Work related stressors

and the development of ischemic heart disease

A reference document on behalf of the Danish Work Environment Research Fund

Nanna Hurwitz Eller

Bo Netterstrøm

Clinic of Occupational Medicine

Hilleroed Hospital, Denmark

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Summary

Introduction: This review was carried out at the request of the Danish Working Environment Research Fund. Clarification of the potential relationships between work related stressors and development of ischemic heart disease (IHD) was requested.

Methods: The review used the following inclusion criteria: 1. Prospective study or a case control study in which exposure assessment was not self-reported. 2. Definite ischemic heart disease. 3. Exposure assessed as a work related psychosocial factor. The quality of the papers was assessed by the use of a predefined scoring system. In most cases one paper presented results of different measures of exposure, one at a time.

Twenty-six papers presenting results from prospective studies and 7 papers presenting results from case control studies were included. Twenty-three papers used exposure measures derived from the Demand Control Model. Four papers included dimensions from the Effort Reward Model. Other exposure measures were downsizing, justice at work, traffic intensity, job insecurity and working hours. Twenty-one of the papers attained a quality score of 7 points or more out of maximum 11, indicating high quality. Most of the papers (17 of those reporting prospective results and five of those reporting case control results) only included men.

Results: *Men*: Demands by any definition were evaluated in 16 studies. Seven studies demonstrated a significant positive association between demands and an increased risk of IHD; in two studies a significant negative association was found whereas the rest of the studies presented non significant results. Control (decision latitude) was evaluated in 13 studies of which three demonstrated a significant positive association between lack of control and increased risk of IHD, and 10 studies presented non significant results. Job strain was evaluated in 15 studies of which three revealed a significant positive association between job strain and increased risk of IHD. Furthermore, three studies demonstrated a significantly increased risk of IHD in the case of iso-strain. Five studies evaluated significance of social support: Three found a significantly increased risk of IHD if the participants experienced lack of social support, while two studies reported non significant results. Among the four papers evaluating the Effort Reward Model, two reported significant positive associations between dimensions of the model and the risk of IHD, and two reported non significant results. The two papers evaluating the Organizational Injustice Model reported a significantly increased risk of IHD if experiencing injustice. Four papers evaluated different terms of job insecurity: Two papers reported a significantly increased risk of IHD and two non significant results.

Studies from the Nordic countries constituted 73% of the studies with significant positive associations.

Women: Demands by any definition were evaluated in 5 studies. One study demonstrated a significant positive association between demands and an increased risk of IHD, where as the rest of the studies presented non significant results. Control was evaluated in four studies of which two demonstrated a significant positive association between lack of control and increased risk of IHD, and two studies presented non significant results. Job strain was evaluated in four studies of which all found non significant associations between job strain and increased risk of IHD. However, one study demonstrated a significantly increased risk of IHD in the case of iso-strain. Four studies evaluated the significance of social support: One found a significantly increased risk of IHD if the participants experienced lack of social support, while three studies reported non significant results. None of the papers concerning the Effort Reward Model or the Organizational Injustice Model included women. One paper concerning job insecurity reported non significant results.

Discussion: The wide variation in exposure measures reflects the many psychosocial factors acting in daily work life. Use of the same stress model and questionnaire is absolutely necessary if researchers want to compare results. When comparing studies it is important that they have been carried out within the same region and are without substantial cultural dissimilarities. It is especially so with relation to the impact of gender on the perception of stressors. The difference between gender in relation to the development of IHD, and the fact that women develop myocardial infarction less frequently and later in life than men highlights the need for an evaluation of the endpoint used when evaluating the significance of psychological stress to IHD. IHD is a multi-factorial disease, and it is therefore difficult to discuss workers compensation in relation to this disease. As risk factors for IHD have a tendency to cluster in the same group of individuals; prevention is seen as the most important aspect. Psychological aspects of the working environment and the interface between work and home have to be discussed and improved.

Conclusion: It is biological plausible and supported by the literature that psychosocial factors are independent risk factors for IHD. In the Nordic countries there is evidence of a predictive significance of high demands, and iso-strain and limited evidence of a predictive significance of lack of control, job strain, lack of social support and job insecurity in relation to the incidence of IHD for men. The literature is too sparse to reach any conclusion regarding other psychosocial factors as well as regarding women. Research should focus on refining measures of exposure, and on the conditions regarding women.

Dansk resume

Introduktion: Denne litteraturgennemgang er foretaget på anmodning af Arbejdsmiljøforskningsfonden, idet man ønskede en afklaring af de mulige sammenhænge mellem arbejdsrelaterede stresspåvirkninger og udvikling af iskæmisk hjertesygdom, IHS.

Metoder: Ved litteraturgennemgangen anvendtes følgende inklusions kriterier: 1. Prospektivt studium eller case-kontrol studium hvor eksponeringen ikke var selv-rapporteret af det enkelte individ. 2. Sikkert diagnosticeret iskæmisk hjertesygdom. 3. Eksponering angivet som en arbejdsrelateret psykosocial faktor. Kvaliteten af de inkluderede studier vurderedes ved anvendelse af et predefineret scorings system. I de fleste tilfælde rapporterede en artikel resultater fra flere analyser, idet flere eksponeringer analyseredes én af gangen. Reviewet inkluderede 26 artikler med resultater fra prospektive studier og 7 artikler med resultater fra case-kontrol studier. Treogtyve artikler anvendte eksponeringsmål, som belyste Krav-Kontrol-modellen. Fire artikler inkluderede dimensioner fra Anstrengelses-Belønnings-modellen. Andre eksponeringer var nedskæringer, retfærdighed på arbejdet, trafik intensitet, usikkerhed i ansættelsen og antallet af arbejdstimer. Enogtyve af artiklerne opnåede en kvalitetsscore på 7 points eller flere af maximum 11. De fleste af artiklerne (17 prospektive og fem case-kontrol) inkluderede kun mænd.

Resultater: *Mænd*: Krav defineret på forskellig måde blev evalueret i 16 studier. Syv studier fandt en signifikant positiv association mellem krav og en øget risiko for IHS, i to studier fandtes en signifikant negativ association, mens resten af studierne ikke var signifikante. Kontrol inkluderedes i 13 studier, blandt hvilke tre demonstrerede signifikante positive associationer mellem mangel på kontrol og øget risiko for IHS, og 10 ikke studier præsenterede signifikante resultater. Job strain blev evalueret i 15 studier, hvoriblandt tre viste signifikante positive associationer mellem job strain og øget risiko for IHS. Desuden fandt tre studier signifikant øget risiko for IHS ved iso-strain. Fem studier evaluerede betydningen af social støtte, tre fandt en signifikant øget risiko for IHS, hvis deltagerne oplevede mangel på social støtte, mens to studier rapporterede ikke signifikante resultater. Af de fire studier som evaluerede Anstrengelses-Belønnings-modellen viste to signifikante positive associationer mellem dimensioner af modellen og risikoen for IHS, mens de andre to var ikke-signifikante. To artikler evaluerede modellen Uretfærdighed i Organisationen og fandt begge signifikant øget risiko for IHS ved oplevet uretfærdighed. Fire artikler evaluerede forskellige typer af job usikkerhed, to af disse rapporterede signifikant øget risiko for IHS og to ikke signifikante resultater. Studier fra de Nordiske lande repræsenterede 73 % af analyserne med signifikante positive associationer.

Kvinder: Krav defineret på forskellig måde blev evalueret i 5 studier. Et studie viste signifikant positiv association mellem krav og øget risiko for IHS, mens de andre ikke viste signifikante resultater. Kontrol blev evalueret i fire studier hvoraf to fandt signifikant positiv association mellem mangel på kontrol og øget risiko for IHS, og to studier ikke præsenterede signifikante resultater. Job strain blev evalueret i fire studier, ingen påviste signifikante associationer. Et studie fandt en signifikant øget risiko for IHS i forbindelse med iso-strain. Fire studier evaluerede betydningen af social støtte, et fandt en signifikant øget risiko for IHS hvis deltagerne oplevede lav grad af social støtte, mens tre studier rapporterede ikke signifikante resultater. Ingen af artiklerne om Anstrengelses-Belønnings-modellen eller modellen om uretfærdighed i organisationen inkluderede kvinder. En artikel om job usikkerhed fandt ikke-signifikante resultater.

Diskussion: De mange forskellige eksponeringsmål viser, at der er mange psykosociale faktorer at tage med i en vurdering af det psykiske arbejdsmiljø. Sammenligning af resultater fra forskellige undersøgelser forudsætter, at det er samme eksponeringsmål, der er undersøgt,

ligesom populationerne skal være sammenlignelige. Studierne bør således være udført i samme kultur, et forhold der ikke mindst er relevant at diskutere i forbindelse med kønnenes forskellige opfattelse af stressorer. Forskellen mellem kønnene i relation til udvikling af IHS og det forhold at kvinder udvikler myokardieinfarkt på et senere tidspunkt i livet end mænd, lægger op til at overveje andre endepunkter, når betydningen af stress for IHS ønskes belyst. IHS er en multifaktoriel sygdom, og det er derfor vanskeligt at diskutere arbejdsskadeerstatning i forbindelse hermed. Da risikofaktorer for IHS ofte forekommer samtidigt hos det enkelte individ, ses forebyggelse som det vigtigste aspekt. Herunder bør psykisk arbejdsmiljø diskuteres og forbedres, og belastninger på baggrund i ønsket om at forene familie og arbejdsliv må undgås.

Konklusion: Det er biologisk plausibelt og støttet af litteraturen at psykosociale faktorer er uafhængige risikofaktorer for IHS. I de nordiske lande fandtes der evidens for, at høje krav og iso-strain er af prediktiv betydning for udvikling af IHS hos mænd. Desuden fandtes begrænset evidens for at lav grad af kontrol, job strain, mangel på social støtte og usikkerhed i ansættelsen er prediktive faktorer for IHS hos mænd. Imidlertid er evidensen ikke tilstrækkelig til, at der kan drages konklusioner i forhold til andre psykosociale faktorer eller vedrørende forholdene for kvinder. Fremtidig forskning bør fokusere på at raffinere eksponeringsmålene og på at belyse forholdene hos kvinder.

Background

Aim

In the spring of 2006, the Danish Working Environment Research Fund, DWERF, called for papers about the relationship between work-related stressors and ischemic heart disease, IHD. The papers will be used by the Danish National Board of Industrial Injuries and the associated Industrial Injuries Committee, IIC, during negotiations about which diseases to include in the Danish Directory of Occupational Diseases. Furthermore, the papers are to be used during the development of guidelines for acknowledgement of industrial injuries irrespective of whether included in the directory or not.

IIC consists of labour market representatives, medical specialists and representatives from the National Board of Industrial Injuries. During the evaluation process of potential occupational diseases, IIC has realized a pressing need for clarification of the relationship between work-related stressors and the development of IHD. This includes the need for a critical evaluation of the character and extent of the potentially increased risk for individuals suffering from stress.

The reform of the occupational health legislation has focused on the importance of gender in the development of occupational disease. It was therefore desired that the gender aspects were considered in the literature review.

In the call for papers from the DWERF it was stated that the scientific reference document should describe, summarise and evaluate possible relationships between occupational stressors and the development of IHD. The scientific reference document should be based on a review of the most important international research findings in the area. The DWERF asked specifically for documentation and scientific evidence of the relationship between work-related stressors and development of IHD. This should also include a description of the potential cause-effect mechanism and an evaluation of the type of stressors that may lead to the development of IHD and to what extent they do so.

Furthermore, the reference document should explain the stress definition used and the implications of this for the project conclusions. Finally, a very broad approach to the concept of stress was requested, including all relevant work-related stressors. The following had to be examined and evaluated:

- The characteristics of the stressor (types of stressors)
- The extent of the stressors (qualitatively and quantitatively)
- The overall extent of the exposure over time
- The onset of the illness in relation to the exposure.

Finally, the reference document should include

- Limits and definition of the effect, i.e. which types of effect and stressor are evaluated.
- Limits and definition of the disease, including the diagnosis, exact information about the background for the diagnosis, and an evaluation of the validity of the results of the study as well as information about the severity of the disease or the symptoms.
- A description and evaluation of the reliability of the documentation concerning the exposure and the weak points of each scientific paper.

- As far as possible, a description and evaluation of the risk related to the specific stressors and overall exposure.
- A description and evaluation of what is known concerning other causes of the diseases.
- The best possible description and evaluation of the existing knowledge about the connection between exposures and responses, including where possible the relationship to specific stressors and the overall exposure, preferably also including the significance of the intensity and the duration of the exposure as well as possible borderline values.
- An explicit evaluation of the prognosis, including to what extent there is evidence that the symptoms and clinical findings persist once the exposure stops, together with the prognostic impact of the exposure.
- A collective and graded evaluation of the scientific evidence.

If the evidence is insufficient to show a relation between occupational stressors and the development of IHD, or if the literature is otherwise inconclusive, this should be described and explained. If more research in this field has been recommended, relevant objectives of such research should be described and included in the overall conclusions of the research project.

On this basis, the following literature review was carried out between January 1th, 2007 and September 1th, 2007. The procedure for creating this document has been the following: Before the application to the Work Environment Research Fund the contractors (authors) asked two researchers in the field to act as reviewers of the document. Professor Töres Theorell, Sweden and Professor Andrew Steptoe, British Heart Foundation and Department of Epidemiology and Public Health, University College, London agreed. The task as supervisor for the process was accepted by Professor Finn Gyntelberg, Clinic of Occupational Medicine, Bispebjerg Hospital, Professor Tage Søndergård Kristensen, National Research Centre for Work Environment and consultant Finn Nielsen, Department of Cardiology, Frederiksberg Hospital. Consultations were held with the three latter and all received June 2007 the first draft of the report. After having received feed back the authors finished the second edition by mid July and a discussion with all parties took place 15th August in Copenhagen. The final version of the reference document was forwarded to the Fund September 2007.

The introductory section will include paragraphs on theoretical stress models, atherosclerosis and IHD, stress physiology and the gender perspective. After this introduction, the epidemiological evidence for an association between work related psychosocial factors and IHD is presented, i.e. the search strategy for and evaluation of epidemiological evidence.

Work related stressors and theoretical stress models

In relation to this study work-related stressors are defined as aspects of the job which can lead to a stress condition. Physical, chemical, biological and psychological factors can lead to stress, but in the present context focus is entirely on the psychosocial stressors. Scientific studies examining the association between psychosocial stressors and diseases have generally used three different measures of exposure: First, stressors can be evaluated objectively, e.g. the number of working hours, the intensity of work, etc. Second, stressors can be self-reported, using different models. Finally, some studies use the so-called ecological method, where the extent and type of psychological work-related factors are based on reports from people with particular types of job in order to avoid that individual experience and strain becoming a measure of exposure (aggregated data).

An objective description of the exposure has only been used in very few studies, as psychological stressors are either very difficult to measure or because documentation is unavailable. On the other hand it is fairly straightforward in scientific studies to ask people how they experience different stressors in their work.

Psychological stressors in the work environment vary to a great extent and depend on the type of job. Of the specific models that have been used to measure psychological strain, the Demand Control Model introduced by Robert Karasek in 1979 (47) has dominated occupational health research during the last 20 years.
The Demand Control Model describes two main dimensions: Demands and control (decision latitude). The latter dimension consists of two sub-dimensions: decision authority and skill discretion. The model is based on the notion that demands per se are not stressful if they are coupled with adequate control over work and the work environment. By combining the two main dimensions, four working conditions are presented: Individuals who experience high demands and have a high control are termed "active" (e.g. lawyers and general practitioners). The combination of high demands and low control is termed "strain" (e.g. assembly line workers and bus drivers), low demands and high control is termed "relaxed" (e.g. craftsmen) and both low demands and low control is termed "passive" (e.g. attendants). According to the Demand Control Model the individuals working under job conditions characterised as "strain" have a larger risk of stress-related disease (48).

Social support at work and/or during spare time has been shown to modify the possible stress-causing effect of strain, and in some studies social support is therefore used in combination with the Demand Control model (45). In this context, it is decisive whether or not the social network provides actual support in the handling of psychosocial strain. Working conditions including both strain and low social support, so called iso-strain, carries the highest risk.

