfatal myocardial infarction or sudden cardiac death (6), recorded deaths from CVD from a nationwide mortality register (43), and recorded CHD death, a first nonfatal myocardial infarction or self-reported or definite angina (47).

The two outcomes for the organizational injustice model were the incidence of CHD (defined as a CHD death, a recorded first nonfatal myocardial infarction, or definite angina) (8) and recorded CVD death from a nationwide mortality register (15).

**Summary estimates of relative risk for coronary heart disease**

An age- and gender-adjusted summary estimate across all of the job-strain studies suggested a risk ratio of 1.43 [95% confidence interval (95% CI) 1.15–1.84] for a combination of high work demands and low job control (figure 3). Eight of the ten individual studies reported a significant or nonsignificant positive association between job strain and CHD, but, in the reports from the Honolulu heart program (40) and the nurses’ health study (38), there was a nonsignificant negative association. After multiple adjustments for risk factors and potential mediators, the overall summary estimate of the relative risk (RR) decreased to 1.16 (95% CI 0.94–1.43) (figure 4).

The summary estimate for the ERI model showed a 1.58-fold (95% CI 0.84–2.97) age- and gender-adjusted excess risk for employees reporting high effort and low reward (table 3). When Kuper et al (47) was replaced by Bosma et al (48), the excess risk was higher (RR 2.52, 95% CI 1.63–3.90). Multiple adjustments did not reduce the overall relative risk for effort–reward imbalance (2.05, 95% CI 0.97–4.32 with Kuper; 2.51, 95% CI 1.58–3.90 with Bosma).

The two studies of organizational injustice and CHD reported an age- and gender-adjusted relative risk of 1.62 (95% CI 1.24–2.13) for organizational injustice (table 3). This risk remained statistically significant after additional adjustments for other risk factors including job strain and effort–reward imbalance (RR 1.47, 95% CI 1.12–1.95).

---

**Study (year) gender**

| Study (year) gender | RR (95% CI) |
|---------------------|-------------|
| Reed (1989), m      | 0.94 (0.65–1.36) |
| Johnson (1989), m   | 1.92 (1.15–3.21) |
| Alterman (1994), m  | 1.48 (0.96–2.24) |
| Bacquer (2005), m   | 1.35 (0.73–2.49) |
| Uchiyama (2005), m  | 1.75 (0.49–6.27) |
| Nattanströml (in press), m | 2.40 (1.01–5.68) |
| Kivimäki (2002), m & w | 2.20 (1.16–4.17) |
| Kuper (2002), m & w | 1.57 (1.26–1.96) |
| Lee (2002), w       | 0.80 (0.48–1.34) |
| Uchiyama (2005), w  | 6.66 (0.93–47.70) |

**Summary estimate**

| Summary estimate | RR (95% CI) |
|------------------|-------------|
|                  | 1.45 (1.15–1.84) |

**Figure 3.** Relative risk (RR) of incident coronary heart disease and cardiovascular events and its summary estimate for the prospective cohort studies on the job-strain model by gender. (95% CI = 95% confidence interval, m = male study population, f = female study population)

| Study (year) gender | RR (95% CI) |
|---------------------|-------------|
| Alterman (1994), m  | 1.03 (0.75–1.41) |
| Stearland (1997), m | 1.08 (0.80–1.45) |
| Eaker (2004), m     | 1.18 (0.89–2.01) |
| Bacquer (2005), m   | 1.26 (0.66–2.41) |
| Uchiyama (2005), m  | 1.86 (0.51–6.77) |
| Nattanströml (in press), m | 2.40 (1.01–5.73) |
| Kivimäki (2002), m & w | 2.22 (1.04–4.73) |
| Kuper (2002), m & w | 1.12 (0.81–1.55) |
| Lee (2002), w       | 0.71 (0.42–1.20) |
| Eaker (2004), w     | 0.61 (0.21–1.76) |
| Uchiyama (2005), w  | 9.05 (1.17–69.93) |

**Summary estimate**

| Summary estimate | RR (95% CI) |
|------------------|-------------|
|                  | 1.16 (0.94–1.43) |

**Figure 4.** Multiple adjusted relative risk of incident coronary heart disease and cardiovascular events and its summary estimate for the prospective cohort studies on the job-strain model by gender. (95% CI = 95% confidence interval, m = male study population, f = female study population)
Test of heterogeneity

We observed heterogeneity between studies regarding the relative risks for job strain (Q=17.5, df=9, P=0.04 in age- and gender-adjusted model; Q=15.4, df=10, P=0.12 in multiple-adjusted model) and effort–reward imbalance (Q=3.9, df=1, P=0.05 in age- and gender-adjusted model; Q=6.4, df=2, P=0.04 in multiple-adjusted model). It was not possible to perform this test for the organizational injustice model due to the too small number of studies.

