

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

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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.

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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
Decision authority	Job does not involve a lot of repetitive work 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 quality⁷

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 valid-

ity 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
<i>Longitudinal studies</i>			
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 immigrants for reasons of language competence; N=79 followed-up	3 Mortality study, excluded survivors with reinfarction or other cardiac complications occurring during follow-up
<i>Case-control studies</i>			
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
Siim, 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
<i>Cross-sectional studies</i>			
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 = psychosocial 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
<i>Longitudinal studies</i>					
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 Whitehall 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 $\alpha=0.67$ & 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
<i>Case-control studies</i>					
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 men	4 Synergy index for demands and decision latitude among men	3	4 Cumulative exposure, all working mainly full-time within last 5 years
Netterstrøm et al, 1999 (58)	3 For women 2 4 items for demands includes physical demands & threat avoidance and vigilance $\alpha=0.51$; 6 items for decision latitude $\alpha=0.65$ & 0.81	1 For women 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	2 Dichotomous for women 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 (61)	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
<i>Cross-sectional studies</i>					
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 $\alpha=0.70$	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
Netterström 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 $\alpha=0.61$), 3 items for control Cronbach $\alpha=0.54$, 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
<i>Longitudinal studies</i>				
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 contraceptives, 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 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
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
<i>Case-control studies</i>				
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, overcommitment 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
<i>Cross-sectional studies</i>				
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 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
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
<i>Longitudinal studies</i>			
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
Suadcani 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
<i>Case-control studies</i>			
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
<i>Cross-sectional studies</i>			
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) infor-

