

# WORK STRESS AND THE RISK OF RECURRENT CORONARY HEART DISEASE EVENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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## Abstract

Though much evidence indicates that work stress increases the risk of incident of coronary heart disease (CHD), little is known about the role of work stress in the development of recurrent CHD events. The objective of this study was to review and synthesize the existing epidemiological evidence on whether work stress increases the risk of recurrent CHD events in patients with the first CHD. A systematic literature search in the PubMed database (January 1990 – December 2013) for prospective studies was performed. Inclusion criteria included: peer-reviewed English papers with original data, studies with substantial follow-up (> 3 years), end points defined as cardiac death or nonfatal myocardial infarction, as well as work stress assessed with reliable and valid instruments. Meta-analysis using random-effects modeling was conducted in order to synthesize the observed effects across the studies. Five papers derived from 4 prospective studies conducted in Sweden and Canada were included in this systematic review. The measurement of work stress was based on the Demand-Control model (4 papers) or the Effort-Reward Imbalance model (1 paper). According to the estimation by meta-analysis based on 4 papers, a significant effect of work stress on the risk of recurrent CHD events (hazard ratio: 1.65, 95% confidence interval: 1.23–2.22) was observed. Our findings suggest that, in patients with the first CHD, work stress is associated with an increased relative risk of recurrent CHD events by 65%. Due to the limited literature, more well-designed prospective research is needed to examine this association, in particular, from other than western regions of the world.

## Key words:

Work stress, Recurrence, Coronary heart disease, Meta-analysis, Epidemiology, Prospective studies

The paper was presented at the 6th ICOH International Conference on Work Environment and Cardiovascular Diseases; 2013 Mar 27–30; Tokyo, Japan. This review work was partly supported by the National Natural Science Foundation of China (Project No. 81360040) and the Natural Science Foundation of Yunnan Province, China (Project No. 2013FB140). Manager of project: Min Zhang, MD, PhD. J. Siegrist was supported by a Senior Professorship grant from the Faculty of Medicine, University of Düsseldorf, Germany. All authors declare that there is no conflict of interest.

Received: February 26, 2014. Accepted: March 28, 2014.

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## INTRODUCTION

Coronary heart disease (CHD) is one of the leading causes of disability and death worldwide, contributing largely to the global burden of disease [1,2]. Based on a large number of prospective cohort studies, psychosocial stress has been identified to increase the risk of CHD in initially healthy populations [3–6]. Furthermore, several psychosocial factors, such as depression [7], anxiety [8], type D personality [9] and financial stress [10,11], are also observed to be predictive of the prognosis of CHD.

Given the observation of increasing incidence rates of CHD among relatively young age groups, particularly in the working population [2,12], contribution of psychosocial work stress to the development and prognosis of CHD in employed people has been drawing increasing attention. Cumulative evidence shows that psychosocial stress at work is repeatedly associated with elevated risks of fatal and non-fatal CHD, and the strongest evidence comes from the investigations that assessed an adverse psychosocial work environment in terms of psychometrically validated measurements based on stress-theoretical models, such as the Demand-Control model or the Effort-Reward Imbalance model [13–16]. The 1st model claims that stress-related ill health results from the combined effects of high job demand and low job control [17], while the latter model emphasizes harmful effects of failed reciprocity between effort spent at work and reward received in turn (high effort/low reward) [18]. So far, few studies have analyzed the role of an adverse psychosocial work environment in the prognosis of cardiac outcomes among patients who survived their first CHD manifestation. As their findings are inconsistent [19–22], we aimed at exploring the current evidence more thoroughly by conducting a systematic review and meta-analysis of the studies that meet defined quality criteria (see below). By doing so, we hope to derive some suggestions that may instruct future research on the topic.

## MATERIAL AND METHODS

In order to perform a systematic review and meta-analysis of epidemiological studies we applied internationally established guidelines [23,24]. We searched the PubMed database by applying the following inclusion criteria:

- time of publication – January 1990 – December 2013,
- study design – a prospective cohort study,
- peer-reviewed English-language article with original data,
- study subjects – patients with the 1st CHD,
- work stress – assessed with reliable and valid instruments,
- end points – cardiac death or nonfatal myocardial infarction,
- follow-up duration – more than 3 years,
- adjustment for relevant confounding factors – such as age, gender, behavior factors, clinical features of CHD, etc.

We performed literature search using (combinations of) the following medical subject headings and key words: work stress, psychosocial work characteristics, job strain, effort reward imbalance, coronary heart disease, myocardial infarction, recurrent, patients, prognosis, death.

