Review

Scand J Work Environ Health 2004;30(2):85-128

doi:10.5271/sjweh.769

Is job strain a major source of cardiovascular disease risk?

by Belkic K, Landsbergis PA, Schnall PL, Baker D

Affiliation: Karolinska Institute, Department of Oncology-Medical Radiation Physics, PO Box 260, Stockholm, SE-17176 Sweden. Karen.Belkic@radfys.ki.se

Refers to the following texts of the Journal: 1996;22(4):241-242 1999;25(2):85-99 1997;23(4):257-265 1998;24(3):197-205 1996;22(2):139-145 1998;24(1):54-61 1998;24(5):334-343

The following articles refer to this text: 2004;30(2):81-83; 2006;32(6):431-442; 2006;32(6):473-481; 2006;32(6):515-527; 2007;33(1):1-3; 2008;34(1):48-54; 2008;34(1):40-47; 2008;34(4):288-296; 2009;35(4):284-293; 2011;37(6):455-463; 2012;38(6):489-502; 2013;39(1):106-111; 2014;40(5):441-456; 2015;41(3):280-287; SJWEH Supplements 2008;(6):33-40; SJWEH Supplements 2008;(6):41-51

Key terms: angina pectoris; cardiovascular death; cardiovascular disease; coronary artery disease; decision latitude; IHD; ischemic heart disease; job control; job strain; myocardial infarction; psychological demand; review; risk; skill discretion; work control

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/15127782

Review

Scand J Work Environ Health 2004;30(2):85–128

Is job strain a major source of cardiovascular disease risk? [1]

by Karen L Belkic, MD,[2,3] Paul A Landsbergis, PhD,[4] Peter L Schnall, MD,[5] Dean Baker, MD[5]

Belkic K, Landsbergis PA, Schnall PL, Baker D. Is job strain a major source of cardiovascular disease risk? *Scand J Work Environ Health* 2004;30(2):85–128.

Empirical studies on job strain and cardiovascular disease (CVD), their internal validity, and the likely direction of biases were examined. The 17 longitudinal studies had the highest validity ratings. In all but two, biases towards the null dominated. Eight, including several of the largest, showed significant positive results; three had positive, nonsignificant findings. Six of nine case–control studies had significant positive findings; recall bias leading to overestimation appears to be fairly minimal. Four of eight cross-sectional studies had significant positive results. Men showed strong, consistent evidence of an association between exposure to job strain and CVD. The data of the women were more sparse and less consistent, but, as for the men, most of the studies probably underestimated existing effects. Other elements of causal inference, particularly biological plausibility, corroborated that job strain is a major CVD risk factor. Additional intervention studies are needed to examine the impact of ameliorating job strain upon CVD-related outcomes.

Key terms angina pectoris, cardiovascular death, coronary artery disease, decision latitude, ischemic heart disease, job control, myocardial infarction, psychological demands, skill discretion, work control.

Clinicians are often called upon to assess the cardiovascular work fitness of patients. As they attempt to make an informed judgment, a fundamental question arises: is the work environment fit, or conducive, to cardiovascular health? With technological advances, jobs characterized *purely* by heavy physical demands have become progressively less common. New types of work-related challenges and burdens primarily affecting the higher nervous system of humans (ie, psychosocial stressors) are more and more frequently encountered. Yet most of the clinical guidelines relevant to the interface between the workplace and the patient's cardiovascular system continue to focus upon levels of physical exertion.

Hu & Speizer (1) underscored the importance of identifying job-related and other environmental hazards that contribute to a given disease process. They noted that "physicians commonly treat the sequelae of such disease in the practice of medicine; however, unless the underlying connection with hazardous exposures is identified and mitigated, treatment of the manifestations rather than the cause at best only ameliorates the condition. At worst, the neglect of hazardous exposures may lead to both failure of treatment and failure to recognize a public health problem with wide significance [p 19]."

Several decades ago, occupational and environmental health research raised the concern that exposure to psychosocial stressors in the modern work environment may be related to cardiovascular disease (CVD). It was clear, however, that the evidence would be difficult to obtain, that a myriad of thorny methodological problems would arise, and that the critical obstacle would be the theoretical conceptualization, modeling, and measurement of workplace stressors. A major breakthrough came in 1979 with the introduction of the job strain (demand-control) model (2). The model was developed for work environments in which stressors are "chronic, not initially life-threatening and the product of sophisticated human organizational decision making. In decision

1 Portions of this paper were presented in abstracts to the 3rd International Congress on the Work Environment and Cardiovascular Disease, International Commission on Occupational Health, March 2002, Düsseldorf, Germany, and to the APA NIOSH Congress: Work, Stress and Health, March 2003, Toronto, Canada.

2 Karolinska Institute, Stockholm, Sweden.

3 Institute for Health Promotion and Disease Prevention Research, University of Southern California School of Medicine, Los Angeles, California, United States.

4 Department of Community Medicine, Mount Sinai School of Medicine, New York, New York, United States.

5 Division of Occupational & Environmental Medicine, Department of Medicine, University of California at Irvine, College of Medicine, Irvine, California, United States.

Reprint requests to: Dr Karen Belkic, Adjunct Associate Professor of Preventive Medicine, Karolinska Institute, Department of Oncology-Medical Radiation Physics, PO Box 260, Stockholm, SE-17176 Sweden. [Karen.Belkic@radfys.ki.se]

making the controllability of the stressor is critical, and it becomes more important as increasingly complex and integrated social organizations develop, with ever more complex limitations on individual behavior [p 78]". The model has two components: "psychological demands, and a combined measure of task control and skill use, or decision latitude [p 78]". Job strain occurs when the human organism is overloaded psychologically and at the same time deprived of control over the work environment, a combination which is predicted to give rise to increased risk of stress-related illness (3, p 78). The basic components of the two dimensions are summarized in table 1. A third dimension, social isolation, was later added to the model, with the worst situation being "iso-strain": high demands, low decision-making latitude, plus lack of social support (5).

Exposure to job strain can be assessed from self-report via a questionnaire, with the dimensions operationalized in the form of short, general instruments, most frequently the job content questionnaire (JCQ) or the psychosocial job strain questionnaire (PSJSQ) (6–8). These measures are feasibly administered in field and epidemiologic studies. Data linkage methods have been developed in the United States and Sweden, so that exposure to job strain (as well as to "iso-strain" in Sweden) can also be inferred from occupational titles alone [ie, the imputation method (9–10)]. External assessment of job characteristics (eg, expert observer) is yet another method for obtaining exposure data. [See the work of Greiner & Krause (11).]

The job-strain model has been the model most widely used for evaluating the psychosocial work environment and its potential impact upon the cardiovascular system,

Table 1. Basic components of the job-strain model, derived from the work of Karasek & Theorell (4).

Component	Demand
Psychological job demands	Job requires very hard work
	Job requires very fast work
	Job requires excessive work
	Job involves conflicting demands
	Job involves not having enough time to get the job done
Decision latitude	
Skill discretion	Job requires learning new things
	Job provides opportunities to develop one's skills
	Job requires a high level of skill
	Job requires creativity
	Job entails a variety of things to do
	Job does not involve a lot of repetitive work
Decision authority	Job allows making one's own decision
	Job provides a lot of freedom as to how the work gets done
	Job provides a lot of say on the job
	Job allows taking part in decisions affecting oneself

with some studies incorporating the third dimension of social isolation as well. Since the introduction of the model, many empirical investigations have been published concerning the relation between job strain and CVD outcomes, including acute myocardial infarction (MI), coronary artery disease (CAD), and CVD-related mortality. Many of these studies report significant positive findings, and job strain is increasingly receiving attention as a potential contributor to CVD (12–14). On the other hand, there have been several nonconfirmatory findings concerning job strain and CVD outcomes published in large-scale studies. These results spurred some questions concerning the strength and consistency of the evidence.

Several in-depth reviews (13, 15–19) have been published concerning the empirical data on the etiologic role of psychosocial workplace factors (in some of these also outside work) and CVD. One of these reviews (16) focused explicitly on job strain. However, a comprehensive and systematic assessment of the internal validity of the current body of reported results is needed. A key issue yet to be addressed is the *direction* in which methodological issues would most likely be acting, delineating situations that would increase the likelihood of obtaining null results and those that could lead to an overestimation of any association.

In this paper, we have used a predefined set of criteria to examine each of the empirical investigations on job strain and CVD. The criteria were developed specifically to assess the methodological issues affecting the internal validity of studies on this topic, and, whenever possible, to identify the direction in which the results would most likely be affected. We have not only addressed the strength and consistency of the association, but also the other major elements of causal inference as well. Particular attention has been devoted to exploring the viability of alternative hypotheses, as well as the question of biological plausibility (ie, what are the possible mechanisms through which job strain could affect the cardiovascular system). This critical review has thereby sought to provide a more definitive answer to the question "Is job strain a major CVD risk factor?" The clinical implications of the conclusion have also been explored.

Methods used for the empirical review

Identification and inclusion of relevant studies

Search strategy

A computer-based search was carried out using Medline, via OVID, from 1966 to January 2002. The search terms were entered as text words in the title, abstract, or other searchable fields (mesh terms, etc). For the independent variable, the search terms were job strain, iso-strain, decision latitude, psychological demands, work control,

job control, skill discretion, decision-making authority and intellectual discretion. These terms were combined with search terms for the dependent variable: myocardial infarction, angina pectoris, ischemic heart disease, coronary artery disease, and cardiovascular death. A senior medical information specialist replicated this strategy. Bibliographies of relevant articles and personal files were also reviewed.

Inclusion criteria and procedure

Articles were chosen for review if they fulfilled the following criteria: (i) exposure to job strain was assessed or imputed via its two major workplace dimensions, psychological demands plus any of the following: decision latitude, skill discretion, decision authority and decision control, as these directly relate to the dependent variable, (ii) any of the following were included as the dependent variable: CAD, manifestations of ischemic heart disease (IHD) (angina pectoris, MI) or mortality from cardiovascular causes, (iii) a case–control, cross-sectional or cohort design was used, (iv) the study was empirical, and (v) the complete study was published in English as a full-length article in a peer-reviewed journal. More than one publication by a given author or authors was included in the review insofar as either the group(s) under study, the endpoints, or the design differed. If two or more studies by the same author(s) offered complementary information but had the same design, endpoint, and study group, they were combined and analyzed together.

Whenever self-report tools other than the JCQ or PSJSQ (7, 20) or their earlier versions were used to assess the demand and control dimensions, two of the authors independently reviewed the described methods to determine whether they were sufficiently compatible with the job-strain model. This procedure was performed in a blinded fashion. Formulations focusing primarily on the individual's subjective reaction to the work environment (eg, "how stressed are you by ...") rather than on its objective characteristics were excluded. As a minimal guideline, it was required that at least one item from each of the major job-strain dimensions be included and that these queries be phrased identically to the original questionnaires or so closely as to be a measure of the original concept (eg, "hectic work" as a measure of psychological job demands). Insofar as the two reviewers disagreed, a third author served as an arbiter.

Included studies

A total of 35 articles was identified that met all the inclusion criteria and needed no further evaluation. Another five articles were independently reviewed by two of the authors, after which those by Hammar et al (21), Sihm et al (22), and Suadicani et al (23) were included, while those by Lynch et al (24) and Murphy (25) were excluded since they did not conform closely enough to the demands or the control dimensions of the job-strain model. Another three, by Billing et al (26), Karasek et al (27), and Messner & Sihm (28)[6] were omitted since only main effects were assessed, and not job strain in relation to the dependent variable. In four instances two or more papers by the same group of authors were combined. The full set of included articles is included in the bibliography.

Assessment of methodological quality[7]

Internal validity assessment

We reviewed all studies fulfilling the aforementioned criteria with respect to their methodological strengths and weaknesses, focusing upon the aspects that would seriously compromise the internal validity of the reported results. The 15 validity criteria grouped into four categories were derived from the work of Stock (29). They are described in the appendix. The first category, *assembly of the sample,* includes the avoidance of selection bias, the avoidance of nonresponse bias, and the application of appropriate exclusion criteria. The validity of *exposure variable assessment* was evaluated by five criteria related to the assessment of point exposure to high psychological demands and to low control, the avoidance of recall bias, the analysis of job strain, the adequate range of variation, and the assessment of temporal aspects of exposure. The four criteria under the category for *confounding and effect modification* were adjustment for relevant demographic confounders, adjustment of relevant biomedical and behavioral confounders, appropriate consideration of gender as an effect modifier, and assessment of other dimensions of the work environment. The validity criteria for the *outcome variable* were related to the assessment of the endpoint itself, whether the assessment of outcome was blinded with respect to exposure status, and the adequate range of variation of the outcome variable.

In most cases, the maximum score was 3 points (optimal). For six of the criteria, there was a possibility for

6 Each of these studies (2 case–control, 1 cross-sectional) had some positive results, such that their omission does not represent a bias towards positive findings. However, because of a substantial number of methodological weaknesses, including confounding (26), low response rates (28), and problems with the assessment of the temporal aspects of exposure (26, 28) and with countermeasures against recall bias (26–28), among others, the positive results do not contribute major supporting evidence for the job strain hypothesis.

7 The internal validity and directionality ratings were performed separately from our review of the results of the studies.

4 points, insofar as the authors had used innovative methods that served to advance the state of the art in this field of investigation. Thus the maximum total score possible was 51. The minimum score for each criterion was usually 1. There was the possibility of a score of 0 for situations that would seriously undermine the validity of a study's conclusions. Two of us independently assessed each of the studies with respect to the 15 validity criteria. In cases of disagreement, a third served as arbiter.

The methodological ratings for each study are presented in tables 2–5 according to the 15 internal validity

Table 2. Internal validity criteria for the assembly of the sample, rated according to the appendix. (CAD = coronary artery disease, CHD = coronary heart disease, CVD = cardiovascular disease, ECG = electrocardiography, IHD = ischemic heart disease, MI = myocardial infarction, MONICA = monitoring of trends and developments of cardiovascular disease, NHANES = National Health and Nutrition Examination Survey)

Study	Internal validity criteria for assembly of the sample		
	Avoidance of selection bias	Avoidance of nonresponse bias	Appropriate clinical exclusion criteria applied
	Score & comment	Score & comment	Score & comment
Longitudinal studies			
Alfredsson et al, 1985 (30)	3 All working men and women in Stockholm	3	1 Previous MI occurrence, cerebrovascular accidents not excluded at baseline
Alterman et al, 1994 (31)	2 67% participation, worker-based, vital status follow-up 100%	2 67% participation, nonrespondents described	3
Bosma et al, 1997 (32); Bosma et al, 1998 (33); Bosma et al, 1998 (34)	2 Worker based cohort: 79% participation at phase 2; 83% in phase 3; subjects with low job control had lower participation rates in phase 2 or 3	2 73% response rate, broken down by employment grade	3 Excluded IHD by clinical examination with ECG, at baseline
Hall et al, 1993 (35)	3 Random population sample, complete follow-up	2 80% response rate, but no description of nonrespondents	1 CVD morbidity assessed at baseline by self-report, but not excluded or taken into account
Hammar et al, 1994 (21); Hammar et al, 1998 (36)	3 Population-based, studied incident cases with nested case-control design, controls chosen at time of case incidence—incidence density sampling	3 Data linkage, implied 100%	3 Linked hospital records to personal identification number ensured that the incident MI was the first hospitalized MI for patients and ruled out hospitalized MI for controls
Hlatky et al, 1995 (37)	0 Evidence for selection attrition (stopped working) among those exposed to job strain or low control and likely selection bias in assembly of original sample	3 99% response rate in Mark et al, 1992 (49)	3 Severe organic heart disease excluded and CHD status at baseline taken into account
Johnson et al, 1989 (38)	3 Population-based cohort, complete follow-up	2 80% participation, nonrespondents not described	1 CVD morbidity assessed at baseline by self-report, but not excluded or taken into account
Johnson et al, 1996 (39)	3 Population-based cohort with nested case-control design, complete follow-up	2 80% participation, nonrespondents not described	1 CVD morbidity assessed at baseline by self-report, but not excluded or taken into account
Karasek et al, 1981 (40)	2 Population-based random sample, nested case-control design—but not incidence-density-sampled controls	2 92% initial response rate, nonrespondents not described	2 Adjusted for self-report of CVD
Kivimäki et al, 2002 (41)	3 Worker-based with 100% follow-up of vital status of cohort	1 Refusals replaced by others on list, no description or figures given	3 Clinical evaluation performed, CVD at baseline excluded
Kuper & Marmot, 2003 (42)	3 Worker-based sample with 99.9% follow-up of vital status, 75.9% follow-up for morbidity in phase 5	2 73–77% nonrespondents broken down by employment grade	3 IHD excluded by clinical examination, with ECG
Lee et al, 2002 (43)	2 Disease-free working survivors 16 years after the initiation of a worker-based (registered nurses) cohort study, 95.5% follow-up	2 78% responded, several characteristics of nonresponders described	3 Those who reported CHD excluded, diagnosis confirmed by review of medical records
Orth-Gomér et al, 2000 (44)	2 Hospital-based selection, clear diagnostic inclusion criteria (acute MI or unstable angina pectoris), <65 years of age; return to work in relation to job strain does not appear to have been assessed	2 43/335 (13%) nonrespondents, 200 participants were working at the time of the examination 3–6 months after the event; nonrespondents included 13 who were too sick and 21 who declined for other reasons, including inability to speak Swedish; no comparison of response rate between those with and without recurrent events	3 Endpoints were recurrent MI and mortality, caseness based on hospital and death registers
Reed et al, 1989 (45)	3 Population-based with complete follow-up of cohort	2 9878/11148, 89% initial response rate, nonrespondents not described	3 CHD excluded, implied by examination
Steenland et al, 1997 (46)	3 Population based sample, 93% follow-up	2 NHANES response rate 70%, nonrespondents described	2 Self-reported CVD

(continued)

Table 2. Continued.

Study	Internal validity criteria for assembly of the sample					
	Avoidance of selection bias		Avoidance of nonresponse bias		Appropriate clinical exclusion criteria applied	
	Score & comment		Score & comment		Score & comment	
Suadicani et al, 1993 (23)	2	Survivors from a 15-year worker-based cohort study	1	75% response rate, nonrespondents not described	3	Self-report confirmed by hospital records
Theorell et al, 1991 (47)	2	Hospital based selection—follow-up of survivors of definite MI occurring prior to age 45 years	2	116/127 (91%) examined within 2 weeks; excluded 6 not working and 31 immigrantes for reasons of language competence; N=79 followed-up	3	Mortality study, excluded survivors with reinfarction or other cardiac complications occurring during follow-up
Case–control studies						
Alfredsson et al, 1982 (50); Alfredsson & Theorell, 1983 (51)	2	Population-based, case-control study	3		3	MI excluded in controls during study period
Bobák et al, 1998 (52)	2	Population-based but survivor bias possible due to case-control design	2	179/191=94% eligible cases, 784/813 (96%) eligible controls, but initial participation rate of controls 75%	3	MONICA protocol
Emdad et al, 1997 (53)	2	CHD patients recruited from the clinic, controls from working population–survivor bias possible	2	13/21 (62%) cases, nonrespondents described, 87/130 (67%) noncase professional drivers were potential participants (based on matching), non-participant noncases not described	2	Noncases had 2-channel ECG during protocol and no known IHD by self-report
Hallqvist et al, 1998 (54); Theorell et al, 1998 (55); Reuterwall et al, 1999 (56); Peter et al, 2002 (57)	2	Population-based, but survivor bias possible due to case-control design	2	Men 82% cases, 75% controls; women 72% cases, 70% controls; some description of nonparticipation among men and women	3	All available medical records scrutinized, health examination of controls performed
Netterstrøm et al, 1999 (58)	2	Consecutive MI cases in two university hospitals, random population sample for controls	2	100% for cases, 90% controls, non-respondents of the latter not described	1	No explicit mention that MI ruled out for controls
Sihm, Dehlholm et al,1991 (22)	2	Hospitalized MI survivors, hospital and population based controls	2	52/54 (96%) eligible cases, 72/86 (84%) eligible controls, non-respondents not described	3	Excluded controls with ECG signs of MI, or history of angina pectoris or intermittent claudication
Theorell et al, 1987 (59)	2	Hospitalized MI survivors, population-based controls	2	116/127 (91%) cases examined, 31 nonnative Swedes excluded, 13 patients excluded because not working; 116/125 (95%) controls agreed to participate, nonrespondents not described	3	History, maximal exercise stress test
Wamala et al, 2000 (60)	2	Cases admitted to cardiac clinic for acute cardiac event, population-based controls	3	292/335 (87%) cases included (of those not included 5 had died); 82.5% controls, controls compared with random population sample, no differences in educational or life-style factors	2	No heart disease symptoms, no hospitalization for previous 5 years among the controls
Yoshimasu & Fukuoka Heart Study Group, 2001 (61)	2	MI cases surviving to rehabilitation, admitted to 22 collaborating hospitals, population-based controls	1	435/507 (86%) cases, 664/1325 (50%) controls, psychosocial characteristics of nonparticipant controls described in detail	2	Referents excluded if prior history of MI, but unclear how assessed
Cross-sectional studies						
Hall et al, 1993 (35)	2	Population-based, cross-sectional	2	80% response rate, nonrespondents not described	3	Cross-sectional study of CVD
Hlatky et al, 1995 (37)	0	Patients coming to tertiary clinical center for angiography to work-up chest pain, no diagnostic entity, 24% had normal coronary arteries, selection bias likely	3	99% response rate from Mark et al (49)	3	Excluded those requiring intensive cardiac care at the time of angiography, pericardial or myocardial disease, baseline CHD status taken into account
Johnson & Hall, 1988 (5)	2	Population-based cross-sectional study	2	79% and 81%, effects of nonresponse on variables concerning illness found to be minimal	3	Cross-sectional study of CVD
Johnson et al, 1989 (38)	2	Population-based, cross-sectional study	2	80% response rate, nonrespondents not described	3	Cross-sectional study of CVD
Karasek et al, 1988 (63)	2	Representative population sample	2	NHANES—response rate 70%, non-respondents described	3	
Netterstrøm et al, 1998 (64)	2	Population-based, cross-sectional study	1	63% response rate, nonrespondents not described	3	
Sacker et al, 2001 (65)	2	Population based, cross-sectional study	1	Response rate not reported	3	Cross-sectional study of CVD
Yoshimasu et al, 200 (66)	0	Patients undergoing angiography for suspected or known IHD, 62% did not have significant CAD, selection bias likely	2	733/838 (87.5%) said to have participated in the study; however, a large number of exclusions were performed for various reasons, such that 197 men remained in the analysis—no description of nonrespondents or of characteristics of the large number of those excluded	3	Caseness defined by extent to coronary artery stenosis, excluded valvular heart disease

Table 3. Internal validity criteria for the assessment of the exposure variables rated according to the appendix. (CAD = coronary artery disease, CHD = coronary heart disease, HANES = Health and Nutrition Examination Survey, HES = Health Examination Survey, JCQ = job content questionnaire, PSJEM = pshychosocial job exposure matrix, PSJSQ = psychosocial job strain questionnaire, QES = quality of employment surveys)

Study	Internal validity criteria for assessment of the exposure variable				
	Valid and reliable assessment of point exposure to psychological demands and control	Avoidance of recall bias for the exposure variable	Analysis of point-exposure to job strain	Adequate range of variation of the exposure variable	Valid and reliable assessment of temporal aspects of exposure
	Score & comment	Score & comment	Score & comment	Score & comment	Score & comment
Longitudinal studies					
Alfredsson et al, 1985 (30)	1 Only 1 item ("hectic job") for demands dimension	3 Imputation study	2 Job strain treated as a dichotomous variable	3	2 1 year follow-up
Alterman et al, 1994 (31)	2 Imputed using QES	3 Imputed	3 Tertile term and analysis of multiplicative interaction	2 Mainly blue-collar workers, use of tertile term only yielded few exposed to job strain	1 25-year follow-up, but stable occupation of cohort
Bosma et al, 1997 (32); Bosma et al, 1998 (33); Bosma et al, 1998 (34)	4 Self-report with White-White-hall validation (4 items for demands) + independent observer	3 Independent observer, self-report in phase I, outcome in phase II or III	3 Multiplicative interaction term calculated, not predictive of outcome, tertiles of control used to assess dose-response	2 All employment grades of white-collar workers, few with job strain (14.7% males, 17.2% females by self-report, 11.9 & 18.8% by external assessment)	3 Exposure assessed twice at 3-year intervals, follow-up of employment during study
Hall et al, 1993 (35)	1 Imputation using PSJEM and 2 items for demands	3 Imputed	2 Dichotomous variable	3	2 7–11 years of follow-up, exposure duration assessed, but not temporal proximity, includes women aged 60–74 years at baseline
Hammar et al, 1994 (21); Hammar et al, 1998 (36)	1 Imputation, demands assessed by two items	3 Imputation	3 All 4 quadrants assessed	3	2 Occupation coded 1–9 years before MI (1970–1975, incident cases 1976–1984), exposure assessed twice—occupationally stable cohort
Hlatky et al, 1995 (37)	3 JCQ with 5 items for demands, but only 6 of the 9 items for decision latitude	3	3 Quotient term and quadrant term	3	2 No repeated exposure, 4-year average follow-up, all employed at baseline
Johnson et al, 1989 (38)	2 Validated questionnaire used, 2 items for demands	3	3 Quintiles	3	1 9-year follow-up, no assessment of cumulative exposure
Johnson et al, 1996 (39)	1 Imputed & 2 items for demands	3 Imputation	3 3 cut points & some description of multiplicative interaction analysis	3	2 Lifetime exposure assessed prior to 14-year follow-up
Karasek et al, 1981 (40)	3 Self-report—2 items for demands, validated and expert ratings	3	2 Dichotomous variable	3	1 No repeated exposure assessment, 9-year follow-up
Kivimäki et al, 2002 (41)	2 4 items for demands, 12 for decision latitude, Cronbach α=0.67 & 0.78, respectively; however, some items inconsistent with dimension (eg, mental strain is an element of job control)	3	3 3 levels of exposure to job strain, demands and decision latitude	3 Both white-collar and blue-collar factory employees	1 Stratified analysis of employees whose occupational group remained unchanged 5 years after assessment of exposure to work stressors but follow-up of vital status >25 years
Kuper & Marmot, 2003 (42)	3 Self-report using Whitehall demand-control questionnaire	3	3 3 levels of exposure to job strain, job demands, and decision latitude, also multiplicative interaction term	2 White-collar workers of various grades	2 11.2-year follow-up, relied upon baseline exposure data, but high correlation between work characteristics in phases 1,2,3 & 5

(continued)

Table 3. Continued.

