Commentary

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Commentary triggered by the Individual Participant Data Meta-Analysis Consortium study of job strain and myocardial infarction risk

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Mika Kivimäki initiated the Individual Participant Data (IPD) Meta-Analysis Consortium, which currently has 50 members. The Consortium recently published several research reports on the relationship between job strain (high psychological demands and low decision latitude at work), on the one hand, and cardiovascular disease and its risk factors, on the other hand. Since IPD represents a novel way to conduct epidemiological research collaboration and as some of the findings from the IPD Consortium have been criticized, this commentary aims to address the rationales behind the approach and discuss some of the main criticisms of the Consortium.

Researchers must tackle many problems when interpreting associations between a psychosocial work environment factor and a health outcome. First of all, work environment factors belong to a "distal" rather than a "proximal" group. In other words, the closer one gets to a biological mechanism relevant for disease development, the more likely it is that a relevant association will be strong. For instance, small samples are needed to establish an individual "brain" factor associated with depression or emotional exhaustion – simply because the brain factor *is* more or less depression. Factors related to work organization, on the other hand, are more "distal" since there are many factors that influence the relationship between the environment and the body's organs. Accordingly, it is sometimes difficult to obtain sufficient statistical power for the establishment of an undisputable association. For instance, the long "distance" between job strain and the outcome, myocardial infarction (MI), explains why we should expect a weaker association than in the study of "proximal" factors, for instance myocardial metabolism in relation to MI. Nevertheless, on a societal level, job strain is very important since it affects many working people, with a prevalence in the working population (in the IPD Consortium study's operational definition) of around 15%. Accordingly, if an unequivocal association is established, it is of major importance to those responsible for work organization and interventions designed to improve working conditions. However, large samples are needed to establish unequivocal proof.

Since Karasek introduced his demand–control model (1), there have been many studies of the association between job strain and risk of MI. These studies have become increasingly sophisticated over the years. In addition, there is accumulated indirect evidence from longitudinal studies of the relationship between job strain, on the one hand, and blood pressure variations and endocrine, metabolic, and immunological parameters, on the other hand. The results from these studies give us a plausible physiological explanation of the assumed relationship between job strain and MI risk.

A reason why this research field has attracted strong attention is that MI is an undisputable illness outcome. The study of MI risk, therefore, serves as a good scientific model for studying the relationship between job strain and adverse health outcomes in general.

Establishment of and rationale behind the IPD Consortium

There have been divided opinions about the relationship between job strain and risk of MI. The main reason for the controversy has been that, despite the relatively large size of several of the published cohort studies with number of observation years often in the range of 50 000, the statistical power has been too small for an unequivocal establishment of an association. As a result, Mika Kivimäki invited a number researchers,

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who had included psychosocial job factors in their study protocols and had or had not published results on the relationship between job strain and MI risk, to establish the IPD Consortium. Including unpublished cohorts was important as this provided a possibility to address the problem of publication bias – the tendency of researchers and journals to publish only positive findings that can lead to inflated associations.

The IPD Consortium received financial support from research foundations in the UK, Sweden, Denmark, France, and Finland. The process started with the goal of testing the hypothesis that job strain is associated with MI risk. Research was divided into several stages, the first of which was to scrutinize questions regarding job strain in the participating cohorts. As expected, there were differences in formulations and response categories and also differences in the number of questions related to psychological demands and decision latitude. However, methodological work overseen by "judges" assessing the similarity between items in the different cohort questionnaires made it possible to establish which cohort questionnaires should be included as well as the minimum number of questions for each dimension in the total IPD study with acceptable precision for the two variables (ie, psychological demands and decision latitude). This was done and the results published (2) before the next phase started. Since the job strain variables in the different studies had been homogenized, it was possible to establish the median values for both demands and decision latitude within each cohort. According to the literature's most common operationalization of job strain, the group with demand above median and, concomitantly decision latitude below median, was defined as the exposed group and the remaining population as the non-exposed. This enabled all individuals (almost 200 000) to be combined in a large cohort study. The average follow-up time was 7.5 years. The assessment of standard risk factors was treated in the same way – criteria were established before the analyses of the association between job strain and MI risk began. Two published articles (3, 4) described the scientific process in the IPD Consortium.