Random-effects modeling was used to perform meta-analysis [25]. We distinguished different levels of work stress and set a group of subjects with a low work stress level as a reference group. Then hazard ratios (HRs) and 95% confidence intervals (CIs) associated with a high work stress level from the selected studies were estimated. We used the Q-test for heterogeneity of the study results [26]. To detect publication bias we explored the funnel plot and the degree of asymmetry by using the Begg's method [27]. Data for different measures of work stress were analyzed separately in a 1st step, then these measures were combined. In addition, all the individual psychosocial work factors defining the theoretical models were identified and included in a further set of analyses for the purpose of a detailed exploration. All analyses were conducted using

statistical program Stata 11 (Stata Corporation, College Station, Texas, USA) [28].

## RESULTS

Based on our literature search, we identified 7 papers derived from 5 prospective studies on associations between work stress and risk of recurrent CHD events [19–22,29–31]. After carefully reading all full texts of the papers, the study of Hlatky et al. was excluded due to the fact that the baseline population was not recruited according to the defined criteria. More specifically, in this study, the subjects with a history of myocardial disease were excluded, as coronary angiography, rather than a clinically defined CHD event, was used to define “coronary artery disease” [19], thus, producing some discordance between the included patient groups [32,33].

We also excluded the study by Leander et al. This paper is based on a prospective study in Sweden, which actually generated 2 publications [21,30]. As both papers were based on the same definition of work stress and included a largely overlapping sample with only 1 year difference in the follow-up observation time, we excluded the study with the shorter observation period from our analysis [30]. However, in another case where 2 papers were produced from 1 prospective study in Canada [22,31], both papers were included in our review for the following reasons. First, the 2 papers were based on different measures of work stress, and 2nd, clearly different periods of follow-up observation were defined. Therefore, 5 papers derived from 4 prospective studies were included into our systematic review (see Table 1).

Among them, 3 studies were conducted in Sweden, and 1 study was from Canada. As far as gender is concerned, 1 study was conducted exclusively among men, and 1 study was restricted to women, whereas the other 3 studies included both men and women. Questionnaires based on the Demand-Control model [34,35], were

used to measure work stress in 4 papers, and the Effort-Reward Imbalance questionnaire [36,37] was applied in 1 paper. The follow-up time varied from 4.0 to 8.5 years. Population of the 5 papers based on 4 prospective studies included 1840 patients with the 1st CHD, and 412 cases of recurrent CHD events. Due to the incomplete statistical information ( $p = 0.017$ , without reporting HR and 95% CI), the earliest study [29] was not included into this meta-analysis. Therefore, remaining 1778 patients with the 1st CHD and 399 cases of recurrent CHD events were finally taken into account.

Figure 1 presents associations between work stress and risk of recurrent CHD events. The pooled analysis for job strain, the measure of the Demand-Control model, indicated a 61% increased risk (HR = 1.61, 95% CI: 1.14–2.28) while, the measure of the alternative work stress model, Effort-Reward Imbalance, was associated with a hazard ratio of 1.75 (95% CI: 0.99–3.08). However, it should be kept in mind that this latter result is based on one single study. Summing up the results, a significant effect of work stress on the risk of recurrent CHD events (HR = 1.65, 95% CI: 1.23–2.22,  $p = 0.001$ ) was observed. Given the limited number of studies, it was not feasible to perform gender-stratified analyses.