Study	Internal validity criteria for assembly of the sample				
	Valid and reliable assessment of point exposure to psychological demands and control	Avoidance of recall bias for the exposure variable	Analysis of point-exposure to job strain	Adequate range of variation of the exposure variable	Valid and reliable assessment of temporal aspects of exposure
	Score & comment	Score & comment	Score & comment	Score & comment	Score & comment
Lee et al, 2002 (43)	3 JCQ	3	3 4 quadrants for exposure to job strain, 3 levels of exposure to demands and control	1 Narrow single occupation—84% registered nurses, as well as working former nurses, although in a variety of settings (out-patient, operating room, administration, variance on relevant job characteristics not demonstrated)	1 Job strain at baseline used to categorize exposure status, 4-year follow-up during which 49% of those with job strain at baseline changed exposure status
Orth-Gomér et al, 2000 (44)	3 Swedish PSJSQ 5 items on demands	3	3 Ratio calculated and quartiles used	3 No apparent restriction of occupation	2 Occupationally stable, median follow-up 4.8 years
Reed et al, 1989 (45)	2 Imputation	3	4 Multiplicative interaction term + dose-response	3	1 18-year follow-up, but number of years on job assessed at baseline
Steenland et al, 1997 (46)	2 Imputed / QES	3	3 Quadrants	3	0 12–16 years of follow-up, single assessment of employment status and job characteristics
Suadicani et al, 1993 (23)	1 Control = 1 item, no mention of validation	3	3 Interactions assessed	3	2 3–4 years of follow-up, no assessment of repeated exposure
Theorell et al, 1991 (47)	2 2 questions for demands, influence (3 items), intellectual discretion or variety (1 item each) Swedish PSJSQ	3	3 Quotient term	3	1 All working at baseline, follow-up time 6–8 years, all who died returned to same job
Case–control studies					
Alfredsson et al, 1982 (50); Alfredsson & Theorell, 1983 (51)	1 Imputed and 1 item for demands	3 Imputation	3 Dichotomous exposure, but multiplicative interaction in 1983 paper	3	1 Occupation coded 4–6 years before MI, no repeated exposure assessment
Bobák et al, 1998 (52)	3 The Whitehall questionnaire, 3 items for demands, selected by factor analysis	1 Cases interviewed 2 weeks post-MI	3 All 4 quadrants assessed	3	2 Currently employed but no repeated exposure assessment
Emdad et al, 1997 (53)	3 Swedish PSJSQ	1 Case status known to subject prior to evaluation of workplace characteristics	3 Quotient term	1 Single occupation multivariate comparisons between professional drivers with CHD and controls-professional drivers with hypertension	2 Temporal proximity to employment among cases not described, number of years in occupation assessed
Hallqvist et al, 1998 (54); Theorell et al, 1998 (55); Reuterwall et al, 1999 (56); Peter et al, 2002 (57)	4 Imputation and self-report via Swedish PSJSQ, detailed comparison between the 2 performed for men 3 For women	3 For men 1 For women	4 Synergy index for demands and decision latitude among men 2 Dichotomous for women	3	4 Cumulative exposure, all working mainly full-time within last 5 years
Netterstrøm et al, 1999 (58)	2 4 items for demands includes physical demands & threat avoid- and vigilance α=0.51; 6 items for decision latitude α=0.65 & 0.81	1 Interview of cases in the coronary care unit, by nurses or physicians who likely knew the caseness, no evidence of overreporting, but denial not ruled out	3 4 quadrant assessment	3	2
Sihm, Dehlholm et al, 1991 (22)	3 Orebro-validated questionnaire, workload = quantity of work & level of strain (difficulty of work tasks), also contradictory demands; opportunity for personal development & growth (3 items); autonomy	1 Questionnaire administered during 1st week of hospitalization	2 A few dichotomous combinations	3	2 Single assessment, excluded those on long-term disability or sick leave or asked about current job

(continued)

Table 3. Continued.

Study	Internal validity criteria for assembly of the sample				
	Valid and reliable assessment of point exposure to psychological demands and control	Avoidance of recall bias for the exposure variable	Analysis of point-exposure to job strain	Adequate range of variation of the exposure variable	Valid and reliable assessment of temporal aspects of exposure
	Score & comment	Score & comment	Score & comment	Score & comment	Score & comment
Theorell et al, 1987 (59)	2 Self-report, 2 items for demands, 1 question for variety, 3 questions on influence over work, 1 question on intellectual discretion	1 Overreport ruled out, but not denial	3 Quotient terms	3	1 Cases had been working at least part-time, but no explicit mention of controls, no repeat exposure, not clear when questionnaire was administered
Wamala et al, 2000 (60)	3 Swedish PSJSQ as per Theorell et al (7)	1	3 Quotient term	3	2 Excluded those not currently working, no repeat exposure assessment
Yoshimasu & Fukuoka Heart Study Group, 2001 (6!)	2 Japanese version of the JCQ, questionnaire-based interview, validated, but only 2 items for demands	1 Self-report within 1 month of acute MI in cases	3 Used quadrant term, assessed high, middle and low strain; also tested tertile term	3	2 Excluded those not having a full-time job from job strain analysis, no repeated exposure assessment
Cross-sectional studies					
Hall et al, 1993 (35)	1 Imputed, 2 items for demands	3	2 Dichotomous variable	3	3 Measured lifetime exposure
Hlatky et al, 1995 (37)	3 JCQ with 5 items for demands, but only 6 of 9 latitude items	2 No relation between angina severity and job strain, baseline clinical status known to participant, but apparently not extent of CAD	3 Quotient term & quadrant term	3	2 Currently employed, no repeat exposure assessment
Johnson & Hall, 1988 (5)	2 Self-report, 2 items for demands, reproducibility 0.92, scalability 0.79; control 11 items Cronbach α=0.70	1	4 Synergy index calculated	3	2 No repeat exposure, currently employed
Johnson et al, 1989 (38)	2 2 items for demands, validated questionnaire	1 Exposure and outcome by self-report from same interview	3 Dose-response: iso-strain	3	2 Employed at baseline, no cumulative exposure
Karasek et al, 1988 (63)	2 Imputed QES	3 Imputational	3 Dichotomous, top 20%, also analyzed as a continuous variable	3	1 HES job exposure assessment 7–17 years prior & HANES 6-years prior to assessment of outcome
Netterstrøm et al 1998 (64)	3 Whitehall methods, 5 demand items, 13 control	2 Assessed association between job strain and other pain, as well as angina pectoris and job satisfaction—no association	3 4 quadrants	3	2 Currently occupationally active, no repeat measures
Sacker et al, 2001 (65)	3 Mainly Whitehall JCQ items: 6 for job control, 3 for job demands	1 Self-report of exposure and outcome from same interview	3 4 quadrants	3	2 Currently working full-time, single assessment of exposure
Yoshimasu et al, 2000 (66)	2 2 items for demands, (Cronbach α=0.61)], 3 items for control Cronbach α=0.54, test-retest reliability 0.51	2 Excluded those with previous MI or long-standing angina pectoris, questionnaires distributed prior to angiography, follow-up blinded interview either before or after angiography, specific instructions to answer questions as prior to symptoms or findings of any abnormal results regarding CAD	2 Median cut-points—10% job strain	2 Blue- and white-collar, no restrictions on occupation, but small percentage exposed to job strain	2 Currently working full-time, no repeated exposure assessment

Table 4. Internal validity criteria for confounding and effect modification according to the appendix. (BMI = body mass index, CAD = coronary artery disease, CHD = coronary heart disease, HDL = high-density lipoprotein, HRT = hormone replacement therapy, LDL = low-density lipoprotein, SCRF = standard cardiac risk factors, SES = socioeconomic status)

Study	Internal validity criteria of confounding and effect modification							
	Adjustment for relevant demographic confounders		Adjustment for relevant biomedical and behavioral confounders		Stratification by gender		Assessment of other dimensions of the work environment	
	Score	Comment	Score	Comment	Score	Comment	Score	Comment
Longitudinal studies								
Alfredsson et al, 1985 (30)	3	Adjusted for nationality, income & residence type	2	Adjusted for age, smoking & some other biomedical SCRF	2	Stratified analysis, but not adjusted for HRT or oral contraceptives	3	Explored interaction between hectic work & sweaty work and between hectic work & heavy lifting, also assessed irregular and long workhours, punctuality, gas and dust exposure, risk of explosion, draft
Alterman et al, 1994 (31)	4	Job strain – SES assessed	3	Strain-biomedical SCRF interaction done—but no results, also no strain-behavioral interaction	3		2	Occupational class
Bosma et al, 1997 (32); Bosma et al, 1998 (33); Bosma et al, 1998 (34)	3	Assessed interaction of SES and dimensions of job strain, London—no assessment of immigrant status or ethnicity	4	Detailed assessment of behavioral factors including interaction effects; adjustment for smoking, cholesterol, high blood pressure, BMI	2	Gender-stratified, no mention of oral contraceptive, HRT, menopause	3	Effort-reward imbalance, social support, employment grade
Hall et al, 1993 (35)	4	Interaction between SES & job characteristics	2	Age-adjusted	2	Only women, no adjustment for oral contracep-, tives, HRT, menopause, LDL, fibrinogen	2	Occupational class
Hammar et al, 1994 (21); Hammar et al, 1998 (36)	3	Adjustment for SES	2	Age-adjusted	2	No HRT, oral contraceptives, menopause, LDL, fibrinogen	3	Interaction assessment for social support, long workhours, noise all by imputation, occupational class
Hlatky et al, 1995 (37)	1	No adjustment for SES which differed significantly by CAD severity, no race or ethnicity adjustment	2	Assume as for cross-sectional, age, smoking, diabetes, hypertension, hypercholesterolemia	1	No gender-stratified analysis, only adjustment, no mention of HRT, oral contraceptives, menopause	3	Workhours, physical demands, occupational status
Johnson et al, 1989 (38)	4	Assessed interaction between SES & iso-strain	2	Age-adjusted	3		2	Social support and occupational class
Johnson et al, 1996 (39)	3	Adjusted for education, class & nationality	2	Age, smoking, exercise	3		3	hazards, physical demands, social support, occupational status
Karasek et al, 1981 (40)	3	Stratified by education	2	Age, smoking	3		1	
Kivimäki et al, 2002 (41)	3		2	Physical activity, smoking, cholesterol, systolic blood pressure, BMI	2	Adjusted for gender, interaction effects with work stressors assessed as not significant, no stratified analysis	3	Full evaluation of effort–reward imbalance and occupational group
Kuper & Marmot, 2003 (42)	3	Assessed interaction between SES and job strain, not race or ethnicity in London	2	Age, smoking, serum cholesterol, hypertension, exercise, BMI, alcohol	2	Nonsignificant interaction between job strain and gender, adjusted but not stratified, no adjustment for HRT, menopause	2	Interaction with SES
Lee et al, 2002 (43)	2	Education, husband's education, no mention of race or ethnicity in United States population	2	Smoking, BMI, hypertension, diabetes, hypercholesterolemia, dietary fat intake, physical activity, family history of MI	3	Women only, past use of oral contraceptives, current use of HRT, menopausal status	2	Nursing type and social support
Orth-Gomér et al, 2000 (44)	2	Adjusted for education, not ethnicity in Stockholm	2	Age, standard biomedical factors, but not behavioral—no multiplicative interaction between work & marital stress, no mention of home workhours or children	3	Women only, adjusted for estrogen status	1	No other job stressors
Reed et al, 1989 (45)	4	Interaction between job strain & education, Japanese language ability	2	Several SCRF	3		1	
Steenland et al, 1997 (46)	2	SES but not race or ethnicity—United States study	2	Several SCRF	3		2	Occupational status

(continued)

Table 4. Continued.

Study	Internal validity riteria of confounding and effect modification							
	Adjustment for relevant demographic confounders		Adjustment for relevant biomedical and behavioral confounders		Stratification by gender		Assessment of other dimensions of the work environment	
	Score & comment		Score & comment		Score & comment		Score & comment	
Suadicani et al, 1993 (23)	3		3	Complete assessment of SCRF + relaxation as a behavioral variable	3		2	Social support, occupational status
Theorell et al, 1991 (47)	3	Adjusted for education, immigrants excluded	3	Smoking, cholesterol, family history, type A behavior,& number of stenosed arteries	3		1	No other job stressors mentioned
Case–control studies								
Alfredsson et al, 1982 (50); Alfredsson & Theorell, 1983 (51)	3		2	Age	3		3	Shift work, lifting, piece rate, noise, vibration, accident risk, overtime work
Bobák et al, 1998 (52)	3	Adjustment of SES using various models, but interaction effects not assessed	2	Age, hypertension, other SCRF	3		1	
Emdad et al, 1997 (53)	2	No adjustment for race or ethnicity in Stockholm-based study	2	Age-adjusted, detailed assessment of SCRF and behavioral risk factors, but not adjusted	3		3	Correlation analysis between occupational stress index and dimensions of job strain
Hallqvist et al, 1998 (54); Theorell et al, 1998 (55); Reuterwall et al, 1999 (56); Peter et al, 2002 (57)	3	Interaction between job strain & social class among men, no adjustment for race or ethnicity in Stockholm	3	Age, smoking, hypertension, lipids, overcommintment as a behavioral factor	3	Men gender-stratified analyses	3	Shiftwork, overtime, supervising, effort–reward imbalance among men
	1	Women			2	Women, lipids assessed but not included in job-strain risk estimate	2	Effort–reward imbalance among women
Netterstrøm et al, 1999 (58)	2	Employment sector, not race or ethnicity, Copenhagen	2	Age, smoking	3		3	Workhours, moonlighting, shiftwork, physical demands, social support, piece work
Sihm, Dehlholm et al, 1991 (22)	3	No significant difference in social class, excluded those with linguistic problems, Aarhus	3	Age, assessed interactions between smoking, cholesterol & hypertension on one hand & workplace stressors on the other, patients versus controls	3		3	Job responsibility, job security, job sociability, extra resources for help, 2 x 2 combinations, but no assessment of workhours, shiftwork, physical exposures
Theorell et al, 1987 (59)	3	Education, immigrants excluded, Stockholm	3	Age-matched, adjusted for tobacco consumption & LDL/HDL; glucose tolerance, heredity, type-A behavior & weight-to-height ratio assessed not significant in multiple regression	3		1	
Wamala et al, 2000 (60)	3	Detailed exploration of social class, no adjustment for ethnicity, Stockholm	3	Age-matched, adjusted for smoking, hypertension, exercise, obesity, lipid status, hopelessness, coping	3	Assessed HRT, adjusted for menopausal status	2	Occupational class
Yoshimasu & Fukuoka Heart Study Group, 2001 (61)	1	Percentage blue-collar jobs lower in nonstrain, P=0.13, occupational status not included in multivariate analysis	4	Adjusted for age, hypertension, diabetes, hyperlipidemia, angina pectoris, obesity, cigarette smoking, alcohol, parental CHD; assessed interaction of job strain and type-A behavior	3	Examination of job strain only among men	3	Shift work, social support, job type
Cross-sectional studies								
Hall et al, 1993 (35)	4	Assessed interaction between SES & job characteristics	2	Age-adjusted	2	No HRT, oral contraceptives, menopause, LDL, fibrinogen	2	Occupational status
Hlatky et al, 1995 (37)	1	No adjustment for SES, this differed significantly according to CAD, fewest white-collar workers among those with significant CAD	2	Age, smoking, diabetes, hypertension, cholesterol	1	Adjusted for gender but no gender stratification, women & men significantly differed on outcome, no mention of HRT, oral contraceptives, menopausal status	3	Workhours, physical demands, occupational status
Johnson & Hall, 1988 (5)	4	Stratified analysis by social class, adjustment for immigrant status	2	Age, smoking, exercise	2	Stratified analysis, no mention of HRT, oral contraceptives, menopause	3	Physical demands adjustment, social support interaction assessed

(continued)

Table 4. Continued.

Study	Internal validity riteria of confounding and effect modification			
	Adjustment for relevant demographic confounders	Adjustment for relevant biomedical and behavioral confounders	Stratification by gender	Assessment of other dimensions of the work environment
	Score & comment	Score & comment	Score & comment	Score & comment
Johnson et al, 1989 (38)	4 Interaction between SES and iso-strain	2 Age-adjusted	3	2 Occupational status
Karasek et al, 1988 (63)	3 Education and race	2 Age, smoking, systolic blood pressure	3	2 Physical demands
Netterstrøm et al, 1998 (64)	2 SES adjusted, but not ethnicity or immigrant status, Copenhagen	2 Age, smoking, systolic blood pressure, HDL-to-total cholesterol ratio	2 Stratified analysis was done for men, not possible for women because of empty cell	3 Workhours, social status, social support, job security
Sacker et al, 2001 (65)	2 SES assessed, but not ethnicity, race, or immigrant status	2 Extensive assessment of standard cardiac risk factors but not behavior unrelated to these	3	2 Blue-collar versus white-collar
Yoshimasu et al, 2000 (66)	3 Adjusted for job type as an indicator of SES	4 Type-A behavior interaction assessed, age, standard biomedical risk-factor adjustment	3	2 Workhours, blue-collar work, social support

Table 5. Internal validity criteria for the outcome variable according to the appendix. (CAD = coronary artery disease, CHD = coronary heart disease, CPK = creatine phosphokinase, CVD = cardiovascular disease, ECG = electrocardiography, HANES = Health and Nutrition Examination Survey, HES = Health Examination Survey, IHD = ischemic heart disease, MI = myocardial infarction, WHO = Work Health Organization)

Study	Internal validity criteria for outcome variable		
	Valid assessment of the outcome variable	Assessment of outcome blinded with respect to exposure	Adequate range of variation of the outcome variable
	Score & comment	Score & comment	Score & comment
Longitudinal studies			
Alfredsson et al, 1985 (30)	2 Hospital registry	3 Linkage	2 Hospitalized cases of MI
Alterman et al, 1994 (31)	2 Mortality from death certificates —main result	3 Linkage, also explicit blinding in Ostfeld	3 Whole cohort followed-up for vital status, all cases included
Bosma et al, 1997 (32); Bosma et al, 1998 (33); Bosma et al, 1998 (34)	1 Self-report of IHD	2 Self-report of outcome, but independent as well as self-report of exposure	2 IHD survivors
Hall et al, 1993 (35)	2 National Death Registry	3 Imputation	3 Whole cohort followed-up for vital status, all cases included
Hammar et al, 1994 (21); Hammar et al, 1998 (36)	3 Registry data with previous validation study	3 Imputation	3 Fatal and nonfatal MI
Hlatky et al, 1995 (37)	1 Unclear how follow-up was carried out, states "all patients were contacted" at follow-up intervals to "document out-come" [p 328]	2 Unclear whether self-report of outcome, not explicitly blinded assessment	3 Presumably all participants followed-up regardless of outcome
Johnson et al, 1989 (38)	2 Registry data	3	3 Whole cohort followed-up for vital status, all cases included
Johnson et al, 1996 (39)	2 Registry data	3 Linkage	3 Whole cohort followed-up for vital status, all cases included
Karasek et al, 1981 (40)	3 Validated death certificate	3	3 All CVD deaths included during follow-up period
Kivimäki et al, 2002 (41)	2 Registry data	3 Use of registry	3 CVD mortality, obtained cause of death for all participants who died during the follow-up period
Kuper & Marmot, 2003 (42)	3 National registry data for mortality, clinical records and ECG reviewed by two trained coders	3 Independent review	3 Fatal and nonfatal incident CHD
Lee et al, 2002 (43)	3 WHO criteria for MI, death certificates corroborated by autopsy or hospital records	3 Explicitly blinded	3 Nonfatal MI and fatal CHD
Orth-Gomér et al, 2000 (44)	3 Validated hospital and death registers	3 Based on registry data	2 Complete follow-up of patients hospitalized for cardiac events
Reed et al, 1989 (45)	3 Panel of physicians reviewed the medical data	3	3 Entire cohort followed-up

(continued)

Table 5. Continued.

