SJWEH Suppl 2008;(6):33–40

What are the next steps for research on work stress and coronary heart disease?

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Kivimäki M, Vahtera J, Elovainio M, Keltikangas-Järvinen L, Virtanen M, Hintsanen M, Väänänän A, Singh-Manoux A, Ferrie JE. **What are the next steps for research on work stress and coronary heart disease?** *SJWEH Suppl.* 2008;(6):33–40.

This paper aimed at identifying gaps in the evidence for work stress as a risk factor for coronary heart disease (CHD) and at providing ideas for more rigorous tests of the association. Evidence in this field is mixed. The risk of type I and II errors would be reduced in future studies if work stress were assessed with predetermined standard instruments repeated over time, if outcomes excluded diagnoses based on subjective symptoms, and if individual participant data from multiple study populations were pooled to allow well-powered subgroup analyses and detailed assessments of the shape of the association. Within the Mendelian randomization and gene × environment interaction frameworks, there may be potential for using genetic data to reduce the risk of confounding and bias and to explicate the biological mechanisms underlying the association between work stress and CHD. If the evidence converges, large-scale intervention studies would be indicated despite the extensive practical problems associated with them.

Key terms cardiovascular disease; psychosocial conditions; working population.

Several studies suggest an association between work stress and increased risk of diseases of major public health relevance, including coronary heart disease (CHD) (1–8). However, there is no consensus on the clinical importance of work stress. For example, work stress is currently not included in the list of established risk factors for CHD (www.americanheart.org) published by the American Heart Association.

In this paper, we have described some of the uncertainties in the empirical evidence on work stress and health and aimed at identifying ways forward in this potentially important area of research.

Biological basis of the stress hypothesis

The central components of the physiological stress system are located in the phylogenetically oldest parts of the brain, the hypothalamus and the brain stem (9). Activating the stress system helps the body to overcome the influence of short-term physical stressors and therefore postpone all functions that may be irrelevant to immediate survival, such as digestion and growth. Although its precise nature varies according to the stressor, the function of a physiological stress response is essentially to prepare for, or maintain, physical exertion through cognitive arousal, sensory vigilance, bronchodilation, tachycardia, raised blood pressure, elevated hemoconcentration, and energy mobilization.

However, although the physiological reactions to short-term stress are assumed to protect survival, this may not be the case if exposure to stress is prolonged (9, 10). In contrast, prolonged overactivity of the stress systems is assumed to cause wear and tear and play a role in CHD and accelerated ageing (9). The foundation for research on these adverse effects was set already in

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the 1920s and 1930s by Cannon (11) and Selye (12, 13). Indeed, the recognition that physiological reactions to stress could damage the body has provided an important basis for epidemiologic research on work stress.

Conceptual models

Contemporary models on work stress aim at describing factors that are likely to represent universal long-term harmful stress at work. The stress model most often cited and most widely tested is the two-dimensional job-strain model (14–16). It proposes that employees who simultaneously have high job demands and low control over work are in a job-strain situation, which, if prolonged, increases the risk of stress-related diseases. Job control (or decision latitude) refers to both socially predetermined control over detailed aspects of task performance (eg, pace, quantity of work, policies and procedures, time of breaks, and scheduled hours) and skill discretion (ie, control over the use of skills by the worker). An expanded version of the job-strain model adds social support to the model as a third component (17). The highest risk of illness is assumed to be related to iso-strain jobs, characterized by high demands, low job control, and low social support.

More-recent developments in the conceptualization of work stress have broadened the view from proximal work characteristics to cover aspects of the person and the labormarket context. A promising example is the effort–reward imbalance model (18). This model maintains that an experienced imbalance between high effort and low reward is particularly stressful, as this imbalance violates core expectations about reciprocity and adequate exchange at work. Not only high demands, but also overcommitment and heavy obligations in private life (eg, debt) may lead to a high expenditure of effort at work. Low rewards can be related to insufficient financial compensation from work, low esteem (eg, lack of help or acceptance by supervisors and colleagues), and poor career opportunities (no promotion prospects, job insecurity, and status inconsistency).