Published findings

The findings of the IPD Consortium have been published in *The Lancet* (5) and the *Canadian Medical Association Journal (CMAJ)* (6). They show a consistent and statistically significant age- and sex-adjusted relationship between job strain and MI risk, which remains even after further adjustments for country, socioeconomic position, and standard risk factors. The findings also show that exclusion of subjects with a short time lag between job strain assessment and onset of MI does not affect the statistical significance of the association – addressing the problem described above with possible vague pre-heart disease illness symptoms possibly influencing the job description. The findings also addressed a second question that had been raised in previous research (7): the risk associated with a combination of high psychological demands and low decision latitude was greater than the risks associated with each one of these two exposures. Finally, the IPD papers provided a response to the question regarding publication bias: Yes, there seemed to be some effect of publication bias since the odds ratio was lower in the unpublished versus published studies. However, even in the unpublished studies, there was a statistically significant relationship between job strain and subsequent MI risk.

Criticism of the IPD findings

Accordingly, the IPD Consortium has delivered clear responses to several of the questions that have been debated ever since Karasek introduced the model. The problem created by a "distal" relationship was solved by means of strict homogenization of the assessments in many cohorts so they could be used as one study. The findings were positive despite many conservative measures safeguarding against factors that could give rise to inflated relationships. Nevertheless, the IPD Consortium has been criticized for several reasons (8–10). The most critical voices have come from researchers involved in work-intervention research. The critical points can be divided into two groups.

Standard risk factors' role in the relationship between job strain and MI. The first and most severe criticism relates to the way in which the role of the standard risk factors for heart disease (diabetes, high blood pressure, smoking, body mass index) has been presented in *The Lancet* and *CMAJ*. The latter article was based only on those cohorts that had full information about relevant lifestyle factors (102 000 participants), and the empirical conclusion has not been debated: job strain adds independently to illness risk even when standard risk factors have been taken into account. And, conversely, standard risk factors add independently to risk regardless of job strain. However, the independent association between job strain and MI risk is much weaker than the corresponding association between the standard risk factors and MI. No one could criticize the IPD Consortium for publishing that finding in itself. However, the practical interpretation formulated in *The Lancet*, "Our findings suggest that prevention of workplace stress might decrease disease incidence; however, this strategy would have a much smaller effect than would tackling of standard risk factors, such as smoking" (5, p1491) has not been endorsed by all members of the IPD. In my mind, the conclusion goes beyond the analyses of

the IPD study. I tried to change these formulations but of course in a large group of researchers (46 authors for *The Lancet* article) one has to compromise, and it becomes practically difficult to discuss changes particularly in the final phase before publication. Critics of the IPD Consortium argue this statement could be used as a justification among clinicians (cardiologists, occupational physicians, and general practitioners) for disregarding the patient's psychosocial working conditions entirely. So what is the role of standard risk factors in the relationship between job strain and MI risk?

In its studies (11, 12), the Consortium has shown that job strain is significantly associated with diabetes, physical inactivity, and obesity as well as to a summarized Framingham risk factor score. According to a recent systematic review (13), job strain is associated with elevated blood pressure, one of the classical standard risk factors. There are divided opinions regarding this relationship with regard to blood pressure assessed in the classical way (at rest in the "doctor's office") but the relationship is more established for blood pressure that has been automatically monitored during normal daily activities (14). As has been pointed out by several authors, long lasting excessive stress may increase the risk of metabolic syndrome, which in itself increases heart disease risk. In addition, excessive intake of carbohydrates and cigarette smoking could be regarded as "external" efforts that an individual could make when the body's own energy mobilization is failing. Accordingly, part of the relationships between job strain and lifestyle factors may mediate the relationship between job strain and MI risk. Thus, the relationships between standard risk factors and job strain make it very difficult to interpret analyses of job strain effects of risk after adjustment for such factors since some of the effect of job strain goes through them.

Adjusting for lifestyle factors is valuable, but one should avoid far-reaching conclusions from the results due to this complexity. There is also a difference between the effect of job strain on different parts of the "ladder of lifestyle risk factors". A closer look at the *CMAJ* table describing the relationship between number of lifestyle risk factors in groups with and without job strain reveals that there is indeed very little added risk going from "no job strain" to "job strain" (from 2.62 to 2.69) when participants (14 000 participants) have at least two of the lifestyle risk factors. But for those with no lifestyle risk factors (N=55 000) and those with only one such risk factor (N=33 000), job strain increases the risk from 1.00 (reference group) to 1.27 and from 1.47 to 1.87, respectively. From a population perspective, we should pay attention to these risk increases in the lower end of the lifestyle risk ladder. The prevalence of cigarette smoking varies vastly between countries. Therefore smoking is a risk factor, for example, with less potential payoff for cardiovascular prevention in Sweden than in many other countries since there are already few smokers in the risk ages in Sweden. Accordingly, it is difficult to make generalized statements regarding the possible pay-off of the potential effects of lifestyle versus work environment interventions.