Study	Internal validity criteria for outcome variable		
	Valid assessment of the outcome variable	Assessment of outcome blinded with respect to exposure	Adequate range of variation of the outcome variable
	Score & comment	Score & comment	Score & comment
Steenland et al, 1997 (46)	2 Hospital records and death certificates	3	3 IHD deaths and hospital discharges for heart disease
Suadicani et al, 1993 (23)	3 Review of death and hospital registry with validity frequently assessed	3 Registry data	3 Complete follow-up of cohort
Theorell et al, 1991 (47)	2 Cardiologist review of reinfarction mortality	2	2 Excluded from analysis those who survived a reinfarction
Case–control studies			
Alfredsson et al, 1982 (50); Alfredsson & Theorell, 1983 (51)	2 Hospital and death registry	3	3 All MI, fatal and nonfatal
Bobák et al, 1998 (52)	3 MONICA protocol	2	2 Survivors of MI
Emdad et al, 1997 (53)	2 Hospitalized cases of IHD events	3 All data analysis performed in a blinded fashion	2 Survivors of IHD events
Hallqvist et al, 1998 (54); Theorell et al, 1998 (55); Reuterwall et al, 1999 (56); Peter et al, 2002 (57)	3 Explicit diagnostic criteria	3 Data linkage in men 2 Women	3 All MI, fatal and nonfatal
Netterstrøm et al, 1999 (58)	2 Severe chest discomfort or ECG signs of MI accompanied by increased CPK to twice the normal level	2 Implied	2 Hospitalized survivors of MI
Sihm, Dehlholm et al, 1991 (22)	2 "Established diagnosis of MI"	2	2 Hospitalized survivors of MI <55 years old
Theorell et al, 1987 (59)	3 WHO criteria for definite MI, CAD by coronary angiography	2	2 Hospitalized survivors of MI <45 years old
Wamala et al, 2000 (60)	3 Explicit diagnostic criteria, including WHO criteria for MI	3	2 Hospitalized survivors of cardiac events
Yoshimasu & Fukuoka Heart Study Group, 2001 (61)	2 Collaborating cardiologists were responsible for the diagnosis of acute MI	2 Implied but not explicit	2 Hospitalized survivors of acute MI
Cross-sectional studies			
Hall et al, 1993 (35)	1 Self-reported CVD	3	2 Survivors only assessed
Hlatky et al, 1995 (37)	3 CAD assessed by coronary angiography, with clear diagnostic criteria	2	2 Excluded patients with unstable angina or other conditions requiring intensive care at time of angiography
Johnson & Hall, 1988 (5)	1	1	2 Survivors only assessed
Johnson et al, 1989 (38)	1 Self-report of IHD, although independent diagnostic system, no objective evidence	1 Self-reported exposure and outcome	2 Only survivors assessed
Karasek et al, 1988 (63)	2 HES review by four physicians, specific ECG, history and blood chemistry for definite MI, reliability assessment made, HANES review of medical records, physical examination, ECG not always available	3 Data linkage	2 Only survivors assessed
Netterstrøm et al, 1998 (64)	1 Self-report only via Rose questionnaire	1 Self-report of exposure and of outcome	2 Only survivors assessed
Sacker et al, 2001 (65)	1 Self-report	1 Self-report of exposure and outcome	2 Survivors of heart disease
Yoshimasu et al, 2000 (66)	3 Explicit diagnostic criteria for stenosis	3	1 Excluded those with long-standing angina pectoris or previous MI

criteria given in the appendix, the criteria being grouped according to their categories, assembly of the sample (avoidance of selection bias, avoidance of nonresponse bias, appropriate clinical exclusion criteria applied) in table 2, assessment of the exposure variable (valid and reliable assessment of point exposure to psychological demands and to control, avoidance of recall bias for the exposure variable, analysis of point-exposure to job strain, adequate range of variation of the exposure variable, valid and reliable assessment of temporal aspects of exposure) in table 3, confounding and effect modification (adjustment for relevant demographic confounders, adjustment for relevant biomedical and behavioral confounders, stratification by gender, assessment of other dimensions of the work environment) in table 4, and the outcome variable (valid assessment of the outcome variable, assessment of outcome blinded with respect to exposure, adequate range of variation of the outcome variable) in table 5.

Directionality

We next asked the question of how these various methodological issues would affect the results and in which direction they would most likely be acting. We examined each of the validity criteria from this perspective, delineating situations that would increase the likelihood of obtaining null results and those that could lead to an overestimation of association. These directionality issues roughly followed the order of the internal validity criteria, although there was no precise one-to-one correspondence between them, since some issues may affect the results in either direction, depending on the specific circumstances. There were also instances in which the way a methodological issue might affect the results could not be determined (eg, a low response rate without any description of the nonrespondents).

The issues that were considered to increase the likelihood of obtaining null results included (i) selection bias in the assembly of the sample, if the participants exposed to job strain but without CVD preferentially entered the study; (ii) selective attrition, if those exposed to job strain or related work stressors selectively stopped working during the follow-up period; (iii) survivor bias (healthy worker effect); (iv) nonexclusion of outcome at baseline leading to dilution of the results; (v) use of the imputation method (imprecise) to define job strain, leading to nondifferential misclassification; (vi) one to two items for assessing psychological demands if the imputation method was used, leading to nondifferential misclassification; (vii) use of a dichotomous variable to define job strain, leading to nondifferential misclassification; (viii) a low percentage of exposure to job strain, leading to a loss of power to detect an existing effect; (ix) single occupation or a limited range of variation of exposure; (x) assessment of exposure to job strain temporally distant from the outcome (studies with long follow-up periods without repeated assessment of exposure status); (xi) lack of a gender-stratified analysis; (xii) likely confounding by another factor, if the relationships were in the opposite direction of the tested association or if several important confounders were not taken into account.

The issues that were considered to increase the likelihood of an overestimation of association were (i) selection bias in the assembly of the sample, if the participants exposed to job strain and with CVD preferentially entered the study; (ii) selective attrition, if those not exposed to job strain or related work stressors selectively stopped working during the follow-up period; (iii) information bias if the outcome was known to the participant at the time of the self-report of exposure; (iv) likely confounding by another factor, if the relationships were in the direction of association. An alternative hypothesis is likely to be operative, whereby a factor other than job strain is the true effect modifier: (v) information bias if the outcome and exposure were both self-reported.

Next, a judgment was made about the overall direction in which the methodological issues were likely to affect the results concerning associations with job strain, as follows: (i) unequivocal bias to the null: several clear and strong biases to the null and no biases to overestimate; (ii) likely bias to the null: a few likely biases to the null and no clear bias to overestimate, (iii) minimal biases: nearly all of the potential sources of bias fully taken into account; (iv) bias possible in both directions; (v) likely bias to overestimate: one or more likely biases to overestimate and no clear bias to the null; and (vi) unequivocal bias to overestimate: several clear and strong biases to overestimate and no biases to the null.

Strength and consistency of the empirical findings with respect to job strain and cardiovascular disease, reviewed in light of the methodological issues affecting the results

The salient details with respect to the results of each of the reviewed longitudinal, case–control, and cross-sectional studies are presented in tables 6, 7, and 8, respectively. Table 9 provides a summary of the relationships between the results and the direction in which the methodological issues were likely to affect each study.

Longitudinal studies

The longitudinal studies (21–23, 30–47) had higher mean total validity ratings than the case–control and cross-sectional studies did. The mean scores of the studies among men were almost identical for the positive, nonsignificant positive, and null studies. The null studies had a somewhat lower mean total score for the women than those that were positive. Of the two longitudinal studies with the highest total scores (score 40), one yielded a significant positive effect estimate (21, 36), while null results were obtained in the other one (45).

Notwithstanding the high overall methodological quality of these investigations, in all but two, biases towards the null dominated. In 11 of the 17 studies, the biases were unequivocal. Biases towards the null were generally due to the use of the imputation method and long follow-up times, with no re-assessment of exposure or even employment status. Persons close to or even above usual retirement age were included in the baseline sample of several of the studies with protracted follow-up (21, 35, 36, 38–40, 44–46); this inclusion would have attenuated the effect estimates even further. The imputation method is particularly problematic for the psychological demand

Table 6. Results of the reviewed longitudinal studies.[a] (BMI = body mass index, CAD = coronary artery disease, CHD = coronary heart disease, CVD = cardiovascular disease, HR = hazards ratio, HRT = hormone replacement therapy, IHD = ischemic heart disease, MI = myocardial infarction, NS = nonsignificant, O = observer-rated, OR = odds ratio, RR = relative risk, SBP = systolic blood pressure, SES = socioeconomic status, SMR = standardized mortality ratio, SR = self-rated, UK = United Kingdom, US = United States, 95% CI = 95% confidence interval)

Study	Participants	Follow-up (years)	Illness outcome	Significant positive associations [b]	Reported nonsignificant, null or significant negative associations [b]	Methodological issues [c] and total validity scores [d]
Studies with significant positive results for job strain and CVD						
Alfredsson et al, 1985 (30)	N=958 096, Swedish, 20–64 years of age, population-based	1	Hospitalized MI (N=1059 men, N=142 women)	Men: punctuality (*age*) SMR 121 (95% CI 110–133), few possibilities to learn new things (*age*) SMR 113 (95% CI 104–123), hectic & monotonous work (*age*) SMR 118 (95% CI 102–135), hectic work & few possibilities to learn new things (*age + income*) SMR≈125 (95% CI≈105–150); women: hectic & monotonous work (*age*) SMR 164 (95% CI 112–233), monotony (*age*) SMR 128 (95% CI 104–157), low influence on workmates (*age*) SMR 133 (95% CI 102–170), low influence on holidays (*age*) SMR 145 (95% CI 114–182)	Men: hectic work (*age*) NS, monotonous work (*age*) NS; women: hectic work (*age*) NS	4 biases to null: non-exclusion of previous MI at baseline, imputation method, 1 item for psychological demands, single cut-point; total validity criteria score 35
Hammar et al , 1994 (21); Hammar et al, 1998 (36)	N=24913 men, N=3535 women, population controls, Swedish, 30–64 years of age, nested case-control study	9	First MI (N=8833 men, N=1175 women)	Men (all): high strain work RR 1.21 (95% CI 1.08–1.35), low decision latitude RR 1.19 (95% CI 1.13–1.25); men (white-collar): hectic work and low influence over workhours RR 1.4 (95% CI 1.1–1.8); women (all): hectic work and few possibilities to learn new things RR 1.3 (95% CI 1.1–1.6), hectic work & low influence on work planning RR 1.3 (95% CI 1.1–1.6), high-strain work RR 1.23 (95% CI 1.01–1.51), low decision latitude RR 1.44 (95% CI 1.25–1.65); women (white-collar): few possibilities to learn new things RR 2.3 (95% CI 1.2–4.6) *(age, county, calendar year)*	Men (blue-collar): hectic work RR 1.2 (95% CI 1.0–1.4), few possibilities to learn new things RR 1.3 (95% CI 0.9–1.9), hectic work & few possibilities to learn new things RR 1.2 (95% CI 1.0–1.4); men (white-collar): hectic work RR 1.0 (95% CI 0.8–1.3), few possibilities to learn new things RR 1.2 (95% CI 1.0–1.4), hectic work & few possibilities to learn new things RR 1.2 (95% CI 1.0–1.6); women (blue-collar): hectic work RR 0.7 (95% CI 0.5–1.1), few possibilities to learn new things RR 2.1 (95% CI 0.9–4.9); women (white-collar): hectic work RR 1.8 (95% CI 0.9–3.7) *(age, county, calendar year)*	3 biases to null: imputation, 2 items for psychological demand, long follow-up outcome (temporally distant to exposure); total validity criteria score 40
Johnson et al, 1989 (38)	N=7219 men, Swedish, 25–65 years of age, population based study	9	CVD mortality (N=193)	Iso-strain (total group) RR 1.92 (95% CI 1.15–3.21), iso-strain (blue-collar) RR 2.58(1.06–6.28) *(age)*	Iso-strain (white-collar) RR 1.31 (95% CI 0.58–2.96) *(age)*	2 biases to null: nonexclusion of CVD at baseline, long follow-up outcome (temporally distant to exposure); total validity criteria score 37
Karasek et al, 1981 (40)	N=1461 men, Swedish, 18–60 years of age, population-based study (nested case-control, N=66 controls)	9	CVD & cerebrovascular mortality (N=22)	High psychological demands OR 4.0 (95% CI 1.2–13.9, high psychological demands & low personal schedule freedom OR 4.0 (95% CI 1.1–14.4) *(age, education, smoking, CHD symptoms matched at baseline)*	Low intellectual discretion OR 1.5 (95% CI 0.4–5.1), low personal schedule freedom OR 1.7 (95% CI 0.6–4.7) (s*ame adjustment as for positive findings)*	3 biases to null: dichotomous variable to assess job strain, long follow-up outcome (temporally distant to exposure), matching controls by CHD symptoms & education attenuated associations; total validity criteria score 36
Bosma et al, 1997 (32); Bosma et al, 1998 (33); Bosma et al, 1998 (34)	N=6895 men, N=3413 women, UK, 35–55 years of age, civil servants	5.3	New self-report: angina (N=177 men, N=151 women), diagnosis IHD (N=124 men, N=42 women), any CHD event (N=401 men, N=253 women)	Men: low control (SR) & angina pectoris OR 1.54 (95% CI 1.05–2.26), low control (SR) & diagnosed IHD OR 1.6 (95% CI 1.01–2.55), low control (SR) & any CHD event OR 1.55 (95% CI 1.20–2.01), low control (O) & any CHD event OR 1.43 (95% CI 1.09–1.88), job strain (SR) & any CHD event OR 1.45 (95% CI 1.03–2.06); women: low control (SR) & any CHD event OR 1.74 (95% CI 1.15–2.64), low control (O) & any CHD event OR 1.73 (95% CI 1.14–2.62) *(age and follow-up time)*	Men: job strain (SR) & angina pectoris OR 1.40 (95% CI 0.93–2.10), job strain (SR) & diagnosed IHD OR 1.16 (95% CI 0.70–1.94), job strain (O) & all outcomes OR 1.03 (95% CI 0.66–1.61); women: low control (SR) & angina pectoris OR 1.20 (95% CI 0.74–1.92), low control (SR) & diagnosed IHD OR 0.85 (95% CI 0.38–1.87), low control (O) & angina pectoris OR 1.46 (95% CI 0.87–2.43), low control (O) & diagnosed IHD OR 1.48 (95% CI 0.53–3.85), job strain (SR) & any CHD event OR 1.14 (95% CI 0.76–1.72), job strain (O) & any CHD event OR 1.22 (95% CI 0.80–1.86) *(age and follow-up time)*	1 bias to null: all white-collar workers (few with job strain), 1 possible bias to overestimate although authors demonstrated that this is unlikely: information bias from self-report of exposure and outcome; total validity criteria score 39

(continued)

Table 6. Continued.

Study	Participants	Follow-up (years)	Illness outcome	Significant positive associations [b]	Reported nonsignificant, null or significant negative associations [b]	Methodological issues [c] and total validity scores [d]
Kivimäki et al, 2002 (41)	N=545 men, N=267 women, Finnish, metal factory employees	Mean 25.6	CVD mortality (N=60 men, N=13 women)	Intermediate job strain HR 1.64 (95% CI 0.85–3.19), high job strain HR 2.22 (95% CI 1.04–4.73) *(age, gender, occupational group, smoking, physical activity, SBP, cholesterol, BMI*)	Low job control HR 1.42 (95% CI 0.72–2.82)*(age, gender, occupational group, smoking, physical activity, SBP, cholesterol, BMI)*	1 or possibly 2 biases to null: long follow-up temporally distant from exposure, no gender-stratified analysis although no significant interaction with work stressors; no information about nonresponders (unclear how this would affect results); total validity criteria score 37
Kuper & Marmot, 2003 (42)	N=6895 men, N=3413 women, UK, 35–55 years of age, civil servants	Mean 11	Incident-validated CHD	High demand and low control & all CHD HR 1.38 (95% CI 1.10–1.75) *(age, gender, occupational grade, coronary risk factors*)	High demand and low control & fatal CHD or nonfatal MI HR 1.16 (95% CI 0.78–1.71) *(age, gender, occupational grade, coronary risk factors)*	1 possible bias to null: no gender-stratified analysis although no significant interaction with job strain; total validity criteria score 39
Theorell et al, 1991 (47)	N=79 men, Swedish, <45 years of age, employed, first MI survivors	6–8	Mortality from repeat MI (N=13)	Demands divided by variety *(univariate)* P=0.03, demands divided by intellectual discretion P=0.02*(biomedical risk factors, education did not differ significantly between groups)*	Demands NS, single aspects of decision latitude NS *(univariate)*	1 bias to null: long follow-up outcome (temporally distant to exposure diluted associations); 1 possible bias to overestimate: all who died had returned to same work as pre-MI (no mention of survivors, could not rule out that survivors, who as a group had lower job strain exposure selectively, did not return to work); total validity criteria score 35
Studies with positive results for job strain and CVD, but none of which were statistically significant						
Alterman et al, 1994 (31)	N=1683 men, US, 38–56 years of age, healthy Chicago Western Electric employees of European ancestry (74% blue-collar)	25	CHD mortality (N=283)	High decision latitude RR 0.76 (95% CI 0.6–0.98) *(age, SBP, cholesterol, smoking, alcohol, family history of CVD)*	Job strain RR 1.40 (95% CI 0.92–2.14), psychological demands RR 0.78 (95% CI 0.48–1.26), decision latitude RR 0.76 (95 % CI 0.59–1.00) *(education & age, SBP, cholesterol, smoking, alcohol, family history of CVD*)	3 biases to null: imputation method, low percentage (7.5%) exposed to job strain, long follow-up (outcome temporally distant to exposure); total validity criteria score 38
Steenland et al, 1997 (46)	N=3575 men, US, 25–74 years of age, population-based study (58% blue-collar)	12–16	Incident heart disease (N=519)	Job control (highest compared with lowest quartile) OR 0.71 (95% CI 0.54–0.93) *(age, education, blood pressure, other coronary risk factors)*	Blue-collar: job strain OR 1.14 (95% CI 0.8–1.63), psychological demands OR 0.64 (95% CI 0.4–1.03), control OR 0.69 (95% CI 0.46–1.02), high control & hight demand OR 0.69 (95% CI 0.48–0.99); white-collar: job strain OR 1.05 (95% CI 0.63–1.77), psychological demands OR 0.93 (95% CI 0.61–1.44), control OR 0.74 (95% CI 0.43–1.26)*(as for positive findings)*	2 biases to null, the latter of which seriously threatened the internal validity of the study: imputation, single assessment of job characteristics temporally very distant to exposure would strongly dilute associations; total validity criteria score 35
Orth-Gomer et al, 2000 (44)	N=292 women, Swedish, 30–65 years old, hospitalized for acute MI or unstable angina pectoris	3.2–6.2 years, median 4.8	Recurrent coronary events (N=81)		Job strain: second quartile HR 1.53 (95% CI 0.58–4.02), upper 2 quartiles HR 1.69 (95% CI 0.72–3.98) *(age);* job strain: second quartile HR 1.33 (95% CI 0.43–4.10), upper 2 quartiles HR 1.67(95% CI 0.64–4.32) *(age, estrogen status, education, diagnosis at index event, symptoms of heart failure, SBP, diabetes mellitis, smoking,* lipids)	1 or possibly 2 biases to null: selective attrition of return to work in relation to job characteristics not ruled out (possible bias), fairly long follow-up outcome (temporally distant to exposure); no adjustment for marital stress or assessment of interaction with job characteristics (uncertain how this affected results); total validity criteria score 37

(continued)

Table 6. Continued.

Study	Participants	Follow-up (years)	Illness outcome	Significant positive associations [b]	Reported nonsignificant, null or significant negative associations [b]	Methodological issues [c] and total validity scores [d]
Studies with null results for job strain and cardiovascular disease						
Hall et al, 1993 (35)	N=5921 women, Swedish, 45–74 years of age, random population sample	7–11	CVD mortality (N=182)	Work control & social support interaction in a multiplicative manner with occupational-class-related risk greater than that attributable to class alone	Blue-collar: psychological demands OR 0.71 (95% CI 0.41–1.24), low control OR 1.07 (95% CI 0.76–1.51), job strain <1; white-collar: psychological demand OR 0.6 (95% CI 0.28–1.31), low control OR 1.4 (95% CI 0.64–3.09), job strain <1 *(age)*	5 biases to null: nonexclusion of CVD morbidity at baseline, imputation, 2 items for psychological demands, single cut point for job strain, follow-up of outcome temporally distant to exposure & inclusion of those 60–74 years of age at baseline; total validity criteria score 35
Hlatky et al , 1995 (37)	N=1132 men, N=357 women, median age 52 years, US, patients undergoing coronary angiography (88% white, 60% white-collar)	Mean 4	Incident non-fatal MI (N=70), cardiac deaths (N=42)		Patients with significant CAD: job strain index and cardiac death RR 0.99 (95% CI 0.96–1.02), quadrant term and cardiac death RR 1.01 (95% CI 0.51–2.01), job strain index & cardiac events RR 1.0 (95% CI 0.98–1.02), quadrant term & cardiac events RR 0.96 (95% CI 0.62–*1.46)(age, gender, ejection fraction, extent of CAD)*; patients without significant CAD (N=6 cardiac events): job strain index & cardiac events RR 0.95 (95% CI 0.87–1.04), quadrant term & cardiac events RR 0.43 (95% CI 0.05–3.67) *(age, gender, ejection fraction, insignificant CAD)*	4 biases to null: selection bias likely in assembly of sample for those exposed to job strain & undergoing angiography but without CAD, selective attrition of those exposed to job strain or low decision latitude, no gender stratification, confounding by SES (job strain higher for white-collar workers, but blue-collar workers had more CAD); total validity criteria score 33
Johnson et al, 1996 (39)	N=12 517 men, Swedish, 25–74 years of age, population-based nested case-control study, N=2422 controls	14	CVD mortality (N=521)	Low control RR 1.83 (95% CI 1.19–2.82), low control & low support RR 2.62 (95% CI 1.22–5.61) *(age, social class, nationality, education, exercise, smoking, last year employed, physical job demands)*	Psychological demands RR range 0.88–1.01 (95% CI 0.66–1.36), job strain NS *(same adjustment as for positive findings)*	4 biases to null: nonexclusion of CVD at baseline, imputation, 2 items for psychological demands, long follow-up outcome (temporally distant to exposure); total validity criteria score 37
Lee et al, 2002 (43)	N=35 038, US, female, registered nurses, 46–71 years of age	4	Incident, non-fatal MI (N=108), fatal CHD (N=38)		Total CHD: high strain RR 0.71 (95% CI 0.42–1.19) *(age, smoking, alcohol, BMI, hypertension, diabetes, cholesterol, menopausal status, HRT, aspirin use, past oral contraceptives, physical activity, education, marital status, husband's education, vitamin E intake, family history, saturated fat intake)*	3 biases to null: survivor bias likely in initial sample, single occupation study limited range of variation of exposure, assessment of job strain temporally distant from outcome; 49% of those exposed to job strain at baseline changed exposure status, but this was not taken into account in the analyses; total validity criteria score 36
Reed et al, 1989 (45)	N=4737 men, US Hawaiians of Japanese descent, 46–65 years of age, population based study	18	Incident definite CHD (N=359)		All calculated forms of job strain NS, psychological demands NS, decision latitude NS; in acculturated group: low job strain (vector score) P<0.05 *(age, blood pressure, other coronary risk factors)*	2 biases to null: imputation, very long follow-up outcome (temporally very distant to exposure); total validity criteria score 40
Suadicani et al 1993 (23)	N=1752 men, Danish, mean age 59.7 years, survivors from a 15-year worker-based cohort study	4	Incident first IHD event (hospitalized and fatal N=46)		Workpace too fast NS, little or no influence on job organization NS, monotonous work NS, interactions of the above NS *(age, social class)*	2 biases to null: survivor bias likely in initial sample, no assessment of occupational stability & fairly long follow-up outcome (temporally fairly distant to exposure); one item to assess self-reported job control (uncertain how this affected results); total validity criteria score 38

[a] All available risk estimates with confidence intervals are shown. For an odds or risk ratio to be considered significant, the 95% CI had to exclude 1.0.
[b] The relevant confounders that were either matched between groups or were adjusted are italicized and indicated in parentheses.
[c] Issues that could affect the directionality of the results of each study are given.
[d] Readers who would like to see additional details about the methodological issues of a particular study or studies may find it helpful to examine the results in this table together with the corresponding validity assessments in tables 2–5.