In the 90's Johannes Siegrist developed a stress model which is based on the individual experience of the balance between the effort made and the reward received (101;105). According to the Effort Reward Model, the most stressful condition is when the effort made is not followed by sufficient reward. Reward is not only a financial matter but also includes the esteem which is associated with the work, job security and future prospects.
The model distinguishes between extrinsic effort, for example time pressure or interruptions whilst working, and intrinsic effort, i.e. individual characteristics or coping patterns such as over-commitment. The third element is the possibility of recognition and reward. An effort-reward imbalance will, according to the model, lead to stress. Individuals with a coping pattern characterised by over-commitment are more likely to accept such an imbalance, and have greater risk of becoming stressed.
The core concept of the Demand Control Model is "personal control" which is believed to be the most important factor in relation to the development of stress. In contrast or merely as a complementary dimension, the basis of the Effort Reward Model is "social reciprocity"(101).

A newer model, the Organizational Injustice Model, claims that stress related disease will occur if the individual does not feel that he / she is treated fairly in the organisation. An indicator of justice at work is whether people believe that their supervisors consider their viewpoints, shares information concerning decision-making, and treats individuals fairly and in a truthful manner (49).

When these stress models are used, a questionnaire is most often filled out by the individual. However, ecological or aggregated data can be used as well. In that case, a job exposure matrix is used to map the work conditions in a large population, for instance in the entire Danish labour market. Measures of work load can be the number of working hours per week or the number of days including overtime work.

Several studies include in their measure of exposure the effects of exposure, e.g. the feeling of being stressed or a individual's general wellbeing. Such studies should not be used to evaluate the correlation between psychological strain and illness and have been excluded in this review. The present literature review has also excluded studies looking into the significance of the placement of working hours, e.g. night time work, as this will be dealt with in another literature review.

Atherosclerosis and Ischemic Heart Disease
All people with a western lifestyle develop atherosclerosis (98). Atherosclerosis is a chronic inflammatory disease affecting the arterial vessels e.g. the aorta, the coronary arteries, and the arteries to the brain and the limbs. Deposition of lipoproteins and other substances and different cells into the wall of the vessels is an essential element of the atherosclerotic process and causes development of atherosclerotic plaques. These plaques can rupture and cause acute occlusive thrombus formation reflecting in for example myocardial infarction or the process can proceed more slowly with progressive narrowing of the vessels causing symptoms (e.g. angina pectoris, heart pain) when the blood supply to the heart, legs or brain is critically reduced.

Atherosclerosis is the most important cause of death in Denmark, as well as in the world (15;98;122). Atherosclerosis has a complex pathogenesis and several risk factors have been pointed out, e.g. male gender, hypercholesterolemia, increased blood pressure, diabetes, obesity, physical inactivity and smoking.

Although the endpoint may be the same, i.e. acute myocardial infarction, AMI, the involved risk factors and the relative importance of these are different among individuals, due to a considerable genetic variation (34), the significance of which has been demonstrated in relation to job strain and atherosclerosis (38). All steps in the atherosclerotic process is affected by this huge genetic variation, i.e. debut of the first signs of atherosclerosis, the speed of progression, variation in the ability of the arterial walls to regenerate, formation of collaterals and an individual variation in the manifestation of atherosclerotic symptoms dependent on the limit of pain and the ability of the tissue to withstand low oxygen tension (34).

The atherosclerotic process is slow and begins early in life without symptoms. The initial stage of the atherosclerotic process involves endothelial (inner lining of the vessel) dysfunction, which is accelerated among smokers due to the toxins in tobacco smoke and among individuals with dyslipidemia and insulin resistance. Shear stress in the arterial walls, different chemical toxins, viral infections (34;98) and leptin from fat cells (9) are other important factors involved in the endothelial dysfunction. The function of the endothelial cells is controlled by the suprachiasmatic nucleus and is subject to diurnal variation (123). One aspect of this is a varying ability to produce the

vasodilating substance nitric oxide (NO), which may explain the diurnal variation in the onset of AMI. The production of NO is increased by oestrogen, which may partly explain the late development of atherosclerosis in women (123).

The atherosclerotic process begins with an injury to the inner layer of the vessel. These injuries are typically seen in vessel segments with high shear stress e.g. at the sites where the vessel divides. Lipoproteins are accumulated in the injured part of the vessels. Normally, the endothelial cells are smooth and non-adhesive. In the case of injuries or endothelial dysfunction an inflammatory response begins with activation of different blood cells such as monocytes and platelets. These cells adhere to the injured area of the vessels and in interaction with lipid substances and smooth muscle proliferation in the vessels the cells are involved in the further atherosclerotic process with formation of foam cells, fatty streaks and fibrous capsules, a so called atheromatous plaque or atheroma. A calcification process with deposits of calcium around the atheromatous plaques develops and the atheroma grows with either partial or total obstruction of the lumen or rupture of the plaque as a final result. When the process causes insufficient blood supply to the organ different symptoms can arise. Angina pectoris, AMI and strokes are some of the most common seen diseases caused by atherosclerosis.

IHD was the cause of hospital admission of 57,083 individuals in 2002 in Denmark; 29,654 were first time admissions. Among the first time admissions in the age group 35-64 years in 2002, 2,395 men, and 716 women were admitted due to an AMI. Since 1978 the admissions rates for IHD in people below 75 years of age have been stable. Mortality from IHD has dropped since 1980. The drop in mortality rate may be caused by a decline in the number of new cases due to a healthier life style, a better prognosis as a result of a changed spontaneous course of the disease or as result of better treatment. The total number of deaths caused by AMI was 2,453 among men and 1,901 among women in 2000. Approximately 45 % of deaths from IHD among men and 23 % of deaths from IHD among women occur before the age of 75 (122).

Stress physiology
The physiological stress response originates in the hypothalamus, where from cortico releasing factor, CRF, is produced and released. In the pituitary gland CRF stimulates the release of adrenocorticotropic hormone, ACTH, which reaches the adrenal glands via the blood. The adrenal glands produce cortisol, the main stress hormone. Along with this activation of the hypothalamus-pituitary-adrenal-axis (HPA-axis) an activation of the sympathetic nervous system (SA-system) occurs. This system functions by means of adrenaline and noradrenaline, partly via neurons (16). These two systems regulate the whole body. It is fundamental that physiological functions, including the production of cortisol, vary diurnally and are controlled by the suprachiasmatic nucleus, the "clock of the body". In order to maintain a healthy body and a normal function of all organs the diurnal rhythm must be intact. This means, that it is healthier to sleep during the night and be awake in the daytime, and furthermore, that it is healthier to be physically active and to eat during the light hours and to rest and sleep during the dark hours (57;81).

The extent to which the HPA-axis and the SA-system are activated in response to a stressor depends on the stressor itself and the individual (56). During foetal life the HPA-axis is programmed. This means that the function of the HPA-axis in the adult is dependent on the life of the mother during pregnancy. If the mother to a child is under strain during pregnancy the foetus will bear a risk of a malfunction of the HPA-axis later on (91).

A malfunction of the HPA-axis can be a very high cortisol secretion in the morning, or a flattened activity –pattern characterised by a small

increase in cortisol secretion in the morning and a rather high secretion of cortisol later in the day in contrast to the normal pattern showing a high increase in cortisol in the morning and a very small secretion of cortisol late in the day. The flattened cortisol secretion pattern has been found to be associated with increased risk of metabolic syndrome (glucose intolerance, insulin resistance, increased waist hip ratio, dyslipideamia, and hypertension), IHD and depression (10;91;97).

The physiological stress research has focused on the activation of the physiological systems. However, recovery from arousal is equally important, as the activation of the nerve vagus during recovery leads to an anti-inflammatory effect (25).

The gender perspective

Gender differences in psychosocial factors, stress and atherosclerosis are innumerable. Gender difference is frequently seen on the labour market and at home. Women tend to take more care of the children and the family (71) even in countries with a high degree of gender equality (26). In general, women's workloads appear to be more diffusely distributed between childcare and housework, whereas men's work effort was focussed on their paid employment. The total workload was greater for women than for men (5-10 hours more per week) (26). The job will presumably change depending on whether the employee is male or female. Males in female dominated jobs tend to become leaders.

However, even when a stressor is perceived in the same way, women and men respond differently. That is, the physiological stress response is different between genders. The stress response in women is less pronounced than in men, presumably due to the female way of coping from old times, the Tend and Befriend response (113). Also, age interacts with gender and influences the differences in stress physiology (61;62).

Finally, IHD seems to be like two different diseases in males and females, respectively (90;111). The incidence of IHD is delayed about ten to fifteen years in women compared to men. Oestrogen protects women from atherosclerosis until menopause. Among several functions, oestrogen has a vasodilating effect. After menopause, the level of cholesterol increases which combined with the decreasing level of oestrogen results in increased risk of IHD. In total there is more death from cardiovascular diseases among women than men, but in the age group below 75 year the number of deaths in men, from cardiovascular diseases, is nearly twice that of women (122). Women are more likely than men to present with unstable angina and experience more atypical symptoms than men. Delayed diagnosis and treatment is more likely to occur in women than in men (44;90;100). Furthermore, medicine known to be of value to men might not be of value to women (90).

Methods

Search strategy

A Medline search was carried out using the limit 'human'. The mesh terms: Ischemic Heart Disease or Coronary Heart Disease or Myocardial Infarction was used in combination with one of the terms listed in table 1. Only studies published in English in peer-reviewed journals were included. Also, the bibliographies of recent reviews (8;53;65;119;121), as well as libraries of the reviewers were revised to insure that all eligible papers were identified.

Inclusion criteria

The focus of the review is on prospective and to a certain degree case control studies dealing with the exposure "psychosocial factors at work" and definite IHD. Table 1 shows the search terms for the measures of exposure, i.e. psychosocial factors, and table 2 shows the search terms for the endpoint, ischemic heart disease. In short the inclusion criteria were:

1. Prospective study or case control study if exposure assessment was not self reported.
2. Definite IHD.
3. Exposure assessed as a work related psychosocial factor.

In case of duplicate reports, the paper with the more specific description of exposure and effect estimate was chosen. After the Medline search the abstract or the full papers were scrutinized by the two authors independently of each other to ensure that the selected papers fulfilled the inclusion criteria.

Papers in which the exposure was among the following issues were excluded from the review: Shift work or night work (these subjects were to be dealt with in another review for DWERF), unemployment, trauma, violence or accidents at work, social capital, social network outside the workplace, personality, coping, overcommitment, burnout, perceived stress, or life course perspective.

According to the chosen endpoint, the following designs were excluded: prognostic studies, papers which exclusively evaluated self reported symptoms or disease, and studies on total mortality.

Among the case control studies 20 studies used self reported exposure assessment and were therefore excluded (11;23;28;29;54;69;75;76;79;84;86-89;94;106;114;124;127;128).

Irrelevant exposure in prospective studies, e.g. perceived stress or job satisfaction, resulted in exclusion of 10 papers (32;33;37;73;74;80;85;93;94;108).

It is obvious that double publications had to be avoided. Due to a more specific description of the exposure the study by Hammar et al. from 1998 was preferred to the one from 1994 (30). Likewise Siegrist et al. from 1992 was preferred to the papers from 1990 and 1994 (102;103).

The Whitehall II Study has resulted in a multitude of papers dealing with psychosocial factors at work and risk factors of IHD. The endpoints used in the papers by Marmot et al. 1997, Bosma et al. 1997, and in Bosma et al.'s papers from 1998 were self reported angina pectoris, severe chest pain or self reported information of doctor-diagnosed or suspected IHD and thereby excluded (12-14;77). In the more recent papers from Whitehall II, among which Kivimäki 2005 was chosen, the endpoint assessment includes clinical records or investigations which can confirm the diagnose of IHD (49;64;66). The paper by Kivimäki et al. from 2006 was excluded as it was a methodological paper (50). Only two papers were included in the review, Ferrie et al.'s paper on job insecurity due to the exposure assessment (24) and Kivimäki et al.'s paper from 2005 due to the estimates not only on justice but also on job strain and effort reward imbalance (49).

This left 33 papers for evaluation.

Quality assessment

The quality of the study was evaluated by use of the criteria shown in table 3. The A score considered exposure assessment. Maximum score, 2, was attained if the questionnaire on exposure was published and it was stated that validation had taken place. The B score was a quality assessment of the end point used. The maximum score 2 was given if the diagnosis, IHD, was certain. It was accepted that IHD was present, if the paper stated that the diagnosis was preceded by a clinical examination, i.e. evaluation of electro cardiograms or blood samples, going through hospital records or if hospital admission registers stated that the diagnosis was IHD. On the other hand, the diagnosis was not considered certain if the participant reported to have angina pectoris (i.e. Rose questionnaire on angina pectoris), or that a doctor had diagnosed myocardial infarction or had suspected the disease. The score 1 was given if the only information on diagnosis was obtained from a register of cause of death, or if the diagnosis was cardiovascular disease. In several papers the endpoint was a combination of both non-fatal cases for which the information originated from hospital records and fatal cases for which the diagnosis was obtained from a death certificate. If the diagnosis had been evaluated, up to 30 % fatal cases was accepted resulting in the score 2. However, if the proportion of fatal cases to non fatal cases was not known or exceeded 30 %, the score 1 was given.

According to the study design score C evaluated exclusion of prevalent cases, which is obviously important. Score D considered the population. A general population was preferred as a restricted population has a risk of too small exposure variation. Score E considered the age of the population. In a rather young and healthy population the chance of finding a difference in incidence of IHD originating in psychosocial factors is larger than in an older population. Also, a population of old people who still work at a high age is probably consisted of people with different working conditions and low psychosocial load compared to the general population. Length of follow-up was evaluated in score F, a short follow-up was preferred. Finally, the analysis was evaluated by score G concerning gender separated analysis and score H concerning confounder control. Multivariate adjustments were preferred. The score 1 was given if adjustment for socio-economic status, behaviour and physiological status was included, while the maximum 2 points were given if adjustment included age, smoking, physical activity, body mass index, blood pressure, lipids, diabetes or blood glucose, and socio-economic status. The maximum score was 11 points. As the mean score was 6.6 among the prospective studies and 6.1 among the case control studies, high quality was defined as a score of 7 or more.

Description of the included papers

An overview of the included papers is shown in table 4.

In all, 26 papers reporting results from prospective studies and 7 papers reporting results from case control studies were selected. The earliest paper was Alfredsson et al. 1982 (1), a case control study from Sweden using aggregated data of hectic work as exposure; the most recent paper from 2007 using self reported data on job strain (52). Twenty of the studies originated from the Nordic countries, 7 from USA, and two from England. Germany, Belgium, and Japan were represented by one study each, and one study was an international study including data from Belgium, France, Spain, and Sweden. In general, the quality of the studies was good. The measures of exposure are, as can be seen in table 4, varied, but relate to the mentioned stress models. The dimensions unified in the Demand Control Model are the focus of 23 papers. Four papers include the dimensions from the Effort Reward Model, and only two papers include both models. The rest of the papers include the following exposures: downsizing, justice at work, traffic intensity, working related life events, job insecurity, closure of a work place, threat to employment, and working hours. These exposures can be grouped as exposures describing work load

(traffic intensity, working hours), job insecurity (downsizing, threat to employment, work related life events, closure of work place) and justice.

Seven of the prospective papers (2;4;5;19;45;92;109) and four of the papers describing case control studies (1;31;46;117) used aggregated data on exposure, all studies on the dimensions of the Demand Control Model. Of the papers using self reported data, 12 included at least one of the dimensions of the Demand Control Model (6;18;27;49-51;55;63;67;83;112;115), four the Effort Reward Model (49;51;72;104), two The Organizational Justice Model (21;49) and three studies used other kinds of exposure assessment (68;78;82).

Referring to gender, three papers on prospective data (2;6;19) and one case control study (31) reported multivariate adjusted results separately for both men and women. Three papers included only women (63;67;68). However, most papers included only men, i.e. 15 prospective (4;18;45;49;52;55;72;78;82;83;92;104;109;112;115) and five case control (1;42;46;107;117).