mation 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
<i>Studies with significant positive results for job strain and CVD</i>						
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 (<i>age</i>) SMR 121 (95% CI 110–133), few possibilities to learn new things (<i>age</i>) SMR 113 (95% CI 104–123), hectic & monotonous work (<i>age</i>) SMR 118 (95% CI 102–135), hectic work & few possibilities to learn new things (<i>age + income</i>) SMR=125 (95% CI=105–150); women: hectic & monotonous work (<i>age</i>) SMR 164 (95% CI 112–233), monotony (<i>age</i>) SMR 128 (95% CI 104–157), low influence on workmates (<i>age</i>) SMR 133 (95% CI 102–170), low influence on holidays (<i>age</i>) SMR 145 (95% CI 114–182)	Men: hectic work (<i>age</i>) NS, monotonous work (<i>age</i>) NS; women: hectic work (<i>age</i>) 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) (<i>age, county, calendar year</i>)	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) (<i>age, county, calendar year</i>)	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) (<i>age</i>)	Iso-strain (white-collar) RR 1.31 (95% CI 0.58–2.96) (<i>age</i>)	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) (<i>age, education, smoking, CHD symptoms matched at baseline</i>)	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) (<i>same adjustment as for positive findings</i>)	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) (<i>age and follow-up time</i>)	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) (<i>age and follow-up time</i>)	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) (<i>age, gender, occupational group, smoking, physical activity, SBP, cholesterol, BMI</i>)	Low job control HR 1.42 (95% CI 0.72–2.82) (<i>age, gender, occupational group, smoking, physical activity, SBP, cholesterol, BMI</i>)	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-vali-dated CHD	High demand and low control & all CHD HR 1.38 (95% CI 1.10–1.75) (<i>age, gender, occupational grade, coronary risk factors</i>)	High demand and low control & fatal CHD or nonfatal MI HR 1.16 (95% CI 0.78–1.71) (<i>age, gender, occupational grade, coronary risk factors</i>)	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 (<i>univariate</i>) P=0.03, demands divided by intellectual discretion P=0.02 (<i>biomedical risk factors, education did not differ significantly between groups</i>)	Demands NS, single aspects of decision latitude NS (<i>univariate</i>)	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
<i>Studies with positive results for job strain and CVD, but none of which were statistically significant</i>						
Altermann 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) (<i>age, SBP, cholesterol, smoking, alcohol, family history of CVD</i>)	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) (<i>education & age, SBP, cholesterol, smoking, alcohol, family history of CVD</i>)	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) (<i>age, education, blood pressure, other coronary risk factors</i>)	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 & high 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) (<i>as for positive findings</i>)	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) (<i>age</i>); 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) (<i>age, estrogen status, education, diagnosis at index event, symptoms of heart failure, SBP, diabetes mellitus, smoking, lipids</i>)	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
<i>Studies with null results for job strain and cardiovascular disease</i>						
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 (<i>age</i>)	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)(<i>age, gender, ejection fraction, extent of CAD</i>); 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) (<i>age, gender, ejection fraction, insignificant CAD</i>)	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) (<i>age, social class, nationality, education, exercise, smoking, last year employed, physical job demands</i>)	Psychological demands RR range 0.88–1.01 (95% CI 0.66–1.36), job strain NS (<i>same adjustment as for positive findings</i>)	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) (<i>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</i>)	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 (<i>age, blood pressure, other coronary risk factors</i>)	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 (<i>age, social class</i>)	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
<i>Studies with significant positive results for job strain and CVD</i>					
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) (<i>age</i>), rushed tempo & low influence over work tempo RR 1.35 (95% CI 1.01–1.81), (<i>age</i>), rushed tempo & not learning new things RR 1.45 (95% CI 1.02–2.04) (<i>age</i>); those 40–54 years of age: hectic work & no influence on workplace 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) (<i>age & immigrant status or education</i>)	Rushed tempo RR 1.06 (95% CI 0.82–1.37), low influence over work tempo RR 1.2 (95% CI 0.93–1.54), 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) (<i>age</i>)	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) (<i>age, employment sector, job category, smoking, social network</i>)	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 (<i>age, education, alcohol and tobacco consumption, body mass index</i>)	Psychological demands NS, influence over work NS, intellectual discretion NS, psychological demands divided by influence over workload NS (<i>as for significant positive</i>); 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) (<i>hypertension, smoking, BMI</i>), low decision latitude (imputed) (all working) OR 1.7 (95% CI 1.3–2.2) (<i>age, catchment area</i>); women (all, self-report): job strain OR for nonfatal 1.51 (95% CI 1.13–2.02) (<i>age, catchment area, overweight, smoking</i>)	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) (<i>hypertension, smoking, BMI</i>), 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) (<i>age, catchment area, social class, coronary risk factors</i>)	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) (<i>age and SES did not differ significantly between patients and controls</i>)	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) (<i>as for significant positive</i>)	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) (<i>age, hypertension, diabetes, hyperlipidemia, angina pectoris, overweight, cigarette smoking, alcohol intake, parental, CHD and shift work</i>)	High job demand RR 1.3 (95% CI 0.7–2.2), low job control RR 1.0 (95% CI 0.5–1.7) (<i>as for significant positive</i>)	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
<i>Studies with positive results for job strain and CVD, but none of which were statistically significant</i>					
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) (<i>age, district, education, hypertension, other coronary risk factors</i>)	Job strain RR 1.31 (95% CI 0.77–2.25), highest psychological demands quartile RR 0.52 (95% CI 0.29–0.93) (<i>as for the significant positive findings</i>)	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 (<i>age</i>)	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
<i>Study with null results for job strain and CVD</i>					
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 (<i>age</i>)	2 biases to null: survivor bias as a case-control study, single occupation, limited range of variation of exposure; 1 bias to over-estimate: 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}
<i>Studies with significant positive results for job strain and CVD</i>					
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) (<i>age, race, education, systolic blood pressure, cholesterol smoking (HANES only) physical exertion</i>)	Psychological demands HES SOR 1.32 (95% CI 0.91–1.9) (<i>as for significant positive findings</i>)	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) (<i>age, dimensions of "iso-strain"</i>)	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) (<i>age, dimensions of "iso-strain"</i>)	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) (<i>age</i>)	White collar: iso-strain PR 1.49 (95% CI 0.91–2.43) (<i>age</i>)	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) (<i>age, age², SES, diet, smoking, leisure-time cholesterol, BMI, diabetes mellitus, blood pressure</i>)		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
<i>Studies with positive results for job strain and CVD, but none of which were statistically significant^e</i>					
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) (<i>age, gender, work hours, psychosocial factors, social status, smoking, systolic blood pressure, HDL:cholesterol ratio</i>)	Men: job strain OR 2.4 (95% CI 0.5–11.5) (<i>age, social status</i>)	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 ($\geq 75\%$ stenosis of ≥ 1 major coronary arteries or $\geq 50\%$ 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) (<i>age, hospital, diabetes, hyperlipidemia, overweight, cigarette smoking, alcohol intake, parental CHD, job type, hypertension</i>)	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
<i>Studies with null results for job strain and cardiovascular disease</i>					
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) (<i>age</i>)	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) (<i>age, gender, smoking status, diabetes hypercholesterolemia, history of MI, typical angina</i>)	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), [†] 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 Netterström 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), 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	–	–	Netterström et al (64), score 32	–	–	Yoshimasu et al (66), score 34	33 1.4
Null	–	–	Johnson (5), ⁱ 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