Gender difference in the job strain–coronary heart disease association

A complete test of gender differences in the association between job strain and CHD was not possible because two studies reported only risk ratios for men and women in combination. However, in both of these studies, two-thirds of the participants were men who also had the vast majority of CHD events. Thus it was possible to compare male or male-dominated samples with female samples.

For all of the male or male-dominated samples, a significant or nonsignificant positive association between job strain and CHD was reported, with the exception of samples from the Honolulu heart project study, which reported an inverse nonsignificant association (40). For the three female samples included in the meta-analysis, a nonsignificant inverse association between job strain and CHD was observed in two studies and a positive association was shown in one study with only two CVD events in the group of women with job strain. The formal test of gender difference failed to reach statistical significance (P=0.21 for age-adjusted model, P=0.25 for multiple-adjusted model).

Lack of studies with female samples prevented the test of gender differences for the ERI and injustice models.

Test of publication bias

We found some evidence for publication bias. The funnel plots for the age- and gender-adjusted and multiple-adjusted job-strain studies appeared to be asymmetric, and the corresponding P-values for publication bias in Begg’s test were 0.09 and 0.04, respectively. However, exclusion of the smaller studies (<1000 participants or <50 CHD or CVD events, 3 studies) (43, 46, 49) had little effect on the overall excess risk related to job strain (the age- and gender-adjusted summary estimate 1.30, 95% CI 1.01–1.68). The first study of the ERI model (6) reported a two times greater hazard ratio for effort–reward imbalance than the later studies testing this model (43, 47), but no evidence was found for publication bias (P=0.32 in Begg’s test), and exclusion of the first ERI study did not alter the summary estimate (RR for effort–reward imbalance 1.52, 95% CI 0.85–2.70, with Kuper et al and 2.24, 95% CI 1.35–3.71, with Bosma). The two studies of the organizational injustice model provided similar hazard ratios for injustice. All of these findings suggested that publication bias was unlikely to have substantially distorted the findings of our meta-analysis.

Discussion

Work stress is currently not included in the American Heart Association list of established risk factors for CHD, but individual response to stress is acknowledged as a potential contributing factor (www.americanheart.org). According to our meta-analysis of prospective cohort studies published by January 2006, work stress is associated with a 50% excess risk of CHD. To our knowledge, this is the first meta-analysis on the best evidence available on this topic, and it was based on 14 studies, of which 6 were not included in the previous...
Work stress in the etiology of coronary heart disease

...noted, the regression dilution-corrected excess risk of long-term job strain as a CHD risk factor (25). In time exposure measures may underestimate the status of long-term strain, but this is not necessarily the case for others with changing job-strain levels. Data from the British Whitehall II study suggest that the use of single-time exposure measures may underestimate the status of long-term job strain as a CHD risk factor (25). Indeed, the regression dilution-corrected excess risk of CHD for job strain was 30% higher than the corresponding uncorrected estimate in these data.

Third, bias and measurement error may have contributed to false negative results. Two cohorts with null findings included participants at postretirement age [the maximum age was 71 years in the nurses’ health study (38) and 77 years in the Framingham offspring study (39)], and, therefore, the likelihood of recall and survivor biases was increased. In the nurses’ health study, 146 incident CHD cases were detected after the assessment of job strain. However, this assessment took place 16 years after the baseline and involved only 29% of the baseline cohort, excluding over 7000 participants who had a diagnosis of CHD, as well as 38 000 baseline participants who were no longer working (38). If job strain predicts an increased risk of CHD and retirement (16, 27, 54), this selective inclusion has a potential for biasing results towards the null. The third study with negative findings, the Honolulu heart program study, used imputed occupation-based job-strain scores derived from United States data as a whole to men of Japanese ancestry in Hawaii (40). The identification of incident CHD cases was, in part, based on obituary notices in local newspapers. Thus both exposure and outcome may have been imprecisely measured.