Results

Overview

The results are presented in table 5. Most of these are depicted in the figures 1-10. As many of the included papers report results of analyses using different exposures as the independent variable and the same endpoint, i.e. analyses of the association between respectively demands and control and IHD, the papers may appear several times in the table. The term "study" is used to nominate a result of an analysis of meaning of one exposure to IHD. In this way one paper is seen as presenting results on several studies.

While many results are presented it should be noticed that only two studies report a significantly decreased risk of IHD in connection with an undesirable psychosocial factor at work, i.e. high demands measured in the form of aggregated data (46;109).

Studies from the Nordic countries represented 73% of the studies with significant positive associations for men. In the 7 papers from USA only three documented a significant association between a psychosocial work factor and IHD (19;78;109).

In the following section results referring to the Demand Control Model, the Effort Reward Model, the Organizational Injustice Model, and to job insecurity are presented, including estimates of risk ratios from high quality studies.

Search terms as overtime work, part time work, and competition at work in combination with IHD yielded no hits.

The Demand Control Model

Demands by any definition were included in 19 papers. *Men*: Demands were evaluated in 17 studies. Eight studies demonstrated a significant positive association between demands and an increased risk of IHD, in two studies a significantly negative association was found whereas the rest of the studies presented non significant results. *Women:* Demands were evaluated in 5 studies. One study demonstrated a significant positive association between demands and an increased risk of IHD, whereas the rest of the studies presented non significant results.

Among the 6 studies using aggregated data on demands none demonstrated a significant positive association, while two studies demonstrated significant negative associations (46;109). Self reported demands were significantly and positively associated with incidence

of IHD in two high quality studies (55;83). Several definitions of "demands" alternative to the definition in the Demand Control Model-questionnaire were significantly associated with risk of IHD (1;2;27;82;107;115).

Risk estimates for demands for men and women according to quality score of the papers are depicted in figures 1 and 2, respectively.

Regarding high demands, estimates of risk ratio, RR (95 % CI), according to the results from high quality studies without serious flaws were:

Demands according to the Demand Control Model (self reported data): RR (fatal or non-fatal myocardial infarction) were: 1.43 (0.80-2.57) (18), 1.4 (1.1-1.6) (83) and 1.46 (1.08-1.97) (55). All these studies included only men. In women, RR (fatal or non-fatal CHD) was 1.4 (0.8-2.3) (63).

Demands according to other definitions (self reported data): Theorell's work load index (e.g. extra work, change of work hours, change in responsibility etc.), RR (fatal or non-fatal myocardial infarction) 1.98 (men) (115). Hectic and monotonous work, RR (myocardial infarction) 1.18 (1.02-1.35) for men age 20-64; 1.53 (1.23-1.87) for men age 20-54, and 1.64 (1.12-2.33) in women age 20-64 (2). In case control design: Working hours last month before myocardial infarction, ≥ 11 hours / day, RR (myocardial infarction) 2.94 (1.39-6.25), and increase in working hours ≥ 3 hours / day, RR 2.49 (1.24-4.99) (107).

Control or decision latitude was evaluated in 15 papers. *Men:* Control was evaluated in 13 studies of which three demonstrated significant positive associations between lack of control and an increased risk of IHD, 10 studies presented non significant results. *Women:* Control was evaluated in four studies of which two demonstrated significant positive associations between lack of control and increased risk of IHD, two studies presented non significant results. In contrast to demands aggregated data on control were significantly associated with risk of IHD in four studies (19;31;46;109), and non-significantly in two (5;117). The study by Eaker et al. demonstrated a significant association between low control and the risk of IHD in women and a non-significant association between the same factors in men. Most studies on self reported control demonstrated no association with the risk of IHD (55;63;67;112).

Risk estimates for control for men and women according to quality score of the papers are depicted in figure 3 and 4, respectively.

Regarding low control, estimates of risk ratio, RR (95 % CI), according to the results from high quality studies without serious flaws were:

Low control: OR (fatal or non-fatal AMI) 1.2 (0.8-2.0) for men (aggregated data) (117). RR (fatal or non-fatal AMI) 0.83 (0.48-1.43) for men (self reported data) (18). RR (fatal or non-fatal AMI) 1.0 (0.9-1.2) for men (83). RR (fatal or non-fatal CHD) 0.7 (0.4-1.2) for women (63).

Job strain was evaluated in 13 papers. *Men:* Job strain was evaluated in 11 studies of which three revealed a significant positive association between job strain and an increased risk of IHD (49;51;83). The term of iso-strain (strain and no support) was significantly and positively associated with the risk of IHD in three studies, with the use of aggregated data (31;45) and self reported data (18). *Women*: Job strain was evaluated in four studies all of which found non significant associations between job strain and increased risk of IHD. Furthermore, one study demonstrated a significantly increased risk of IHD in relation to iso-strain (31).

Risk estimates for job strain for men and women according to quality score of the papers are depicted in figure 5 and 6, respectively.

Regarding job strain, estimates of risk ratio, RR (95 % CI), according to the results from high quality studies without serious flaws were:

Job strain (self reported data): RR (fatal or non-fatal AMI) 1.26 (0.66-2.41) for men (18). RR (fatal or non-fatal CHD) 1.44 (1.01-2.05) for men age 35-55 (49). RR (fatal or non-fatal CHD) 2.4 (1.0-5.7) for men (83). RR (fatal or non-fatal AMI) 1.17 (0.67-2.06) for men and 1.29 (0.44-3.85) for women (6). RR (fatal or non-fatal CVD) 1.70 (0.96-3.01) for men aged 19-55 years (52). RR (fatal or non-fatal CHD) 1.0 (0.5-1.9) for women (63).
Iso-strain (self reported data): RR (fatal or non-fatal CHD) 1.92 (1.05-3.54) for men (18).

Social support

Lack of social support was examined in 7 papers. *Men:* Five studies evaluated the effect of social support, three found a significantly increased risk of IHD if the participants experienced lack of social support (18;31;82), while two studies reported non significant results. *Women:* Four studies evaluated the effect of social support, one found a significantly increased risk of IHD if the participants experienced lack of social support (6), while three studies reported non significant results. The study by André-Petersson et al. demonstrated an association for women but not for men.
Risk estimates for lack of social support for men and women according to quality score of the papers are depicted in figure 7 and 8, respectively.
Regarding lack of social support, estimates of risk ratio, RR (95 % CI), according to the results from high quality studies without serious flaws were:
Lack of social support (self reported data): RR (fatal or non-fatal CHD) 2.36 (1.38-4.01) for men age 35-59 (18). RR (myocardial infarction) 1.00 (0.69-1.45) for men and RR (myocardial infarction) 2.72 (1.42-5.22) for women (6). RR (fatal or non-fatal CHD) 1.2 (0.7-2.1) for women (63).

The Effort Reward Model

The Effort Reward Model was evaluated in only four papers, none including women. *Men:* The study by Siegrist et al. (1992) considered status inconsistency and intrinsic effort (104). The coexistence of high effort and low reward was significantly and positively associated with an increased risk of IHD in one study using proxy measures for effort and reward (51). Lynch et al. (1997) demonstrated a non-significant positive association between a measure of effort reward imbalance in a life course perspective and the risk of IHD (72), while one study using proxy measures from Whitehall II showed no association (49).
Risk estimates for of the Effort Reward Model according to quality score of the papers are depicted in figure 9, men only. All studies were connected with serious flaws.

The Organizational Injustice Model

Feeling of justice was significantly negatively associated with the risk of IHD in two studies on men (21;49). Results are not depicted.
Regarding organizational injustice, estimates of risk ratio, RR (95 % CI), according to the results from high quality studies without serious flaws were:
Injustice (self reported data): RR (fatal or non-fatal CHD) 1.45 (1.02-2.04) for men age 35-55 (49).

Job insecurity

Five papers evaluated problems referring to *job insecurity* (24;42;68;78;120). Two studies showed significant positive associations (78;120), both studies of men.

Risk estimates for job insecurity according to the quality score of the papers are depicted in figure 10, men only. The association between risk estimate and quality was tested by the means of one-way ANOVA, showing no association (p 0.07)

Regarding job insecurity, estimates of risk ratio, RR (95 % CI), according to the results from high quality studies without serious flaws were:

Job insecurity (self reported data): New job, demotion, business failure etc., more than 2 events: RR (fatal CHD) 1.35 (1.03-1.76) for men (78). RR (diagnosed myocardial ischemia) 1.40 (0.9-2.2) for men and 1.69 (0.8-3.3) for women (24).

Discussion

The present review was carried out at the request of the Danish National Board of Industrial Injuries and the Industrial Injuries Committee as clarification of the potential relationships between work related stressors and the development of IHD was requested. The review was carried out as a systematic review and included 33 papers presenting 52 studies including men, 17 studies including women and 7 studies including both genders. Of the 69 studies including only one gender, 27 showed a significant positive association between an undesirable psychosocial factor at work and an increased risk of IHD. Only two studies showed significant negative associations between an undesirable psychosocial factor at work and an increased risk of IHD. The review demonstrates a large variation in measurement of exposure and in study design.

Several reviews of the evidence of associations between psychosocial factors and disease have been published during the recent years. The review by Belkic et al. (8) evaluated the evidence of an association between job strain and cardiovascular disease, Tsutsumi et al. (119) examined the validity of the Effort Reward Model, and van Vegchel et al. (121) evaluated evidence of the concepts of the Effort Reward Model. The two latter reviews were carried out to discuss methodology. The reviews by Hemmingway et al. (36), and by Kuper et al. (65) come from the same group and have a broader focus than the one presented here, i.e. the exposure "psychosocial factors" included personality, depression and anxiety. This review concluded that 10 out of 13 included etiologic papers on psychosocial work characteristics reported a moderate or strong association with an increased risk of IHD.

Finally, Kivimäki et al. have recently published a meta-analysis of the evidence considering the Demand Control Model, the Effort Reward Model and the Organizational Injustice Model (53). The focus of the review was to estimate the relative risk of coronary heart disease associated with work stress, as indicated by these models. Compared with the present review the review by Kivimäki et al. is more selective and includes a meta-analysis. This meta-analysis reported the following multivariate adjusted summary estimates of risk ratios for IHD across studies regardless of gender: Job strain 1.16 (95 % CI: 0.94-1.43), effort reward imbalance 2.05 (95 % CI: 0.97-4.32), and organizational injustice 1.47 (95 % CI: 1.12-1.95). It was chosen not to combine the results of the present review in a new meta-analysis for several reasons. The exposures were more varied than in Kivimäki et al.'s review and several of the exposures were included in only one or few studies. Also, as a methodological consideration the studies were hard to compare, especially culturally, and according to gender and age.

Generally, the papers included in the review were of good quality as demonstrated by the quality score constructed for the purpose. Construction of a quality score is difficult and is associated with the danger of automatic rating, and as seen in table 4 some papers reached a rather high quality score despite serious flaws. The publication of such papers may be a result of publication bias as journals may have been preoccupied in publishing statistically significant negative or positive results.

The review revealed many non significant results. Studies like Reed 1989 (92), Alterman 1994 (4), Eaker 2004 (19), Andersen 2004 (5), Kivimäki 2002 (51), and Kornitzer 2006 (55) have such serious flaws, that the results can not be taken as evidence of no association. The prevailing problem is not confounding but rather selection and problems related to exposure assessment (see below). Inclusion of old

participants includes a risk of healthy worker effect and dilutes exposure assessment in several manners: people who work in their old age presumably work in professions in which they are not exposed to psychosocial loads, or they are especially dedicated to their work. On the other hand, old age in it self constitutes a significant risk factor for IHD. The population studied has to vary sufficiently in exposure, i.e. inclusion of only one occupational group may be a problem. At the same time, the participants have to belong to the same culture as the meaning of stressors has to be comparable.

Precision of the measure of exposure
The variation in measurement of exposure mirrors the fact that psychosocial factors acting as stressors in daily work life are multifarious. The review includes two main stress models but also a large number of other exposures. The exposures used originate in various working environments and various cultures. Other exposure measures may coexist. For instance, bullying at the work place (54) may be of importance to health. The use of theoretically based stress models may be a strength, but at the same time it is important that use of the models do not stand in the way of exploration of other stressors. During the last 10-20 years the labour market has changed and fewer are employed in production, i.e. industry and farming, while more are employed in education, administration, health care and knowledge production. This means that the stress models usable in the 80's might have to be further developed to be used today. In the 70's when the Demand Control Model was developed job strain showed stronger association with disease than demands and control separately. However, the level of decision authority has generally increased, though it is still different between groups. On the other hand, skill discretion has increased in society during the 80's. This increased educational level in the working population as well as the increased demands on the labour market has to be followed by adjustments of the exposure measures. What is seen empirically in the form of no association of job strain to disease therefore may originate in changes in society. For this reason the development of COPSOQ (Copenhagen psychosocial questionnaire) (60) is an important continued process, which may in fact never end. As a result of this process evidence of change in the psychosocial work environment is emerging. In today's labour market, social and emotional demands rather than quantitative are of significance and justice, support from leaders, trust and social capital, play significant roles.
An important problem is whether researchers are measuring the stressor they want to. Steenland et al. argues in relation to the finding of a lack of an association between demands and risk of IHD that they might not have measured what they intended to (109). Different occupations meet different kinds of psychological demands, and occupations held by people in higher status layers tend to be related to higher psychological demands. (77). This methodological challenge is discussed by Kristensen et al. who ask the researchers in the field to make a distinction between intensification (faster work pace, blue-collar workers) and extensification (longer working hours, white collar workers) of demands (59). The Demand Control Model is the most prominent stress model but the dimensions of the model have to be further elucidated (58;59).
To make a precise description of the exposure, which can be compared between studies several methodological considerations have to be taken into account. Use of the same stress model and questionnaire are obvious necessities, but it is also a precondition that the studies are comparable with regard to culture. Cultural differences may be the reason for the many positive Nordic studies in contrast to the non significant / negative studies from USA. Comparing results between cultures reveals information about differences and similarities between the cultures, but does not determine whether a certain psychosocial job condition involves an increased risk of disease or not. Seen

in this perspective, the studies from the Nordic countries presented evidence of an increased risk of IHD when exposed to hectic work, high workload or demands, and low support especially for men.

However, if one concludes that a certain psychosocial factor at work implies an increased risk of disease in a specific culture, this psychosocial factor has to be clearly defined and the relevant time of exposure to this factor has to be stated. As an example, one might hypothesize, that high psychological demands are associated with an increased risk of IHD. A study of this would require a clear and unequivocal definition of "demands", a culture in which the defined type of demands is unwanted, and a population in which a sufficient exposure contrast is present. Furthermore, a precondition for developing IHD on the basis of atherosclerosis is that the exposure is prolonged, i.e. years. So, if the "demands" are not clearly defined, if "demands" are a preferred condition, no exposure contrasts are present, or the exposure is of a short duration a significant association is not to be expected. Examples of studies representing these methodological problems are Alfredsson et al. (1985) (2), Reed et al. (1989) (92), and Lee et al. (2002) (67). The first study included nearly 1 million citizens (high exposure contrast), and the exposure was clearly defined ("hectic work" in a culturally homogenous population). The follow up period was only one year. This is rather short for developing atherosclerotic disease but sufficient as the huge number of participants includes people who vary to a large extent concerning predisposition and stages of atherosclerosis. On the other hand, Reed et al. used aggregated data obtained in USA in a population of Japanese origin in Honolulu. As few as 359 men were followed for 18 years. The data on exposure have presumably not fit the culture of the population, and the follow up was far too long (the exposure may have changed several times). In the study by Lee et al. (2002), the included population consisted of female registered nurses in USA. As the Demand Control Model describes demands and control among assembly line workers rather than among nurses this model may not be useful to understand the demands perceived by nurses in USA. A questionnaire on hiding feelings, having the responsibility for other people's lives, or questions on the problems originating from being both a mother and a nurse (double exposure (70;118)) might have been more relevant.

Most of the studies use measurement of exposure solely at baseline. In the case of a large population study this is the most feasible. However, as in the study by Reed et al. (1989), exposure may have changed during a long follow up. A negative change can be important as demonstrated by Theorell et al. (1998) (117). For workers experiencing the same level of work stress during the follow up period, exposure measured at one point in time may be sufficient (50). This may be evaluated by stratification according to whether or not the participants have the same job during the follow up period as it is done in Kivimäki et al. 2002 (51), where a stronger association was seen among those whose occupational group was unchanged. A significant change in exposure occurs when the participant retires. Therefore, follow up beyond the age at which most people in the specific population retire is inexpedient.