While effort–reward imbalance defines disproportionate costs for an employee in terms of gains received (ie, a distributive injustice condition), the latest research on work stress has focused on the two remaining aspects of justice (19–22). Procedural justice indicates whether decision-making procedures include input from affected parties, are consistently applied, suppress bias, are accurate, are correctable, and are ethical (20). Relational justice refers to supervisors treating workers with fairness, politeness, and consideration (20). As justice is a fundamental value in social interaction and the organization of society, enduring problems in procedural and relational justice have been hypothesized to form an important source of stress at work, the organizational injustice model (21, 23).

Existing evidence from prospective cohort studies

Previous narrative reviews of the evidence on work stress and CHD have come to conflicting conclusions. Some of them support the status of work stress as a major coronary risk factor (2), while others suggest that the evidence is still incomplete (24). An advantage of a systematic meta-analysis over narrative reviews is that it provides an objective summary of the selected studies. At least one meta-analysis of evidence from prospective cohort studies on work stress and CHD is available. Prospective cohort studies are assumed to represent observational data with the strongest internal validity. This meta-analysis summarized a total of 14 studies on the three work-stress models published by January 2006 (3).

Work stress was associated with a 50% excess risk of CHD, the greatest number of studies being related to the job-strain model. (3) However, the review noted that only a few studies have focused on women. There was little standardization in the assessment of work stress. This lack of standardization reduces the between-study comparability and raises doubt that exposure measures were not determined prehoc. Significant heterogeneity in the effects of stress was observed between studies (ie, while most of the studies supported the status of work stress as a risk factor); notable exceptions with negative findings also existed.

The identification of potential reasons for inconsistencies in the evidence is crucial to the clarification of the true effect of work stress on CHD. A conventional starting point is to consider sources of type I error and type II error in previous studies. In the field of work-stress research, type II error is often expected to be a greater problem than type I.

Factors preventing the observation of true positive associations

Exposure misclassification contributes to false negative findings (type II error). In the meta-analysis, all of the studies with null findings assessed work stress at one point in time only (3). As CHD develops over a long time span, long-term, rather than short-term, levels of work stress are assumed to have an impact on CHD incidence. For employees with stable overload, a single-time measurement may provide an accurate estimate of

long-term stress, but this is not necessarily the case for others with changing work-stress levels.

Data from the Whitehall II study of British civil servants suggest that the use of single-time exposure measures may underestimate the status of long-term work stress as a CHD risk factor (25). Indeed, the regression dilution-corrected excess risk of CHD for job strain was 30% higher than the corresponding uncorrected estimate in these data. In the Finnish Valmet study of industrial employees, the effect of effort–reward imbalance on cardiovascular mortality was stronger in a stratified analysis for the employees who did not change workplaces during the first 5 years of the follow-up (26).

Age may play a role in stress effects. Findings from the Whitehall II study and the Swedish WOLF (work, lipids and fibrogen) study show that the inclusion of older employees in a study sample results in a substantial reduction of the effect of work stress on CHD (27). In line with this finding, an association between job strain or its components and CHD was found in studies using younger cohorts, such as the Western Electric study of men aged 38–56 years (28), the Whitehall II study of civil servants aged 35–55 years (29), a random sample of the male Swedish working population aged 18–65 years (17), and the Valmet study of men and women aged 17–65 years (26). In contrast, such an association was not observed in the Framingham offspring study of men and women aged up to 77 years (30), the women's health study of nurses aged 46–71 years (31), or the Malmo diet and cancer study of men and women at the mean age of 55 years (32).

At least the following five factors may contribute to the effect attenuation after the inclusion of older employees in a cohort: (i) retirement during the follow-up removes work stress and leads to exposure misclassification, (ii) a healthy-worker survivor bias operates in older cohorts (healthy-worker survivor bias occurs when healthier workers remain at work and those with health problems drop out), (iii) even with a similar absolute difference in CHD events between stress and nonstress groups, an increasing number of other age-related causes of CHD may diminish risk ratios as these other causes figure into both the numerator and denominator of the ratio, (iv) older workers may become accustomed to work stress and report lower levels even if exposed to the same stress-producing stimuli as younger workers, and (v) current work stress models may not adequately define stressors for older workers.

Other potential reasons suggested as contributors to false negative findings in work-stress research include, for example, the use of ecological work-stress measures that are insensitive to individual-level differences in work stress, the use of single-occupation or single-workplace samples leading to constricted variation in work stress, and item contents in work-stress measures that do not accurately capture stresses that are relevant to the target population (2, 33). However, little research is available that directly tested these propositions.