Fourth, it is also important to consider type I error (false positive) as a source of mixed findings (ie, the possibility that the observed positive associations between work stress and CHD are spurious), the null findings representing the true estimates. Publication bias may increase the risk of false positive findings, but we found little evidence suggesting that this type of bias would have distorted findings in our meta-analysis. Confounding due to some unmeasured third factors (eg, risk factors from the preemployment period) may artificially inflate associations, a possibility that cannot fully be ruled out in any observational study. However, there is some evidence suggesting that preemployment factors do not substantially confound the association between job strain and CHD risk (55).

Directions of future research

Further studies with more sophisticated assessment strategies are needed to develop a more complete picture of the role of work stress in the etiology of CHD. There has been little standardization in the assessment of work stress, as the survey instruments have varied between studies and many studies have made modifications to the scales. Moreover, the standard questionnaires for the ERI and organizational injustice models have only recently been published; thus the existing follow-up studies on these models rely on preliminary scales or secondary analyses of data originally collected for other primary purposes. Thus replications of work-stress studies with standard instruments (11, 56–58) would be vital to ensure independent assessment of exposure and outcome.
At the same time, however, it is important to recognize that worklife is under continuous change, and this process causes variation in the relative importance of existing stressors and the possibility of new stressors emerging. An interdisciplinary approach may help to update stress models in the future. The job-strain model was developed in the context of industrialization in parallel to a widely applied work-motivation theory with some core aspects of work that are close to the job-control concept (ie, task variety, and autonomy) (59, 60). The ERI model shares elements with the distributive justice model, another work motivation theory (10), and taps features of postmodern flexible worklife, such as temporary employment and job insecurity (61). The most recent developments in work motivation theories involve procedural and relational justice at work (11, 13), which has been shown to be an important moderator of employee responses (62–65). A further parallel between work motivation theories and stress models is the application of the organizational injustice concept in studies of stress as an etiological factor for CHD.

The pathways through which work stress may elicit harmful effects on CHD have remained unclear. This meta-analysis showed that the association between work stress, as indicated by job strain, and CHD substantially decreased after adjustment for covariates, such as socioeconomic position, body mass index, blood pressure, cholesterol concentration, smoking, and sedentary lifestyle. While the interpretation of this finding is not unambiguous, the decrease may provide information about factors that mediate the association between work stress and CHD. Stress has been associated with sleep disturbances (20), increased smoking intensity (21), reduced leisure-time physical activity (22), unhealthy diet (23), increased weight gain and obesity (66, 67), metabolic and hemostatic disturbances (18, 68), reduced heart rate variability and vagal tone (9, 68, 69), early atherosclerosis (70), impaired inflammatory and immune response (71, 72), accelerated cellular aging (19), and other risk factors (1, 17). To determine whether these associations indicate stress mediators, studies directly linking epidemiologic evidence with subsequent intermediate biological and behavioral mechanisms and with cardiovascular endpoints are needed.

Attenuation of the stress–CHD association after adjustments may also imply confounding and a risk marker status for work stress. The long latency period between some distant risk factors and manifest CHD (73, 74) and the fact that CHD is a multietiological disease make it difficult to distinguish between single causal risk factors and risk markers, although this distinction is essential in terms of policy implications. Favorable change in causal risk factors, but not in risk markers, would reduce the risk of CHD and therefore form the target for interventions. In the future, attempts to carry out large-scale work stress intervention studies with long follow-up periods would be of vital importance, as they may increase the understanding of both causality and means of prevention. Additional studies taking advantage of naturally occurring worklife changes could also be helpful. One example of such changes is organizational downsizing, a proxy measure for increases in job strain and effort–reward imbalance among those who keep their jobs (75). In a recent study, downsizing was associated with an increased risk of CVD mortality among such employees, and the greatest excess risk was found in the years immediately following the personnel reductions (76). This time-dependent effect pattern supports a causal, rather than a confounded, association between downsizing and CVD mortality, but further research is needed for confirmation.

