Review

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Is job strain a major source of cardiovascular disease risk?

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Table 9. Continued.

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

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

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

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

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

selectively stop working, another potential bias towards the null.

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

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

Case–control studies

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

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

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

Cross-sectional studies

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

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

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

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

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

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

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

Further considerations

Unpublished data and publication bias

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

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

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

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

Combining results—meta-analytical calculations

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

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

Dose–response relationships

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

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

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

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

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

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

Temporal nature of the association

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

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

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

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

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

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

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

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

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

Confounding and alternative hypotheses

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

Sociodemographic factors

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

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

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

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

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

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

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

Other work environment models and factors

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

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

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

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

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

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

rate of the original sample with respect to paid employment.

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

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

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

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

Gender and gender-related factors

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

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

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

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

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

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

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

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

Social psychological mechanisms

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

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

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

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

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

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

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

Standard cardiac risk factors

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

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

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

Atherosclerosis

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

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

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

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

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

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

Autonomic or neuroendocrine mechanisms

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

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

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

Possible cardiovascular consequences of exposure to job strain among vulnerable persons

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

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

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

be triggered in vulnerable people by mentally stressful situations.

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

Coherence with broader research and with sociohistorical trends—convergent validation

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

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

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

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

Concluding remarks—clinical implications

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

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

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

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

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Appendix

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

Assembly of the sample

1. Avoidance of selection bias

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

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

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

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

2. Avoidance of nonresponse bias

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

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

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

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

3. Appropriate clinical exclusion criteria applied

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

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

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

Assessment of the exposure variable

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

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

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

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

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

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

5. Avoidance of recall bias for the exposure variable

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

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

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

6. Analysis of point-exposure to job strain

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

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

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

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

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

7. Adequate range of variation of the exposure variable

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

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

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

8. Valid and reliable assessment of temporal aspects of exposure

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

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

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

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

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

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

Confounding and effect modification

9. Adjustment for relevant demographic confounders

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

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

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

Score 1
- failure to adjust for socioeconomic status

10. Adjustment for relevant biomedical and behavioral confounders

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

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

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

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

11. Stratification by gender

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

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

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

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

12. Assessment of other dimensions of the work environment

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

Score 3

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

2 For example, negative affect, hostility, etc.

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

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

Score 1
- no other job stressors assessed

Outcome variable

13. Valid assessment of the outcome variable

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

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

Score 1
- only by self-report

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

14. Assessment of outcome blinded with respect to exposure

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

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

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

15. Adequate range of variation of the outcome variable

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

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

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

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