Use of aggregated data instead of self reported data may provide the possibility of including a large population at the expense of specificity of exposure. The studies using aggregated data found no associations between demands and IHD, while control and IHD more consistently was associated. This may point to a distinction between the two dimensions: The items included in the dimension demands cover the feeling of having enough time to do the job etc. This is clearly an individual feeling. The control dimension includes items about who tells you what to do at work and how to do it, i.e. structural factors at work. Originally, the Demand Control Model did not state that demands per se are stressful if coupled with sufficient control (48). The results of the studies using aggregated data are in line with this. The fact that self reported demands are associated with an increased risk of IHD may express that people who state that they experience high demands do not feel in control. Self reported control seems not to be associated with IHD. According to the discussion on the cultural aspects of

stress, this may be caused by the fact that the degree of control over ones work situation is very high in the Nordic countries, i.e. exposure contrast is low.

Job strain is significantly associated with risk of IHD in several studies. An interaction between demands and control was found in only one study (83), and was not demonstrated others (6;18;55). Only positive results are presented for the iso-strain theory (18;31;45). This may be due to a strong effect of support (18;31).

The Effort Reward Model and the Organizational Injustice Model are examples of new theories that have to be evaluated by more studies before it is possible to determine the effect of the included dimensions. This also applies to job insecurity. The results till now point to a significance of all three, but standard questionnaires have not been used in study designs included in this review.

Precision of the endpoints

The use of IHD as the end point may be discussed. One of the inclusion criteria was "definite coronary heart disease". The endpoints used were angina pectoris (objectively assessed), acute myocardial infarction, cardiovascular or coronary death, among others sudden death. These endpoints were chosen as they are "hard" endpoints. Self reported disease may be questioned as symptoms tend to be felt more strongly when one has difficulties at the job, than otherwise. Therefore, results for self reported angina pectoris were not included in this review.

Bias in the form of misclassification might occur due to the difference in incidence of the endpoints of atherosclerosis in men and women. It is believed that acute myocardial infarction is a "hard" endpoint that can be used with a large precision as the ultimate state of atherosclerosis. However, the assumption for using it is that all cases of severe atherosclerosis result in angina pectoris or myocardial infarctions, which are objectively assessed. However, among patients < 65 years significantly more women than men present with unstable angina, and significantly fewer women than men with ST-elevation (95). In patients with non-ST-elevation coronary syndromes biomarkers are used to rule out the diagnosis. However, troponin which is the today's choice of biomarker is less frequently elevated in women than in men. The reason for this may be as simple as the choice of cut-off value, which has been chosen on the basis of a predominantly male population (22). "Silent MI", i.e. myocardial infarction without symptoms, or MI's not diagnosed may thus result in misclassification since coronary heart disease in women generally is more frequently undiagnosed than in men (22;44;90;100;111). Some studies include women in the collection of data but exclude women in the analysis due to few incident cases (55;83). It is important to note that it is not necessarily evidence of good coronary health in women.

Another kind of misclassification may occur in countries in which health care is not free, like in USA. IHD may not be found if the individual experiencing symptoms does not have the financial background for hospitalisation or treatment. At the same time the more prosperous may be examined more carefully. This may lead to misclassification, i.e. overrepresentation of the high status layer and under representation of the low status layer, which again may lead to a null/negative finding.

Sudden death is included as endpoint in some studies. The reason for sudden death may not only be myocardial infarction. Among other reasons, arrhythmia may very well be caused by the same conditions as IHD on the basis of atherosclerosis; however the time from exposure to endpoint may be considerably shorter (35).

In the early days of research of psychosocial factors and IHD, the pathogenic mechanism of atherosclerosis was believed to be first of all a question of high levels of cholesterol and blood pressure. Now, atherosclerosis is known to be an inflammatory disease. This means that

lack of associations between psychosocial factors and conventional coronary risk factors are not evidence of lack of association between psychosocial factors and atherosclerosis. This is increasingly demonstrated in research using atherosclerosis as the endpoint. As the increased risk of IHD originates in an increased atherosclerotic development, it might be a better alternative to use the size of the vessel wall as the endpoint. Using the intima media thickness of the carotid, IMT, an 11 % increased risk of IHD has been demonstrated each 0.1 mm increase in IMT (99). A follow up study from 1998 demonstrated that a progression rate of IMT of 0.03 mm / year was associated with an significantly increased risk of IHD of 2.2 (40). The demonstration of an association between work-related stressors and progression in IMT is also evidence for an association between work-related stressors and an increased risk of IHD. An association between psychosocial factors and increased IMT has been demonstrated by Hintsanen et al. (2005). In this study job strain 9-10 years before measuring IMT was associated with increased IMT in 478 men, but not in 542 women (both groups: mean age 32) (39). However, in another study IMT progression was found to be associated with the Effort Reward Model, and with private factors but not with the Demand Control Model (both genders) (20). Coronary luminal diameter change over 3 years has been shown to be increased in women with stress derived from either work or family compared to those experiencing no stress (125).

Length of exposure
The reviewed literature is not sufficient to determine any dose response relationship between exposure to a psychosocial factor at work and incidence of IHD. One study, Johnson 96, aims at establishing a dose response relationship between the dimensions of the Demand Control Model and cardiovascular mortality. The study demonstrates an increasing risk till 10-15 years of exposure but a decreasing risk hereafter (46). This is to be expected, as the exposure has to be present a considerable time until it can be demonstrated that the atherosclerotic condition progresses with higher speed than otherwise. Those who are diseased leave the work place, and the people still working after 15 or 20 years are believed to have a genetically constitution not prone to develop IHD.
With regard to the length of exposure the age of the population included in the study is important. As argued before a long follow up is accompanied with a risk of change in exposure, especially the change due to retirement. The effect of work stress seems most pronounced in the younger age groups, presumably because the effect of other risk factors take over during age, or the stressors are perceived as more uncontrollable by younger individuals (31;52).

Analytical strategy
In this review, it was decided to present risk estimates with multivariate adjustments. This may be an over-adjustment. However, the multivariate adjustments did not change the results much. On the other hand, it is important to realise that among the most frequent factors predisposing to IHD, several factors may in fact be caused by the physiological stress response. Psychosocial factors might be associated to hypertension in itself (110;126), as well as choice of diet and development of obesity (3;7) and smoking (43). The point is, that if all were healthy and did not smoke, have hypertension or hypercholesterolemia then the significance of psychosocial factors might be huge.
As the stress response as well as the perception of stressors is different between the two genders, it is of paramount importance that researchers evaluate stressors and data accordingly, i.e. separate the genders in the analyses. In the study by Alfredsson et al. (1985) hectic and monotonous work was associated with an increased risk of IHD in both genders, i.e. RR 1.18 for men and 1.64 for women (2). In Eaker et al.'s study (2004) low decision latitude was associated with an increased risk for women but not for men, i.e. RR 0.99 for men and 1.98

for women (19). André-Petersson et al. (2007) found a significantly increased risk of IHD for women with low social support but not for men (6). However, the sparse literature is not consistent, as Hammar et al. (1998) found risk estimates of similar sizes for the two genders (31).

Influence of night work
Night work has to be minimised as disturbance of the diurnal rhythm of physiology in the long run may harm (57;81). A healthy life is dependent on sufficient recovery and sleep. During the last century mean duration of sleep has decreased. In severe chronic stress the HPA-axis is disturbed and a flattened pattern of secretion including relatively high levels of cortisol throughout the 24 hours is seen. As this flattened pattern is found to be associated with abdominal obesity, insulin resistance and metabolic syndrome, the incidence of which is increasing, this is alarming (16;96;97).

Prognosis
The review did not include studies which discussed the significance of work-related psychosocial factors for the prognosis of IHD. The topic has only been sparsely examined. Theorell et al. found that male coronary patients below age 45 who returned to work and died during the following 5 years had more psychologically demanding jobs than those who survived (116). Hoffmann et al. followed 222 men aged 30 to 60 years included in the study within 7 weeks after their first myocardial infarction. A poor medical outcome defined as death, re-infarction, severe symptoms or poor exercise capacity, was among other factors associated with high workload (41). Data from The Stockholm Female Coronary Risk Study demonstrated a worsened prognosis for women's coronary heart disease as the risk of recurrent heart disease was 5.7 (95 % CI 1.3 – 24.3) for women experiencing both marital and work related stress compared to the risk in women with no stressors (87).

Evaluation of excess risk in individuals contrary to groups
The above mentioned results, i.e. the relative risk ratios for IHD in connection with various exposures, express associations in a specific population. It is difficult to extrapolate these results to be used in evaluation of individual risk estimation. The first challenge is to describe and quantify the exposure. The measures of exposure used in the literature are not suited to be used in the clinical or the juridical setting. The next problem to be discussed is the concept of risk and risk factors. The individual risk for developing IHD depends on many factors, among others genetics, foetal environment, and psychosocial environment during childhood and adolescence in combination with risk factors in adulthood, i.e. smoking, diet, physical activity and psychosocial factors at work. An individual with no known conventional coronary risk factors (low blood pressure, normal values of BMI, cholesterol etc) is at a low absolute risk for IHD. An increase in risk as indicated in the literature on psychosocial factors at work of approximately 2, doubles the risk. On the other hand, if an individual has several risk factors, i.e. smoking, high cholesterol, high blood pressure etc, the extra increase in risk due to psychosocial factors at work is of less significance, as these risk factors are far more important. As an example a smoking male, aged 50 with se-cholesterol 6 mmol/l, and systolic blood pressure 160 mmHg has a 7 times increase in the10-year relative risk of death due to cardio-vascular disease (17).

Workers compensation

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IHD is such a multi factorial disease, that it is difficult to discus workers compensation claims. In cases known to be in good health before engaging in a job condition including low degree of control, high demands and effort and / or low degree of support and reward, it might be relevant to compensate a worker for the development of IHD. The exposures which might qualify for compensation would have to be discussed. As atherosclerosis and risk factors for metabolic syndrome and IHD are very common and possible to influence, prevention should be given high priority. Psychological aspects of the working environment have to be discussed and improved.

Future research
In future research more precise exposure measures are needed. Most studies until now have had no evaluation of the duration or the intensity of a given exposure. Such evaluation cannot be obtained by means of postal or internet based questionnaires alone. In addition interviews in depth although standardised can be applied in order to gather more information on the quality and quantity of stressors. Using information from other sources might be a way to validate the exposure. Even though in the case of emotional strain other sources might be lacking.
All this can be obtained by using a nested case control design. Cases have to be incident cases well characterised diagnostically. To gather a sufficient number of cases a case control design is the only feasible way. The cases could be derived from a cohort study with exposure assessment several times prior to the follow up as done in the Danish National Cohort of Working Environment in order to estimate the duration of exposure and the relation between exposure and onset of IHD. Confounding factors must include private stressors as well as the commonly used co-variables obtained in many of the referred studies. The analyses should be stratified for gender.
As the quality regarding design of several of the referred studies is high, adjustments, as described above, of measures applied in these studies might to some extent improve their validity.
The reviewed literature included very few data on women, and it is therefore recommended that future studies include both genders.

Conclusion

The literature review revealed the following about different psychosocial exposures at work:

Demands:

Men: Demands by any definition were evaluated in 16 studies, 7 demonstrated a significant positive association, two a significant negative association and 7 non significant results. *Women:* Demands by any definition were evaluated in 5 studies; one demonstrated a significant positive association, whereas the rest of the studies presented non significant results. *Level of relative risk was 1.2-2.9 for males.*

Due to serious flaws in the non significant studies evidence points to self-reported demands as a significant predictor of IHD for men. For women, data were too few and inconsistent to draw any conclusion.

Control or decision latitude

Men: Control was evaluated in 13 studies, three using aggregated data, demonstrating significant positive associations, and 10 showing non significant results. *Women:* Control was evaluated in four studies, two demonstrated significant positive associations, and two studies presented non significant results. *Level of relative risk was 1.4-1.8 for males.*

Due to serious flaws in the non significant studies, it was concluded that there is only limited evidence for lack of control (aggregated data) as a significant predictor of IHD for men. Data for women were too few to draw any conclusion.

Job strain

Men: Job strain were evaluated in 15 studies, four revealed a significant positive association between job strain and increased risk of IHD. The term of iso-strain (strain and no support) was significantly and positively associated with risk of IHD in three studies. *Women*: Job strain was evaluated in four studies of which all found non significant associations. However, one study demonstrated a significantly increased risk of IHD in the case of iso-strain. *Level of relative risk was 1.4-2.4 for males.*

It was concluded that there is only limited evidence for job strain as a predictor for IHD, while iso-strain were concluded to be significant predictor of IHD for men. Data for women were too few and inconsistent to draw any conclusion.

Lack of social support

Men: Of 5 studies evaluated meaning of social support, three found a significantly increased risk of IHD if the participants experienced lack of social support, while two studies reported non significant results. *Women:* Four studies evaluated the meaning of social support, one found a significantly increased risk, while three studies reported non significant results. *Level of relative risk was 1.3-2.7 for both genders.*

The data show limited evidence of an association between lack of social support and incidence of IHD for both men and women.

Effort Reward imbalance and *Feeling of justice*

There are too few data to draw any conclusion.

Job insecurity

Men: Of four studies on job insecurity, two (one including both genders) showed a significant positive association and two non significant results. *Women:* One non significant study, as well as the one study including both men and women. *Level of relative risk was 1.4 for males.*

The data show limited evidence of an association between job insecurity and the incidence of IHD for men. Data were too few to draw any conclusion regarding women.

The following was concluded:

- It is biological plausible and supported by the literature that psychosocial factors at work are risk factors for IHD.

- In the Nordic countries, evidence is sufficient to state that high demands, and iso-strain, are independent risk factors for IHD for men. Furthermore, there is limited evidence of an association between the following factors: Lack of control, job strain, lack of social support and job insecurity, and the risk of IHD for men. Regarding the women, there is limited evidence of an association between lack of social support and the risk of IHD.

- In order to develop IHD on the basis of atherosclerosis an exposure of 5-10 years is believed to be sufficient. However, sudden death on the basis of arrhythmia is possible after a shorter duration of the work load. Men and women are at different risks as definite IHD is seen about ten years later in women than in men. Also, the way IHD expresses itself varies between the two genders.

- As the significance of any stressor depends on the perceiving individual due to genetic and environmental predispositions it is considered to be extremely difficult to make an exposure assessment in individuals for the purpose of workers compensation.

- According to the aim of this review future research is suggested to focus on

  o Refinement of exposure measures, including evaluation of intensity and duration

  o Changes in psychosocial work environment in Denmark

  o Conditions in women, and gender differences

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Table 1. Measures of exposure used as search terms, i.e. included psychosocial factors.

Inclusion	Work
	Working hours, overtime work, part time work.
	Downsizing, threats to employment security, job insecurity, loss of employment
	Demand control model, demands, control, social support, strain, iso-strain
	Effort reward model, effort, reward, effort reward imbalance, ERI
	Organizational justice, injustice
	Competition at work
	Bullying at work
	Salary, wages, esteem, status inconsistency

Table 2. Search terms describing ischemic heart disease, i.e. included endpoints.

Inclusion	Ischemic heart disease, coronary heart disease, myocardial ischemia, myocardial infarction
	Diagnosed fatal or non fatal ischemic heart disease (clinical examination, clinical / hospital records, register based hospitalization or mortality)

Table 3. Quality criteria used to assess quality of the papers.