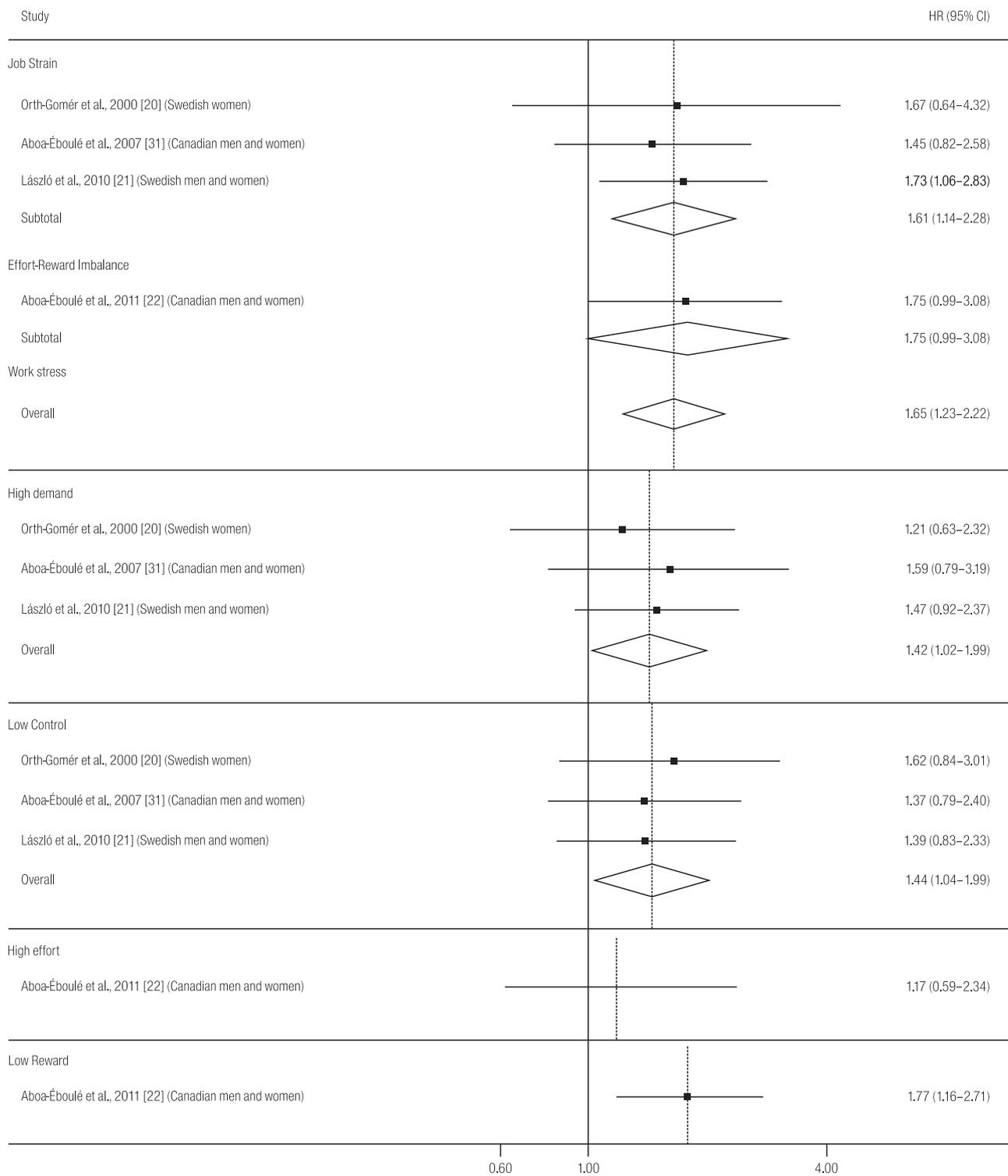
In the case of the individual psychosocial work factors defined by the 2 work stress models, the pooled HR for high demand and low control indicated elevated risks of 42% and 44%, respectively, suggesting that the effect of job strain was produced, to some extent, by additive interaction between high demand and low control. In the case of high effort and low reward, respective risks of recurrent CHD events were increased by 17% and by 77%, respectively, and thus, indicating that the reward component exerted primary contribution to the model of Effort-Reward Imbalance.

The Q-test did not indicate heterogeneity between the selected studies for this meta-analysis ( $p = 0.965$ ), and we found no evidence of publication bias in any analyses using funnel plot or the Begg’s asymmetry method ( $p = 0.734$ ).

**Table 1.** Summary of the prospective studies on work stress and the risk of recurrent coronary heart disease (CHD) events