Working conditions and lifestyle. The most important argument concerning working conditions and lifestyle, however, is based upon clinical experience: employees with a poor work environment may be unwilling to follow lifestyle health promotion advice. In contrast, when subjects feel that their working conditions improve they may feel more motivated to follow individual health promotion advice. Admittedly there is little scientific hard core evidence for this. However, of relevance is my research group's observation in a controlled job-intervention study (a year-long program for improvement of psychosocial know-how among managers) showing that, after a year's intervention, decision authority had developed statistically significantly more favorably among the intervention group's employees (reporting to managers in the experimental group). At the same time, the morning plasma cortisol concentration (related to the metabolic syndrome) as well as the plasma concentration of the liver enzyme gamma glutamyl transferase and (among women only) the serum concentration of triglycerides had improved among employees in the intervention but not the control group. These findings indicate that an improved psychosocial work environment may contribute to an improved risk factor profile among the employees (15). Sorensen has discussed the effect of occupational class on smoking habits and its potential role for anti-smoking propaganda (16). It should also be pointed out that – with the use of terminology introduced above – lifestyle factors should be regarded as "more proximal" (thus likely to be associated with stronger direct associations with heart disease risk) in relation to the illness processes than psychosocial work environment factors.

Studies showing that subjects with job strain who have suffered a MI are more likely than others during follow-up to experience a new cardiac event (17–19) illustrate that job strain is of importance to heart disease.

The interrelationships between work environment and lifestyle risk factors should be studied preferably with more sophisticated statistical models. Karasek has more recently expanded his demand–control theory and discussed the complex nature of these relationships (20). He points out that the key factor in relationships that gives rise to long-term stress reactions at work is the control of storage and release of energy in the task of maintaining stable physiological self-regulation. He notes that in order to resolve current scientific dilemmas, one should ideally study multiple and linked levels of

both proximal (even more proximal than we currently study) and more distal (for instance work organization and global economy) factors. Karasek and collaborators (21) have recently described the design of a possible large-scale study that would take these intermediary mechanisms into account.

According to the IPD Consortium's article in the *CMAJ*, "For many people, avoidance of stress at work is unrealistic. The absence of strong evidence for effective interventions to reduce job strain therefore raises the challenge of identifying additional approaches for dealing with the health impact of stress in the workplace" (6, p764). This has caused tension among the readership. In mass media and comments from cardiologists following the IPD publications, this seems to give the impression that organizational job interventions have no scientific basis (although this was emphatically not stated in the articles). While it is true that large-scale controlled intervention studies aimed at reducing job strain on a collective organizational level, with subsequent follow-up of health effects providing strong evidence for an effect on heart disease risk, have not been published, there are still publications indicating this could be worth a closer look. For a review, see La Montagne et al (22). Bourbonnais et al's study (23) showed beneficial three-year effects of a work organization improvement program on the mental health of employees, with no similar change in the control group. Another study by Bond and Bunce (24) randomizing six offices to intervention and control groups, respectively, showed that mental health, sick leave, and self-rated productivity improved after one year in the intervention but not control group; this study also showed that increased perception of control was the mediating factor. In the study that my own group (15) performed on the effects of improved management on employee health, parameters related to the metabolic syndrome and decision authority reportedly improved for the employees in the intervention but not control group.

Strength of the association between job strain and MI. The second area of criticism leveled at the IPD findings relates to statements about the strength of the association between job strain and MI risk. It is true that in some of the IPD texts (for instance in the abstract of *The Lancet* article), the formulations regarding the studied associations were expanded to work stress in general. This is clearly a mistake since the analysis presented was on the effect of job strain – which is only one aspect of workplace stress. The IPD researchers are involved in research on other kinds of workplace stress, such as effort–reward imbalance (25), job insecurity (26) organizational justice (27), and leadership (28, 29), and the IPD Consortium plans to add exposures (effort–reward imbalance, job insecurity, and long working hours) to its study of job strain. This will enable the group to examine whether different kinds of psychosocial adverse factors compound risk. There are indications of this in previous literature (30, 31).