	Issue evaluated	Scoring	Comment
A	Exposure assessment valid and reproducible?	0 (exposure assessed by questionnaires not published) 1 (exposure assessed by published questionnaires) 2 (exposure assessed by published and validated questionnaires)	To reproduce and to interpret the results, it is important to know the method used. If the paper did not permit reproduction of exposure assessment, "0" was scored. If the items or questionnaire had been published (table in paper or the like) "1" was scored. Also, aggregated data yielded a score of 1. Maximum score was achieved if it was stated that validation of the questionnaire or method had taken place and only if the data were self reported.
B	End point assessment?	0 (endpoint assessment not described) 1 (cause of death from register) 2 (endpoint assessment from clinical examination, hospital records, register of cause of admission to hospital)	If the paper did not state from which source the diagnosis originated score "0" was given. "1" was scored by papers using information from death registers, because information can be biased and may be not clinically based. Score 2 was given in the case of a positive diagnosis. If the endpoint was mixed, exploration of cause of death and max 30% deaths also scored 2.
C	Exclusion of prevalent cases	0 (no exclusion or not described) 1 (exclusion of prevalent cases)	Prevalent cases of disease had to be excluded before analysis.
D	Population	0 (population restricted to occupation or firm) 1 (general population)	In a restricted population there is a risk of too small exposure variation and of selection bias.
E	Age of population	0 (mean age >55 years, upper range above 65) 1 (mean age ≤ 55 years, upper range below 65)	The years around retirement are problematic, because subjects experiencing psychosocial load may tend to retire prematurely more often whereas subjects with no psychosocial load may even tend to continue working after the age of regular retirement more often than other people.
F	Follow-up period	0 (> 10 years) 1 (≤ 10 years)	Age is a strong risk factor for IHD. As a very long follow-up period is naturally accompanied by a corresponding increase in the age of the participants, a very long follow-up has to be avoided. Exposure may change during a long follow up period.
G	Gender separated	0 (studies using gender as a covariate) 1 (studies including only one gender or using gender separated analyses)	According to the different pathophysiology of atherosclerosis and different socio-cultural circumstances in the two genders, analysis has to be carried out separately for men and women, respectively.
H	Confounder adjustment (age, socio-economic status, smoking, physical activity, BMI, lipids, diabetes, blood pressure)	0 (only adjustment for confounders in one or two groups) 1 (adjustment for confounders describing socio economic status, behavior and physiological status) 2 (adjustment for all mentioned confounders)	Confounders can be grouped in three groups: socio economic variables, behavioral variables and physiological variables. Adjustment for age is found to be fundamental. Beyond age, adjustment for variables from all three groups was preferred. Maximum score was only achieved if adjustment for the mentioned variables had taken place.

Table 4. Characteristics of papers included in the review. Risk estimates are fully adjusted with the mentioned confounders, if nothing else is stated. Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease.

Aggregated exposure								
First author / year	Exposures (quality score A)	Outcome (quality score B)	Population (quality score C, D, E)	Cases / Follow-up (quality score F)	Risk estimate, men or *both genders* (95% confidence -interval) (quality score G)	Risk estimate, women (95% confidence -interval)	Confounders (quality score H)	Quality score (summed of A-H, max 11)
The Demand Control Model								
Alfredsson 1985 (2)	Early job strain: hectic and monotonous work, hectic work with little opportunity to learn new things, hectic and little influence over work tempo (1)	Myocardial infarction, hospitalization data (2)	Sweden, 958 096 citizens (20-64 years) (0, 1, 1)	1201 / 1 year (1)	Age 20-64 years: Standardized morbidity ratio: Hectic and monotonous work: 1.18 (1.02-1.35). Hectic work with little opportunity to learn new things: 1.28 (1.09-1.48). Age 20-54 years: Hectic and monotonous work: 1.53 (1.23-1.87). Hectic work with little opportunity to learn new things: 1.57 (1.25-1.94). (1)	Age 20-64 years: Standardized morbidity ratio: Hectic and monotonous work: 1.64 (1.12-2.33).	Univariate analysis (0)	7
	Strengths: Inclusion of nearly 1 million citizens, short follow-up. Flaws: Only univariate adjustments, different kinds of exposure are included in the measures used, i.e. hectic and monotonous work. Comments: The exposure is measured in a form which hides the meaning of the single terms included. As development of IHD takes place over several years the short follow-up period may be a problem. Notice increased risk in the younger stratus.							
Reed 1989 (92)	Demands, decision latitude, strain (1)	Non fatal and fatal CHD, register-based and clinical records. (2)	USA, Honolulu, 4 737 men of Japanese origin (45-65 years) (1, 1, 0)	359 / 18 years (0)	Age-adjusted relative incidence for high / low demands 0.86, high / low decision latitude 1, strain 0.94 (calculated by author). (1)		Age, smoking, blood pressure, cholesterol, glucose, exercise (0)	6

	Strengths: A rather large cohort, use of clinical records to insure the diagnoses are correct. Flaws: Very long follow-up period. Exposure estimated on the basis of data from a white population. Comments: As the included population is of Japanese origin there is a risk of misclassification. The long follow-up increases the risk of change in exposure.							
Johnson 1989 (45)	Iso-strain (low social support, high demands, low control) (1)	Fatal CVD, register-based (1)	Sweden, 7 219 employed men (1, 1, 0)	193 / 9 years (1)	Iso-strain RR: All: 1.92 (1.15-3.21) Blue-collar: 2.58 (1.06-6.28) White-collar: 1.31 (0.58-2.98) (1)		Age, stratification on social status (0)	6
	Strengths: Large population, relatively short follow-up. Flaws: Use of cardiovascular death as the endpoint, as this includes coronary deaths, death due to stroke etc. Comments: The data are only analysed according to iso-strain and mostly in figures. This is a problem when one wants to compare results.							
Alterman 1994 (4)	Decision latitude, demand, strain (1)	CHD (clinical data) (2)	USA, 1 683 men (38-56 years) (1, 0, 1)	115 CHD / 10 years (1)	Low decision latitude 0.87 (0.57-1.31), high demands 1.07 (0.54-2.12), job strain 1.5 (0.85-2.80) (1)		age, smoking, blood pressure, cholesterol, alcohol, family history of CVD, education (1)	8
	Strengths: Use of clinical data to insure reliable diagnosis. Relatively short follow-up. Flaws: A rather large proportion of the population had to be excluded as job titles could not be linked to exposure data (338 of 2107 men). Comments: The non-significant result may originate in a lack of variation in exposure.							
Steenland 1997 (109)	Control, demands, strain (1)	Incident CHD, hospital admission data and death certificates (23%) (1)	USA, 3 575 men (25-74 years) (1, 1, 0)	519 / 12-16 years (0)	Low control 1.41 (1.07-1.85), high demands 0.81 (0.61-1.09), high demands /low control 1.08 (0.81-1.49). Blue-collar: high demands / low control 1.14 (0.80-1.63) White-collar: high demands/ low control 1.05 (0.63-1.77) (1)		Age, blood pressure, education, body mass index, cholesterol, smoking, self-reported diabetes (1)	7
	Strengths: Large cohort, many incident cases. Flaws: Long follow-up, inclusion of old participants. Comments: Though the participants were all working, the population includes very old men in which the age in it self comprises a large increase in risk.							

Andersen 2004 (5)	Decision authority, skill discretion	Register based fatal (35%) and non fatal MI	Denmark, 16 216 (44 % women) (20-75 years), data from several population-studies	610 male, 121 female cases / different follow-up	*Low decision authority and low SES 1.47 (0.93-2.31), low skill discretion and low SES 1.07 (0.72-1.60)*		Cohort of investigation, age, sex, cohabitation, smoking, alcohol, exercise, BMI, blood pressure, cholesterol, socio-economic status	4
	(1)	(1)	(0, 1, 0)	(0)	*(0)*		(1)	
	Strengths: A very large population including women. Flaws: Very old participants, use of gender as confounder. Comments: The combination of data from several cohorts carries a risk of uneven exposure-assessment and it is difficult to know what the study adds.							
Eaker 2004 (19)	Decision latitude, demands, strain	CHD morbidity	USA, 3 039 (1711 men and 1328 women) (18-77 years)	149 incident CHD / 10 years	Low decision latitude 0.99 (0.98-1.02), high demands 1.00 (0.97-1.04). High strain 1.18 (0.69-2.0) (calculated by author).	Low decision latitude 1.98 (1.26-3.10), high demands 0.99 (0.93-1.06). High strain 0.61 (0.21- 1.75) (calculated by author).	Blood pressure, body mass index, cigarette smoking, diabetes, total cholesterol / HDL-cholesterol	8
	(1)	(2)	(1, 1,0)	(1)	(1)		(1)	
	Strengths: A large population including women, rather short follow-up. Flaws: Inclusion of very old people, use of aggregated data from 1980 to estimate exposure in 1984-1987. Comments: It is a problem to include participants who are old. Their exposures have changed during their lifetime and age in it self constitutes a high risk.							
Downsizing								
Vahtera 2004 (120)	Downsizing	CHD mortality, register based	Finland, 5 909 men and 16 521 women (19-62 years)	79 CHD death / 7.5 years	*2.00 (1.02-3.92)*		Age, sex, socio economic status and type of employment	3
	(0)	(1)	(0, 1, 0)	(1)	*(0)*		(0)	

	Strengths: Large cohort, short follow-up. Flaws: Few cases, gender used as confounder. Comments: The authors used a rough measure of exposure, i.e. % reduction in different occupational groups.							

Self reported exposure

First author / year (quality score A)	Exposures (quality score A)	Outcome (quality score B)	Population (quality score C, D, E)	Cases / Follow-up (quality score F)	Risk estimate, men or *both gender* (95% confidence -interval) (quality score G)	Risk estimate, women (95% confidence -interval)	Confounders (quality score H)	Quality score (sum of A-H, max 11)

The Demand Control Model

First author / year	Exposures	Outcome	Population	Cases / Follow-up	Risk estimate, men or both gender	Risk estimate, women	Confounders	Quality score
Theorell 1977 (115)	Workload index (e.g. extra job, change of work hours, change in responsibility, problems with superiors) (1)	Fatal or non-fatal myocardial infarction, hospital records (2)	Sweden, 5 187 building construction workers (all males, 41-61 years) (1, 0, 1)	51 / 2 years (1)	RR, work load: 1.98 (p < 0.01) (1)		Age (0)	7
	Strengths: A large sample and short follow-up. Flaws: One occupational group, no adjustments except for age, exposure assessed as an index of different work-associated problems. Comments: The study includes rather few cases.							
Haan 1988 (27)	Job strain scale composed of three subscales: physical strain, variety, control (0)	Non fatal and fatal CHD, register-based (1)	Finland, 902 employees of a metal company (33 % women, 17-65 years) (1, 0, 0)	60 / 10 years (1)	*The summed job strain, OR: 4.95 (p= 0.03)* *(0)*		Age, sex, smoking, alcohol, relative weight, cholesterol, systolic blood pressure (0)	3
	Strengths: Inclusion of both women and men. Relatively short follow-up Flaws: The used job strain scale includes both physical and psychological factors. Gender used as covariate. Comments: The design of the study makes the results difficult to interpret.							
Suadicani 1993 (112)	Job influence, work pace, monotony	Non fatal and fatal CHD (24%), register-	Denmark, 1 638 men (55-74 years)	46 / 4 years	Job influence 0.93 (ns *) Work pace 1.25 (ns *) Monotony 0.91 (ns *) * calculated by author		Social status, tobacco, alcohol, exercise, blood	8

(1)		based (2)	(1, 1, 0)	(1)	(1)		pressure, BMI, lipids (1)	
Strengths: A rather large population and short follow-up. Flaws: Inclusion of rather old participants as age in it-self increases the risk of IHD significantly. Comments: The paper focused on the finding of significantly increased risk in those participants who were not able to relax after work.								
Kivimäki 2002 (51)	Demand, control, job strain effort, reward, effort reward imbalance (ERI) (1)	Register based CVD mortality (1)	Finland, 545 men and 267 women (1, 0, 0)	73 / mean 25.6 years (0)	*Adjustment only for age and sex: High demands 1.35 (0.77-2.36). High effort 1.63 (0.90-2.96). Low reward 2.04 (1.21-3.43). Multivariate adjustment: Low control 1.42 (0.72-2.82), strain 2.22 (1.04-4.73), ERI 2.42 (1.02-5.73). (0)*		Age, sex, occupational group, smoking, exercise, blood pressure, cholesterol, body mass index (1)	4
Strengths: Inclusion of both men and women. Flaws: Very long follow-up, use of cardio-vascular register-based mortality as endpoint. Use of gender as covariate. Comments: The authors discuss the problem of exposure assessment one or more times. The association between exposure and IHD was stronger in those having the same job 5 years after exposure assessment.								
Lee 2002 (67)	Demands, control, support, strain (1)	Non fatal myocardial infarction (medical records) and fatal CHD (26%) (2)	USA, 35 038 women (30-55 years) (1, 0, 1)	146 / 4 years (1)	(1)	Low strain 1.00, passive 1.12 (0.67-1.84), active 0.75 (0.40-1.42), high strain 0.63 (0.34-1.17). High demands 0.80 (0.52-1.24), low control 0.97 (0.65-1.45), low support 1.15 (0.80-1.64)	Age, smoking, alcohol, BMI, history of hypertension, diabetes or hypercholesterolemia, menopausal status, education (1)	8
Strengths: A very large middle-aged population and short follow-up. Diagnosis very certain. Flaws: Only nurses included. Comments: When only one occupational group is included in a study there is a risk of too small variation in exposure. This may be a reason for the finding of no association. Furthermore, among nurses the demand of hiding feelings or the like may be a more relevant exposure to be assessed.								
De Bacquer	Demands,	Fatal (23%)	Belgium,	87 /	High demands 1.43 (0.80-		Age, education,	11

2005 (18)	control, support, strain, iso-strain model	and non fatal AMI, clinical records	14 987 men (35-59 years)	mean 3.15 years	2.57), low decision latitude 0.83 (0.48-1.43), low social support 2.36 (1.38-4.01), strain 1.26 (0.66-2.41), iso-strain 1.92 (1.05-3.54)		BMI, smoking, diabetes, systolic blood pressure, serum total cholesterol, international standard classification of occupations code and company	
	(2)	(2)	(1, 1, 1)	(1)	(1)		(2)	
	Strengths: Reliable diagnoses, large sample, short follow-up. Full adjustment for confounders. Flaws: Other psychosocial factors may have been included. Comments: A very nice study.							
Kiwimäki 2005 (49)	Effort reward imbalance (ERI), job strain, justice at work (2)	Register based CHD-death, non fatal CHD (clinical records) (1)	England, 6 442 men (35-55 years) (1, 1, 0)	250 / 8.7 years (1)	Job strain 1.44 (1.01-2.05), ERI 0.95 (0.65-1.40), high justice 0.69 (0.49-0.98). (1)		Age, employment grade, and strain, ERI, justice (0)	7
	Strengths: Large cohort and fairly short follow-up. Flaws: Only few adjustments. Comments: Whitehall II study. For some participants exposure was assessed at both phase 1 and 2, for others only at one occasion.							
Kornitzer 2006 (55)	Demands, control, job strain (2)	Fatal and non fatal MI, register based or clinical records (1)	Belgium, France, Spain, Sweden, 20 435 male (35-59 years) (0, 1, 1)	180 / 40 months (1)	High demands 1.46 (1.08-1.97), low control 1.00 (0.74-1.34), job strain 1.47 (0.96-2.25). (1)		Age, smoking, blood pressure (0)	7
	Strengths: Large cohort, short follow-up. Flaws: Inclusion of participants from different cultures, few adjustments, exposure assessed by different questionnaires,. Comments: The results should have been stratified by country.							
Kuper 2006	Demands,	Incident fatal	Sweden,	89 / 135		Low control 0.7	Age, socio	8

(63)	control, job strain, support	(10%) and non fatal CHD, register based	19 565 women (30-50 years)	months		(0.4-1.2), high demands 1.4 (0.8-2.3), job strain 1.0 (0.5-1.9), low support 1.2 (0.7-2.1)	economic status, body mass index, alcohol, cigarettes, diabetes, high blood pressure, exercise	
	(1)	(2)	(1, 1, 1)	(0)	(1)		(1)	
	Strengths: Reliable endpoints, large cohort, short follow-up, analyses stratified by full-time and part-time workers. Flaws: A minor flaw is the lack of adjustment for lipids. Other psychosocial factors might have been included. Comments: A reliable study.							
Netterstrom 2006 (83)	Demands, decision latitude, strain (2)	Incident fatal and non fatal CHD, register based (2)	Denmark, 659 men (mean age 44.3 years) (1, 1, 0)	47 /14 years (0)	High demands 1.4 (1.1-1.6), decision latitude 1.0 (0.9-1.2), job strain 2.4 (1.0-5.7). (1)		Age, social status, exercise, alcohol, lipids, blood pressure, smoking (1)	8
	Strengths: Danish study, reliable exposure assessment according to the Demand Control Model. Flaws: Long follow-up. Comments: The study included an objective assessment of job strain, which did not support the Demand Control Model.							
André-Petersson 2007 (6)	Social support, job strain (2)	First time myocardial infarction (2)	Sweden, 4 740 women (54.2 years) and 3 063 men (55.5 years) (1, 1, 1)	205 / 7.8-9 years (1)	Unadjusted: Low support 1.00 (0.69-1.45), job strain 1.17 (0.67-2.06). No results from multivariate analyses. (1)	Unadjusted: strain 1.29 (0.44-3.85). Multivariate adjusted: Low support 2.72 (1.42-5.22).	age, blood pressure, use of antihypertensive drugs, prevalent diabetes, BMI, treatment for hyperlipidemia, alcohol, smoking, education and occupation (1)	10
	Strengths: Reliable diagnoses, large cohort, short follow-up, inclusion of both men and women. Flaws: No male results from multivariate analyses. Comments: Very reliable study.							
Kivimäki	Job strain	Incident fatal	Sweden,	93 / 9.7	Job strain,		Age	9

2007 (52)		(23%) or non-fatal CVD, hospital records and register-based	3 160 men (19-65 years)	years	Men aged 19-65, 1.24 (0.73-2.10) Men aged 19-55, 1.70 (0.96-3.01)			
	(2)	(2)	(1, 1, 1)	(1)	(1)		(0)	

Strengths: Large cohort and relatively short follow-up. Reliable exposure assessment and endpoint.
Flaws: Few adjustments, inclusion of old participants.
Comments: Notice an increased relative risk when the population is restricted to those aged 19-55.