Finally, little research has been done to establish risk profiles for people exposed to work stress. The same environmental challenges or stressors are not likely to induce similar stress reactions in all people, but factors determining groups at greatest risk of CHD under stress have remained unclear. Thus future research should also focus on interactions between work stress, genetic predispositions, and health behavior to improve the predictive validity of stress models.

Concluding remarks

Traditional occupational hazards, such as exposures to toxic chemicals, cold, and noise, may account for only part of the effect of work on health. Work stress refers to the aspects of work design, organization, and management, and their social and organizational contexts, that have the potential to cause harm to employee health. This paradigm, in addition to the conventional physicochemical approach, is suggested to form an essential part of contemporary occupational health research. We found an overall predictive association between work stress and CHD with about 50% excess risk among stressed employees, but we also acknowledged several methodological limitations in the existing evidence. A meta-analysis provides an objective summary of current evidence, but is open to the same threats of validity as the single studies that form the combined data base. Thus further research in contemporary worklife is needed to clarify the role of work stress in the etiology of CHD.

Acknowledgments

This study was supported by the Finnish Work Environment Fund and the Academy of Finland (projects 117604, 105195, and 110451).
Dr Kouvonen was a visiting scientist at the University of Nottingham when this paper was prepared.

References

1. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998;338:171–9.
2. Karasek RA. Job demands, job decision latitude and mental strain: implications for job redesign. Adm Sci Q. 1979;24:285–307.
3. Karasek R, Baker D, Marxer F, Ahlbom A, Theorell T. Job decision latitude, job demands, and cardiovascular disease: a prospective study of Swedish men. Am J Public Health. 1981;71:694–705.
4. Karasek R, Theorell T. Healthy work: stress, productivity, and the reconstruction of work life. New York (NY): Basic Books; 1990.
5. Johnson JV, Hall EM. Job strain, work place social support, and cardiovascular disease: a cross-sectional study of a random sample of the Swedish working population. Am J Public Health. 1988;78:1336–42.
6. Siegrist J, Peter R, Junge A, Cremer P, Seidel D. Low status control, high effort at work and ischemic heart disease: prospective evidence from blue-collar men. Soc Sci Med. 1990;31:1127–34.
7. Siegrist J. Adverse health effects of high-effort/low-reward conditions. J Occup Health Psychol. 1996;1:27–41.
8. Kivimäki M, Ferrie JE, Brunner E, Head J, Shipley MJ, Vahtera J. Job strain and leisure-time physical activity in female and male public sector employees. Prev Med. 2005;41:532–9.
9. Wardle J, Gibson EL. Impact of stress on diet: processes and implications. In: Stansfeld S, Marmot M, editors. Stress and the heart: psychosocial pathways to coronary heart disease. London: BMJ Books; 2002:124–49.
10. Macleod J, Davey Smith G, Heslop P, Metcalfe C, Carroll D, Hart C. Psychological stress and cardiovascular disease: empirical demonstration of bias in a prospective observational study of Scottish men. BMJ. 2002;324:1247–51.
11. Kivimäki M, Head J, Ferrie JE, Brunner E, Marmot MG, Vahtera J, et al. Why is evidence on job strain and coronary heart disease mixed?: an illustration of measurement challenges in the Whitehall II study. Psychosom Med. 2006;68:398–401.
12. Kuper H. Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. Semin Vasc Med. 2002:2:267–314.
13. Belkic KL, Landsbergis PA, Schnall PL, Baker D. Is job strain a major source of cardiovascular disease risk? Scand J Work Environ Health. 2004;30:85–128.
14. van Veghel N, de Jonge J, Bosma H, Schaufeli W. Reviewing the effort-reward imbalance model: drawing up the balance of 45 empirical studies. Soc Sci Med. 2005;60:1117–31.
15. Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. Annu Rev Public Health. 2005;26:469–500.
16. Egger M, Davey Smith G, Altman DG. Systematic reviews in health care: meta-analysis in context. 6 ed. London: BMJ Publishing Group; 2005.
17. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283:2008–12.
18. Karasek RA, Theorell T, Schwartz JE, Schnall PL, Pieper CF, Michela JL. Job characteristics in relation to the prevalence of myocardial infarction in the US Health Examination Survey (HES) and the Health and Nutrition Examination Survey (HANES). Am J Public Health. 1988;78:910–8.
19. Woodward M. Epidemiology: study design and data analysis. Boca Raton (FL): Chapman & Hall; 2005.
20. Sterne JAC, Bradburn MJ, Egger M. Meta-analysis in Stata. In: Egger M, Davey Smith G, Altman DG, editors. Systematic reviews in health care: meta-analysis in context. 6th ed. London (UK): BMJ Publishing Group; 2005. p 347–72.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315:629–34.
22. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50:
1088–101.