Study (country)	Subjects	Period of follow-up (years)	Measurement of work stress	Measurement of recurrent CHD events	Return to work and retirement	Statistical adjustment
Theorell et al., 1991 [29] (Sweden)	62 men with the 1st myocardial infarction before the age of 45	5.0	job strain at baseline (within 2 weeks of discharging from the referring hospital)	ischaemic heart disease death (13 cases)	all returned to the same work; nobody was retired	number of stenosed coronary arteries, degree of coronary atherosclerosis, and age at the onset of the 1st myocardial infarction
Orth-Gomér et al., 2000 [20] (Sweden)	130 working women aged 30–65 years with the 1st acute myocardial infarction or unstable angina pectoris	4.8	job strain at baseline (3–6 months after hospitalization)	cardiac death, acute myocardial infarction, or revascularization procedures (38 cases)	all returned to the same work; no information on retirement	age, estrogen status, educational level, marital stress, diagnosis at index event, symptoms of heart failure, systolic blood pressure, diabetes mellitus, smoking, triglyceride level, and high-density lipoprotein cholesterol level
Aboa-Éboulé et al., 2007 [31] (Canada)	972 subjects (866 men, 106 women) aged 35–59 years with the 1st myocardial infarction	5.9	job strain at baseline (6 weeks after return to work)	fatal CHD, nonfatal myocardial infarction, or unstable angina (206 cases)	all returned to work (M: 3.6 months after the 1st myocardial infarction); no information on retirement	age, gender, marital status, education, perceived economic situation, smoking status, body mass index, alcohol consumption, physical activity, number of recommended medications, hypertension, dyslipidemia, diabetes, family history of coronary heart disease < 60 years, left ventricular ejection fraction, number of prior comorbid conditions, thrombolysis, number of in-hospital events, chronic social support at work, number of physical and chemical exposures at work, alexithymia, hostile affect, suppressed anger, number of adverse work organization factors, social support outside work, and psychological distress
László et al., 2010 [21] (Sweden)	676 working subjects (78.9% men) aged 45–65 years with the 1st myocardial infarction	8.5	job strain at baseline (a few days after the 1st myocardial infarction)	cardiac death or non-fatal myocardial infarction (155 cases)	no information	age, gender, education, occupational class, managerial status, overtime work, shiftwork, and household work
Aboa-Éboulé et al., 2011 [22] (Canada)	738 subjects (669 men, 69 women) aged 35–59 years with the 1st myocardial infarction	4.0	Effort-Reward Imbalance at baseline (2 years after the 1st myocardial infarction)	fatal CHD, nonfatal myocardial infarction, or unstable angina (96 cases)	all returned to work (M: 3.6 months after the first myocardial infarction); no information on retirement	age, gender, the number of prior comorbid conditions, thrombolysis, the number of recommended medications, the number of adverse work organization factors, social support outside work, alexithymia, and job strain

M – mean.



HR – hazard ratio; CI – confidence interval.

**Fig. 1.** Associations between work stress and the risk of recurrent coronary heart disease events

## DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis concerning association between work stress and prognostic cardiac outcomes in patients who survived their first CHD event. Although based on a limited number of studies, our results suggest that work stress increases the relative risk of recurrent CHD events to a significant extent (i.e., HR = 1.65).

Several explanations have been proposed to account for the observed association. On one hand, distinct stress-physiological processes may be triggered by recurrent exposure to an adverse psychosocial work environment, with harmful effects on a compromised myocardium, such as excessive activation of the autonomic nervous system and the neuro-endocrine stress axis of the body [38,39]. For instance, a decreased heart rate variability, a marker of sympathetic overdrive, and increased levels of cortisol secretion, a marker of a dysregulated hypothalamic-pituitary – adrenocortical stress axis, were observed to precede major adverse cardiovascular events in CHD patients [40,41]. In addition to neuronal and neuro-hormonal factors, several indicators of the reduced immune competence due to chronic work stress [42] may contribute to an increased susceptibility to recurrent cardiac events. Recently, also a low serum level of interleukin-17 was found to be associated with a higher risk of major cardiovascular events in CHD patients [43].

On the other hand, work stress can affect the cardiovascular system through significant changes in behavioral factors that matter for cardiovascular health, such as the increased amount of cigarette smoking or alcohol consumption, altered dietary habits or reduction of physical activity [44]. Moreover, disrupted sleep patterns and an increased prevalence of depression/anxiety induced by work stress and onset of a CHD event may matter as these latter conditions were shown to increase the risk of recurrent cardiac events [7,8,45,46]. While all these proposed explanations are in line with available evidence on the risk and

protective factors of CHD, to our knowledge, no single study has yet combined data on work stress, physiological markers, behavioral patterns and cardiac outcomes in a prospective design.

The results of our review and meta-analysis should be interpreted with caution for a number of limitations of the evidence. The first limitation concerns variations in return to work after the onset of the first CHD. Except for one Swedish study [21], all the remaining studies included in this review provided robust information that all the studies' participants returned to work. Cumulative evidence indicates that severity of the disease, high level of work stress, and low level of job satisfaction are the major risk factors for non-return to work following CHD [47–49]. Thus, lack of information on the reasons for not returning to work and lack of information concerning giving-up work during the observation period runs the risk of misclassifying the exposure assessment and the related risk estimation. Interestingly, in the Canadian study [31] an additional analysis of CHD patients who discontinued their work career was performed. The results indicated that CHD patients who stopped working for a period of 6 months or longer experienced a somewhat lower risk of recurrent CHD events, compared to those who continued working during the whole observation period (HR = 0.81, 95% CI: 0.34–1.90).