The Effort Reward Model

Siegrist 1992 (104)	Reward (status consistency) and intrinsic effort	Non fatal and fatal CHD, register-based, clinical records	Germany, 323 blue-collar workers, men (25-55 years)	27 / 6.5 years	Status inconsistency 2.9 (1-8) High intrinsic effort 3.6 (1.2-10.5)		Age, BMI, blood pressure, lipids, exercise, smoking	7
	(1)	(1)	(1, 0, 1)	(1)	(1)		(1)	

Strengths: Middle-aged participants, short follow-up.
Flaws: As the study introduces a new stress model and questionnaire, the population is rather small.
Comments: The study must be seen as one introducing a new stress model, and therefore the results have to be confirmed in other settings.

Lynch 1997 (72)	Demands, resources, income	Non fatal and fatal CHD, register-based (acute myocardial infarction register)	Finland, 1 727 men (42, 48, 54 and 60 years at inclusion)	89 cases / 8.1 years	High demands, low resources, low income, RR: 1.57 (0.78-3.18)		Age, lipids, exercise, blood pressure, BMI, alcohol, tobacco, prevalent disease incl. diabetes, marital status	9
	(1)	(2)	(1, 1, 0)	(1)	(1)		(2)	

Strengths: Rather large, middle-aged population and short follow-up. Reliable endpoint.
Flaws: The measure used to estimate exposure is mixed and describes conditions other than work.
Comments: The exposure assessment may be better used in a "life course" perspective.

Kivimäki 2002 (51)	Demands, control, job	Register based CVD	Finland, 545 men	73 / mean 25.6 years	*Low control 1.42 (0.72-2.82), job strain 2.22 (1.04-4.73),*		occupational group, smoking,	4

	strain effort, reward, effort reward ratio (ERI) (1)	mortality (1)	and 267 women (1, 0, 0)	(0)	*ERI 2.42 (1.02-5.73).* *(0)*		exercise, systolic blood pressure, cholesterol, BMI (1)	
	Strengths: Inclusion of both men and women. Flaws: Proxy measures for effort and reward were constructed on the basis of questionnaires from 1973, but the included items were not exemplified. Very long follow-up, use of cardio-vascular register-based mortality as endpoint. Use of gender as covariate. Comments: The authors discuss the problem of exposure assessment one or more times. The association between exposure and IHD was stronger in those having the same job 5 years after exposure assessment.							
Kiwimäki 2005 (49)	Effort reward imbalance (ERI) (proxy measures), job strain, justice at work (1)	Register based CHD-death, non fatal cases (clinical records) (1)	England, 6442 men (35-55 years) (1, 1, 0)	250 / 8.7 years (1)	Job strain 1.44 (1.01-2.05), ERI 0.95 (0.65-1.40), injustice 1.45 (1.02-2.04). (1)		age, employment grade, and job strain, ERI, justice (0)	6
	Strengths: Large cohort and fairly short follow-up. Flaws: Only a few adjustments. Exposure assessment in the form of proxy measures for effort and reward were constructed on the basis of items, which merely mirrored demands and social support / job satisfaction, respectively (questionnaire in Kuper et. al. 2002). Comments: Whitehall II study. For some participants exposure was assessed at both phase 1 and 2, for others only at one occasion.							
Justice at work								
Kiwimäki 2005 (49)	Effort reward imbalance (ERI), job strain, justice at work (2)	Register based CHD-death, non fatal CHD (clinical records) (1)	England, 6442 men (35-55 years) (1, 1,0)	250 / 8.7 years (1)	Job strain 1.44 (1.01-2.05), ERI 0.95 (0.65-1.40), injustice 1.45 (1.02-2.04). (1)		Age, employment grade, and job strain, ERI, justice (0)	7
	Strengths: Large cohort and fairly short follow-up. Flaws: Few adjustments. It is unclear what "justice" is as the concept included level of information, willingness of the superior to listen to problems and appraisal. Comments: Whitehall II study. For some participants exposure was assessed at both phase 1 and 2, for others only at one occasion. The demonstrated association may not be describing justice but something about support and predictability.							
Elovainio	Justice at work	Register	Finland,	73 / 25.6	*High justice 0.61 (0.36-1.00)*		Sex, age,	4

2006 (21)		based CVD-mortality	804 engineering-industry employees (33% women) (17-65 years)	years			occupational group, smoking, physical activity, systolic blood pressure, cholesterol, BMI, job strain, effort-reward imbalance	
	(1)	(1)	(1, 0, 0)		*(0)*		(1)	

Strengths: Justice measured by the use of one relevant question.
Flaws: Use of CVD-deaths as endpoint. Long follow-up, use of gender as covariate.
Comments: A weak study.

Various exposures

Netterstrom 1988 (82)	Work load (objective: traffic intensity. Subjective: work pace too high, work pace higher than 5 years ago), social contact in spare time (1)	Non fatal and fatal CHD (34%), register-based	Denmark, 2 045 male bus drivers (20 - 64 years)	62 cases, 50 without symptoms at inclusion / 6 years	High traffic intensity 4.4 (1.2-16.4) Higher work pace than 5 years ago 2.7 (1.1-7.1) No social contact 2.0 (1.0-3.8)		Smoking, age	5
	(1)		(1, 0, 0)	(1)	(1)		(0)	

Strengths: Rather large population, short follow-up. Work load assessed both as an objective and subjective measure.
Flaws: Few adjustments.
Comments: The association between traffic intensity and IHD may originate in pollution.

Matthews 2002 (78)	Work stress measure containing 7 work related life events (e.g. change to a new job, demotion, business failure) Marital stress (e.g. separation)	Register based CHD mortality	USA, Multiple Risk Factor Intervention Trial: 6 428 in intervention group and 6 438 in control	771 / 9 years	CHD: More than 2 work events, RR 1.35 (1.03-1.76)		age, study group, education, non fatal CHD event, smoking, diastolic blood pressure, alcohol, cholesterol	7

First author / year	Exposures	Outcome	Population	Cases	Risk estimate, men or *both genders* (95% confidence -interval)	Risk estimate, women (95% confidence - interval)	Confounders	Quality score
	(1)	(1)	group, men (35-57 years) (0, 1, 1)	(1)	(1)		(1)	
Strengths: Large population, short follow-up. Flaws: The combined measure of exposure as this does not describe work environment but merely employment status etc. Comments: A study which demonstrates the significance of both job and family.							
Lee 2004 (68)	Job insecurity (1)	CHD (clinical records) (2)	USA, 36 910 women (46-71 years) (1, 0, 0)	154 / 4 years (1)	(1)	Non fatal MI, 1.28 (0.82-2.00)	Age, follow up period, smoking, alcohol, BMI, history of hypertension, diabetes and hypercholesterolemia, menopausal status, exercise, education (1)	7
Strengths: Large cohort, short follow-up, reliable endpoint. Flaws: Inclusion of old participants as age is a significant risk factor in it self. Comments: Job insecurity may be seen as an example of universal lack of control.							

Case Control Studies

First author / year	Exposures (quality score A)	Outcome (quality score B)	Population (quality score C, D, E)	Cases (quality score F – left out)	Risk estimate, men or *both genders* (95% confidence -interval) (quality score G)	Risk estimate, women (95% confidence - interval)	Confounders (quality score H)	Quality score (summed score, max 10)

Various exposures

First author / year	Exposures	Outcome	Population	Cases	Risk estimate, men	Risk estimate, women	Confounders	Quality score
Alfredsson 1982 (1)	Aggregated data, hectic work, monotony, low influence (1)	Fatal /non fatal AMI (1)	Sweden, 882 controls, men (1, 1, 1)	334	Low influence, hectic work 1.35 (1.01-1.81). Not learning new things, hectic 1.45 (1.02-2.04). (1)		Age (0)	6
Strengths: Large case-control study. Flaws: Only adjustment for age. The use of aggregated data and no information on job title of the individual make the exposure assessment rather uncertain.							

	Comments: As social status has significant meaning this should have been included as confounder.							
Iversen 1989 (42) (1)	Aggregated data, closure of a shipyard (1)	Hospital admission, disease of circulatory system (1)	Denmark, 441 controls, men (1, 0, 0)	887	1.60 (0.78-3.25) (1)		Age (0)	4
	Strengths: A "natural experiment". Flaws: Use of hospital admission due to CVD-disease as endpoint. Only adjustment for age. Comments: The study describes the significance of closure of a workplace to the health of the employees.							
Johnson 1996 (46) (1)	Aggregated data, control, demands, support (1)	CVD-death (1)	Sweden, 2 422 controls, men (24-74 years) (1, 1, 0)	521	RR (10 years employment): Low control 1.83 (1.19-2.82), high demands 0.93 (0.71-1.22), low support 1.09 (0.81-1.46). (1)		Age, year last worked, survey year, smoking, exercise, education, social class, and nationality (0)	5
	Strengths: Report of results according to exposure duration, 5, 10, 15, 20, 25 and 26+ years. Flaws: Use of CVD-death as endpoint, inclusion of old participants. Comments: The study aims to answer the question "how long do you have to suffer from a psychosocial factor at work to have an increased risk for IHD? Low risk after 25 years of exposure may be due to a "healthy worker" effect.							
Ferrie 1998 (24) (1)	Aggregated data on threat to employment (1)	Diagnosed cardiac ischemia (2)	England, 5347 men and 2477 women with stable employment (1, 1, 1)	513 men and 153 women, department sold	1.40 (0.9-2.2) (1)	1.69 (0.8-3.3)	Age and grade (0)	7
	Strengths: Inclusion of both men and women, natural experiment. Flaws: Few adjustments. Comments: Whitehall II study. Cases were employees at a department which was out-sourced.							
Hammar 1998 (31)	Aggregated data, demands, decision latitude, support, job strain, iso-strain	Fatal /non fatal AMI, hospital discharge register and	Sweden, controls 24 913 men and 3 553 women	8 833 men, 1 175 women	Low decision latitude 1.37 (1.25-1.50), high demands 0.93 (0.89-1.02), low social support 1.28 (1.17-1.41), iso-strain 1.35 (1.16-1.58)	Low decision latitude 1.12 (1.05-1.19), high demands 0.95 (0.89-1.01), low	Age, county of residence, and calendar year	6

		death register (1)	(30-64 years) (1)			(1)	social support 1.10 (0.99-1.17), iso-strain 1.31 (0.99-1.73)	(0)	
	Strengths: Inclusion of many cases and both genders Flaws: Few adjustments. Comments: Though the diagnoses originated from the hospital discharge-register the study is seen as reliable.								
Theorell 1998 (117)	Aggregated data, Inferred decision latitude (1)	Fatal (23%) and non fatal AMI, hospital discharge register and death register (2)	Sweden, controls 300, men (45-64 years) (1, 1, 1)	1047	Low decision latitude OR, 1.2 (0.8-2.0). Negative change in decision latitude OR 1.4 (1.0-2.0) (1)			Age, hospital catchment area, smoking, LDL-HDL ratio, social class, history of hypertension, and chest pain. (1)	8
	Strengths: Inclusion of many cases. Flaws: Aggregated data. Comments: Reliable study.								
Sokejima 1998 (107)	Self report (information from table of salary) working hours (1)	First time AMI, hospital admission (2)	Japan, controls 331, men (30-69 years) (1, 1, 0)	195	Daily working hours last month before infarction: < = 7 hours 2.0 ((1.52-5.28), 7-11 hours 0.96 (0.58-1.60) > = 11 hours 2.94 (1.39-6.25). Increase in working hours > = 3 hours 2.49 (1.24-4.99) (1)			Age, occupation category, hypertension, hypercholesterolemia, diabetes, BMI, smoking habits, proportion of sedentary work, and burn out index (1)	7
	Strengths: Working hours are an objective measure of workload. Flaws: Risk of bias as the data from the table of salary were reported by the participant. Comments: Exposure was reported by the use of table of salary and was seen as "objective".								

Table 5. Men, evidence of association between measures of psychosocial load at work and incidence of IHD. Writing in *italics* indicate, that the analyses were carried out using gender as a confounder.

	Significant positive association	Significant negative	Non-significant studies

		association	
Demands by any definition	Alfredsson 1985, Sweden Theorell 1977, Sweden Kornitzer 2006, international * Netterstrøm 2006, Denmark Netterstrøm 1988, Denmark Alfredsson 1982, Sweden * Sokejima 1998, Japan	Steenland 1997, USA * Johnson 1996, Sweden	Reed 1989, USA * Alterman 1994, USA * Eaker 2004, USA * Suadicani 1993, Denmark * *Kivimäki 2002, Finland* * De Baquer 2005, Belgium Hammar 1998, Sweden
Control	Steenland 1997, USA * Johnson 1996, Sweden Hammar 1998, Sweden		Reed 1989, USA * Alterman 1994, USA * *Andersen 2004, Denmark* * Eaker 2004, USA * Suadicani 1993, Denmark * *Kivimäki 2002, Finland* * De Baquer 2005, Belgium Kornitzer 2006, international * Netterstrøm 2006, Denmark Theorell 1998, Sweden
Job strain	Johnson 1989, Sweden (iso-strain) *Haan 1988, Finland* * De Baquer 2005, Belgium (iso-strain) Kivimäki 2005, England Netterstrøm 2006, Denmark *Kivimäki 2002, Finland* * Hammar 1998, Sweden (iso-strain)		Reed 1989, USA * Alterman 1994, USA * Steenland 1997, USA * Eaker 2004, USA * De Baquer 2005, Belgium André-Peterson, Sweden Kornitzer 2006, international * Kivimäki 2007, Sweden
Social support	De Baquer 2005, Belgium Netterstrøm 1988, Denmark Hammar 1998, Sweden		André-Peterson 2006, Sweden Johnson 1996, Sweden
Effort Reward model	Siegrist 1992, Germany * *Kivimäki 2002, Finland* *		Lynch 1997, Finland * Kivimäki 2005, England *
Organizational Injustice	Kivimäki 2005, England Elovainio 2006, Finland *		
Job	*Vahtera 2004, Finland* Mathews		Iversen 1989, Denmark *

insecurity	2002, USA		Ferrie 1998, England

Asterisk * indicates that one or more serious flaws have to be considered.

Table 6. Women, evidence of association between measures of psychosocial load at work and incidence of IHD.

