

Extended Abstract

TITLE: Effect of job strain on incident cardiovascular disease: confounding and mediation by lifestyle habits. An overview of systematic reviews.

Background: In 2016, an estimated 17.9 million people died from cardiovascular (CVD), representing 31% of all global deaths, making CVD the leading cause of death worldwide (1). Psychosocial stressors at work (PSW) may be important contributors to the increasing CVD burden (2-4). PSW are commonly defined by Karasek's demand-control model, which postulates that exposure to high psychological demands, combined with low job control, causes a high stress condition (*i.e.* job strain) that can lead to health problems (5, 6). About 20 to 25% of workers in industrialized countries are exposed to job strain (7). Two recent systematic reviews (SR) with meta-analysis have reported that job strain is associated with increased risk of coronary artery disease (CAD) by 26% (8) and stroke by 22% (9). PSW reduction represents a promising avenue for CVD prevention efforts (10-12).

PSW, in contrast with recognized lifestyle habits, are not yet integrated within clinical practice guidelines (13, 14). Currently, both international primary prevention guidelines (15-17) as well as recent SR (18, 19) on CVD prevention recommend smoking cessation, increased physical activity and moderate alcohol consumption to mitigate the risk of CVD. Subsequently, much less recommendations concerning PSW reduction have been put in place to prevent CVD (20-22) although interventional studies demonstrated that PSW are modifiable (23-26), as are lifestyle habits (27-29). It has been estimated that the elimination of job strain could prevent up to 62% of CVD cases (30).

Large prospective studies have observed that the association between job strain and CVD risk remains after adjusting for unhealthy lifestyle habits. This supports an important independent effect of strain on CVD risk, over and above that of lifestyle habits (22, 31-35). However, the nature of the relation between PWS and lifestyle habits on CVD has never been investigated systematically.

The role of lifestyle habits on the causal relationship of PSW on CVD remains unclear (10). In addition to the potential independent effect of PSW and lifestyle habits on CVD, lifestyle habits have also been postulated to represent a mediating pathway by which PSW acts on CVD (36-38). Under that premise, adjustment for lifestyle habits could underestimate the strength of association and mask the true effect of job strain on CVD risk (39). A conceptual diagram illustrates these potential confounding and intermediate roles. Clarifying the role of lifestyle habits in the relationship between job strain and CVD would contribute to strengthen the quality of evidence on the causal effect of job strain.

Objective: This overview of systematic reviews aimed to examine how lifestyle habits, namely smoking, excessive alcohol consumption and physical inactivity, have been considered in systematic reviews evaluating the effect of job strain and cardiovascular diseases incidence. The specific objectives were to determine how these reviews discussed potential confounding and mediation effects by these lifestyle habits.

Methods: An overview of the literature was performed in order to identify SR assessing the effect of job strain on CVD incidence. To do so, several literature databases (PubMed; OVID; Web of Science and CINHAL from 1979 to 2018) were consulted. To be included, reviews had to be systematic. Hence, non-systematic, narrative or scoping reviews were not included.

Two reviewers (C.R. & M.L.R.) extracted data from SR in a standardized grid. Information relating to lifestyle habits in the inclusions criteria, evaluation of study quality, reported results as well as in the discussion were extracted. Results have then been reviewed, summarized and critically evaluated in order to evaluate if and how lifestyle habits have been considered in SR reporting on job strain and CVD incidence.

Results: We identified 13 systematic reviews, including four with meta-analyses. Lifestyle habits have been considered as potential confounders in ten out of the 13 systematic reviews identified in either the inclusion criteria, evaluation of study quality, results or discussion. Five SR reports that an association between job strain and cardiovascular incidence remains after adjusting for lifestyle habits. Eight systematic reviews discussed lifestyle habits as potential mediators in the association of interest and five systematic reviews postulated a potential underestimation of effects due to overadjustment for lifestyle habits. None of these systematic reviews investigated the magnitude of this potential overadjustment bias.

Implications for Future Research: Future research should aim to investigate potential mediating mechanisms, and clarify the causal association between job strain and CVD in order to explain the observed effect (2, 43). Although our overview of SR strongly suggests that the effect of job strain on CVD risk is independent of that of lifestyle habits, their role as potential confounders cannot be excluded (43). Indeed, evaluation between confounding and mediating pathways is complex when considering behavioural factors (53). Due to a probable confounding and mediating effect of lifestyle habits (43), our overview of current SR in occupational epidemiology does not clarify if adjustment for lifestyle habits should be performed (confounding) or avoided (mediator) when estimating the effect of job strain on CVD risk. Rather, our work highlights the need for longitudinal studies with repeated measures in order to clarify the temporal sequence between exposure to PWS and lifestyle habits as causal factors preceding CVD incidence (52, 53). The need for such studies has long been identified in order to inform on lifestyle habits role in the effect of PWS on CVD (2, 40, 43).

Moreover, confounding and mediating factors are similar from a statistical (54, 55) and conceptual point of view (56, 57). The approach of comparing the strength of association before and after controlling

for the mediator provides a starting point for estimating the mediated effect (57). However, this method cannot be applied to more complex models involving multiple mediators or variables acting as both mediator and effect modifier. It is important to note that the effect modification hypothesis is compatible with both the confounding and the mediator role of lifestyle habits (52). Furthermore, ruling on the direction of the bias due to adjustment for mediating factors that could introduce simultaneously effect modification is complex (52). Although, it is often assumed that adjustment for mediating factors leads to an underestimation of the effect (51), it may reveal more complex in the present context (58). Solely proper mediation analysis could provide further information on this question.

Mediation analysis could contribute to improving our understanding of underlying mechanisms by which PWS acts on CVD incidence (59). These analyses could be particularly relevant due to the complexity of exploring these mechanisms in a laboratory setting, normally done for acute stress mechanisms. Similarly, mediation analyses could support the development of effective PWS intervention by identifying key targets (*i.e.* lifestyle habits) (2, 45). PWS could prove important factors in CVD primary prevention since exposure to work stressors could obstruct important behavioural changes such as smoking cessation, increased physical activity and moderate alcohol consumption (10, 60, 61).

Conclusion: According to this overview of SR, the effect of job strain on CVD is independent of lifestyle habits. However, the presence of great heterogeneity in the way lifestyle habits are considered in systematic reviews do not allow to draw sound conclusions about their potential role as mediators in the relationship between job strain and cardiovascular disease. Overadjustment for lifestyle habits could lead to an underestimation of the magnitude of the true causal effect of job strain on CVD incidence. To this day, the potential magnitude of this underestimation has never been assessed in the SR. These findings may have important implications for public and occupational health policies as well as the development of interventions. Clarifying how PSW contribute, either directly or indirectly through lifestyle habits, to the CVD burden could contribute to an increased consideration of PSW in primary prevention.

Key Words: Job Strain, Psychosocial Work Stressors, Lifestyle Habits, Smoking, Alcohol, Physical Inactivity, Cardiovascular Diseases, Mediation Analyses, Intermediary Pathway.

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