37. Steenland K, Johnson J, Nowlin S. A follow-up study of job strain and heart disease among males in the NHANESI popula-
mation. Am J Ind Med. 1997;31:256–60.

38. Lee S, Colditz G, Berkman L, Kawachi I. A prospective study of job strain and coronary heart disease in US women. Int J Epidemiol. 2002;31:1147–53.

39. Eaker ED, Sullivan LM, Kelly-Hayes M, D’Agostino RB Sr, Benjamin EJ. Does job strain increase the risk for coronary heart disease or death in men and women?: the Framingham Offspring study. Am J Epidemiol. 2004;159:950–8.

40. Reed DM, LaCroix AZ, Karasek RA, Miller D, MacLean CA. Occupational strain and the incidence of coronary heart dis-
case. Am J Epidemiol. 2004;159:495–502.

41. Johnson JV, Hall EM, Theorell T. Combined effects of job strain and social isolation on cardiovascular disease morbidity and mortality in a random sample of the Swedish male working population. Scand J Work Environ Health. 1989;15:271–9.

42. Alterman T, Shekelle RB, Vernon SW, Burau KD. Decision latitude, psychologic demand, job strain, and coronary heart disease in the Western Electric Study. Am J Epidemiol. 1994;139:620–7.

43. Kivimäki M, Leino-Arjas P, Luukkonen R, Riihimäki H, Vahtera J, Kirjonen J. Work stress and risk of cardiovascular mortality: prospective cohort study of industrial employees. BMJ. 2002;325:857–61.

44. Kuper H, Marmot M. Job strain, job demands, decision latitude, and risk of coronary heart disease within the Whitehall II study. J Epidemiol Community Health. 2003;57:147–53.

45. De Bacquer D, Pelfrene E, Clays E, Mak R, Moreau M, de Smet P, et al. Perceived job stress and incidence of coronary events: 3-year follow-up of the Belgian Job Stress Project cohort. Am J Epidemiol. 2005;161:434–41.

46. Oishiyan T, Kurasawa T, Sekizawa T, Nakasaku H. Job strain and risk of cardiovascular events in treated hypertensive Japanese workers: hypertension follow-up group study. J Occup Health. 2005;47:102–11.

47. Kuper H, Singh-Manoux A, Siegrist J, Marmot M. When reciprocity fails: effort-reward imbalance in relation to coronary heart disease and health functioning within the Whitehall II study. Occup Environ Med. 2002;59:777–84.

48. Bosma H, Peter R, Siegrist J, Marmot M. Two alternative job stress models and the risk of coronary heart disease. Am J Public Health. 1998;88:68–74.

49. Netterström B, Kristensen TS, Sjöl A. Psychological job de-
mands increase the risk of ischaemic heart disease: a 14-year cohort study of employed Danish men. Eur J Cardiovasc Prev Rehabil. 2006;13:414–20.

50. Lundberg U, Mardberg B, Frankenhaeuser M. The total workload of male and female white collar workers as related to age, occupational level, and number of children. Scand J Psychol. 1994;35:315–27.

51. Viäinenä A, Kevin MV, Ala-Mursula L, Pentti J, Kivimäki M, Vahtera J. The double burden of and negative spillover between paid and domestic work: associations with health among men and women. Women Health. 2004;40:1–18.

52. Chandola T, Kuper H, Singh-Manoux A, Bartley M, Marmot M. The effect of control at home on CHD events in the Whitehall II study: gender differences in psychosocial domest-
ic pathways to social inequalities in CHD. Soc Sci Med. 2004;58:1501–9.

53. Krantz G, Berntsson L, Lundberg U. Total workload, work stress and perceived symptoms in Swedish male and female white-collar employees. Eur J Public Health. 2005;15:209–14.

54. Krause N, Lynch J, Kaplan GA, Cohen RD, Goldberg DE, Salonen JT. Predictors of disability retirement. Scand J Work Environ Health. 1997;23:403–13.