Factors preventing the observation of a true null association

Type I error (false positive) is also a potential source of mixed findings (ie, the observed positive associations between work stress and CHD may be spurious, the null findings representing the true estimates). Publication bias (selective publication of positive findings) and the lack of predetermined instruments for the assessment of work stress may increase the risk of false positive findings. Residual confounding due to some unmeasured third factors may artificially inflate associations, a possibility that cannot fully be ruled out in any observational study. For example, CHD is associated with a large variety of risk factors from adulthood, as well as from the preemployment periods of childhood and adolescence. The possibility of false positive findings arises when these risk factors are additionally associated with work stress. A Swedish study found childhood socioeconomic adversity to be associated with low job control in adulthood (indicated by an occupation-based proxy measure), and this early risk explained a substantial part of the association between low control and increased risk of cardiovascular disease (34). The effects on job strain were not reported in that study. In a Finnish study, socioeconomic status and coronary risk factors in adolescence did not attenuate the association between job strain (individual assessment) and increased carotid intima-media thickness, a preclinical predictor of CHD (35).

Reporting bias (or common method bias) is a further potential source of type I error for studies using exposures and outcomes that are potentially affected by subjective reporting. It is important to recognize that this potential bias is not only restricted to self-reported outcomes, such as Rose angina, but may also influence outcomes based on hospital admission data that include conditions influenced by subjective reporting (eg, ill-defined heart disease, hemorrhoids, or "other" circulatory disorders). No evidence is available for this bias in relation to work stress, but the effects of daily stress on CHD have been shown to vary depending on whether or not the outcome included an element of subjective reporting (36).

Reversed causality (eg, if early manifestations of CHD bias perceptions of stress) would also increase the likelihood of type I error. Although healthy population studies typically remove participants with prevalent CHD at baseline, this action does not necessarily eliminate the possibility of reverse causality. CHD may also present itself as unmeasured chronic angina or nonspecific

chest pain, and these early manifestations of CHD may bias perceptions of work stress. If this were the case, short-term effects of work stress would be stronger than longer term effects because underlying disease would increase the likelihood of disease manifestation (37). However, stronger short-term effects could also be the result of exposure misclassification (type II error), which is more likely for long follow-ups during which, for a substantial proportion of stressed employees, exposure to work stress may change over time. Moreover, if the effects of work stress on CHD are mainly explained by mechanisms triggering manifest disease among populations with subclinical disease, only short-term effects would be expected.

Future challenges in conventional prospective cohort studies

To date, the number of prospective cohort studies on work stress and CHD is still relatively small (3). However, further replication serves little purpose. Instead future studies should attempt to reduce the potential for type I and II errors more effectively. We recommend that at least the following five points be taken into account when new prospective cohort studies on work stress and CHD are designed:

1. Use of predetermined standard survey instruments to assess work stress: Such use would reduce the possibility of type I error caused by the selective reporting of results. The use of standard measures would also indicate whether harmful work stress can be assessed with reproducible methods.
2. Multiple measurements of work stress over time to improve the estimation of long-term exposure and reduce type II error.
3. Inclusion of objective measures of work stress (in addition to individual assessments) and the use of outcome measures that include only diagnoses based on objective criteria (eg, electrocardiography, enzymes, and computed tomography or magnetic resonance imaging). Such procedures would minimize reporting bias.
4. Inclusion of established standard coronary risk factors as time-dependent covariates in models of the association between work stress and CHD to distinguish whether they act as confounding factors or underlying mediators. In the first case, adjustment for these factors is necessary, whereas in the latter case it would result in overcontrol and artificial effect attenuation. Indeed, very little research has taken into account the levels and changes in potential intervening factors over time in assessments of work stress and CHD follow-up.
5. The pooling of individual participant data from multiple study populations with identical measurements of exposure, outcome, and covariates to enable subgroup analyses and the accounting for potential effect modification by factors such as age group or career stage, gender, and occupational position. Analyses of pooled data would provide sufficient power for the detection of potential small and moderate effects and the description of the shape of the association in more detail.

In addition to performing further prospective cohort studies, other sources of evidence, such as genetic association studies, should also be considered for obtaining information about the potential benefits of reducing work stress in terms of preventing CHD.