Table 7. Results of the reviewed case-control referent studies.[a] (BMI = body mass index, CHD = coronary heart disease, CVD = cardiovascular disease, MI = myocardial infarction, NS = nonsignificant, OR = odds ratio, RR = relative risk, SES = socioeconomic status, 95% CI = 95% confidence interval)

Study	Participants	Illness outcome	Significant positive associations[b]	Reported nonsignificant, null or significant[b]	Methodological issues[c] and total validity scores[d]
Studies with significant positive results for job strain and CVD					
Alfredsson et al, 1982 (50); Alfredsson & Theorell, 1983 (51)	Swedish men, <65 years of age, N=334 cases, N=882 population controls	Hospitalized and or fatal MI	Total study population: monotony RR 1.32 (95% CI 1.02–1.70) (*age*), rushed tempo & low influence over work tempo RR 1.35 (95% CI 1.01–1.81), (*age*), rushed tempo & not learning new things RR 1.45 (95% CI 1.02–2.04)(*age*); those 40–54 years of age: hectic work & no influence on workpace RR≈1.7 (95% CI≈1.3–2.8), hectic work & few possibilities to learn new things RR≈2.0 (95% CI≈1.3–3.2) *(age & immigrant status or education)*	Rushed tempo RR 1.06 (95% CI 0.82–1.37), low influence over work tempo RR 1.2 (95% CI.93–1.54), not learning new things RR 1.19 (95% CI 0.93–1.54), rushed tempo & monotony RR 1.26 (95% CI 0.92–1.72) *(age)*	4 biases to null: survivor bias as a case–control study, imputation method, 1 item for psychological demands, assessment of occupation 4–6 years prior to study; total validity criteria score 38
Netterstrøm et al, 1999 (58)	Danish men, <60 years of age, N=76 cases, N=176 worker controls	Hospitalized acute MI	Job strain OR 2.3 (95% CI 1.2–4.4) *(age, employment sector, job category, smoking, social network)*	Low decision latitude OR 1.21 (95% CI 0.7–2.1), high psychological demands OR 1.62 (95% CI 0.9–2.8)	3 biases to null: survivor bias as case–control study, MI not explicitly ruled out for controls, outcome known to participants at the time of self-report of exposure (over-report ruled out but not denial), physician & nurses performed interview—could motivate some patients to deny work stressors if they wanted to return to work; total validity criteria score 32
Theorell et al, 1987 (59)	Swedish men, <45 years of age, N=85 cases, N=116 community controls	Hospitalized nonfatal MI coronary artery atherosclerosis (patients)	Variety of worktasks P=0.01, psychological demands divided by variety of worktasks P=0.01, psychological demands divided by intellectual discretion P=0.04 (*age, education, alcohol and tobacco consumption,body mass index)*	Psychological demands NS, influence over work NS, intellectual discretion NS, psychological demands divided by influence over workload NS *(as for significant positive);* for the patients the degree of coronary atherosclerosis and quotient terms or main effects NS	2 biases to null: survivor bias as a case–control study, outcome known to participants at time of self-report of exposure (over-report ruled out but not denial); total validity criteria score 34
Hallqvist et al, 1998 (54); Peter et al, 2002 (57); Reuterwall et al, 1999 (56); Theorell et al, 1998 (55)	Swedish men, 45–64 years of age, N=1047 cases, N=1450 population controls; Swedish women, 45–70 years of age, N=392 cases (nonfatal), N=533 population controls	First hospitalized or fatal MI or both	Men (all working, self-report): job strain quartile RR 2.2 (95% CI 1.2–4.1) [optimal RR 9.2 (95% CI 3.3–25.6)], synergy index quartile RR 4.0 (95% CI 0.5–30.8) [optimal RR 7.5 (95% CI 1.8–30.6)]; men (manual workers, self-report): job strain quartile RR 10.0 (95% CI 2.6–38.4) [optimal RR 46.1 (95% CI 4.9–429)], synergy index quartile RR 11.1 (95% CI 1.2–107) [optimal RR 23.9 (95% CI 2.1–277)], low decision latitude (not imputed) RR 2.3 (95% CI 1.1–4.9) *(hypertension, smoking, BMI),* low decision latitude (imputed) (all working) OR 1.7 (95% CI 1.3–2.2) *(age, catchment area);* women (all, self-report): job strain OR for nonfatal 1.51 (95% CI 1.13–2.02)*(age, catchment area, overweight, smoking)*	Men (nonmanual workers, self-report): job strain quartile RR 1.5 (95% CI 0.6–3.5), psychological demands quartile RR 1.2 (95% CI 0.8–1.6), low decision latitude RR 1.0 (95% CI 0.6–1.7); men (manual workers, self report): psychological demands RR 1.2 (95% CI 0.5–3.1) *(hypertension, smoking, BMI)*, low decision latitude (imputed) RR 1.2 (95% CI 0.8–2.0), negative change in decision latitude RR 1.4 (95% CI 1.0–2.0) *(age, catchment area, social class, coronary risk factors)*	1 bias to null: survivor bias as a case–control study; other potential sources of bias taken into account for men; 1 bias to overestimate (for women): self-report of job characteristics only (outcome known to participants at time of self-report of exposure); total validity criteria score 46 for men & 36 for women
Sihm et al, 1991 (22)	Danish men, <55 years of age, N=52 cases, N=72 community & hospital controls	Survivors of MI	Heavy workload & contradictory demands RR 1.96 (95% CI 1.19–3.24), heavy workload & low responsibility RR 1.78 (95% CI 1.05–3.02), low workload & good social interaction RR 0.58 (95% CI 0.35–0.95) *(age and SES did not differ significantly between patients and controls)*	High workload RR 1.54 (95% CI 0.96–2.44), low autonomy RR 0.82 (95% CI 0.54–1.24), low influence RR 1.00 (95% CI 0.66–1.53), contradictory demands RR 1.33 (95% CI 0.87–2.02), low growth & development RR 0.81 (95% CI 0.53–1.24) *(as for significant positive)*	1 bias to null: survivor bias as a case–control study; 1 bias to overestimate: outcome known to participants at time of self-report of exposure; total validity criteria score 36

(continued)

Table 7. Continued.

Study	Participants	Illness outcome	Significant positive associations [b]	Reported nonsignificant, null or significant [b]	Methodological issues [c] and total validity scores [d]
Yoshimasu & Fukuoka Heart Study Group, 2001 (61)	Japanese men, 40–79 years of age, N=173 cases, N=303 community controls	Hospitalized survivors of first acute MI	High job strain OR 2.2 (95% CI 1.1–4.5) *(age, hypertension, diabetes, hyperlipidemia, angina pectoris, overweight, cigarette smoking, alcohol intake, parental, CHD and shift work)*	High job demand RR 1.3 (95% CI 0.7–2.2), low job control RR 1.0 (95% CI 0.5–1.7) *(as for significant positive)*	1 or possibly 2 biases to null: survivor bias case–control study, those not exposed to job strain more frequently blue-collar (P=.13) but occupational status not included in multivariate risk estimate; 1 or possibly 2 biases to overestimate: nonparticipant referents had significantly higher job demands than participating referents, outcome known to participants at time of self-report of exposure; significantly more nonparticipant referents in blue-collar jobs (unclear how this would affect results); total validity criteria score 33
Studies with positive results for job strain and CVD, but none of which were statistically significant					
Bobák et al, 1998 (52)	Czech men, 25–64 years of age, N=179 cases, N=784 controls, all full-time employed	First nonfatal MI	Highest decision latitude quartile RR 0.43 (95% CI 0.24–0.79) (*age, district, education, hypertension, other coronary risk factors)*	Job strain RR 1.31 (95% CI 0.77–2.25), highest psychological demands quartile RR 0.52 (95% CI 0.29–0.93) *(as for the significant positive findings)*	1 bias to null: survivor bias as a case–control study; 1 possible, though unlikely, bias to overestimate: outcome known to participant at time of self-report of exposure, although the inverse relation to demands argues the opposite—denial; total validity criteria score 35
Wamala et al, 2000 (60)	Swedish women, ≤65 years of age, N=292 cases, N=292 population controls	Hospitalized acute MI or unstable angina pectoris, survivors	Job control P=0.03, job strain ratio P=0.02 *(age)*	Job control, job strain did not substantially explain the increased CHD risk in the lowest occupational strata	1 attenuated bias to null : survivor bias partially taken into account in assessment of results for those not currently working; 1 bias to over-estimate: outcome known to participants at time of self-report of exposure; total validity criteria score 38
Study with null results for job strain and CVD					
Emdad et al, 1997 (53)	Swedish men, <52 years of age, N=13 cases, N=12 hypertensive controls, all professional drivers	Hospitalized ischemic heart disease		Job strain NS, psychological demand NS, decision latitude NS, skill discretion NS, control NS *(age)*	2 biases to null: survivor bias as a case-control study, single occupation, limited range of variation of exposure; 1 bias to overestimate: outcome known to participant at time of self-report of exposure; total validity criteria score 33

[a] All available risk estimates with confidence intervals are shown. For an odds or risk ratio to be considered significant, the 95% CI had to exclude 1.0.
[b] The relevant confounders that were either matched between groups or were adjusted are italicized and indicated in parentheses.
[c] Issues that could affect the directionality of the results of each study are given.
[d] Readers who would like to see additional details about the methodological issues of a particular study or studies, may find it helpful to examine the results in this table together with the corresponding validity assessments in tables 2–5.

Table 8. Results of the reviewed cross-sectional studies.[a] (BMI = body mass index, CAD = coronary artery disease, CHD = coronary heart disease, CVD = cardiovascular disease, HANES = Health and Nutrition Examination Survey, HES = Health Examination Survey, HDL = high-density lipoprotein, MI = myocardial infarction, OR = odds ratio, PR = prevalence ratio, RR = risk ratio, SES = socioeconomic status, SOR = standardized odds ratio, 95% CI = 95% confidence interval)

Study	Participants	Illness outcome	Significant positive associations [b]	Reported nonsignificant, null or significant [b]	Methodological issues and total validity scores [c, d]
Studies with significant positive results for job strain and CVD					
Karasek et al, 1988 (63)	US men, age 18–79 years, N=2409 HES, N=2424 HANES, population samples (87% & 88% white, respectively)	MI prevalence (N=39 HES, N=30 HANES)	Job strain: HES SOR 1.50 (95% CI 1.07–2.1), HANES SOR 1.61 (95% CI 1.07–2.41); psychological demands: HANES SOR 2.05 (95% CI 1.28–3.28); decision latitude: HES SOR -1.52 (95% CI -1.02– -2.25), HANES SOR -2.0 (95% CI -1.39– -2.87) *(age, race, education, systolic blood pressure, cholesterol smoking (HANES only) physical exertion)*	Psychological demands HES SOR 1.32 (95% CI 0.91–1.9) *(as for significant positive findings)*	3 biases to null: survivor bias as a cross-sectional study, imputation, assessment of exposure to job strain temporally distant from outcome (7–17 years prior for HES, 6 years for HANES); total validity criteria score 36
Johnson & Hall, 1988 (5)	N=7165 men, N=6614 women, Swedish, age 16–65 years, population sample	Self-reported CVD (N=409 men, N=395 women)	Men (blue-collar): high psychological demands & low control PR 3.55 (95% CI 1.64–7.69), high psychological demands & low control & low support PR 7.22 (95% CI 1.6–37.4); men (white-collar): high psychological demands & low support PR 1.81 (95% CI 1.02–3.22), 3-factor multiplicative interaction ratio 1.09; women (blue-collar) high psychological demands & low support PR 1.68 (95% CI 1.07–2.63); women (white-collar): high psychological demands & low support PR 2.06 (95% CI 1.05–4.01) *(age, dimensions of "iso-strain")*	Men (blue-collar): high psychological demands PR 1.36 (95% CI 0.99–1.86), low control PR 1.42 (95% CI 0.96–2.09); men (white-collar): high psychological demands PR 1.32 (95% CI 0.93–1.86), control PR 1.03 95% CI 0.6–1.75), high psychological demands & low control PR 1.03 (95% CI 0.36–2.91); women (blue-collar): high psychological demands PR 1.21 (95% CI 0.88–1.66), low control PR 1.12 (95% CI 0.77–1.62), high psychological demands & low control PR 1.43 (95% CI 0.88–2.3); women (white-collar): high psychological demands PR 1.14 (95% CI 0.76–1.70), low control PR 1.07 (95% CI 0.7–1.66), high psychological demands & low control PR 1.13 (95% CI 0.36–2.91) *(age, dimensions of "iso-strain")*	1 bias to null: survivor bias as a cross-sectional study; 2 biases to overestimate: outcome known to participants at time of self-report of exposure, self-report of exposure & outcome; total validity criteria score 34
Johnson et al, 1989 (38)	N=7219 men, Swedish, age 25–65 years, population sample	Self-reported CVD (N=407)	All: iso-strain PR 1.77 (95% CI 1.28–2.44); blue-collar: iso-strain PR 2.04 (95% CI 1.24–3.36) *(age)*	White collar: iso-strain PR 1.49 (95% CI 0.91–2.43) *(age)*	1 bias to null: survivor bias as a cross-sectional study; 2 biases to overestimate: outcome known to participants at time of self-report of exposure, self-report of exposure & outcome; total validity criteria score 33
Sacker et al, 2001 (65)	N=4235 men, population-based, England, age 20–64 years	Self-reported heart disease: angina 1.1%, possible MI 6%, physician-diagnosed heart disease 5%, any heart disease 9%	High strain: angina OR 2.46 (95% CI 1.23–4.92), possible MI OR 1.46 (95% CI 1.01–2.12), physician diagnosed heart disease OR 1.50 (95% CI 1.02–2.20), any heart disease OR 1.60 (95% CI 1.20–2.13) *(age, age^2, SES, diet, smoking, leisure-, time cholesterol, BMI, diabetes mellitus, blood pressure*		2 biases to null: survivor bias as a cross-sectional study, low percentage (15%) job strain; 2 biases to overestimate: outcome known to participants at time of self-report of exposure, self-report of exposure and outcome; total validity score 31
Studies with positive results for job strain and CVD, but none of which were statistically significant [e]					
Netterstrøm et al, 1998 (64)	N=512 men, N=537 women, Danish, 30–59 years of age, population-based	Self-reported angina pectoris (N=25 men, N=10 women)	Job strain OR 2.3 (95% CI 1.2–4.4) *(age, gender, work hours, psychosocial factors, social status, smoking, systolic blood pressure, HDL:cholesterol ratio)*	Men: job strain OR 2.4 (95% CI 0.5–11.5) *(age, social status)*	1 bias to null: survivor bias as a cross-sectional study; 2 attenuated biases to overestimate: outcome known to participants at time of self-report of exposure, self-report of exposure & outcome (however, no association found between job strain and other somatic pains or between job satisfaction and angina pectoris); low response rate (unclear how this affects results); total validity criteria score 32

(continued)

Table 8. Continued.

Study	Participants	Illness outcome	Significant positive associations [b]	Reported nonsignificant, null or significant [b]	Methodological issues and total validity scores [c, d]
Yoshimasu et al, 2000 (66)	N=197 men, Japan, undergoing coronary angiography, but without long-standing angina pectoris or previous MI, mean age 54.7 (SD 8.9) years	Presence of CAD (≥75% stenosis of ≥1 major coronary arteries or ≥ 50% stenosis of left main coronary artery)		Job strain OR 1.7 (95% CI 0.6–5.3), psychological demands OR 1.3 (95% CI 0.6–2.6), low control OR 0.8 (95% CI 0.4–1.5) (*age, hospital, diabetes, hyperlipidemia, overweight, cigarette smoking, alcohol intake, parental CHD, job type, hypertension)*	4 biases to null: selection bias likely in assembly of sample [large percentage (62%) of those undergoing angiography had no CAD; may have been selected, at least in part, because of exposure to untoward job conditions], survivor bias as a cross-sectional study, single cut point for job strain, low percentage (10%) job strain, exclusion of those with long-standing angina, or previous MI indicating limitation of range for outcome (uncertain how this affects results); total validity score 34
Studies with null results for job strain and cardiovascular disease					
Hall et al, 1993 (35)	N=5921 women, Swedish, 45–74 years of age, random population sample	Self-reported CVD (N= 1147)	Work control & social support interact in a multiplicative manner with occupational class, indicating risk greater than that attributable to class alone	White-collar: job strain <1, psychological demands OR 0.81 (95% CI 0.62–1.06), low control OR 1.23 (95% CI 0.9–1.69); blue-collar: job strain <1, psychological demand OR 0.76 (95% CI 0.6–0.97), low control OR 1.02 (95% CI 0.87–1.2) *(age)*	4 biases to null: survivor bias as a cross-sectional study, imputation method, 2 items for psychological demands, single cut point for job strain; information bias unlikely since only outcome self-reported; total validity criteria score 35
Hlatky et al, 1995 (37)	N=1132 men, N=357 women, median age 52 years, US patients undergoing coronary angiography (88% white, 60% white-collar)	Degree of coronary atheromatosis		Job strain: quadrant term RR 0.98 (95% CI 0.71–1.36), index RR 1.0 (95% CI 0.99–1.01) (*age, gender, smoking status, diabetes hypercholesterolemia, history of MI, typical angina)*	4 biases to null: selection bias likely in assembly of sample for those exposed to job strain and undergoing angiography but without CAD, survivor bias cross-sectional study, no gender stratification, confounding by SES, job strain higher among white-collar workers, but blue-collar workers had more CAD; total validity criteria score 33

[a] All available risk estimates with confidence intervals are shown. For an odds or risk ratio to be considered significant, the 95% CI had to exclude 1.0.
[b] The relevant confounders that were either matched between groups or were adjusted are italicized and indicated in parentheses.
[c] Issues that could affect the directionality of the results of each study are given.
[d] Readers who would like to see further details about the methodological issues of a particular study or studies may find it helpful to examine the results in this table together with the corresponding validity assessments in tables 2–5.
[e] When gender stratified.

Table 9. Job strain and cardiovascular disease outcomes: summary table. (CHD = coronary heart disease, IHD = ischemic heart disease, MI = myocardial infarction)

Job strain results	Unequivocal bias to overestimate	Likely bias to overestimate	Bias possible in both directions	Minimal biases	Likely bias to null	Unequivocal bias to null score	Total validity score
	Study & score	Study & score	Study & score	Study & score	Study & score	Study & Score	Mean SD
Longitudinal studies							
Men							
Significant positive association	–	–	Theorell et al (47), score 35	Kuper & Marmot (42) [a, b]	Bosma et al (32–34), [c] score 39 Kivimäki et al (42), [a] score 37	Alfredsson et al (30), score 35 Hammar et al (21, 36), score 40 Johnson et al (38), [d] score 37 Karasek et al (40), score 36	37.3 1.9

(continued)

Table 9. Continued.

Job strain results	Unequivocal bias to overestimate	Likely bias to overestimate	Bias possible in both directions	Minimal biases	Likely bias to null	Unequivocal bias to null score	Total validity score	
	Study & score	Study & score	Study & score	Study & score	Study & score	Study & Score	Mean	SD
Nonsignificant positive association	–	–	–	Kuper & Marmot (42) [a, e]	Bosma et al (32–34), [f] score 39	Alterman et al (31), score 38 Steenland et al (46), score 35	37.8	1.9
Null	–	–	–	–	Suadicani et al (23), score 38	Hlatky et al (37), [a] score 33 Johnson et al (39), score 37 Reed et al (45), score 40	37	2.9
Significant negative association	–	–	–	–	–	–	.	.
Total	.	.	.	.	.	.	37.3	2.1
Women								
Significant positive association	–	–	–	Kuper & Marmot (42) [a, b]	Kivimäki et al (41), [a] score 37	Alfredsson et al (30), score 35 Hammar et al (21, 36), score 40	37.8	2.2
Nonsignificant positive association	–	–	–	Kuper & Marmot (42) [a, e]	Bosma et al (32–34), [g] score 39 Orth-Gomér et al (44), score 37	–	38.3	1.2
Null	–	–	–	–	–	Hall et al (35), score 35 Hlatky et al (37), [a] score 33 Lee et al (43), score 36	34.7	1.5
Significant negative association	–	–	–	–	–	–	.	.
Total	.	.	.	.	.	.	37	2.3
Case-control studies								
Men								
Significant positive association	–	–	Sihm et al (22), score 36 Yoshimasu & the Fukuoka Heart Study Group (60), score 33	Hallqvist et al (54) & Theorell et al (55), [h] score 46	–	Alfredsson et al (50, 51), score 38 Netterstrøm et al (58), score 32 Theorell et al (59), score 34	36.5	5.1
Nonsignificant positive association	–	–	–	–	Bobak et al (52), score 35	–	35	.
Null			Emdad et al (33), score 33				33	.
Significant negative association	–	–	–	–	–	–	.	.
Total	.	.	.	.	.	.	35.9	4.5
Women								
Significant positive association	–	–	Reuterwall et al (56) & Peter et al (57), score 36	–	–	–	36	.
Nonsignificant positive association	–	Wamala et al (60), score 38	–	–	–	–	38	.
Null	–	–	–	–	–	–	.	.
Significant negative association	–	–	–	–	–	–	.	.
Total	.	.	.	.	.	.	37	1.4
Cross-sectional studies								
Men								
Significant positive association	–	–	Johnson & Hall (5)[i], score 34 Johnson et al (38), [d] score 33 Sacker et al (65), score 31	–	–	Karasek et al (63), score 36	33.5	2.1

(continued)

Table 9. Continued.

Job strain results	Unequivocal bias to overestimate	Likely bias to overestimate	Bias possible in both directions	Minimal biases	Likely bias to null	Unequivocal bias to null score	Total validity score	
	Study & score	Study & score	Study & score	Study & score	Study & score	Study & Score	Mean	SD
Nonsignificant positive association	–	–	Netterstrøm et al (64), score 32	–	–	Yoshimasu et al (66), score 34	33	1.4
Null	–	–	Johnson (5),[j] score 34	–	–	Hlatky et al (37),[a] score 33	33.5	0.7
Significant negative association	–	–	–	–	–	–	.	.
Total	.	.	.	.	.	.	33.4	1.5
Women								
Significant positive association	–	–	–	–	–	–	.	.
Nonsignificant positive association	–	–	Johnson & Hall (5), score 34	–	–	–	34	.
Null	–	–	–	–	–	Hall et al (35), score 35 Hlatky et al (37),[a] score 33	34	1.4
Significant negative association	–	–	–	–	–	–	.	.
Total	.	.	.	.	.	.	34	1.0

[a] Results not gender-stratified.
[b] All CHD (score 39).
[c] Any CHD end point (self report).
[d] Results for iso-strain.
[e] Nonfatal MI or fatal CHD (score 39).
[f] Angina, diagnosed IHD (self-report).
[g] Self-report.
[h] Except for survivor bias as in case–control studies.
[i] Blue-collar.
[j] White-collar.

dimension since its main source of variance is within-occupation. This problem may explain the discrepant findings of a significant positive association between job control and CVD but the lack of such discrepancy for psychological demands in several of the longitudinal studies (31, 39, 46) that relied only on imputation. Another problem with imputation was found in the study by Reed et al (45), the only study in which a significant inverse relation ($P<0.05$) was found between job strain and incident coronary heart disease (CHD). This inverse finding was apparent for only one subgroup (acculturated Japanese American men in Hawaii). Exposure status in that study was imputed on the basis of data from the United States as a whole. The authors suggested the possibility "that the actual working conditions to which this cohort was exposed were not accurately represented by this method" [and also] "that the different patterns of results shown by the men divided into Westernized and traditional Japanese groups, indicate that such cultural differences can affect the associations [p 501–502]".