55. Kivimäki M, Hintsanen M, Keltikangas-Järvinen L, Elovainio M, Pulkki-Råback L, Vahtera J, et al. Early risk factors, job strain and atherosclerosis among men in their 30s: the cardio-
vascular risk in young Finns study. Am J Public Health. In press.

56. Siegrist J, Starke D, Chandola T, Godin I, Marmot M, Niedhammer I, et al. The measurement of effort-reward imbalance at work: European comparisons. Soc Sci Med. 2004;58:1483–90.

57. Karasek RA, Theorell T. Stress, productivity and reconstruc-
tion of working life. New York (NY): Basic Books; 1990.

58. Hackman JR, Oldham GR. Work redesign. Reading (MA): Addison-Wesley; 1980.

59. Siegrist J, Peter R. Threat to occupational status control and cardiovascular risk. Isr J Med Sci. 1996;32:179–84.

60. Siegel PA, Post C, Brockner J, Fishman AW, Garden C. The moderating influence of procedural fairness on the relationship between work-life conflict and organizational commit-
ment. J Appl Psychol. 2005;90:13–24.

61. Elovainio M, Kivimäki M, Vahtera J. Organizational justice: evidence of a new psychosocial predictor of health. Am J Public Health. 2005;95:105–8.

62. Siegel PA, Post C, Brockner J, Fishman AW, Garden C. The moderating influence of procedural fairness on the relationship between work-life conflict and organizational commit-
ment. J Appl Psychol. 2005;90:13–24.

63. Elovainio M, Kivimäki M, Vahtera J. Organizational justice: evidence of a new psychosocial predictor of health. Am J Public Health. 2005;95:105–8.

64. Kivimäki M, Elovainio M, Vahtera J, Virtanen M, Stansfeld SA. Association between organizational inequity and inci-
dence of psychiatric disorders in female employees. Psychol Med. 2003;33:319–26.

65. Elovainio M, Kivimäki M, Helkama K. Organization justice evaluations, job control, and occupational strain. J Appl Psychol. 2001;86:418–24.

66. Kivimäki M, Head J, Ferrie JE, Shipley MJ, Brunner E, Vahtera J, et al. Work stress, weight gain and weight loss: evidence for bidirectional effects of job strain on body mass index in the Whitehall II study. Int J Obes. 2006;30:982–7.

67. Dallman MF, Pecoraro N, Akana SF, LaFleur SE, Gomez F, Houkshar H, et al. Chronic stress and obesity: a new view of “comfort food”. Proc Natl Acad Sci USA. 2003;100:11696–701.

68. Vrijkotte TG, van Doornen LJ, de Geus EJ. Work stress and metabolic and hemostatic risk factors. Psychosom Med. 1999;61:796–805.

69. Vrijkotte TG, van Doornen LJ, de Geus EJ. Effects of work stress on ambulatory blood pressure, heart rate, and heart rate variability. Hypertension. 2000;35:880–6.

70. Hintsanen M, Kivimäki M, Elovainio M, Pulkki-Råback L, Keski-Vaara P, Juonala M, et al. Job strain and early atheroscle-rosis: the cardiovascular risk in young Finns study. Psychosom Med. 2005;67:740–7.

71. Cohen S, Tyrrell DA, Smith AP. Psychological stress and suscepti-ility to the common cold. N Engl J Med. 1991;325:606–12.

72. Kiecolt-Glaser JK, Marucha PT, Malarkey WB, Mercado AM,
Work stress in the etiology of coronary heart disease

Glaser R. Slowing of wound healing by psychological stress. Lancet. 1995;346:1194–6.

73. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA. 2003;290:2277–83.

74. Galobardes B, Smith GD, Lynch JW. Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. Ann Epidemiol. 2005;16:91–104.

75. Kivimäki M, Vahtera J, Pentti J, Ferrie JE. Factors underlying the effect of organisational downsizing on health of employees: longitudinal cohort study. BMJ. 2000;320:971–5.

76. Vahtera J, Kivimäki M, Pentti J, Linna A, Virtanen M, Virtanen P, et al. Organisational downsizing, sickness absence, and mortality: 10-town prospective cohort study. BMJ. 2004;328:555.

Received for publication: 30 January 2006