Evidence from quasi-experiments

Observing natural experiments has been seen as a more feasible option than randomized trials in this field, and they are thought to help to eliminate some of the uncertainties inherent in conventional observational cohort studies, such as reporting bias or confounding material factors. Since the recessions that hit most industrialized countries in the 1980s and 1990s, evidence has accumulated on the health risks of survivors of corporate downsizing. One of the first studies in the field was conducted among the municipal employees of a town called Raisio in Finland (38). The Raisio study found a marked increase in sickness absence, job demands, and job insecurity and a decrease in job control among the employees who worked in heavily downsized groups when they were compared with those in nondownsized groups (38–40). Adverse effects on the health of the survivors of downsizing, including an elevated risk of fatal cardiovascular disease, have since been reported in several other studies (41, 42). It is noteworthy that, as there is no concurrent change in socioeconomic status, salary, or chemical hazards at work among those who keep their jobs, downsizing represents a proxy for a condition in which work stress increases while these material factors remain constant. Thus such studies could provide complementary evidence for conventional prospective cohort studies on the potential effects of work stress on health.

However, some recent studies using national data on changes in the size of firms (rather than corporate records checked for validity by the researchers) have found mixed associations between downsizing and stress, major downsizing being sometimes associated

with reduced rather than increased work stress among the survivors (43, 44). This result indicates that changes in staff numbers may not always represent a proxy for increased work stress. A further limitation of downsizing studies involves the fact that such organizational restructuring is not necessarily randomly targeted towards different employee groups. This situation introduces a source of selection bias common in observational epidemiologic studies.

Potentials of genetic association studies

Overcoming the fundamental problems of residual confounding and bias in conventional observational studies will mean that the limited funds to test the effectiveness of large-scale work-stress interventions will be directed towards what are likely to be the most effective targets. Genetic data are increasingly available for on-going cohort studies and may provide a new source of evidence with which to test the status of work stress as a risk factor for CHD. If the findings were promising, it would be easier to justify the funding of expensive large-scale trials. At least two approaches might have potential in this regard: (i) Mendelian randomization and (ii) gene × environment interaction.

Mendelian randomization

The Mendelian randomization approach uses genetic variants as instrumental variables or proxies for potentially modifiable behavioral or environmental risk factors (45). The assumption underlying Mendelian randomization in studies of work stress would be that alleles are randomly allocated from parents to offspring at conception. Thus people with genetic variants associated with a higher risk of experiencing stress will have, in effect, been randomly allocated to somewhat higher levels of stress across their life course than those with genotypes related to a lower risk of experiencing stress. These differences in stress should therefore translate into differences in CHD risk if stress were causally related to CHD. An assumed strength of this approach, compared with conventional observational data, is that the genetic variants affecting the risk of stress represent proxies for stress that are largely free of reverse causation bias (ie, genetic variants are determined at conception) as well as confounding by other risk factors (allocation of alleles that construct the genetic variant is based on a random assortment of maternally and paternally derived chromosomes).

The Mendelian randomization approach has been utilized to determine the magnitude of a causal association for cholesterol (46), C-reactive protein (CRP) (47, 48), and estrogen response (49) with CHD risk, but no such study on stress reaction is available and, to our knowledge, no genetic variants causing a variation in such reactions have been identified. However, considering the rapid expansion in genomic knowledge, future research may identify genetic variants suitable for Mendelian randomization studies, to mimic unconfounded variation in exposure to stress reactions. If stress genes are indeed identified, examining the association between the genetic variants and disease outcome is equivalent to a randomized controlled trial, but with the advantages that the actual study design is likely to be considerably less expensive, less time-consuming, less problematic ethically, more feasible, and more generalizable. Obviously, such a study would involve testing the effects of general stress or stress reactions on CHD, as genetic variants related to stress reactions cannot be specified to work stress. However, there is no reason to expect that stress reactions would be fundamentally different in relation to work stress than to stress in general. Thus a successful demonstration of an effect of overall stress would make the status of work stress as a causal coronary risk factor more plausible in the same way that failures to demonstrate an effect would provide evidence against a causal role.