	Significant positive association	Non-significant studies
Demands by any definition	Alfredsson 1985, Sweden	Eaker 2004, USA * Lee 2002, USA * Kuper 2006, Sweden Hammar 1998, Sweden
Control	Eaker 2004, USA * Hammar 1998, Sweden	Lee 2002, USA * Kuper 2006, Sweden
Job strain	Hammar 1998, Sweden (iso-strain)	Eaker 2004, USA * Lee 2002, USA * André-Peterson 2006, Sweden Kuper 2006, Sweden
Social support	André-Peterson 2006, Sweden	Lee 2002, USA * Kuper 2006, Sweden Hammar 1998, Sweden
Job insecurity		Lee 2004, USA *

Asterisk * indicates that one or more serious flaws have to be considered.

Figure 1. Risk estimates for the association between demands by any definition and IHD (men) are shown on the X-axis. Y-axis indicates quality, i.e. increasing quality upwards. Asterisk * indicates that the analysis included both genders and sex were used as a confounder.
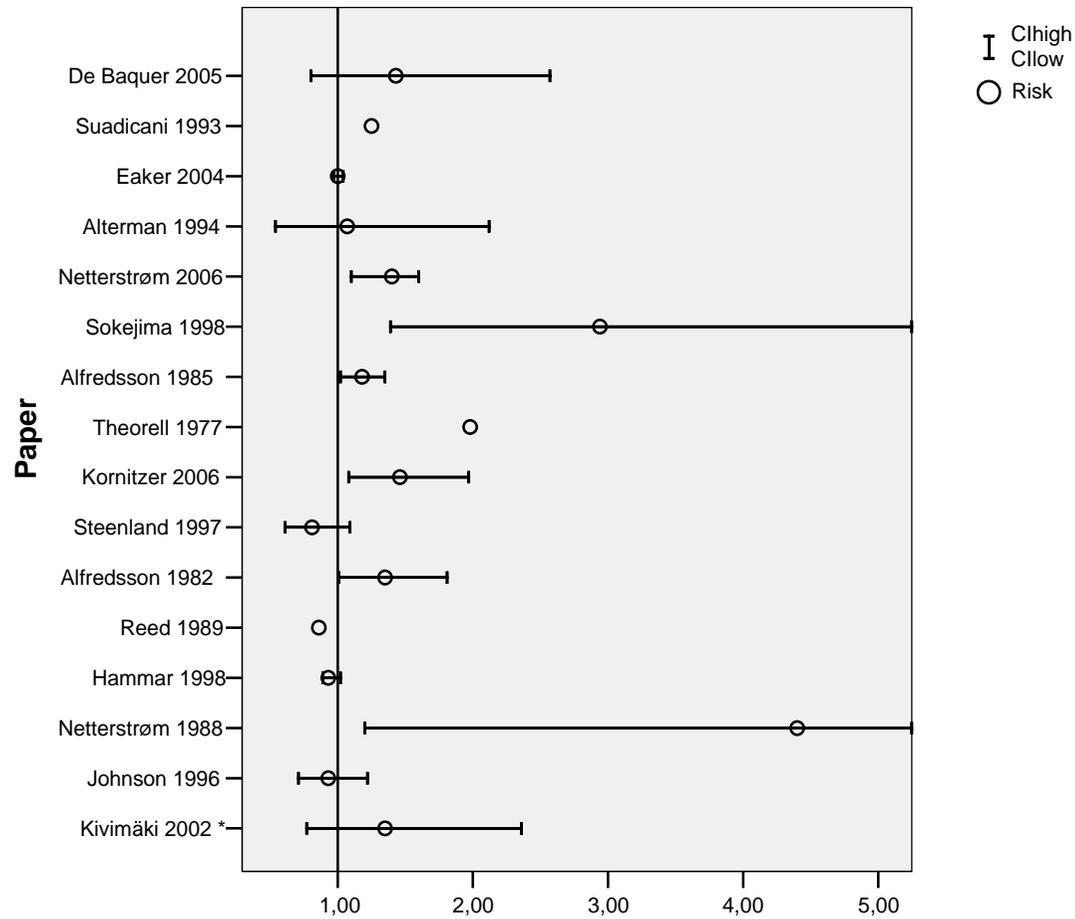
Figure 2. Risk estimates for the association between demands by any definition and IHD (women) are shown on the X-axis. Y-axis indicates quality, i.e. increasing quality upwards.
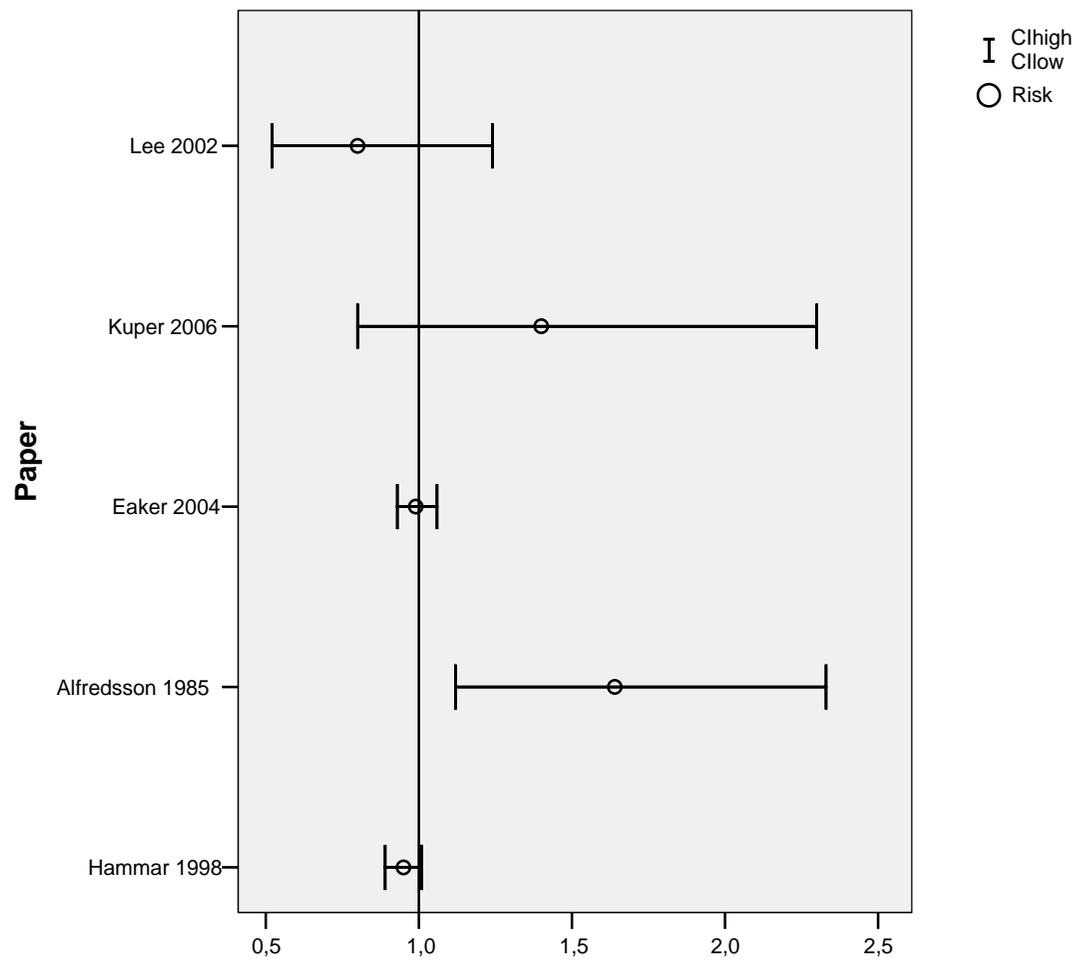
Figure 3. Risk estimates for the association between lack of control and IHD (men) are shown on the X-axis. Y-axis indicates quality, i.e. increasing quality upwards. Asterisk * indicates that the analysis included both genders and sex were used as a confounder.
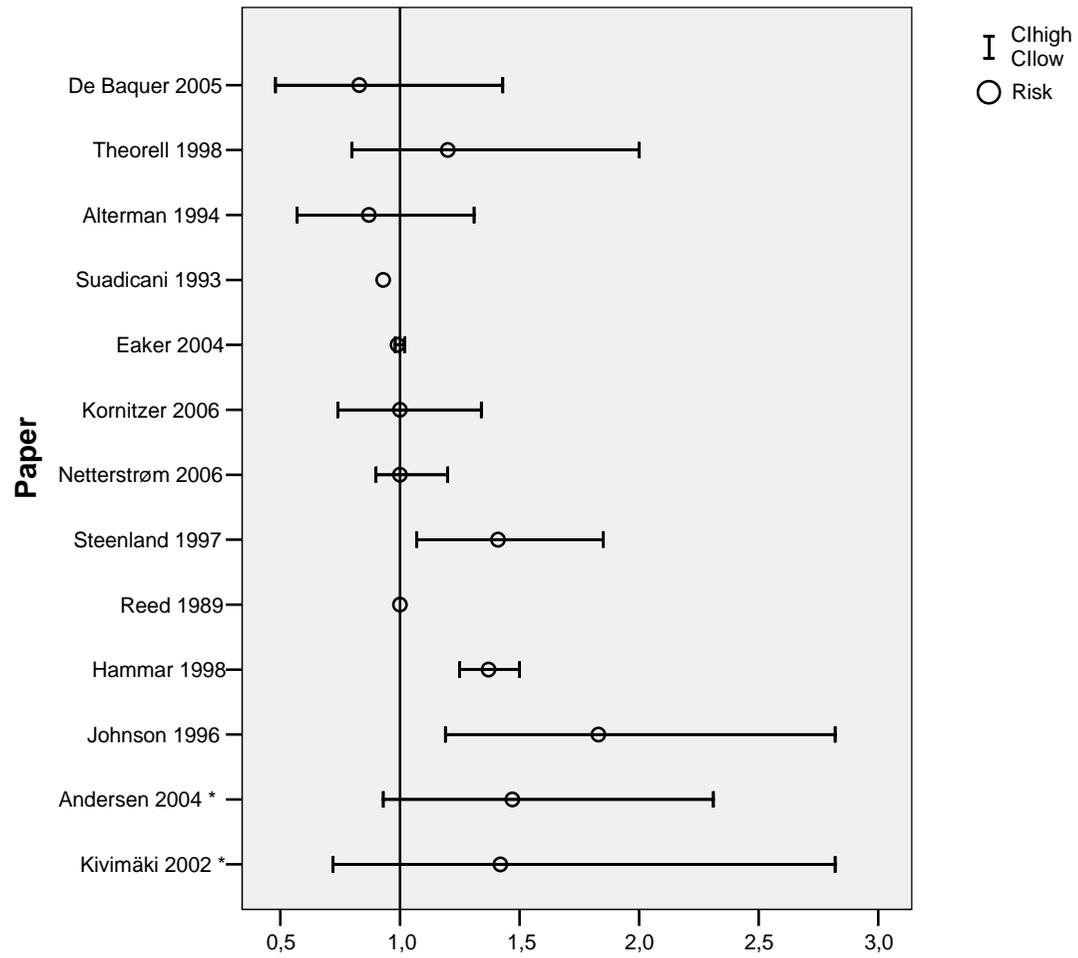