In two of the studies with null findings (23, 43), the participants had taken part in a previous cohort study, and therefore survivor bias was likely to have been operative in the assembly of the sample. In the research by Lee et al (43) the assessment of these psychosocial job characteristics was performed some 16 years after the initiation of the study, and after which more women in the cohort had actually stopped paid employment than were included in the part of the study concerned with job strain. The likelihood is therefore high that a strong healthy worker effect was operative in the assembly of the sample with respect of the assessment of the effects of job strain on incident CHD. Moreover, 49% of those exposed to job strain at baseline changed their exposure status during the follow-up period. This change, which undoubtedly attenuated the findings, was not taken into account in the analyses.

Selective attrition from high-strain jobs has been reported to be common among working women generally (48). In respect to a longitudinal study (44) comprised of women who had been hospitalized for an ischemic cardiac event, it is plausible that many of those who had previously been exposed to job strain did not return to work after enduring an episode of CHD. The authors did not provide evidence that would rule out this possibility. Moreover, while the direction in which a likely confounder (marital stress) would affect the results is unclear, the effect of *combined exposure* to marital stress and job strain was not tested. It is not unreasonable to argue that women falling into that category would

Table 9. Continued.

Job strain results	Unequivocal bias to overestimate	Likely bias to overestimate	Bias possible in both directions	Minimal biases	Likely bias to null	Unequivocal bias to null score	Total validity score	
	Study & score	Study & score	Study & score	Study & score	Study & score	Study & Score	Mean	SD
Nonsignificant positive association	–	–	Netterstrøm et al (64), score 32	–	–	Yoshimasu et al (66), score 34	33	1.4
Null	–	–	Johnson (5),[j] score 34	–	–	Hlatky et al (37),[a] score 33	33.5	0.7
Significant negative association	–	–	–	–	–	–	.	.
Total	.	.	.	.	.	.	33.4	1.5
Women								
Significant positive association	–	–	–	–	–	–	.	.
Nonsignificant positive association	–	–	Johnson & Hall (5), score 34	–	–	–	34	.
Null	–	–	–	–	–	Hall et al (35), score 35 Hlatky et al (37),[a] score 33	34	1.4
Significant negative association	–	–	–	–	–	–	.	.
Total	.	.	.	.	.	.	34	1.0

[a] Results not gender-stratified.
[b] All CHD (score 39).
[c] Any CHD end point (self report).
[d] Results for iso-strain.
[e] Nonfatal MI or fatal CHD (score 39).
[f] Angina, diagnosed IHD (self-report).
[g] Self-report.
[h] Except for survivor bias as in case–control studies.
[i] Blue-collar.
[j] White-collar.

dimension since its main source of variance is within-occupation. This problem may explain the discrepant findings of a significant positive association between job control and CVD but the lack of such discrepancy for psychological demands in several of the longitudinal studies (31, 39, 46) that relied only on imputation. Another problem with imputation was found in the study by Reed et al (45), the only study in which a significant inverse relation ($P<0.05$) was found between job strain and incident coronary heart disease (CHD). This inverse finding was apparent for only one subgroup (acculturated Japanese American men in Hawaii). Exposure status in that study was imputed on the basis of data from the United States as a whole. The authors suggested the possibility "that the actual working conditions to which this cohort was exposed were not accurately represented by this method" [and also] "that the different patterns of results shown by the men divided into Westernized and traditional Japanese groups, indicate that such cultural differences can affect the associations [p 501–502]".

In two of the studies with null findings (23, 43), the participants had taken part in a previous cohort study, and therefore survivor bias was likely to have been operative in the assembly of the sample. In the research by Lee et al (43) the assessment of these psychosocial job characteristics was performed some 16 years after the initiation of the study, and after which more women in the cohort had actually stopped paid employment than were included in the part of the study concerned with job strain. The likelihood is therefore high that a strong healthy worker effect was operative in the assembly of the sample with respect of the assessment of the effects of job strain on incident CHD. Moreover, 49% of those exposed to job strain at baseline changed their exposure status during the follow-up period. This change, which undoubtedly attenuated the findings, was not taken into account in the analyses.

Selective attrition from high-strain jobs has been reported to be common among working women generally (48). In respect to a longitudinal study (44) comprised of women who had been hospitalized for an ischemic cardiac event, it is plausible that many of those who had previously been exposed to job strain did not return to work after enduring an episode of CHD. The authors did not provide evidence that would rule out this possibility. Moreover, while the direction in which a likely confounder (marital stress) would affect the results is unclear, the effect of *combined exposure* to marital stress and job strain was not tested. It is not unreasonable to argue that women falling into that category would

selectively stop working, another potential bias towards the null.

Null results were also obtained in the longitudinal portion of the study by Hlatky et al (37), who examined incident nonfatal MI and cardiac death. There was evidence of selective attrition during the follow-up period, since the patients with CAD who reported low decision latitude or job strain had disproportionately stopped working at the 1-year follow-up (49); this attrition would have attenuated any association between the point exposure to job strain at entry into the study and subsequent cardiac events. Confounding by socioeconomic status was in the direction opposite that of disease severity, and yet there was no reported adjustment for socioeconomic status. This would also bias the results towards the null, as would the lack of gender stratification, particularly since the pattern of job strain exposure was highly gender-specific. Another bias towards the null in the study by Hlatky et al (37) was due to the likely selection bias in the assembly of the original sample towards those with self-reported exposure to job strain but no CAD. [See the cross-sectional results section for further discussion on these points.]

Overall, eight investigations, including several of the largest, showed significant positive results with effect sizes, the odds ratio (OR) ranging from 1.21 [95% confidence interval (95% CI 1.08–1.35)] (21, 36) to 4.0 (95% CI 1.1–14.4) (40) for the men and from 1.3 (95% CI 1.1–1.6) (21, 36) to a standardized mortality ratio (SMR) of 164 (95% CI 112–233) (30) for the women. In addition another three studies with positive, although statistically nonsignificant findings. Overall these results provided strong and consistent evidence, particularly for the men, that exposure to job strain is associated with an increased risk of cardiac events and death from CVD. The magnitude of this association appears to have been substantially underestimated, since bias towards the null was present in nearly all of these studies. There was also compelling evidence that low job decision latitude is predictive of future cardiovascular morbidity and mortality.

Case–control studies

Among the case–control studies (22, 50–61), those of Hallqvist et al (54) and Theorell et al (55) received the highest total validity rating (rating 46, also the highest of all those included in this review), having addressed nearly all of the methodological issues, with the exception of survivor bias. This was, by far, the largest case–control study, and its effect estimates were among the largest for exposure to job strain and risk of first MI. The next highest total validity rating (rating 38) was found for the second largest case–control study (50, 51), in which significant positive findings were reported, and for the study by Wamala et al (60), with statistically nonsignificant positive results for the women. Major threats to internal validity (scores of 0) were not attributed to any of the case–control studies.

Recall bias possibly leading to overestimation appears to have been, overall, fairly minimal in these investigations. First of all, two of the studies, by Alfredsson et al (50, 51) and by Hallqvist et al and Theorell et al (54, 55), at least in part, relied upon imputed data. In their study, Netterstrøm et al (58) ruled out the possibility of overreporting. On the other hand, since exposure data were obtained by nurses or physicians who were probably aware of the participants' clinical status, the patients may have been motivated to deny adverse work conditions, perhaps to facilitate return to work. This possible source of underestimation with respect to effect size was not addressed. Similarly, Theorell et al (59) showed that information bias leading to the overreporting of exposure to job strain among the cases of MI did not occur, but they did not rule out denial. At the time of the self-report of exposure, the clinical status (case versus control) was known to the participants in the studies by Reuterwall et al (56) and Peter et al (57)[8] and Sihm et al (22). The possibility of information bias (either to overestimate or to deny) was not ruled out. However, it has been pointed out that an inflation of effect estimates due to recall bias, if it occurs, usually affects self-reports of psychological job demands, but not decision latitude. Therefore the likelihood of overestimating exposure to job strain, per se, was diminished even if the study participants knew their disease status prior to reporting exposure (62). Survivor bias, leading to an underestimation of existing associations, was likely in all but one of the case–control studies.

We therefore concluded that the six case–control studies (of the nine) with significant positive results, with overall effect sizes ranging from a relative risk of 1.45 (95% CI 1.02–2.0) (50, 51) to an odds ratio of 2.3 (95% CI 1.2–4.4) (58), also provide consistent evidence in favor of an association between job strain and CVD among men and some, though not entirely consistent, support for this association among women.

Cross-sectional studies

The mean total validity ratings for the cross-sectional studies (5, 35, 37, 38, 63–66) were practically identical

8 A comparison between imputation and self-reporting was made only for men in the studies by Hallqvist et al (54) and Theorell et al (55).

for the positive, statistically nonsignificant positive, and null studies. The highest total score (score 36) was found for the study by Karasek et al (63), in which significant positive results appeared and in which information bias was not operative, since the exposure data were imputed and the outcome (MI prevalence) was objectively assessed. The next highest score (score 35) was for the imputational study by Hall et al (35) with null results for self-reported CVD among the women. Both of these studies had several other biases towards the null.

The two cross-sectional studies (37, 66) with angiographically assessed CAD as the outcome were both vulnerable to selection bias in the assembly of the sample, which would have underestimated existing associations. In the study by Yoshimasu et al (66), a large percentage (62%) of the patients undergoing angiography did not have CAD according to the authors' definition. Patients with chest pain and normal coronary arteries have been described as a group with a high prevalence of occupational and behavioral difficulties (67–69). It appears that such patients were selectively included in the study, the result being *differential* misclassification of the type that tends to bias the results negatively. In the study by Hlatky et al (37), the sample was comprised of persons reporting chest pain (or "equivalent ischemic symptoms") who underwent coronary angiography at a university hospital. The frequency of reported chest pain was higher, by at least an order of magnitude (70), for the study patients than for a population of similar age. A total of 38% of the patients had insignificant CAD (>0% and <75% lumenal narrowing) or normal coronary arteries. These patients belonged to the white-collar group far more often than those with significant CAD (P<0.001). Altogether 35% of the patients with completely normal coronary arteries were classified as being exposed to job strain, compared with 26% and 25% of those with insignificant or significant CAD, respectively. When these results are considered together, it can be argued that patients complaining of chest pain in the higher socioeconomic strata and who reported exposure to adverse psychosocial work conditions preferentially entered the study group. This occurrence would have distorted the etiologic relationship between exposure to job strain and the presence of CAD and therefore biased the results towards the null. Given that socioeconomic status and CAD were inversely related, failure to adjust for this confounder would also bias the results towards the null. Lack of gender stratification further obfuscates etiologic relations. Forty-three percent of the women, but only 23% of the men, fell into the job-strain category. On the other hand, women comprised 48% of the patients with normal coronary arteries versus 14% of those with significant CAD. No mention was made of syndrome X, characterized by enhanced ventricular pain sensitivity (71) and normal epicardial coronary arteries and a high prevalence among women (72).

Four of the eight cross-sectional studies relied upon self-report both of exposure and of CHD, such that information bias was possible, although, as has already been discussed, information bias was less likely for the control dimension, and therefore for job strain as a whole. Significant positive associations were found for the male participants in three of these investigations.

Thus, the cross-sectional studies, with effect sizes ranging from a standardized odds ratio of 1.5 (95% CI 1.07–2.1) for a physician-diagnosed prevalence of MI (63) to a standardized odds ratio of 2.46 for self-reported angina pectoris (65), provide additional evidence of an association between job strain and CVD among men, although biases leading to overestimation, as well as to the null, could have been operative in several studies.

Thus, overall, among the men, there was strong and consistent evidence of an association between exposure to job strain and CVD, across study designs and across a somewhat limited number of examined populations.[9] The data for women were more sparse, and not quite as consistent, although, as was the case for the men, the majority of the studies was likely to have underestimated existing effects.

Further considerations

Unpublished data and publication bias

It is always difficult to gauge the impact of noncommunication of results on a body of knowledge based upon empirical findings. Publication bias (ie, nonpublication of null or negative results) is a potentially serious issue, which could lead to an inflated view of the consistency and strength of associations (73).

With regard to the topic of this review, a substantial number of papers has been published that reported no association between exposure to job strain and CVD. We are not aware of any investigations on job strain and CVD outcomes with null or negative results that have not been published. On the other hand, positive 10-year longitudinal data (74) exist for 548 men and 328 women from the Framingham study, which was not included in our review because the results were not published as a full-length journal article. La Croix & Haynes (74) found that self-reported exposure to high job demands

9 Significant positive findings were obtained from Sweden, Japan, the United Kingdom, Denmark, and the United States (US), with positive but only nonsignificant results from the Czech Republic and null results for US Hawaiians of Japanese descent.

plus low supervision clarity among women was associated with a risk ratio of 2.9, and, for clerical female workers, the risk ratio was 5.2. Imputed data from the Framingham study also yielded a highly significant relative risk for job strain among women and men. Preliminary data from a multicenter European project (JACE) also suggest an increased risk of incident IHD events for 18 592 working men with self-reported job strain, after adjustment for age, job title, smoking, and systolic blood pressure (hazard ratio 1.66, 95% CI 1.0–2.7) (75).

Combining results—meta-analytical calculations

Partanen (76) has pointed out that, besides publication bias, heterogeneity is also a key reason for skepticism towards meta-analyses of nonexperimental studies. The limitations and pitfalls of combining results in clinical medicine are manifold, and, increasingly, the need for qualitative approaches and an identification of the best evidence for estimating effect size is underscored (77–79). In our review, we did not undertake formal meta-analytical calculations because data were not available that fulfilled the criteria for homogeneity in methods used to assess job strain, adjustment for confounders, and outcome measures, as well as being free of important biases potentially affecting internal validity.

Other causal criteria concerning the relation between job strain and cardiovascular disease

Dose–response relationships

Several, but not all, of the reviewed investigations have suggested that a dose–response relationship exists between exposure to job strain and CVD risk. In their prospective study, Kivimäki and his colleagues (41) reported an increase in the hazards ratio of workers exposed to high levels of job strain (high or intermediate demands combined with low control) when compared with the hazards ratio of workers with intermediate job strain levels. This dose–response finding appeared in five different models, including that with adjustment for all the considered confounders. Indirect evidence of a temporal dose–response relationship was also reported in this study; namely, a stratified analysis with workers whose occupational group remained unchanged over 5 years revealed a higher hazard ratio, 2.9 (95% CI 1.25–6.71), than that of the entire cohort.

In their case–control study, Yoshimasu et al (61) reported a fully adjusted odds ratio of 1.2 for acute MI with respect to "middle levels" of job strain (active or passive quadrants) and 2.2 with respect to high strain, each compared with low strain. Of the five adjusted models for each of the four self-reported CVD outcomes presented by Sacker et al (65), nearly all showed a dose–response pattern, the largest odds ratios being determined for high strain, followed by the passive and active quadrants compared with the relaxed quadrant. In several of these models the trend was statistically significant. Although the associations were not statistically significant, Orth-Gomér et al (44) obtained an adjusted hazards ratio [10] of 1.33 for recurrent coronary events among women with CHD in the second job strain quartile (moderate) when compared with a hazards ratio of 1.67 for those in the upper two quartiles (severe). Defining job strain as the lowest 7% of decision latitude and highest 37% of job demands, compared with the quartile term, Hallqvist et al (54) reported that the relative risk of MI increased from 2.2 to 9.2. On the other hand, dose–response patterns were not found in studies by Hammar et al (36), Lee et al (43), and Netterstrøm et al (58, 64).

A dose–response effect has also been found for decision latitude alone in several studies. Hallqvist et al (54) found an increased relative risk for MI as the levels of job decision latitude decreased (eg, when exposure to decision latitude was defined as the top 25% exposed versus 7%, the relative risk for MI increased from 1.2 to 1.8). Bobák et al (52) observed a clear dose–response relationship between four levels of job control and risk of MI; this trend was highly significant after adjustment for confounders. The cohort studies of Bosma et al (32, 33) also showed a dose–response relation with respect to intermediate and low job control and self-reported occurrence of each of the self-reported outcome measures, with a significant test for trend for angina and any coronary event. Quartiles of job control and risk of incident heart disease also showed a dose–response pattern in the study of Steenland et al (46), although the trend was not statistically significant. In contrast, no dose–response relationship was apparent between exposure to progressively lower levels of job control and CVD mortality in the study by Johnson et al (39).

The finding of a graded effect upon outcome with various levels of point exposure represents one element of causal inference, although it is neither necessary nor sufficient to demonstrate a causal relationship (77). Causal relationships may demonstrate patterns other than a linear gradient between exposure and outcome (eg, threshold or ceiling effects). Moreover, besides the job-strain hypothesis, the demand–control model also postulates the active learning hypothesis, whereby jobs

10 Job-strain levels were calculated as the quotient of psychological demands and control.

with high (although not overwhelming) demands and high decision latitude represent a healthy combination through long-term positive changes in coping behavior (2). For this reason, the association between the four quadrants (relaxed → active → passive → high strain) of the demand–control model and health outcomes such as CVD might not be strictly monotonic.

Temporal nature of the association

Prospective cohort studies offer the means to determine whether exposure preceded outcome (ie, that a putative cause occurred before the effect) (77). As concluded earlier, given the numerous methodological issues that would bias the results towards the null, the body of findings from the longitudinal studies, particularly for men, can be considered strong and consistent. This strength and consistency support the contention that the temporal relationship is in the expected direction, namely, that exposure to job strain preceded the occurrence of cardiovascular events.

The strongest evidence for the temporality criterion from a single investigation can be derived from that of Hammar et al (21, 36). This population-based study examined incident cases of first MI identified from hospital and death registers whose validity was independently verified. All the identified incident cases (over 10 000) were included in the study. A nested case–control design was employed, with at least two age- and gender-matched controls chosen from the total population at the time of case incidence. Exposure data were imputed from occupational title assessed twice over a 5-year interval, prior to the follow-up period; these data were obtained for 99% of all the cases and controls. Previous hospitalized MI was ruled out with the help of data linkage systems, although it was not possible to assess subclinical or silent disease. The follow-up period (9 years) was sufficiently long to capture the temporal sequence, including an eventual latency period.

Kivimäki and his colleagues (41) also provided strong evidence for the temporality criterion with over 25 years of complete follow-up with respect to the vital status of 812 Finnish metal factory workers. All of the participants were clinically examined, and only those free of CVD at baseline were included in the study. National mortality register data including cause and date of death were obtained for all the 73 study participants who died during the follow-up period. Information about exposure to job strain was obtained via self-report using a validated instrument, and an assessment of job stability at baseline and at the end of a 5-year follow-up was performed.

A random population-based sample of 1461 Swedish men was followed over 9 years in the study of Karasek et al (40). The initial participation rate was 92%, with no loss to follow-up with respect to vital status. Over the 9 years, there were 22 deaths from CVD or cerebrovascular disease, confirmed by validated death certificates. Three controls from the cohort were blindly matched by baseline CHD symptoms, age, and education to each case (nested case–control design). Data on exposure to high psychological demands and aspects of job control had been obtained at baseline from all the participants via self-report. The risk estimate for exposure to job strain and CVD was the highest of all the longitudinal investigations; however, the precision was the lowest due to the relatively small size of the groups. Nevertheless, this study also corroborates the temporality criterion.

The large prospective study of Johnson et al (38), reporting an odds ratio of 1.92 for exposure to iso-strain and future CVD mortality, also achieved complete follow-up of a population-based cohort over a 9-year period with respect to clinical outcome. Self-report data on job characteristics were obtained at baseline, with an 80% initial participation rate. Persons with self-reported CVD at baseline were not excluded from the longitudinal study, nor were the analyses adjusted for prevalent CVD.

Alfredsson and his colleagues (30) linked registers to obtain complete information about job title and incident hospitalization for MI in their population-based study of nearly one million working men and women in Sweden. Because the follow-up period was relatively short (1 year) and previous MI was not excluded at baseline, the inferences that can be made from this study about the temporal relationship between exposure to job strain and risk of future MI are somewhat limited.

The study of Bosma et al (32–34) provides some support for the temporality criterion with respect to job strain and self-reported IHD, with stronger support for this criterion in relation to low job control. Over 10 000 civil servants from the United Kingdom, free from clinically diagnosed IHD at intake, were followed over an average of 5.3 years. The initial participation rate was 73%. Exposure data were obtained at baseline, as well as at the end of a 3-year follow-up (phase 2) from both self-report and expert ratings; the outcome was self-reported incident IHD. As mentioned, the authors demonstrated that information bias from self-report of both exposure and outcome was unlikely. There was 79% follow-up in phase 2, 72% participating in all three phases. The clinical status of those lost to follow-up was not mentioned. For the men but not the women, a significant positive odds ratio was obtained for exposure to job strain based on the basis of self-report and incident CHD events. Associations with other self-reported outcomes, while positive, were not statistically significant, although as previously noted, the relatively small

number of persons exposed to job strain diminished the power of the study to detect existing effects. On the other hand, low job control was a significant predictor of future self-reported IHD among both the men and the women, with very consistent data for the former.

Seventy-nine men who had suffered a first MI before the age of 45 years were followed for 6 to 8 years by Theorell and his colleagues (47). Self-report data on psychosocial job characteristics were obtained within 3 to 6 months of the infarct. The 13 patients who died from reinfarction during the follow-up period were compared with the 49 who had no post-MI cardiac complications, and exposure to job strain significantly and independently predicted death from reinfarction. The authors stated that all the 13 patients who died had returned to the same job as before the MI, but, as mentioned, it was unclear whether this was also the case for the 49 in the latter group, and, if not, the possibility of overestimation of effect arises. Nevertheless, these data suggest that returning to high strain work after acute MI may increase the risk of future fatal cardiac events.

Confounding and alternative hypotheses

The possibility that observed and plausible empirical associations between psychosocial exposures and disease are, in fact, due to confounding, as has been raised by Macleod et al (80), will now be addressed with respect to the findings concerning job strain and CVD.

Sociodemographic factors

Socioeconomic status. A substantial body of evidence links low socioeconomic status to an increased incidence and prevalence of CHD (81–84). Consequently, an alternative hypothesis might be that the observed associations between job strain and CVD were due to social class. This possibility is unlikely, however, because most of the positive studies accounted for socioeconomic status.