However, there are potential problems that should be taken into account when the applicability of the Mendelian randomization technique is considered in tests of the association between work stress and CHD (45). First, the fact that stress reactions may have multiple pathways that all contribute to CHD risk [eg, through the autonomic nervous system and the hypothalamic-pituitary-adrenal axis (HPA) (9)] means genetic variants need to be identified for each of these pathways. It is likely that the proportion of variance in stress levels explained by stress genes will also remain small. Thus, in the study of stress, Mendelian randomization methods would probably require very large data sets, pooled samples, and research consortia. Furthermore, anxiety and depression, both based on a polygenic form of etiology, share common elements with stress reactions and may thus confound the results (50).

Second, even if some genetic variants associated with stress levels are identified, they may not necessarily be suitable instruments for unconfounded and unbiased stress effects (45), since it is possible that the genetic variant related to stress is also associated with other functional genetic variants (ie, in linkage disequilibrium), or the genetic variant influencing stress levels may have multiple effects influencing other potential environmentally modifiable risk factors in addition to stress (pleiotropy) (45). In all of these cases, the genetic instrument for stress may be confounded.

Third, a further potential problem of the Mendelian randomization approach arises from developmental

compensation. This phenomenon occurs when a genetic variant expressed during fetal development or postnatal growth influences the expression of a wide range of other genes and leads to changes that may compensate for the influence of the original genetic variant (called canalization) (45). In case of stress, developmental compensation could occur if a person who developed and grew from the intra-uterine period with increased stress reactions, due to a genetic variant that inflated stress reactions, becomes resistant to the influence of lifelong elevated stress levels, through permanent changes in tissue structure and function that counterbalance the effects of the genetic variant. Moreover, increased stress reactivity may lead to "behavioral compensation". In this scenario, the individual actively avoids situations that may trigger a stress response and thus introduce selection bias. One way to reduce such bias is to collect environmental information in order to control this environmental variation, as has been done in gene × environment interaction studies.

Gene × environment interaction studies

Genetic variants that modify the effects of work stress on CHD risk may be potentially useful in examining causality. In this application of the gene × environment interaction approach, the effects of stressful work characteristics are thought to be dependent on the genetic variants that relate to stress reactivity. To date, the only study that has examined such interactions focused on the neuregulin-1 gene (NRG-1) (51). To achieve sufficient statistical power, this study quantified CHD risk by a continuous trait measure, carotid intima-media thickness (cIMT), a surrogate marker of atherosclerosis and a valid presymptomatic predictor of CHD (52).

Animal studies show that neuregulin-1 protein may contribute to the development of the sympathetic nervous system and the maintenance of parasympathetic activation, which balances excess beta-adrenergic activation (53–55). Variants in the NRG-1 gene produce variation in the synthesis of neuregulin-1 protein. The gene × environment interaction study of work stress hypothesized that people with a T/T variant in the NRG-1 gene may generate exceptionally high sympathetic activity during job strain and, if there is a causal association between work stress and cIMT that is mediated by sympathetic overactivity, the association between job strain and cIMT would be particularly strong. Indeed, the study found such an interaction as job strain was associated with increased cIMT among men with the T/T variant but the association was not apparent among other men (51).

Although these findings supported the hypothesis that the activation of biological systems related to stress is related to increased CHD risk, this evidence should be regarded as preliminary, since, first, the exact function of the genetic variant is not understood and sympathetic activity was not measured in that study—thus the possible operation of pleiotropy and canalization cannot be ruled out. Second, there is a huge number of potential stress × genetic variant interactions available for testing; thus it is likely that a large number of published reports on such interactions would be chance findings (56). Furthermore, the power to detect meaningful gene × environment interaction is low with most nonpooled samples (57).

Concluding remarks

This paper has aimed at providing a roadmap to a more rigorous testing of the status of work stress as a causal risk factor for CHD. There is clearly a need for conventional prospective cohort studies in this field to reduce the risk of type I and type II error through improved research designs and data collection methods. We have described future potentials related to the use of genetic data as a complementary source of evidence for conventional observational data, but substantial developments in knowledge in genetics is still needed before these potentials can be actualized.

Finally, even if all these sources of evidence did provide robust evidence supporting a potential causal role for work stress, we would still need to undertake appropriate large-scale intervention studies (randomized controlled trials if possible) to determine the most effective means (individual, organizational, legislative) of decreasing population levels of work stress (or stress levels among those most at risk) and thereby reducing CHD.

Acknowledgments

MK and JV were supported by the Academy of Finland (grants 117604, 124327, and 124332).

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