Figure 4. Risk estimates for the association between lack of control and IHD (women) are shown on the X-axis. Y-axis indicates quality, i.e. increasing quality upwards.
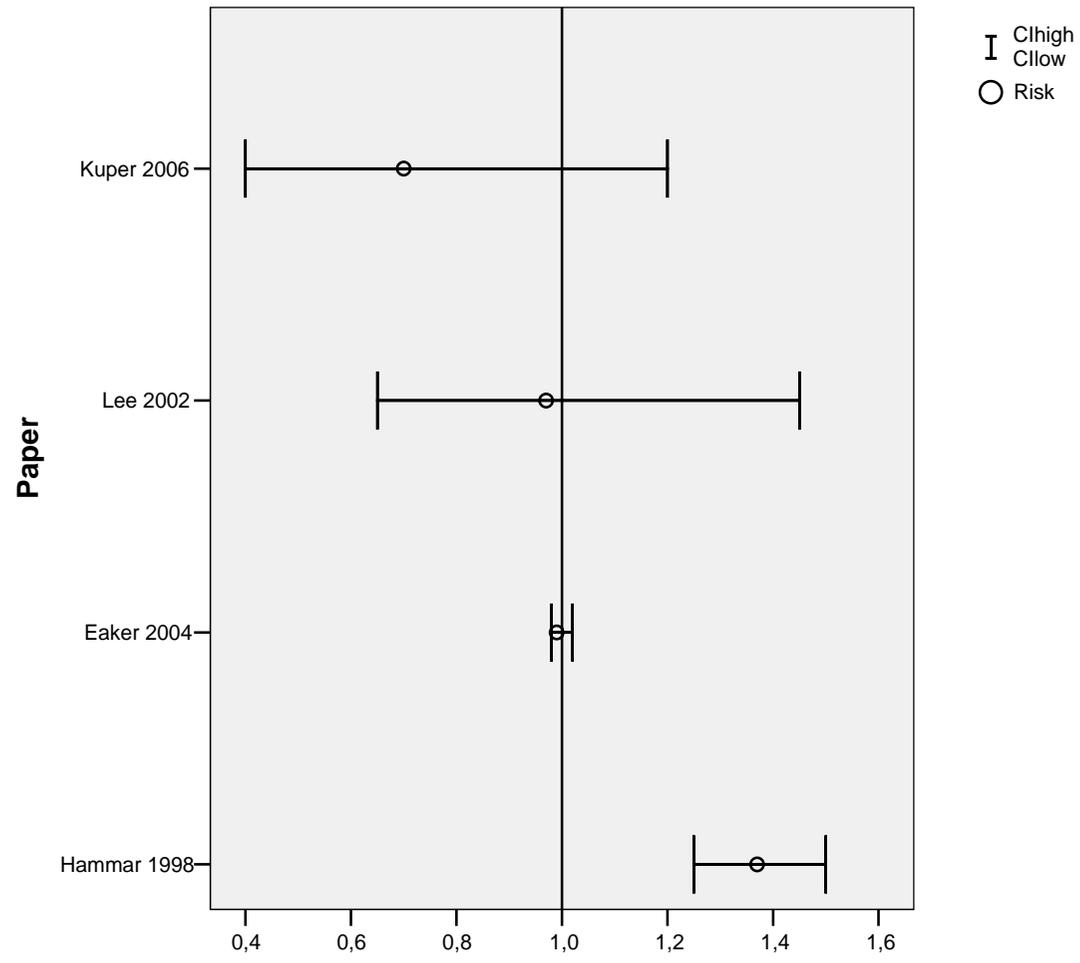
Figure 5. Risk estimates for the association between job strain and IHD (men) are shown on the X-axis. Y-axis indicates quality, i.e. increasing quality upwards. Asterisk * indicates that the analysis included both genders and sex were used as a confounder.
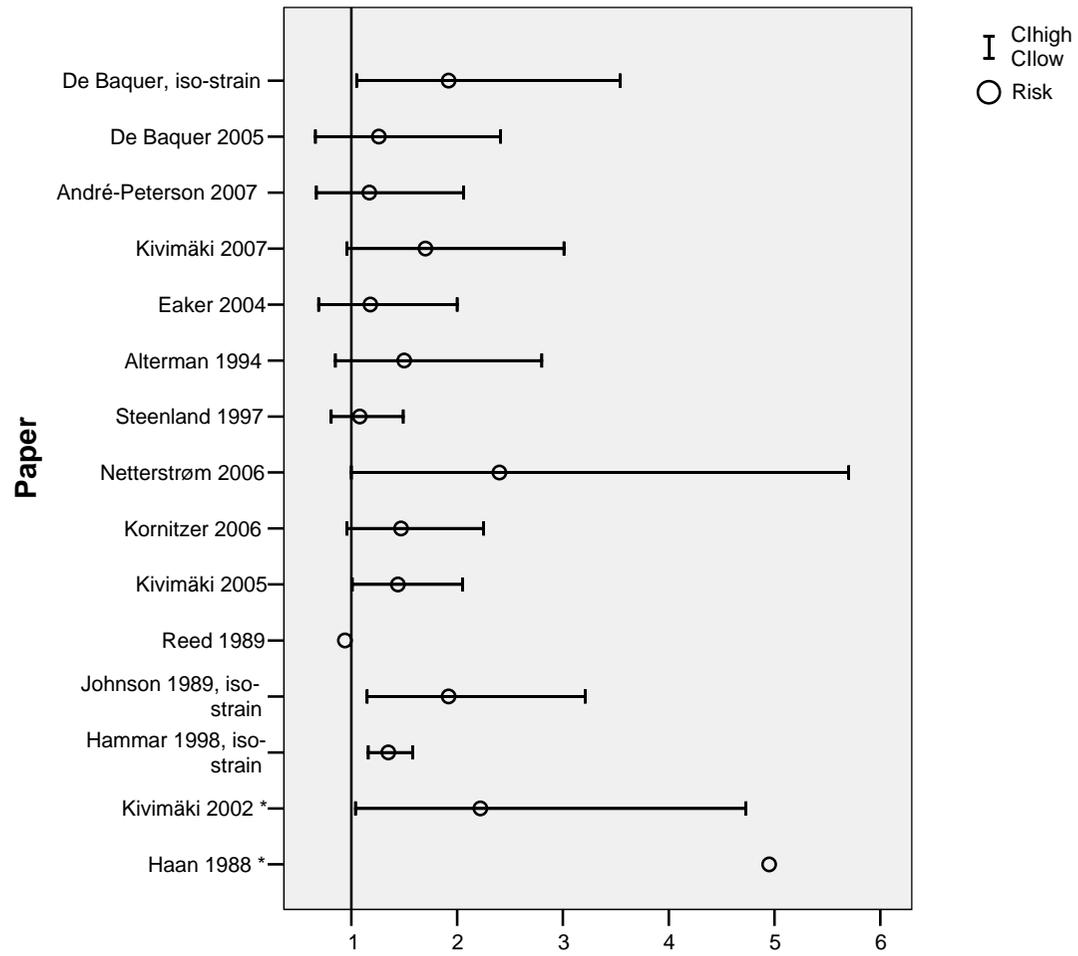
Figure 6. Risk estimates for the association between job strain and IHD (women) are shown on the X-axis. Y-axis indicates quality, i.e. increasing quality upwards.
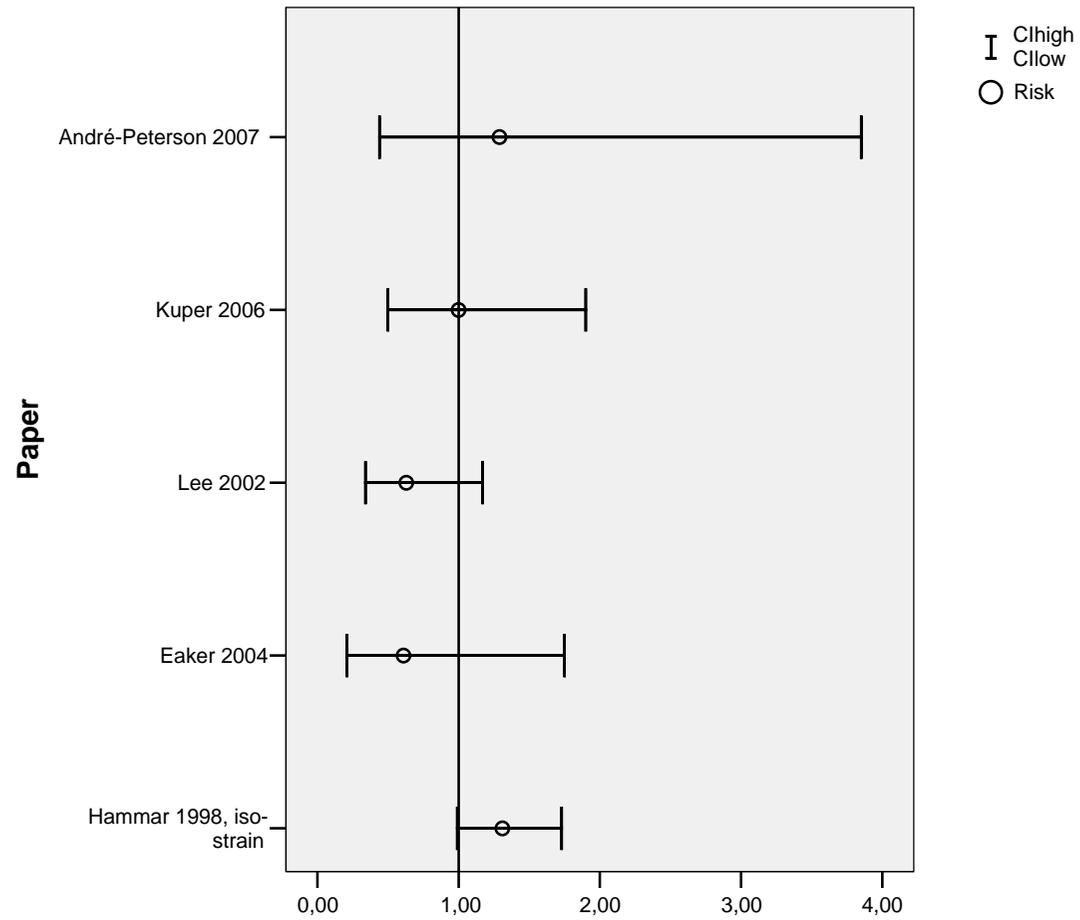
Figure 7. Risk estimates for the association between lack of social support and IHD (men) are shown on the X-axis. Y-axis indicates quality, i.e. increasing quality upwards.
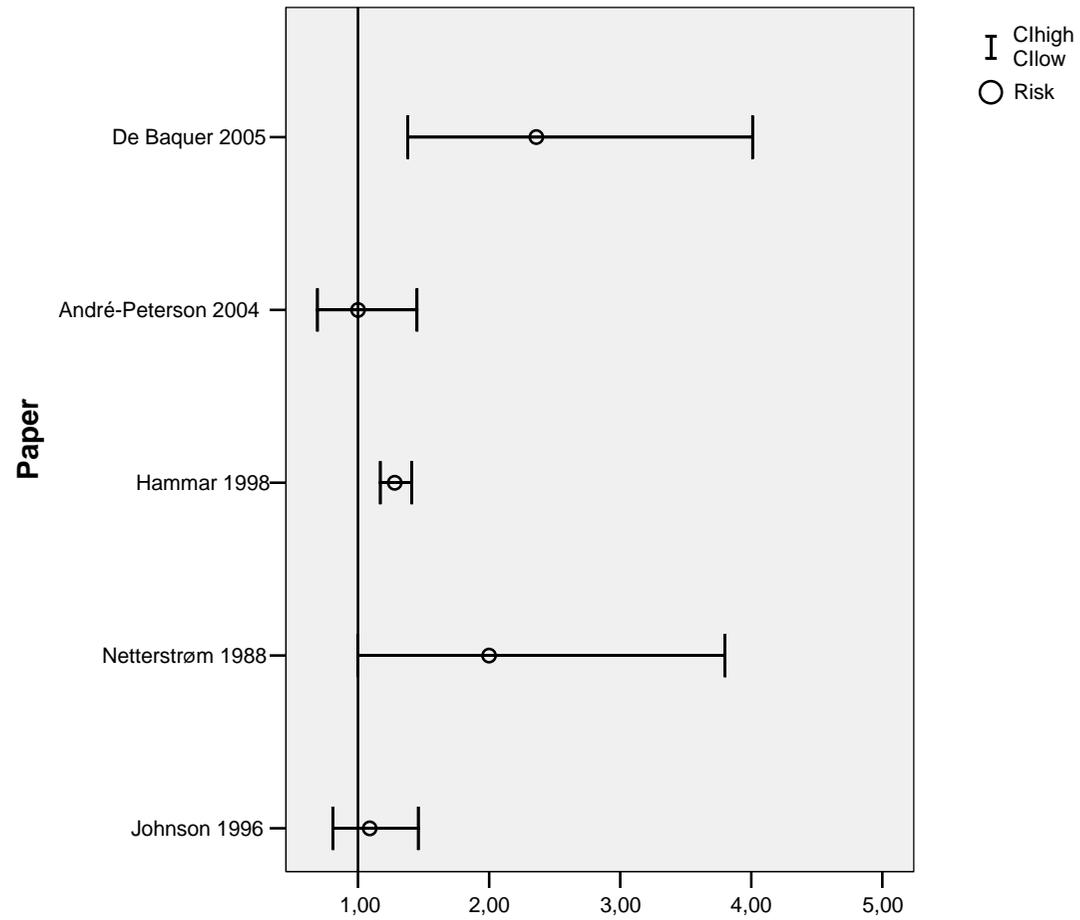
Figure 8. Risk estimates for the association between lack of support and IHD (women) are shown on the X-axis. Y-axis indicates quality, i.e. increasing quality upwards.
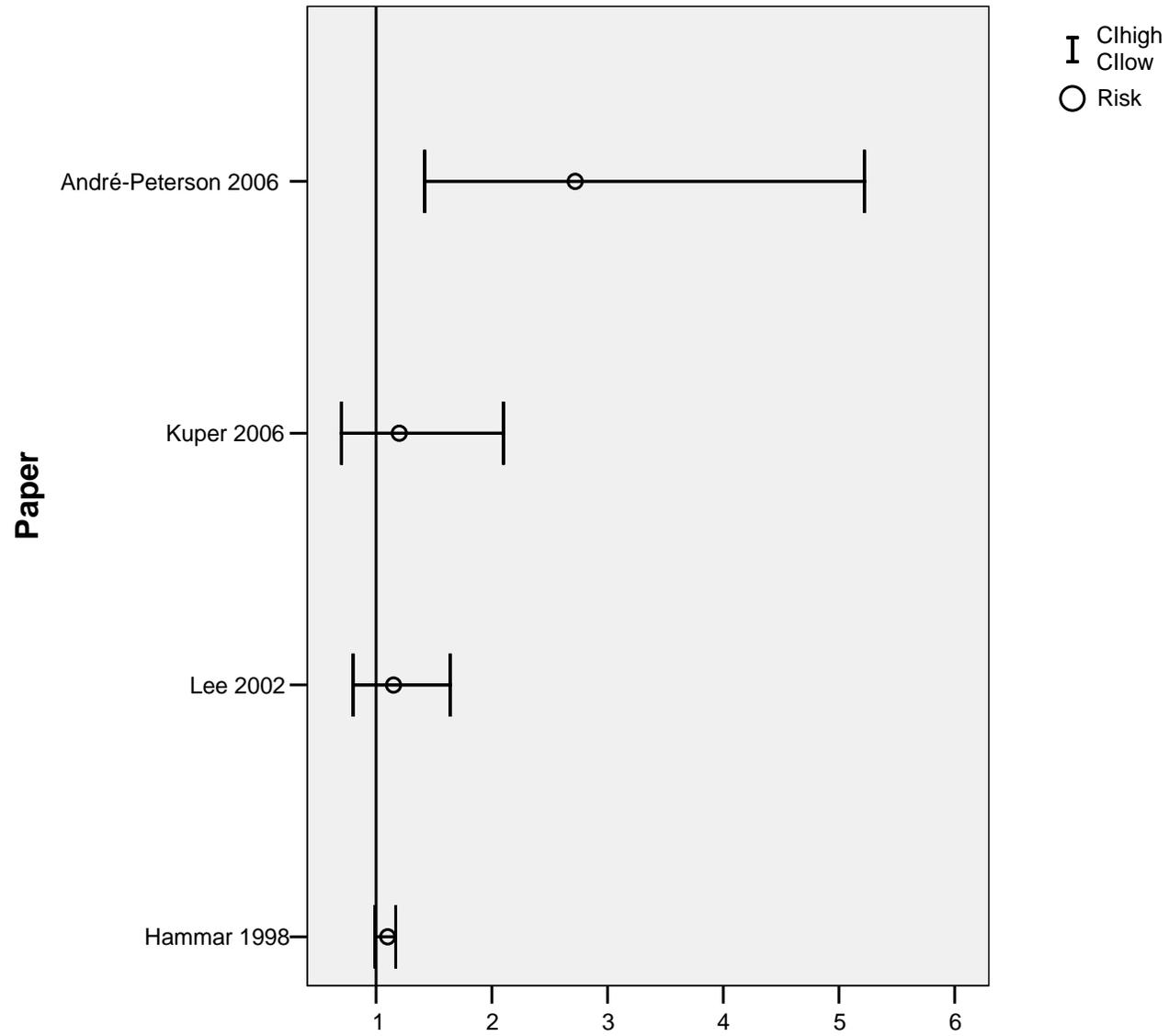
Figure 9. Risk estimates for the association between concepts of the Effort Reward Model and IHD (men) are shown on the X-axis. Y-axis indicates quality, i.e. increasing quality upwards.
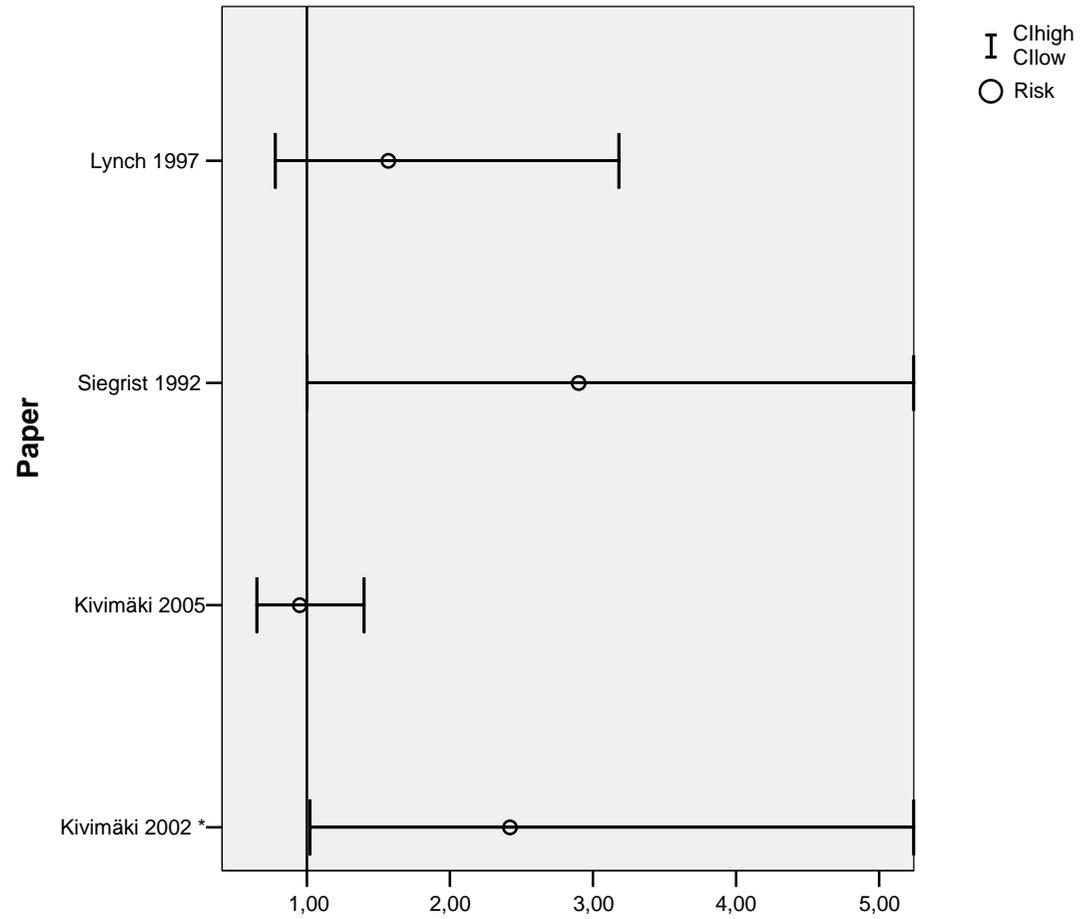
Figure 10. Risk estimates for the association between job insecurity and IHD (men) are shown on the X-axis. Y-axis indicates quality, i.e. increasing quality upwards.