Social class probably acts as an effect modifier, since the impact of exposure to job strain upon the risk of developing CVD differs according to socioeconomic status. For men, nearly all of the investigations with stratified analyses reported much higher risk estimates among blue-collar workers than among white-collar ones. For example, the adjusted relative risk for MI was 10 (95% CI 2.6–38.4) for manual workers versus 1.5 (95% CI 0.6–3.5) for nonmanual workers in the case–control study by Hallqvist et al (54). Class differences in the effect of job strain upon CVD were less apparent among female workers in the few studies in which stratified analyses were performed.

Moreover, exposure to job strain is not uniform across social class. Lack of decision latitude at work is much more common among those in the lower socioeconomic status groups (38, 54, 85). High psychological work demands have been ascribed to white-collar occupations ("active jobs") (38, 54). Contingent or precarious employment also generally entails very high job demands (86). Workers in these unstable jobs often belonged to the lowest socioeconomic status strata and are thus likely to have low job control as well. Much of the occupational exposure data, especially from the longitudinal studies, have been gathered from full-time working persons with some degree of occupational stability. The exclusion of temporary workers, a group likely to be exposed to job strain, could attenuate risk estimates.

Race and ethnicity. Race and ethnicity are often closely related to socioeconomic status. Working persons of minority backgrounds, especially those without full language proficiency in the country in which they were working, were not included in some of the reviewed studies (22, 31, 47, 59). According to logic similar to that introduced earlier, it is conceivable that these persons were exposed to job strain and that their exclusion could have attenuated the reported findings.

Several, but not all, of the positive studies performed in a multi-ethnic or multiracial setting adjusted for race or ethnicity. In contrast, three of the studies with null results from the United States (37, 43, 46) were likely to have examined racially diverse groups, but did not account for this factor.

The potential for effect modification also needs to be considered. Johnson & Hall (87) emphasized that the "effects of race on labor market access and the exposure to racist remarks, practices, or attitudes on the job need to be studied as an important aspect of occupational stress for minority workers [p 370]". There is some evidence from descriptive studies suggesting that African Americans working in stressful jobs may have a greater risk for CHD mortality than white Americans in the same occupation (87). African Americans also have much higher age-adjusted prevalence rates of hypertension than non-Hispanic whites in the United States (88) and among the highest rates of hypertension in the world (89).[11] The need to examine the relationship between job strain and CVD among groups from a wider range of racial and ethnic origin, in various parts of the world, has been underscored (16).

11 This high prevalence of hypertension is likely of environmental and not genetic origin since in rural west Africa (from whence African-Americans underwent forced migration to the United States) the prevalence of hypertension is among the lowest in the world (89).

Other work environment models and factors

Social support—a third dimension of the job strain model. As mentioned earlier, social support at work has been added as a third dimension of the job strain model, with the worst combination, job strain plus social isolation, termed *iso-strain*. The risk of self-reported CVD was markedly greater for men and women exposed to iso-strain than for those exposed to job strain alone in the study by Johnson & Hall (5). This finding was the most striking for male blue-collar workers whose prevalence ratio was 3.55 for exposure to job strain alone and 7.22 for iso-strain. Iso-strain was also a strong predictor of future CVD mortality among men in a 9-year longitudinal investigation (38). Combined exposure to high demands, low control, and low social support was associated with the highest risk for the 1-year incidence of MI among men aged 30–54 years in the imputational study by Hammar et al (36), although not among women nor among the entire cohort of men aged 30–64 years. When also imputing job characteristics from occupational title, Johnson et al (39) reported the highest risk estimates for future CVD mortality for men exposed to the combination of low job control and low social support.

Social support has also been treated as a potential confounder of job strain. The highest odds ratio for MI among all the case–control studies of job strain was obtained by Netterstrøm et al (58), after adjustment for social network at work, as well as other potential confounders. Significant positive risk estimates for job strain and self-reported CVD or angina were also reported after adjustment for social support in the cross-sectional studies of Johnson & Hall (5) and Netterstrøm et al (64), respectively.

The effort–reward imbalance model. An alternative, yet complementary way of looking at psychosocial work stressors is embodied in the effort–reward imbalance model (90). This model emphasizes lack of reciprocity between efforts spent and rewards received. The latter include monetary rewards, as well as esteem, career opportunities, and job security. Efforts can be both extrinsic (job demands and obligations) and intrinsic (overcommitment by the individual to work). A substantial body of cross-sectional and longitudinal investigations, primarily among men, has shown a significant positive association between effort–reward imbalance and acute MI, as well as CVD-related mortality. [For an overview, see Belkic et al (17).]

Peter et al (57) examined the combined effects of exposure to job strain and effort–reward imbalance upon the risk of acute MI in the Stockholm Heart Epidemiology case–control study. Among the men, exposure to job strain together with high extrinsic effort and low rewards yielded a substantially higher adjusted effect estimate (OR 2.02, 95% CI 1.34–3.07) than exposure to job strain only or effort–reward imbalance only (OR 1.30 and 1.42, respectively). This was a gender-specific finding in that, among the women, it was only intrinsic effort (overcommitment) plus job strain that yielded a combined effect. [See the section on gender and that on behavior, for further discussion.]

Peter et al (57) pointed out that assessing the joint effects of the two models is much more informative than treating the alternative model as a confounder. Controlling one model for the other, in order to test independent effects, did not yield systematically increased effect estimates in their study. Bosma et al (33) found that, although job control remained a significant independent predictor of self-reported CHD after adjustment for effort–reward imbalance, the effect estimate diminished. They also reported a significant association between job control and effort–reward imbalance in that those with low job control reported effort–reward imbalance more often than those with high job control. This association is not surprising since the control dimension is integral to both models, although, for job strain, it is primarily control over task performance, whereas the effort–reward imbalance model views control at the "macro-level", over larger issues such as salary, career advancement, and the like. The extrinsic effort and psychological demand dimensions have substantial similarity, and they show moderate statistical correlation (57). Kivimäki and his colleagues (41) reported a significant association between exposure to high job strain and high effort–reward imbalance, and similar risk estimates for each of these. Thus, while the two models have clear conceptual and operational differences, they also overlap. Most importantly, the "combination of information derived from the two models [captures] a broader range of stressful experience at work, and thus, result[s] in an improved risk estimate [p 294]" (57).

Work schedules, threat avoidant vigilance, physical and chemical factors. Nightshift work has also been implicated in CVD risk. According to a recent review (91) shift workers are estimated to have about a 40% increased CVD risk when compared with day workers. Shiftwork has been associated with low decision latitude, monotony, and not learning new things (51, 92). The combined effects of exposure to job strain and shiftwork have not, however, been reported. The limited data available indicate that shiftwork does not confound the association between job strain and acute MI, since effect estimates remain significant when this factor is taken into account in case–control studies (58, 61). The shiftwork status of the registered nurses was not included in the analyses by Lee et al (43). This is clearly an important occupational stressor in the nursing profession, and it may have contributed to the high attrition

rate of the original sample with respect to paid employment.

The epidemiologic data concerning long workhours and CVD is somewhat sparse and inferential, although this is a plausible relationship and its importance has been emphasized in clinical observations (93–95). "*Karoshi*", cardiovascular or cerebrovascular death due to long hours of demanding work, is a recognized entity in Japan (94), and it is becoming acknowledged elsewhere as well (96). Thus far, however, there have not been any reported risk estimates for working long hours in a high-strain job. Job strain still showed a significant association with self-reported angina after adjustment for long workhours in the study by Netterstrøm et al (64).

Threat avoidant vigilance is defined as the need to maintain a high level of attention in order to avoid the disastrous consequences that could occur with a momentary lapse or a wrong decision. A multifaceted body of evidence is emerging linking this factor to the risk of CVD, especially noting the high cardiac risk among urban mass transit operators and other categories of professional drivers, for whom threat avoidant vigilance is an essential feature of work (97–98). Risk estimates for combined exposure to job strain and threat avoidant vigilance have not been reported, nor has threat avoidant vigilance been taken into account as a potential confounder of the job strain–CVD relationship.

Physical factors such as heavy lifting, noise, vibration, and excessive heat or cold are considered potentially harmful to the cardiovascular system (especially as possible trigger mechanisms), although, as yet, there is little *direct* evidence linking these exposures to hard CVD outcomes (99). The combined effect upon CVD risk of exposure to these physical factors plus job strain has not been described. However, inferred data (50) indicate a significantly increased risk of MI among men exposed to high psychological job demands (rushed tempo) together with vibration, sweaty work or heavy lifting. The significant positive risk estimate for prevalent MI in the study by Karasek et al (63) included adjustment for physical exertion at work. Exposure to certain chemicals (eg, carbon disulfide, nitroglycerin, and carbon monoxide) is directly associated with an increased risk of CVD (99). There are no published studies in which these factors are examined together with exposure to job strain.

Overall, from the limited available data, we concluded that the significant positive risk estimates for job strain do not appear to have been confounded by other occupational factors. On the other hand, consideration of the potential combined effects of job strain and other work-related exposures upon the risk of CVD is a promising avenue for further investigation.

Gender and gender-related factors

Gender is obviously a critical effect modifier for which stratified analysis is essential. An estimated 80% of the workforce is employed in gender-segregated occupations (87). Women are more likely than men to have low levels of control over their work (100). Furthermore, women working in jobs with low decision latitude are far more apt to also have high psychological demands. Consequently, "women are several times more likely than men to hold high-strain jobs in the general working population. By contrast, men's high-demand jobs generally are accompanied by somewhat higher decision latitude [p 83]" (3). Not only does the nature of job exposures differ markedly by gender, but the patterns of CVD manifestation and age-related prevalence are also highly gender specific (101). A notable example is syndrome X. As discussed earlier, lack of gender stratification is undoubtedly one important contributor to the null findings of Hlatky et al (37) concerning job strain and CAD.

Hormones. With the exception of the studies by Lee et al (43), Orth-Gomér et al (44), and Wamala et al (60), none of the studies of women took into account estrogen status or the use of hormone replacement therapy. Reuterwall et al (56) reported elevated risk estimates for MI among women with hyperlipidemia. This is one of the major important consequences of low estrogen levels. However, these authors (56) did not adjust for hyperlipidemia in their risk estimate for MI in relation to job strain. Only one of the studies (43) adjusted for use of oral contraceptives, which appears to increase the risk of MI among some groups of women (smokers over 35 years of age) (102). It is difficult to ascertain how hormone status and the use of exogenous hormone preparations affected the results, particularly in light of the most recent unexpected data indicating an *increased* risk of CVD events among women taking combined hormone replacement therapy (103). Overall, it seems plausible that a lack of adjustment for hormone-related risk among women may have diluted the effect estimates.

Additional burden: home and family responsibilities. Women bear a major burden outside the arena of paid worklife (ie, responsibility for home and family). This responsibility has remained essentially unchanged, despite women's markedly increased levels of paid employment in recent decades (104). As pointed out by Hall (100, 105), among women, the psychological burden of the home situation appears to interact more with the work situation to generate illness symptoms than it does among men. Thus information about the home situation is essential for studies of work and health among women, and it is more difficult to establish an association between CVD and job strain among women than

among men. In a similar vein, Messing (106) has noted that multiple roles and complex exposures make it hard to pin down risks for working women. Moreover, the burden of unpaid labor appears to be inversely related to socioeconomic level (107).

Brisson et al (48) showed that, among university-educated,[12] white-collar, female workers, combined exposure to heavy load from family and domestic work, plus exposure to job strain, produced the highest levels of diurnal blood pressure. This finding is also broadly complementary to the gender-specific finding linking over-commitment plus exposure to job strain to risk of MI among women (57).

A nonwork burden, marital stress, was evaluated among women with CHD in the longitudinal study of Orth-Gomér et al (44). It was found to be a significant independent predictor of recurrent coronary events. However, no analysis was described of exposure to *both* marital stress and job strain, nor did the authors report adjustment for marital stress in their risk assessment of exposure to job strain. When it is considered that these are potential additive burdens, it is conceivable that female patients with ischemic heart disease and exposed to both severe marital stress *and* job strain could be at very high risk of recurrent cardiac events. This would be a clinically important hypothesis, which warrants empirical testing.

Few of the other investigations of job strain and CVD that included women took into account stressors related to home and family responsibilities. In their study of registered nurses, Lee et al (43) found no interaction between exposure to job strain and hours of care giving in the home (for children and for sick relatives). These authors emphasized the need for "a more complete assessment of the stress in the home environment [p 1152]".

Potential mediating mechanisms: plausibility of a job strain–cardiovascular disease relationship

Social psychological mechanisms

Negative emotions have been postulated as a potential mediator in the causal pathway between occupational stressors and CHD (108). Exposure to job strain has been found to predict depressive symptoms significantly in a longitudinal study of over 10 000 electrical company employees (109). Cross-sectional relationships between job strain and negative emotions have also been reported (110, 111), although null findings have been seen as well (112). In turn, there is substantial data linking depression with CHD, especially mortality post-MI (13, 108, 113), and anxiety with cardiac death (19, 113). Kubzansky & Kawachi (113) have concluded that there is "growing evidence that negative emotions may influence the development of CHD [p 323]".

There are also some data showing a relationship between the main components of job strain and various psychological markers. In a 1.5-year follow-up of 11 121 working men, psychological workload was associated with a 1.4 times higher risk of a new visit for psychiatric treatment (114). Among female blue-collar workers in Israel, short-cycle, repetitive work was significantly related to psychological distress (anxiety-irritability, depression, and somatic complaints) (115). Low job control was significantly associated with negative affectivity among male civil servants (34). However, risk estimates of self-reported heart diseases due to low job control were not substantially changed in models with and without adjustment for negative affectivity (32), the finding suggesting that negative affectivity was not a mediator of the job control–CHD association.

A type-A behavior pattern, taken in its entirety, is probably not a mediator of the pathway between job strain and CVD, since it is primarily related to the higher status, success-oriented jobs characteristic of the "active" quadrant, rather than to jobs in the high strain quadrant (16, 112). However, the hostility component of type-A behavior pattern has been associated with low levels of job control among both men and women (34). Adjustment for hostility lowered the odds ratio somewhat for newly reported CHD in association with low control among men, but not among women. There is some, though not entirely consistent, prospective evidence linking hostility to future cardiac events in healthy persons and to ischemic complications in patients with CAD. [See Rozanski et al (19) for a review.]

The type-A behavior pattern also includes a measure of overinvolvement in work; this component is very similar to the intrinsic effort or overcommitment component of the model for effort–reward imbalance. For women, the combination of exposure to job strain plus the presence of overcommitment yielded a much higher risk of MI (OR 2.19) than either exposure to job strain without overcommitment (OR 1.23) or overcommitment without job strain (OR 1.19) (57). Thus overcommitment could mediate (or moderate) the job strain–MI relationship for women.

Job strain, as well as overcommitment (high intrinsic effort), has also been associated with burnout or vital exhaustion in cross-sectional studies of nurses and teachers, professions in which women are heavily represented (116–118). In turn, vital exhaustion (especially in the early stage) and burnout have been prospectively associated with CVD (14, 119, 120).

12 But not nonuniversity-educated, white-collar working women.

Additional multivariate prospective studies using structural equation models would help elucidate the nature of the relationships between job strain, potential behavioral or psychological mediators, and CVD.

Standard cardiac risk factors

Hypertension. The strongest empirical evidence linking job strain to standard cardiac risk factors is found for hypertension. A substantial body of data indicates that exposure to job strain is cross-sectionally and longitudinally associated with significant elevations in ambulatory blood pressure of a clinically important magnitude, greatest at work, but also evident at home and during sleep (121–123). [For a review see Belkic et al (17).] Increased ambulatory blood pressure, particularly during work, is closely linked to left ventricular hypertrophy (124–126). Moreover, exposure to job strain has been directly associated with increased left ventricular mass (127). It is therefore plausible that long-term exposure to job strain leads to a sustained elevation in blood pressure, which in turn causes structural changes in the left ventricle. Considering the strong, independent relation between increased left ventricular mass and cardiac events, this pathophysiological process may account for a substantial part of the reported association between job strain and CVD-related morbidity and mortality.

Several of the adjusted effect estimates for job strain and CVD have included blood pressure or hypertension as a potential confounder (31, 44–46, 52, 61, 63–66). Overcorrecting for intermediates in the etiologic chain can lead to the masking of a true effect (128). Adjustment for hypertension may have thereby attenuated the effect sizes, given the evidence that this represents an important mediating mechanism between job strain and CVD.

Smoking and other standard cardiac risk factors. Substantial data, although not entirely consistent, indicate a positive relation between exposure to job strain and smoking intensity (17). Three-year longitudinal findings revealed that increased decision-latitude was positively associated with smoking cessation among men (129). Significantly more than the expected number of patients with high demands were smokers (100%), compared with the controls (60%), in the study by Sihm et al (22). This finding suggests a possible interaction between smoking and high demands, such that "smoking seemed to add significantly to the psychosocial risk associated with high job demands [p 208]" (22). On the other hand, as yet, limited evidence is available to support an association between exposure to job strain and obesity, sedentary leisure-time activity, hypercholesterolemia, or glucose intolerance (17). Most of the reviewed investigations adjusted for at least some of the standard cardiac risk factors. The exception was a few of the imputational studies (21, 35, 36).

Atherosclerosis

Broadly speaking, a relationship between job strain and the development of CAD is plausible. Job-strain-induced hypertension could play a role. Sustained elevations in blood pressure contribute to atherogenesis by creating shear stress at branching points on the arterial tree, and they also have a direct pro-inflammatory effect (130). Nitric oxide production, upon which endothelial function depends, is impaired among patients with hypertension (131). Liu et al (125) has shown that working persons with elevated daytime ambulatory blood pressure, but normal casual clinic blood pressure, as well as those with sustained hypertension, had a significantly higher prevalence of discrete carotid artery atherosclerotic plaques, compared with those with normal blood pressure, both during daily activities and in the clinic.

Exposure to job strain has also been associated with increased catecholamine excretion, in some studies. [See the next section.] Beta-adrenergic mechanisms are implicated in endothelial-injury (132), and epinephrine is known to activate platelets.

The evidence thus far does not suggest that job strain promotes atherogenesis via increased lipoprotein levels, nor are there data supporting an effect upon fibrinogen. In the Whitehall II study, elevated fibrinogen was reported to be associated with low workplace control, after adjustment for socioeconomic status (133). However, in a study by Ishizaki et al (134), neither job strain nor its major dimensions were significantly associated with plasma fibrinogen levels, although psychological demands were inversely related to tissue plasminogen activator levels. Møller & Kristensen (135) also failed to find a significant, independent relation between job strain and plasma fibrinogen levels.

As noted earlier, the studies of Yoshimasu et al (66) and of Hlatky et al (37) cannot be used to make valid inferences in relating job strain to coronary atherosclerosis. In particular, selection bias concerning who came to coronary angiography altered the findings vis-à-vis the etiologic relationship between exposure to job strain and CAD. Nor was the degree of coronary atherosclerosis found to be associated with exposure to job strain in the relatively small series of young men with post-MI in the study by Theorell et al (59), and selection bias did not appear to be an important factor for that study.

High-resolution carotid ultrasound provides a proxy measure for CAD and can be used to screen working populations (130). When this method was applied, a significant, independent relation was reported between high demands and low economic rewards at work and 4-year progression of carotid atherosclerosis among Finnish

men (136). Recent data (137) have revealed a significant cross-sectional association between exposure to job strain and plaque prevalence in the carotid artery and intima-medial thickness at carotid bifurcations, after adjustment for standard cardiac risk factors in a population-based sample of working women in Sweden. No such findings concerning exposure to job strain were reported for the men in that study, although a low odds ratio for carotid plaque prevalence was found for the men in active jobs

Autonomic or neuroendocrine mechanisms

The effort–distress paradigm: high demands and low control in the laboratory. The job strain model is closely akin to the effort–distress paradigm, in which demanding tasks are coupled to low control situations in the laboratory (138). The underlying biological construct is that, when the human organism is overloaded psychologically and at the same time deprived of control over the work environment, a high degree of arousal together with distress ensues. This situation has been found to activate the sympathoadrenomedullary and hypothalamo-pituitary-adrenocortical axes, a deleterious combination for the cardiovascular system (139). One of the experimental paradigms applied in this context has been the performance of a monotonous vigilance task versus a self-paced, reaction-time task. Both of these tasks elicited similar effort, but the former also created distress, while the latter was rather enjoyable. During the vigilance task, both epinephrine and cortisol increased, while during the reaction-time task, there was a rise only in epinephrine (140). More recently, Peters et al (141) found that a high effort–low control task not only elicited a rise in catecholamine and cortisol, but also an increase in blood pressure.

Field studies: catecholamine, cortisol and inhibition of anabolism. Neuroendocrine changes consistent with activation of the sympathoadrenomedullary axis have been reported for metallurgists performing high-strain, paced assembly-line work (142). Other field studies have shown elevated catecholamine excretion in association with high strain work (143) or low decision latitude (144). Long-lasting energy mobilization has also been associated with the inhibition of anabolism ("adaptive redirection of energy"). Theorell et al (145) found that increasing job strain was associated with decreasing plasma testosterone levels among working men. An improvement in the work conditions of policemen was associated with increased plasma testosterone and an improved profile for standard cardiac risk factors (146).

Field studies: heart rate variability. Recent evidence also suggests that exposure to job strain may alter the vago–sympathetic balance, as reflected by heart rate variability. van Amelsvoort et al (147) reported a significant increase in normalized low-frequency power among healthy workers exposed to job strain when they were compared with those with low demands and high control (relaxed quadrant), after adjustment for age, gender, leisure-time physical activity, and smoking status. Indices of diminished heart rate variability have been found to predict cardiovascular morbidity and mortality in healthy populations (148, 149). No studies have yet been published that have examined the relation between heart rate variability and return to high strain work after MI, although depressed heart rate variability is recognized as a powerful independent predictor of mortality and the risk of life-threatening arrhythmias among post-MI patients (150).

Possible cardiovascular consequences of exposure to job strain among vulnerable persons

Myocardial ischemia. Two of the major determinants of imbalance between myocardial oxygen demand and supply, namely, systolic blood pressure and left ventricular hypertrophy, are directly associated with exposure to job strain. It is plausible, although it has not been directly demonstrated, that job-strain-related elevations in blood pressure and catecholamine could lead to endothelial dysfunction, which increases vulnerability to vasospasm. It is also plausible, although it has not been directly demonstrated, that job strain could promote coronary atherosclerosis.

As noted earlier, among healthy persons, exposure to job strain has been associated with diminished heart rate variability (147). Among patients with CAD, the onset and severity of ischemic events have been found to be related to low heart rate variability (151). Mentally stressful paradigms have been shown to trigger silent myocardial ischemia in the laboratory in 40–70% of patients with various stable ischemic syndromes (19, 152, 153). However, published field studies on the relation between myocardial ischemia and exposure to job strain or other psychosocial work stressors are lacking.

Cardiac electrical instability. As yet, there is no direct evidence linking job strain to disturbances in cardiac electrical stability. However, several contributory stress-mediated mechanisms are associated with exposure to high-strain work. They include sympathetic overdrive, altered vago–sympathetic balance and left ventricular hypertrophy (154–157). In the setting of the ischemic myocardium, autonomic outflow, profoundly affected by exposure to stressors, has been shown to be a critical determinant of whether or not life-threatening arrhythmias will ensue (154, 158, 159). Moreover, as has already been discussed, myocardial ischemia itself can

be triggered in vulnerable people by mentally stressful situations.