Another question arising in the critique is whether adding health outcomes to one another would provide a more useful analysis of the total impact of the psychosocial work environment. The IPD Consortium has already published a study showing that job strain is associated with increased diabetes risk (11), while an ongoing study examines whether job strain is prospectively related to the risk of stroke. A study of job strain in relation to depression is also being planned. Therefore, in the future, we will see studies from the IPD group addressing the extent to which an adverse work environment (with several exposures) adds to the risk of developing any of these illnesses that are metabolically related to one another.

Critical methodological questions have been made regarding the effect of the job strain assessment in the IPD study. A careful analysis of the questionnaires in the different cohort studies was performed and decisions were made regarding "sufficient homogeneity". The statistical analyses showed that little information was lost with the applied criteria. However, it could still be that the standard Job Content Questionnaire which has been the international standard for job strain assessment is a better questionnaire than the methodological compromise that we achieved. Precision may have been lost due to this and, according to my understanding, it is more likely that this has given rise to random error than systematic overestimation of risk.

Another important point is that there has only been one assessment of job strain (at start of follow-up) in the IPD study. In a previous study, Kivimäki et al (32) have shown that stable job strain lasting through at least two measurements with an interval of two years is a stronger predictor than one measurement alone. People change jobs and stop working. Accordingly, precision in predictions will improve when there are several longitudinal measurements.

An additional problem is that subjects with the worst job conditions may not participate in this type of study. This is a methodological problem that is not only confined to the IPD Consortium studies. "Overstressed" subjects may have difficulties participating in our studies for practical reasons (irregular work exposure for instance). Also, those who have already developed a disease or illness caused by adverse working conditions will not be included. We know too little about the effects of this kind of non-participation. There is reason to believe that it may give rise to an underestimation of true risks, as discussed by Collins et al (33). Another limitation is that our study represents a Western European perspective. In the European countries participat-

ing in our study, work democracy has been an important topic in societal discussions for several decades. It is possible that the relationships would be different in Southern Asian, South American, and African countries for instance.

The IPD Consortium also examines health outcomes other than cardiovascular disease. The first publication in this group (34) focused on colorectal, lung, breast, and prostate cancers. No significant associations were found between job strain and the incidence of these forms of cancer.

Concluding remarks

The IPD Consortium has great potential to provide solid knowledge in the field of psychosocial factors and health. IPD represents a new collaborative approach. Participating researchers have to search ways of homogenizing their exposure and outcome assessments in order make it possible to form very big cohorts in which every participant contributes equally. This is an improvement on the usual meta-analysis procedure. A possible drawback of the need to compromise is that the final number of questions that can be used is more limited than in the original study cohorts, possibly decreasing precision. Another issue is the complexity of managing collaboration between so many researchers. The IPD Consortium has presented good opportunities for everyone to provide input during the production of articles, but under time constraints (eg, the final phase of *The Lancet* article) it is difficult, if not impossible, to include opinions from 46 coauthors. Perhaps a formalized structure would have helped (eg, a small group could be democratically elected by all the participating researchers to act on their behalf in "critical situations").

The fact that there is an independent relationship between job strain and MI risk already provides an important rationale for employers to deal with psychosocial stress, regardless of the size of the association – simply because MI is a serious illness which gives rise to suffering, risk of death, and productivity loss both for the company and society as a whole. It should be pointed out that there are a number of other valid reasons for the employer to deal with employee stress, not the least financial ones (see, for instance, 35). Psychosocial stress at work may cause much more financial damage than employers know. The IPD Consortium will, in the near future, examine the total effect of job strain, job insecurity, and effort–reward imbalance on important health outcomes that to some extent have a shared etiology (depression, diabetes, stroke, and MI). One critique of the IPD Consortium is that our strategy may lead to over-interpretation of "bits and pieces" of findings. From that point of view, a joint analysis of all the exposures and outcomes already from the start would have been better. However, the IPD Consortium has worked very rapidly and effectively with its scientific process. Transparency has been key in its empirical analysis. A requirement that publications would have had to include all the possible exposures and outcomes in one analysis from start would have delayed the process considerably (possibly for several years) and may not have been feasible given the financing terms. However, the current intense debates put even more pressure on the scientific community to join forces to unravel the "proximal/distal" controversy. The IPD Consortium has shown an interesting example of the strong potential of scientific collaboration.

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