Second, there was not sufficient information on the effect of retirement on CHD across the studies. Of the 4 studies in our review, only 1 study stated that none of the participants had been retired [29]. In the case of the other studies it remains unclear whether some participants had early retirement or received disability pension during the follow-up period. Since the exposure to work stress is discontinued at the moment of retirement, accordingly, the risk of CHD is expected to be decreased. Alternatively, other sources of stress originating from the transition into retirement may be present, such as loss of status and feeling of worthlessness. Some new prospective

investigations observed that retirement would increase the risk of CHD [50–52]. However, different patterns of health trajectory after statutory retirement vs. retirement due to ill health were also observed [53]. As a result, for early retirees and disability pensioners with CHD, it is difficult to disentangle whether elevated risks of recurrent CHD events are due to the stress at work, stress associated with retirement or conditions related to the 1st CHD itself.

Third, the timing of measuring work stress is critical. Two studies measured work stress after the patients with the 1st CHD returned to work [20,22,31]. In these cases, work stress referred to the conditions experienced after the 1st CHD. By contrast, the other 2 studies measured work stress within 2 weeks following the onset of 1st CHD (even still during the hospitalization period) [21,29], and therefore, assessed work stress experienced before the onset of the 1st CHD. We assume that there are significant changes in the perception and evaluation of psychosocial working conditions by patients, depending on whether they refer to their situation before or after having experienced a significantly threatening life event i.e., a CHD incidence.

Moreover, results of the studies on associations between work stress and CHD vary according to the number of exposure assessments. There is a clear indication that repeated measures of work stress improve the risk estimation, compared to a single exposure assessment [54]. The Canadian study [22,31] supports this notion. A single measure of job strain at time 1 (6 weeks after return to work following the 1st CHD) or at time 2 (2 years after the 1st CHD) did not significantly predict recurrent CHD events (HR = 1.45, 95% CI: 0.82–2.58; and HR = 1.33, 95% CI: 0.75–2.34, respectively). However, chronic job strain (exposure to job strain at both time points) was associated with a considerable increase in the risk of recurrent CHD events (HR = 2.38, 95% CI: 1.37–4.13).

Fourth, so far, the measurement of work stress was mainly based on the Demand-Control model [17] or the

Effort-Reward Imbalance model [18]. Future studies should enlarge the range of predictors related to an adverse psychosocial work environment. For instance, organizational justice, a model focusing on employees' perceptions of fairness in the workplace [55], was associated with a reduced risk of the 1st CHD in 2 prospective studies [56,57]. Job insecurity [58,59] and overtime work [60] are additional relevant factors in this context.

Fifth, given significant gender differences in work stress [61], in the prevalence and incidence of CHD [12] as well as in the strength of effects of work stress on CHD [13–16], this issue deserves more intense inquiry. In the studies included in our review, men accounted for more than 80% of the total sample. As mentioned, due to the small number of studies, we were not able to analyze gender differences in work stress and recurrent CHD events. However, in the Swedish study restricted to women only, it is of interest to note that work stress was associated with the elevated risk of recurrent CHD events but did not reach statistical significance, whereas marital stress did predict adverse outcomes [20]. A challenging task of future research relates to the analysis of double exposure to work stress and family stress in women suffering from CHD and their potential adverse effect on cardiac recurrence.

Finally, while heterogeneity between the selected studies and publication bias were not detected in our meta-analysis, one needs to bear in mind that the presence of bias cannot be ruled out, given the fact that the low number of studies compromises the statistical power of bias assessment [62,63]. This methodological limitation can be extended by a limitation related to the generalization of the reported findings. All empirical evidence is restricted to CHD populations returning to work in 2 Western countries, Sweden and Canada. In view of the current socioeconomic and epidemiologic transition in rapidly developing countries, work stress [64] and CHD [65,66] in these regions have become pandemic during the past 2 decades. Therefore, respective evidence on the role of work stress

in influencing the onset and the recurrence of CHD events is urgently needed.

## CONCLUSIONS

In conclusion, despite these limitations, our systematic review and meta-analysis support the notion that stressful work in terms of high demand and low control, or of high effort and low reward, is associated with a significantly increased relative risk of recurrent cardiac events in men and women with the first CHD. From a preventive perspective, interventions in the workplace that aim at reducing work stress by improving the psychosocial work environment are warranted [67,68], not only for healthy workers, but also for employees working with CHD. Nevertheless, due to the limited literature available, more well-designed research is needed to examine the associations between work stress and recurrent CHD events in the future, particularly from other regions of the world, such as non-western societies.

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