There are several reports in the literature of a septadian overrepresentation of life-threatening arrhythmias and acute cardiac events on Mondays (160–162). Exposure to the stress of work after a weekend of leisurely activities has been suggested as a potential trigger of these events (155, 157). There are numerous plausible mechanisms by which exposure to job strain could contribute to the occurrence of acute cardiac events in vulnerable persons. The finding that young men who returned to high-strain work after acute MI were at particularly high risk of lethal ischemic events (47) suggests that activation of these mechanisms could well be more important than we have heretofore appreciated.

Coherence with broader research and with sociohistorical trends—convergent validation

On many levels, a causal relationship between exposure to job strain and CVD can be considered coherent with our understanding of how the CVD epidemic has arisen. Gaziano (163) speaks of the "age of degenerative and man-made diseases", such as CVD, and links these to urban industrial life, including "radical changes in work-related activities [p 3]". The epidemic of CVD seems to parallel profound changes in the social organization of work that have taken place over the last 200 years: from craft work to machine-based, mass production, exemplified by Taylorism, and most recently, to lean production (164). Job strain captures essential features of these processes. A very similar sociohistorical dynamic has been observed for hypertension (165), which is well recognized as a powerful CVD risk factor, and, as already discussed, is one of the major pathways through which job strain is likely to affect the pathogenesis and manifestation of ischemic heart disease.

More broadly, the importance of social factors in the etiology of CVD is becoming increasingly apparent, from the large body of evidence concerning the impact of social isolation versus support networks (166–169), socioeconomic status (81–84), and classical studies on the impact of immigrating from regions of low to high CHD prevalence (170), among other things. Rozanski et al (19), in their exhaustive review of clinical, epidemiologic and experimental findings, concluded that there is "clear and convincing evidence that psychosocial factors contribute significantly to the pathogenesis and expression of CAD [p 2192]". More recently, Kuper et al (15) presented a systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of CHD and arrived at similar conclusions for depression, social support, and psychosocial work characteristics.

Insights from cognitive ergonomics and brain research have also provided support for the job-strain concept. In particular, a consideration of cognitive energy mobilization confirms the need for a two-dimensional model, which includes both task demands and the possibilities for control (171). Thus, from the vantage point of cognitive ergonomics, the indelible coupling between these two dimensions becomes eminently clear: with sufficient decision-latitude, or control, a worker can modulate even a fairly onerous, *though not overwhelming*, psychological workload to meet his or her moment-to-moment needs and capacities (3, 172). Furthermore, when psychological workload was operationalized on the basis of the theory of human information transmission (173), the criterion validity of the demand dimension was improved (53, 172). It has therefore been emphasized that, when psychologically demanding work is considered, it is helpful to go beyond queries about "working hard" and "working fast", to analyze tasks in terms of the allocation of mental resources (172). This step becomes particularly important for occupations in which many of the most taxing demands are not readily apparent (eg, professional driving and health professions, for which job-strain assessments using standard self-report instruments did not yield significant findings with respect to CVD) (172).

Finally, the association between job strain and CVD is coherent with clinical intuition and observations. Clinicians have long sensed that workplace stressors can have a profound impact upon patients' cardiovascular health. In 1958 Russek & Zohman (93) published a seminal paper from their own medical practice, in which they identified "occupational stress and strain" as the factor that most sharply distinguished their young patients with IHD from a group of healthy controls. Their analyses relied upon descriptive data obtained from patient histories. Nowadays, these types of clinical observations can be tested with the use of validated questionnaires or other methods that assess exposure to job strain without relying exclusively upon self-report.

Concluding remarks—clinical implications

In addition to the strong, consistent evidence of an association between exposure to job strain and CVD, especially among men, many other elements of causal inference, particularly biological plausibility, have been shown in this review to support the conclusion that job strain is indeed a major CVD risk factor. It is well recognized that the most definitive evidence regarding causality is obtained from randomized trials (174, 175). The limited existing data generally show that workplace interventions that increase decision-making latitude or

diminished psychological demands (eg, by reducing time pressure) resulted in favorable changes in mediators relevant to the cardiovascular system, such as blood pressure or the catecholamine and lipid profile (176–178). There is clearly a need for larger-scale primary intervention studies that examine the effects of lowering job strain upon a broader range of cardiovascular-related outcomes, if possible using the interrupted time series with a switching replication study design (179).

Thus far, no intervention studies have examined the effect of ameliorating exposure to job strain among those at a high risk of developing CVD or on patients who have already suffered a cardiac event. As discussed earlier, there is observational evidence from among young men who have suffered an acute MI that return to work in a high-strain job is an independent predictor of subsequent IHD-related death. The predictive strength of return to high-strain work was found to be of comparable magnitude to degree of angiographically assessed coronary atheromatosis and to be more powerful than left ventricular ejection fraction (47). Observational data also indicate that men with hypertension who change from exposure to nonexposure to job strain over 3 years show a pronounced fall in ambulatory blood pressure [13] at work and at home (123).

We began by posing the question of whether the work environment is conducive to cardiovascular health, pointing out that this is a key issue to be addressed when judgments must be made about the cardiovascular work fitness of patients. We underscored the need for guidelines that not only take into consideration the levels of physical exertion on the job, but also the relevant psychosocial work stressors. The practical challenge is to offer the cardiac patient a style of life and of work that protects both his or her health and right to be productive (180); this challenge includes avoiding iatrogenically compromising employability (181). Modification of work schedules is among the most immediately feasible ways to ameliorate the effects of job strain and other potentially cardio-deleterious exposures (181). These and other strategies should be explored in randomized clinical trials, which would not only provide a needed link in etiologic research, but would also be helpful for developing evidence-based guidelines for the prevention-oriented care of working patients at high risk of CVD or with manifest CVD.

Acknowledgments

This work has been a long collaborative effort, and we are grateful to many of our colleagues for their helpful discussions, particularly at the International Conference on the Work Environment and Cardiovascular Disease, held in Düsseldorf, Germany, in March of 2002 and at the 5th Interdisciplinary Conference on Occupational Health and Stress, held in Toronto, Canada, in March of 2003, at which portions of this paper were presented. We wish to thank Pam Corley, Senior Medical Information Specialist at the USC School of Medicine, for her help with and advice on the search strategy by which the empirical articles were identified.

References (* = included in the empirical review)

1. Hu H, Speizer FE. Influence of environmental and occupational hazards on disease. In: Braunwald E, Fauci AS, Kasper DL, Hauser DL, Longo D, Jameson JL, editors. Harrison's principles of internal medicine. 15th ed. New York (NY): McGraw-Hill, Inc; 2001. p 19–21.
2. Karasek RA. Job demands, job decision latitude and mental strain: Implications for job redesign. Adm Sci Q 1979;24:285–307.
3. Karasek RA, Theorell T. The demand-control-support model and CVD. In: Schnall PL, Belkic K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 78–83. Occupational medicine: state of the art reviews, vol 15.
4. Karasek R, Theorell T. Healthy work: stress, productivity and the reconstruction of working life. New York (NY): Basic Books; 1990.
*5. Johnson JV, Hall EM. Job strain, workplace 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. Karasek R, Brisson C, Kawakami N, Houtman I, Bongers P, Amick B. The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics. J Occup Health Psychol 1998; 3:322–55.
7. Theorell T, Perski A, Åkerstedt T, Sigala F, Ahlberg-Hultén G, Svensson J, et al. Changes in job strain in relation to changes in physiological states: a longitudinal study. Scand J Work Environ Health. 1988;14:189–96.
8. Landsbergis P, Theorell T. Self-report questionnaires. In: Schnall PL, Belkic K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 163–171. Occupational medicine: state of the art reviews, vol 15.
9. Johnson JV, Stewart WF. Measuring work organization exposure over the life course with a job-exposure matrix. Scand J Work Environ Health 1993;19:21–8.
10. Schwartz JE. Imputation of job characteristics scores. In: Schnall PL, Belkic K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 172–5. Occupational medicine: state of the art reviews, vol 15.
11. Greiner BA, Krause N. Expert-observer assessment of job

13 –11.3— –5.8 mm Hg for workplace blood pressure, after adjustment for age, body mass index, alcohol, and smoking status.

characteristics. In: Schnall PL, Belkic K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 175–83. Occupational medicine: state of the art reviews, vol 15.
12. Barsky AJ. Psychiatric and behavioral aspects of cardiovascular disease. In: Braunwald E, Zipes DP, Libby P, editors. Heart disease. a textbook of cardiovascular medicine. Philadelphia (PA): WB Saunders Co; 2001. p 2244–61.
13. Hemingway H, Marmot M. Psychosocial factors in the aetiology and prognosis of coronary heart disease: systematic review of prospective cohort studies. BMJ 1999;318:1460–7.
14. Kristensen TS, Kornitzer M, Alfredsson L. Social factors, work, stress and cardiovascular disease prevention. Brussels: The European Heart Network; 1998.
15. Kuper H, Marmot M, Hemingway H. Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. Semin Vasc Med 2002;2:266–314.
16. Schnall PL, Landsbergis PA; Baker D. Job strain and cardiovascular disease. Annu Rev Public Health 1994;15:381–411.
17. Belkic K, Landsbergis P, Schnall P, Baker D, Theorell T, Siegrist J, et al. Psychosocial factors: review of the empirical data among men. In: Schnall PL, Belkic K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 24–46. Occupational medicine: state of the art reviews, vol 15.
18. Brisson C. Women, work and CVD. In: Schnall PL, Belkic K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 49–57. Occupational medicine: state of the art reviews, vol 15.
19. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular diseases and implications for therapy. Circulation 1999;99:2192–217.
20. Karasek RA. Job content instrument: questionnaire and user's guide. Lowell (MA): University of Massachusetts; 1985.
*21. Hammar N, Alfredsson L, Theorell T. Job characteristics and the incidence of myocardial infarction. Int J Epidemiol 1994;23:277–84.
*22. Sihm I, Dehlholm G, Hansen ES, Gerdes LU, Faergeman O. The psychosocial work environment of younger men surviving acute myocardial infarction. Eur Heart J 1991;12:203–9.
*23. Suadicani P, Hein HO, Gyntelberg F. Are social inequalities as associated with the risk of ischaemic heart disease a result of psychosocial working conditions? Atherosclerosis 1993;101:165–75.
24. Lynch J, Krause N, Kaplan GA, Tuomilehto J, Salonen JT. Workplace conditions, socioeconomic status and the risk of mortality and acute myocardial infarction: The Kuopio Ischemic Heart Disease Risk Factor Study. Am J Public Health 1997;87:617–22.
25. Murphy LR. Job dimensions associated with severe disability due to cardiovascular disease. J Clin Epidemiol 1991;44:155–66.
26. Billing E, Hjemdahl P, Rehnqvist N. Psychosocial variables in female vs male patients with stable angina pectoris and matched healthy controls. Eur Heart J 1997;18:911–8.
27. Karasek RA, Gardell B, Lindell J. Work and non-work correlates of illness and behaviour in male and female Swedish white collar workers. J Occup Behav 1987;8:187–207.
28. Messner T, Sihm H. Psychosocial risk factors for ischaemic heart disease among men in the subarctic area. Int J Circumpolar Health 1997;56:12–20.
29. Stock SR. Workplace ergonomic factors and the development of musculoskeletal disorders of the neck and upper limbs: a meta-analysis. Am J Ind Med 1991;19:87–107.
*30. Alfredsson L, Spetz CL, Theorell T. Type of occupation and near-future hospitalization for myocardial infarction and some other diagnoses. Int J Epidemiol 1985;14:378–88.
*31. 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.
*32. Bosma H, Marmot M, Hemingway H, Nicholson AC, Brunner E, Stansfeld SA. Low job control and risk of coronary heart disease in Whitehall II (prospective cohort) study. BMJ 1997;314:558–65.
*33. 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.
*34. Bosma H, Stansfeld SA, Marmot MG. Job control, personal characteristics and heart disease. J Occup Health Psychol 1998;3:402–9.
*35. Hall EM, Johnson JV, Tsou T-S. Women, occupation, and risk of cardiovascular morbidity and mortality. Philadelphia (PA): Hanley & Belfus Inc; 1993. p 709–19. Occupational medicine: state of the art reviews, vol 8.
*36. Hammar N, Alfredsson L, Johnson JV. Job strain, social support at work and incidence of myocardial infarction. Occup Environ Med 1998;55:548–53.
*37. Hlatky MA, Lam LC, Lee KL, Clapp-Channing NE, Williams RB, Pryor DB, et al. Job strain and the prevalence and outcome of coronary artery disease. Circulation 1995; 92:327–33.
*38. 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.
*39. Johnson JV, Stewart W, Hall EM, Fredlund P, Theorell T. Long-term psychosocial work environment and cardiovascular mortality among Swedish men. Am J Public Health 1996; 86:324–31.
*40. 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.
*41. 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;325:857–60.
*42. 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.
*43. 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.
*44. Orth-Gomér K, Wamala SP, Horsten M, Schenck-Gustafsson K, Schneiderman N, Mittleman MA. Marital stress worsens prognosis in women with coronary heart disease: The Stockholm Female Coronary Risk Study. JAMA 2000;284:3008–14.
*45. Reed DM, LaCroix AZ, Karasek RA, Miller D, MacLean CA. Occupational strain and the incidence of coronary heart disease. Am J Epidemiol 1989;129:495–502.
*46. Steenland K, Johnson J, Nowlin S. A follow-up study of job strain and heart disease among males in the NHANES1 population. Am J Ind Med 1997;31:256–60.

*47. Theorell T, Perski A, Orth-Gomér K, Hamsten A, deFaire U. The effects of the strain of returning to work on the risk of death after a first myocardial infarction before age of 45. Int J Cardiol 1991;30:61–7.
48. Brisson C, LaFlamme N, Moisan J, Milot A, Masse B, Vézina M. Effect of family responsibilities and job strain on ambulatory blood pressure among white-collar women. Pyschosom Med 1999;61:205–13.
49. Mark DB, Lam LC, Lee KL, Clapp-Channing NE, Williams RB, Pryor DB, et al. Identification of patients with coronary disuse at high risk for loss of employment: a prospective validation study. Circulation 1992:86:1485–94.
*50. Alfredsson L, Karasek R, Theorell T. Myocardial infarction risk and the psychosocial work environment: an analysis of the male Swedish working force. Soc Sci Med 1982;16:463–7.
*51. Alfredsson L, Theorell T. Job characteristics of occupations and myocardial infarction risk: effect of possible confounding factors. Soc Sci Med 1983;17:1497–503.
*52. Bobák M, Hertzman C, Škodová Z, Marmot M. Association between psychosocial factors at work and nonfatal myocardial infarction in a population-based case–control study in Czech men. Epidemiology 1998;9:43–7.
*53. Emdad R, Belkić K, Theorell T, Cizinsky S, Savić Č, Olsson K. Work environment, neurophysiologic and psychophysiologic models among professional drivers with and without cardiovascular disease: seeking an integrative neurocardiologic approach. Stress Med 1997;13:7–21.
*54. Hallqvist J, Diderichsen F, Theorell T, Reuterwall C, Ahlbom A, SHEEP Study Group. Is the effect of job strain on myocardial infarction due to interaction between high psychological demands and low decision latitude: results from Stockholm heart epidemiology program (SHEEP). Soc Sci Med 1998;46:1405–15.
*55. Theorell T, Tsutsumi A, Hallqvist J, Reuterwall C, Hogstedt C, Fredlund P, et al. Decision latitude, job strain and myocardial infarction. Am J Public Health 1998;88;382–8.
*56. Reuterwall C, Hallqvist J, Ahlbom A, de Faire U, Diderichsen F, Hogstedt C, et al. Higher relative, but lower absolute risks of myocardial infarction in women than in men: analysis of some major risk factors in the SHEEP study. J Intern Med 1999;246:161–74.
*57. Peter R, Siegrist J, Hallqvist J, Reuterwall C, Theorell T, the SHEEP Study Group. Psychosocial work environment and myocardial infarction: improving risk estimation by combining two complementary job stress models in the SHEEP study. J Epidemiol Community Health 2002;56:294–300.
*58. Netterstrøm B, Nielsen FE, Kristensen TS, Back E, Møller L. Relation between job strain and myocardial infarction: a case–control study. Occup Environ Med 1999;56:339–342.
*59. Theorell T, Hamsten A, de Faire U, Orth-Gomér K, Perski A. Psychosocial work conditions before myocardial infarction in young men. Int J Cardiol 1987;15: 33–46.
*60. Wamala SP, Mittleman MA, Horsten M, Schenck-Gustafsson K, Orth-Gomér K. Job stress and the occupational gradient in coronary heart disease risk in women: the Stockholm Female Coronary Risk Study. Soc Sci Med 2000;51:481–9.
*61. Yoshimasu K, The Fukuoka Heart Study Group. Relation of Type A behavior pattern and job-related psychosocial factors to nonfatal myocardial infarction: a case–control study of Japanese male workers and women. Psychosomatic Med 2001;63:797–804.
62. Theorell T, Karasek R. Current issues relating to psychosocial job strain and cardiovascular disease research. J Occup Health Psychol 1996;1:9–26.
*63. 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 (HANES) and the Health and Nutrition Survey. Am J Public Health 1988;78:910–8.
*64. Netterstrøm B, Kristensen TS, Møller L, Jensen G, Schnohr P. Angina pectoris, job strain and social status: a cross-sectional study of employed urban citizens. Int J Behav Med 1998;5:312–22.
*65. Sacker A, Bartley MJ, Frith D, Fitzpatrick RM, Marmot MG. The relationship between job strain and coronary heart disease: evidence from an English sample of the working male population. Psychol Med 2001;31:279–90.
*66. Yoshimasu K, Liu Y, Kodama H, Sasazuki S, Washio M, Tanaka K, et al. Job strain, type A behavior pattern, and the prevalence of coronary atherosclerosis in Japanese working men. J Psychosom Res 2000;49:77–83.
67. Pickering TG. Should studies of patients undergoing coronary angiography be used to evaluate the role of behavioral risk factors for coronary heart disease? J Behav Med 1985;8:203–13.
68. Pickering TG. Job strain and the prevalence and outcome of coronary artery disease. Circulation 1996;94:1138–9.
69. Lantinga LJ, Sprafkin RP, Mc Croskery JH, Baker MT, Warner RA, Hill NE. One-year psychosocial follow-up of patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1988;62:209–13.
70. Reeder BA, Liu L, Horlick L. Sociodemographic variation in the prevalence of cardiovascular disease in Saskatchewan: results from the Saskatchewan Heart Health Survey. Can J Cardiol 1996;12:271–7.
71. Pasceri V, Lanza GA, Buffon A, Montenero AS, Crea F, Maseri A. Role of abnormal pain sensitivity and behavioral factors in determining chest pain in Syndrome X. J Am Coll Cardiol 1998;31:62–6.
72. Wenger NK. Rehabilitation of the patient with coronary heart disease. In: Alexander RW, Schlant RC, Fuster V, O'Rourke RA, Roberts R, Sonnenblick EH, editors. Hurst's The Heart. 9th edition. New York (NY): McGraw-Hill; 1998. p 1619–31.
73. Boissel J-P, Haugh MC. The iceberg phenomenon and publication bias: the Editors' fault? Clin Trials Met Anal 1993; 28:309–15.
74. La Croix A, Haynes SG. Occupational exposure to high demand/low control work and coronary heart disease incidence in the Framingham cohort. Am J Epidemiol 1984;120;481.
75. Kornitzer M, de Smet P, Boulenguez C, De Backer G, Ferrario M, Houtman I, et al. The Demand-Control Model and incidence of coronary heart disease (CHD) in a multicenter European project: the JACE study. In: Proceedings of the 3rd International Congress on the Work Environment and Cardiovascular Diseases; 2002 Mar 20–22; Düsseldorf, Germany. European Science Foundation Scientific Programme.
76. Partanen T. What's with epidemiologic meta-analyses? Scand J Work Environ Health 1996;22(4):241–2.
77. Rothman KJ, Greenland S. Modern epidemiology. Philadelphia (PA): Lippincott-Raven; 1998.
78. Sacks HS. Meta-analyses of randomized controlled trials. N Engl J Med 1987;316:450–5.
79. Spitzer WO. Meta-meta-analysis: unanswered questions about aggregating data. J Clin Epidemiol 1991;44:103–7.
80. Macleod J, Davey Smith G, Heslop P, Metcalfe C, Carroll D,

Hart C. Are the effects of psychosocial exposures attributable to confounding? Evidence from a prospective observational study on psychological stress and mortality. J Epidemiol Community Health 2001;55:878–84.
81. Gonzales A, Artalejo FR, Calero JR. Relationship between socioeconomic status and ischaemic heart disease in cohort and case control studies: 1960–1993. Int J Epidemiol 1998;27:350–8.
82. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation 1993; 88:1973–98.
83. Marmot M, Theorell T. Social class and cardiovascular disease: the contribution of work. In: Johnson JV, Johansson G, editors. The psychosocial work environment: work organization, democratization and health: essays in memory of Bertil Gardell. Amityville (NY): Baywood Publications; 1991. p 34–48.
84. Wamala SP, Mittleman MA, Horsten M, Schenck-Gustafsson K, Orth-Gomér K. Potential explanations for the educational gradient in coronary heart disease: a population-based case–control study of Swedish women. Am J Public Health 1999;89:315–21.
85. Marmot MG, Bosma H, Hemingway H, Brunner E, Stansfeld S. Contribution of job control and other risk factors to social variations in coronary heart disease incidence. Lancet 1997;350:235–9.
86. Quinlan M, Mayhew C, Bohle P. The global expansion of precarious employment, work disorganization and consequences for occupational health: a review of recent research. Int J Health Serv 2001;31:335–414.
87. Johnson JV, Hall EM. Dialectic between conceptual and causal inquiry in psychosocial work-environment research. J Occup Health Psychol 1996:1:362–74.
88. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, et al. Prevalence of hypertension in the US adult population: results from the third National Health and Nutrition Examination Survey, 1988–1991. Hypertension 1995; 25:05–313.
89. Cooper RS, Rotimi CN, Ward R. The puzzle of hypertension in African-Americans. Sci Am 1999;280:36–43.
90. Siegrist J. Adverse health effects of high-effort/low-reward conditions. J Occup Health Psychol 1996;1:27–41.
91. Bøggild H, Knutsson A. Shift work, risk factors and cardiovascular disease [review]. Scand J Work Environ Health 1999;25(2):85–99.
92. Tenkanen L, Sjöblom T, Kalimo R, Alikoski T, Härmä M. Shift work, occupation, and coronary heart disease over 6 years of follow-up in the Helsinki Heart Study. Scand J Work Environ Health 1997;23(4):257–65.
93. Russek HI, Zohman BI. Relative significance of heredity, diet, and occupational stress in coronary heart disease of young adults. Am J Med Sci 1958;235:266–75.
94. Shimomitsu T, Odagiri Y. Working life in Japan. In: Schnall PL, Belkić K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 280–1.Occupational medicine: state of the art reviews, vol 15.
95. Steenland K. Shift work, long work hours and cardiovascular disease: a review. In: Schnall PL, Belkic K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 7–17. Occupational medicine: state of the art reviews, vol 15.
96. Michie S, Cockcroft A. Overwork can kill: especially if combined with high demand, low control, and poor social support. BMJ 1996;312:921–2.
97. Belkic K, Emdad R, Theorell T. Occupational profile and cardiac risk: possible mechanisms and implications for professional drivers. Int J Occup Environ Health 1998;11:37–57.
98. Winkleby MA, Ragland DR, Fisher, JM, Syme SL. Excess risk of sickness and disease in bus drivers: a review and synthesis of epidemiological studies. Int J Epidemiol 1988;17:255–62.
99. Fine L. Chemical and physical factors. In: Schnall PL, Belkić K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 18–24. Occupational medicine: state of the art reviews, vol 15.
100. Hall EM. Gender, work control, and stress: a theoretical discussion and an empirical test. Int J Health Serv 1989; 19:725–45.
101. Douglas PS. Coronary artery disease in women. In: Braunwald E, Zipes DP, Libby P, editors. Heart disease: a textbook of cardiovascular medicine. Philadelphia (PA): WB Saunders Co; 2001. p 2038–51.
102. The World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case–control study. Lancet 1997;349:1202–9.
103. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288:321–33.
104. Lundberg U. Influence of paid and unpaid work on psychophysiological stress responses of men and women. J Occup Health Psychol 1996;1:117–30.
105. Hall EM. Double exposure: the combined impact of the home and work environments on mental strain and physical illness. Int J Health Serv 1992;22:239–60.
106. Messing K. Multiple roles and complex exposures: hard-to-pin-down risks for working women. In: Goldman MB, Hatch MC, editors. Women's health. San Diego (CA): Academic Press; 2000. p 455–62.
107. Terán L, Belkic K, Johnson CA. An exploration of psychosocial determinants of obesity among Hispanic women. Hisp J Behav Sci 2002;24:92–103.
108. Rugulies R. Are negative emotions a step in the causal pathway between occupational stress and illness?: a meta-analysis on depression and coronary heart disease. In: Proceedings of the 3rd International Congress on the Work Environment and Cardiovascular Diseases; 2002 Mar 20–22; Düsseldorf, Germany. European Science Foundation Scientific Programme.
109. Niedhammer I, Goldberg M, Leclerc A, Bugel I, David S. Psychosocial factors at work and subsequent depressive symptoms in the Gazel cohort. Scand J Work Environ Health 1998;24(3):197–205.
110. Bourbonnais R, Brisson C, Moisan J, Vézina M. Job strain and psychological distress in white-collar workers. Scand J Work Environ Health 1996;22(2):139–45.
111. Williams RB, Barefoot JC, Blumenthal JA, Helms MJ, Lueckeen L, Pieper CF, et al. Psychosocial correlates of job strain in a sample of working women. Arch Gen Psychiatry 1997;54:543–8.
112. Landsbergis PA, Schnall PL, Dietz DK, Friedman R, Pickering T. The patterning of psychological attributes and distress

by 'job strain' and social support in a sample of working men. J Behav Med 1992;15:379–405.
113. Kubzansky DL, Kawachi I. Going to the heart of the matter: do negative emotions cause coronary heart disease? J Psychosom Res 2000;48:323–37.
114. Uehata T. Stress, daily habits and health: from the epidemiologic survey on work stress and health. Bull Inst Publ Health 1993;42:385–401. [In Japanese: As cited by: Kawakami N, Haratani T. Epidemiology of job stress and health in Japan: review of current evidence and future direction. Ind Health 1999;37:174–86.]
115. Melamed S, Ben-Avi I, Luz J, Green MS. Objective and subjective work monotony: effects of job satisfaction, psychological distress and absenteeism in blue-collar workers. J Appl Psychol 1995;80: 29–42.
116. Amick III BC, Kawachi I, Coakley EH, Lerner D, Levine S, Colditz GA. Relationship of job strain and iso-strain to health status in a cohort of women in the United States. Scand J Work Environ Health 1998;24(1):54–61.
117. Bourbonnais R, Comeau M, Vézina M, Dion G. Job strain, psychological distress, and burnout in nurses. Am J Ind Med 1998;34:20–8.
118. Cropley M, Steptoe A, Joekes K. Job strain and psychiatric morbidity. Psychosom Med 1999;29:1411–66.
119. Appels A, Mulder P. Excess fatigue as a precursor of myocardial infarction. Eur Heart J 1988;9:758–64.
120. Appels A, Otten F. Exhaustion as precursor of cardiac death. Br J Clin Psychol 1992;31:351–6.
121. Laflamme N, Brisson C, Moisan J, Milot A, Mâsse B, Vézina M. Job strain and ambulatory blood pressure among female white-collar workers. Scand J Work Environ Health 1998;24(5):334–43.
122. Schnall PL, Schwartz JE, Landsbergis PA**,** Warren K, Pickering TG. Relation between job strain, alcohol and ambulatory blood pressure. Hypertension 1992;19:488–94.
123. Schnall PL, Schwartz J, Landsbergis PA, Warren K, Pickering TG. A longitudinal study of job strain and ambulatory blood pressure: results of a three year follow-up. Psychosom Med 1998;60:697–706.
124. Devereux RB, Pickering TG, Harshfield GA, Kleinert HD, Denby L, Clark L, et al. Left ventricular hypertrophy in patients with hypertension: Importance of blood pressure response to regularly recurring stress. Circulation 1983; 68:476–9.
125. Liu J, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. Ann Intern Med 1999;131:564–72.
126. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M et al. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. Hypertension 1994;24:793–801.
127. Schnall PS, Pieper C, Schwartz JE, Karasek RA, Schlussel Y, Devereux RB, et al. The relationship between "job strain", workplace diastolic blood pressure, and left ventricular mass index: results of a case–control study. JAMA 1990; 263:1929–35.
128. Hernberg S. Work related disease—some problems in study design. Scand J Work Environ Health 1984;10 (special issue):367–72.
129. Landsbergis PA, Schnall PL, Dietz DK, Warren K, Pickering TG, Schwartz JE. Job strain and health behaviors: results of a prospective study. Am J Health Promot 1998;12:237–45.
130. Steptoe A, Marmot M. Atherogenesis, coagulation, and stress mechanisms. In: Schnall PL, Belkic K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 136–8. Occupational medicine: state of the art reviews, vol 15.
131. Cardillo C, Kilcoyne CM, Cannon RO, Panza JA. Impairment of the nitric oxide-mediated vasodilator response to mental stress in hypertensive, but not in hypercholesterolemic patients. J Am Coll Cardiol 1998;32:1207–213.
132. Skantze HB, Kaplan J, Pettersson K, Manuck S, Blomqvist N, Kyes R, et al. Psychosocial stress causes endothelial injury in cynomolgus monkeys via beta 1-adreoceptor activation. Atherosclerosis 1998;136:153–61.
133. Brunner E, Davey Smith G, Marmot M, Canner R, Beksinska M, O'Brien J**.** Childhood social circumstances and psychosocial and behavioral factors as determinants of plasma fibrinogen. Lancet 1996;347:1008–13.
134. Ishizaki M, Tsuritani I, Noborisaka Y, Yamada Y, Tabata M, Nakagawa H. Relationship between job stress and plasma fibrinolytic activity in male Japanese workers. Int Arch Occup Environ Health 1996;68:315–20.
135. Møller L, Kristensen TS. Plasma fibrinogen and ischaemic heart disease risk factors. Arterioscler Thromb 1991;11:344–50.
136. Lynch J, Krause N, Kaplan GA, Salonen R, Salonen JT. Workplace demands, economic reward and progression of carotid atherosclerosis. Circulation 1997;96:302–7.
137. Rosvall M, Östergren P-O, Hedblad B, Isacsson S-O, Janzon L, Berglund G. Work-related psychosocial factors and carotid atherosclerosis. Int J Epidemiol 2002;31:1169–78.
138. Frankenhaeuser M. The sympathetic-adrenal and pituitary-adrenal response to challenge: comparison between the sexes. In: Dembroski TM, Schmidt TH, Blomchen G, editors. Biobehavioral bases of coronary heart disease. Basel: Karger;1983. p 91–105.
139. Theorell T. Neuroendocrine mechanisms. In: Schnall PL, Belkić K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 139–46. Occupational medicine: state of the art reviews, vol 15.
140. Lundberg U, Frankenhaeuser M. Pituitary-adrenal and sympathetic-adrenal correlates of distress and effort. J Psychosom Res 1984;24:125–30.
141. Peters ML, Godaert GL, Ballieux RE, van Vliet M, Willemsen JJ, Sweep FC, et al. Cardiovascular and endocrine responses to experimental stress: effects of mental effort and controllability. Psychoneuroendocrinology 1998;23:1–17.
142. Timio M, Gentili S, Pede S. Free adrenaline and noradrenaline excretion related to occupational stress. Br Heart J 1979;42:471–4.
143. Evans GW, Carrere S. Traffic congestion, perceived control and psychophysiologic stress among urban bus drivers. Appl Psychol 1991;76:658–63.
144. Härenstam AB, Theorell TPG. Work conditions and urinary excretion of catecholamine: a study of prison staff in Sweden. Scand J Work Environ Health 1988;14:257–64.
145. Theorell T, Karasek R, Eneroth P. Job strain variations in relation to plasma testosterone fluctuations in working men—a longitudinal study. J Intern Med 1990;227:31–6.
146. Grossi G, Theorell T, Jurisoo M, Setterlind S. Psychophysiological correlates of organizational change and threat of unemployment among police inspectors. Integr Physiol Behav Sci 1999;34:30–42.
147. van Amelsvoort LGPM, Schouten EG, Maan AC, Swenne CA, Kok FJ. Changes in frequency of premature complexes

and heart rate variability related to shift work. Occup Environ Med 2001;58:678–81.
148. Liao D, Cal J, Rosamond WD, Barnes RW, Hutchinson RG, Whitsel EA, et al. Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study. Am J Epidemiol 1997;145:696–706.
149. Tsuji H, Venditti FJJ, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort: The Framingham Heart Study. Circulation 1994;90:878–83.
150. Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Eur Heart J 1996;17:354–81.
151. Dilaveris PE, Zervopoulos GA, Psomadaki ZD, Michaelides AP, Gialofos JE, Toutozas PK. Assessment of time domain and spectral components of heart rate variability immediately before ischemic ST segment depression episodes. Pacing Clin Electrophysiol 1996;19:1337–45.
152. Jain D, Burg M, Soufer R,Zaret BL. Prognostic implications of mental stress-induced silent left ventricular dysfunction in patients with stable angina pectoris. Am J Cardiol 1995:76:31–5.
153. Krantz DS, Kop WJ, Santiago HT, Gottdiener JS. Mental stress as a trigger of myocardial ischemia and infarction. Cardiol Clin 1996;14:271–87.
154. Huikuri HV. Heart rate dynamics and vulnerability to ventricular tachyarrhythmias. Ann Med 1997;29:321–5.
155. Lown B. Sudden cardiac death: biobehavioral perspective. Circulation 1987;76 (suppl 1):I-186–I-197.
156. Messerli FH, Grodzicki T. Hypertension, left ventricular hypertrophy, ventricular arrhythmias, and sudden death. Eur Heart J 1992;13 Suppl D: 66–9.
157. Willich SN, Maclure M, Mittleman M, Arntz HR, Muller JE. Sudden cardiac death: support for a role in triggering causation. Circulation 1993;87:1442–50.
158. Carpeggiani C, Skinner JE. Coronary flow and mental stress: experimental findings. Circulation 1991;83 (suppl 2):II-90–II-93.
159. Lown B. Role of higher nervous activity in sudden cardiac death. Japan Circ J 1990;54:581–602.
160. Rabkin SW, Mathewson FAL, Tate RB. Chronobiology of cardiac sudden death in men. JAMA 1980;44:1357–58.
161. Peters RW, McQuillan S, Resnick SK, Gold MR. Increased monday incidence of life-threatening ventricular arrhythmias: experience with a third-generation implantable defibrillator. Circulation 1996:94:1346–9.
162. Willich SN, Löwel H, Lewis M, Hörmann A, Arntz H-R, Keil U. Weekly variation of acute myocardial infarction: Increased Monday risk in the working population. Circulation 1994:90:87–93.
163. Gaziano JM. Global burden of cardiovascular disease. In: E. Braunwald, DP Zipes, Libby P. editors. Heart disease: a textbook of cardiovascular medicine. Philadelphia (PA): WB Saunders Co; 2001. p 1–18.
164. Landsbergis PA, Cahill J, Schnall PL. The impact of lean production and related new systems of work organization on worker health. J Occup Health Psychol 1999;4:1–23.
165. Schnall PL, Belkic K, Landsbergis PA, Baker D. Why the workplace and cardiovascular disease? In: Schnall PL, Belkic K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 1–5. Occupational medicine: state of the art reviews, vol 15.
166. Berkman LF, Leo-Summers L, Horwitz RI. Emotional support and survival after myocardial infarction. Ann Intern Med 1992;117:1003–9.
167. Egolf B, Lasker J, Wolf S, Potvin L. The Roseto effect: a 50-year comparison of mortality rates. Am J Publ Health 1992; 82:1089–92.
168. Orth-Gomér KA, Unden AL, Edwards ME. Social isolation and mortality in ischemic heart disease. Acta Med Scand 1988;224:205–15.
169. Wolf S. Psychosocial forces in myocardial infarction and sudden death. Circulation.1969;39–40 (suppl 4):IV-74–IV-81.
170. Marmot M, Syme L. Acculturation and coronary heart disease in Japanese-Americans. Am J Epidemiol 1976;104:225–47.
171. Gaillard AWK. Comparing the concepts of mental load and stress. Ergonomics 1993;36:991–1005.
172. Belkic K. The occupational stress index: an approach derived from cognitive ergonomics and brain research for clinical practice. Cambridge (England): Cambridge International Science Publishing; 2003.
173. Welford AT. The measurement of sensory-motor performance: survey and reappraisal of twelve years' progress. Ergonomics 1960;3:189–230.
174. Maclure M. Refutation in epidemiology: why else not? In: KJ Rothman, editor. Causal inference. Boston (MA): Epidemiology Resources Inc; 1988. p 131–8.
175. Kristensen TS. Workplace intervention studies. In: Schnall PL, Belkic K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 293–305. Occupational medicine: state of the art reviews, vol 15.
176. Melin B, Lundberg U, Söderlund J, Granqvist M. Psychophysiological stress reactions of male and female assembly workers: a comparison between two different forms of work organization. J Organ Behav 1999;20:47–61.
177. Orth-Gomér K, Eriksson I, Moser V, Theorell T, Fredlund P. Lipid lowering through work stress reduction. Int J Behav Med 1994;1:204–14.
178. Rydstedt LW, Johansson G, Evans GW. The human side of the road: Improving the working conditions of urban bus drivers. J Occup Health Psychol 1998;3:161–71.
179. Beehr TA. O'Hara K. Methodological designs for the evaluation of occupational stress interventions. In: Kasl SV, Cooper CL, editors. Research methods in stress and health psychology. Chichester: John Wiley & Sons, Ltd; 1987. p 79–112.
180. Maisano G. Summary and conclusions towards guidelines for return to work after myocardial infarction and myocardial revascularization. Eur Heart J 1988 (suppl L):9:120–2.
181. Belkic K, Schnall P, Uglješić M. Cardiovascular evaluation of the worker and workplace: a practical guide for clinicians? In: Schnall PL, Belkić K, Landsbergis P, Baker D, guest editors. The workplace and cardiovascular disease. Philadelphia (PA): Hanley & Belfus Inc; 2000. p 213–22. Occupational medicine: state of the art reviews, vol 15.

Received for publication: 25 June 2003

Appendix

Internal validity criteria for empirical studies examining the relation between exposure to job strain and cardiovascular disease

Assembly of the sample

1. Avoidance of selection bias

Score 3, optimal
- worker- or population-based sample
- all potential workers included, or, if not, random method used for selection
- survivor bias avoided (ie, cohort or concurrent case–control study with at least 75% follow-up, no evidence of selective attrition, incidence density sampling performed)

Score 2
- volunteer or survivor bias possible (cross-sectional and case–control designs)
- if cohort study, less than 75% follow-up but no evidence of selective attrition
- if clinic-based study, inclusion based upon specified and confirmed diagnostic entity

Score 1
- selection methods not reported
- nonrandom selection
- response rate not reported
- for cohort studies: follow-up rate <60%, follow-up rate not reported, or evidence of selective attrition

Score 0 (internal validity may be *seriously* undermined)
- selection bias likely (distortion of the etiologic relationship between the exposure and outcome variable)

2. Avoidance of nonresponse bias

Score 3, optimal
- 80% or greater response rate in each comparison group and documentation that there is no differential nonrespondent rate between the groups

Score 2
- response rate 60–79% in each comparison group or inadequate or no documentation that there was no differential nonrespondent rate between the comparison groups

Score 1
- response rate <60%
- response rate not reported
- in case–control studies, large discrepancy between response rate of comparison groups (>30%)

- *Deduct one point from (3) or (2) above, if no description of the nonrespondents*

3. Appropriate clinical exclusion criteria applied

Score 3, optimal
- caseness adequately ruled out for controls in case–control studies or at baseline in prospective studies

Score 2
- indirect assessment of caseness (eg, self-report) for controls in case–control studies or at baseline in prospective studies

Score 1
- failure to rule out caseness for controls in case–control studies or at baseline in prospective studies

Assessment of the exposure variable

4. Valid and reliable assessment of point exposure to psychological demands and control

Score 4, optimal with use of innovative methods
- two or more validated methods used

Score 3
- self-report method only using a reliable and valid instrument or valid observer rating alone

Score 2
- use of imputation method (nondifferential misclassification may occur)
- only two items for the demand dimension

Score 1
- only one item per dimension or instrument not validated

- *If only two items for demand, and the imputation method is used, score 1*

5. Avoidance of recall bias for the exposure variable

Score 3, optimal
- exposure assessed by imputation or independent observer
- self-report of exposure made before outcome known to participant

Score 2
- outcome status known to participant prior to self-report of exposure, but potential recall bias assessed and appeared not to be operative

Score 1
- outcome status known to participant prior to self-report of exposure, recall bias could be operative

6. Analysis of point-exposure to job strain

Score 4, optimal, with use of innovative methods
- detailed exploration of the interaction between high demands and low control, providing insight into the nature of the interaction, especially identification of threshold for effect

Score 3
- assessed the interaction of demands and control as a quotient term (continuous variable) or as a multiplicative interaction term or used various cut points to provide insight into dose–response relationships.

Score 2
- assessed job strain only as a dichotomous variable (nondifferential misclassification possible)

Score 1
- no assessment of the interaction between high demands and low control

- *In order for a study to be given maximum points for this criterion, at least three items are needed for the demand dimension*

7. Adequate range of variation of the exposure variable

Score 3, optimal
- various occupations included with a broad range of occupational status levels, including white- and blue-collar

Score 2
- restriction to a single occupational class or single occupation title but study demonstrated sufficient variance in relevant job characteristics

Score 1
- single occupation title and study did not demonstrate sufficient variance in relevant job characteristics

8. Valid and reliable assessment of temporal aspects of exposure

Score 4, optimal, with use of innovative methods
- dynamic change or lifetime exposure to job strain assessed, as well as temporal proximity in cohort studies

Score 3
- repeated exposure measures made and temporal proximity to the outcome variable assessed

Score 2, no repeated exposure assessment but
- follow-up on employment status in temporal proximity to the outcome (long-term cohort studies, within 5 years).
- in case–control studies, temporal proximity of employment assessed and reasonably close (within 2 years)

Score 1, no repeated exposure assessment and
- in cohort studies, a large segment of the cohort likely to be temporally quite far removed from exposure (5–10 years). If over 10 years, then assessment of the occupational stability of the cohort or some other quasi measure for cumulative exposure is made (eg, seniority)
- in case–control or cross-sectional studies: current employment status and temporal proximity of employment not assessed or over 2 years removed

Score 0 (internal validity may be *seriously* undermined)
- no repeated exposure assessment and in cohort studies a large segment likely to be temporally very far from exposure (over 10 years) and no assessment of the occupational stability of the cohort or some other quasi measure for cumulative exposure is made (eg, seniority)

- *One point should be subtracted if there is evidence of sizable change in exposure status over follow-up, and it is not taken into account in the analysis*

Confounding and effect modification

9. Adjustment for relevant demographic confounders

Score 4, optimal, with use of innovative methods
- assessment of interactive effects between socioeconomic status or race or ethnicity and job strain

Score 3
- adjustment for socioeconomic status (and for race or ethnicity, if relevant)

Score 2
- failure to adjust for race or ethnicity in a multiracial or multiethnic population

Score 1
- failure to adjust for socioeconomic status

10. Adjustment for relevant biomedical and behavioral confounders

Score 4, optimal, with use of innovative methods
- assessment of interactive effects between biomedical or behavioral factors and job strain

Score 3
- adjustment for age
- accounted for standard cardiac risk factors[1], other behavioral indices[2]

Score 2
- no adjustment for other behavioral indices, adjustment for at least some of the standard cardiac risk factors (including age)

Score 1
- no adjustment for any of the standard cardiac risk factors (including age)

11. Stratification by gender

Score 3, optimal
- single gender study or stratified analysis performed if both genders included
- *If women included, the following gender-specific factors considered:* (i) use of oral contraceptives and (ii) hormone replacement therapy, menopause or the relevant risk factors which these affect (low-density lipoprotein cholesterol, fibrinogen)

Score 2
- stratified analysis performed, but no adjustment for use of oral contraceptives
- no consideration of hormone replacement therapy, menopause or for the risk factors these most affect (low-density lipoprotein cholesterol, fibrinogen)
- men and women included in the study, no gender-stratified analysis performed, adjustment made for gender and interaction effects assessed

Score 1
- men and women included in the study, and no gender-stratified analysis performed, and, although adjustment made for gender, no interaction effects assessed

Score 0 (internal validity may be *seriously* undermined)
- men and women included in the study and no adjustment made for gender

12. Assessment of other dimensions of the work environment

Score 4, optimal, with use of innovative methods
- explored the interaction between job strain or its major dimensions and other workplace factors (besides occupational status or employment grade)

Score 3

1 Here we have included both biological and behavior-related standard cardiac risk factors: smoking, obesity, hypercholesterolemia, hypertension, and sedentary leisure-time activity.

2 For example, negative affect, hostility, etc.

- the full job content questionnaire or other methods used to assess at least three other major job stressors (shiftwork, workhours, rest breaks, job security, physical demands, hazards, etc)

Score 2
- some job stressors assessed, but several major job stressors not evaluated (job status as part of effort–reward imbalance would be included here)

Score 1
- no other job stressors assessed

Outcome variable

13. Valid assessment of the outcome variable

Score 3, optimal
- systematic review of all participants by independent clinical observers who followed explicit diagnostic criteria; if registry data or hospital and death certificates used, quality assurance procedures applied

Score 2
- use of registers, hospital and death certificates as they stand with appropriate diagnostic entities

Score 1
- only by self-report

Score 0 (internal validity may be *seriously* undermined):
- incorrect criteria or evidence of systematic error in the assessment of outcome

14. Assessment of outcome blinded with respect to exposure

Score 3, optimal
- complete blinding of assessors as to exposure status, explicitly stated, or linkage of data sets

Score 2
- failure to explicitly state that outcome measure assessed without knowledge of exposure status

Score 1
- self-reported exposure and self-report of outcome, raising the possibility of report bias for outcome

15. Adequate range of variation of the outcome variable

Score 3, optimal
- broad range of variation in the dependent variable, all cases of coronary heart disease or cases of cardiovascular disease including nonsurvivors and out-of-hospital deaths

Score 2
- some limitation of range of variation (eg, cases being hospitalized survivors of cardiac events in a case–control study)

Score 1
- clearly limited range of variation (eg, only hospitalized survivors of cardiac events, without any comparison group)

- *Note, this criterion refers to outcome and not to the exclusion of those with the disease at entry in longitudinal studies*