The association between work stressors and cardiovascular disease, a methodological approach

THE ASSOCIATION BETWEEN WORK STRESSORS AND CARDIOVASCULAR DISEASE, A METHODOLOGICAL APPROACH

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Introduction

Cardiovascular disease and its prevalence

Cardiovascular disease (CVD) is a group of disorders of the heart and the blood vessels and includes: coronary heart disease (disease of the blood vessels supplying the heart muscle), cerebrovascular disease (disease of the blood vessels supplying the brain), peripheral arterial disease (disease of the blood vessels supplying the arms and legs), rheumatic heart disease (damage to the heart muscle and heart valves from rheumatic fever), congenital heart disease (malformations of the heart structure existing at birth) and deep vein thrombosis and pulmonary embolism (blood clots in the leg veins that can dislodge and move to the heart and lungs) (1).

CVD constitutes a major public health problem in the world and affects many people. CVD is related to high mortality and the consequences of the disease are chronic/ long-lasting. Worldwide, CVD is the number one cause of death. It is estimated that 17.3 million people died from CVD in 2008, which is 30% of all global deaths. Of these deaths, 7.3 million were due to coronary heart disease (CHD) and 6.2 million were due to stroke (1). In the EU, CVD is the main cause of death among women. For men this is true for all EU-countries except for the Netherlands, France, Slovenia and Spain (2). Besides the most common cause of death, it is also one of the most prevalent chronic diseases in Western societies. Hospital discharge rates for CVD measure the number of patients who leave a hospital after receiving care for CVD. In the EU, discharge rates for all CVD were around 2400 per 100,000. For CHD, the discharge rate was just over 600 per 100,000 and for stroke it was just over 390 per 100,000 (2). In 2009, the number of hospitalizations due to CVD in the Netherlands was 364,666 (3).

The societal impact of cardiovascular disease

The consequences of CVD are considerable for both the society and the individual, in terms of economic costs and well-being. The Disability Adjusted Life Years (DALY) is an aggregate for the number of healthy life years lost in a population due to disease. It expresses the burden of disease in a population. Within the calculation of DALY's the number of people suffering from the disease, the severity of the disease, the number of deaths due to the disease and the age at which death occurs are taken into account. In European countries, 17% of all DALY's lost in 2004 were due to CVD, making it the second largest single cause after neuropsychiatric disorders (2). In the Netherlands, 15% of all DALY's lost were due to CVD, making it the third largest cause, after cancer (18%) and psychiatric disorders (26%) (4). The economic costs related to CVD are enormous. Overall CVD is estimated to cost the EU economy almost 196 billion a year. 54% of the costs are due to direct health care, 24% are due to productivity losses and 22% are due to informal care of people with CVD (2). In the Netherlands, in 2009, 8% of the total health care costs were due to CVD (2,5). The total non-health care costs were around 4,8 million euro of which 48% were due to morbidity related production losses, 24% were due to mortality related production losses and 28% were due to informal care.

Production losses due to CVD contribute greatly to the overall financial burden (2). Current

detailed information about time to work resumption after a myocardial infarction (MI) is unavailable. In the Netherlands, in 1997, the mean sickness absence duration due to MI was 272 days with substantial variation (6). This is high, in comparison to the mean sickness absence of 7,6 days in 2010 (7). Also internationally the variation is substantial, ranging from 60 days in the US to 120 days in Sweden. In case of an uncomplicated and adequately treated MI, most employees return to work within three to twelve months. The percentage of employees returning to work varies internationally between 36% and 85%, although in most literature the percentage is above 75%. The substantial variation in work resumption is mainly due to social economic (for example the presence of work disability pensions) and social psychological factors (8). Factors that mainly determine work resumption are the motivation of the patient and the subjective perception of the work capacity (9, 10), the viewpoint of the patient that work is the causal factor that has led to the occurrence of MI (8, 11) and the presence of depression (12). These factors are included in the guideline 'Acting of the occupational physician in case of employees with ischaemic heart disease', which was developed with the aim to prevent unnecessary sickness absence and thereby reducing the risk of long term work disability (13). On average, two years after experiencing a MI a stable situation has been achieved. Limitations and comorbidities due to MI usually have manifested during this period. After this 2 year period, an assessment is made of the functional possibilities, the prognosis concerning the (length of the) work disability and re-evaluations of the work disability (13). After two years, there is still a large number of MI patient who have not returned to work; in 2011, CVD accounted for 6% of the total WAO benefits in the Netherlands (7).

For the individual, CVD impacts various dimensions of one's life. Around 25% of the patients with a MI die within one hour after occurrence of the complaints. Among the hospitalized patients, 10% of the patients die in the hospital. This percentage is strongly related to the age of the patient, but also having a CVD history or diabetes is related to a worse prognosis. After 5 years, around 68% of the male patients and 55% of the female patients are still alive (8).
After the acute phase, the prognosis is strongly determined by the remaining left ventricular function, the size and the severity of the remaining ischemia, the susceptibility of the heart for tachycardia and/ or heart fibrillation and the presence of other cardiovascular risk factors and comorbidity (8). In addition, MI and stroke patients have an increased risk of recurrent events (14-18). Furthermore, experiencing a MI is a major life event (19, 20), it has a major impact on one's life and can cause intense emotions. Therefore CVD does not only affect physical health, it also affects psychosocial health. Individuals who have experienced a MI or stroke are at increased risk of developing psychological disorders such as anxiety or depression (21-25), where 15-45% of the MI patients develop depression and 30% develop anxiety (8). In addition, the occurrence of CVD also negatively impacts quality of life (25-28).
Due to the considerable consequences of CVD for both the society and the individual, in terms of economic costs and well-being, prevention aimed at reducing risk factors for CVD is important.

Risk factors for cardiovascular disease
CVD is a multi- causal disease and since 1945 epidemiological research has established several individual risk factors for CVD. The most common types of CVD are stroke and coronary heart disease (CHD) (1). The main pathological process underlying coronary heart disease and stroke is atherosclerosis (29-31). It starts early in life and progresses gradually through life (32-34). Risk factors for atherosclerosis can be divided into non-modifiable (gender, age, positive family history for CVD) and modifiable risk factors (35). The progression rate of atherosclerosis is influenced by behavioural related risk factors such as tobacco use, unhealthy diet and physical inactivity (resulting in obesity), elevated blood pressure (resulting in hypertension), abnormal blood lipids (resulting in dyslipidaemia) and elevated blood glucose (resulting in diabetes). Continuing exposure to these risk factors leads to further progression of atherosclerosis, resulting in unstable atherosclerotic plaques, narrowing of blood vessels and obstruction of blood flow to vital organs, such as the heart and the brain (36-38). Depending on the location of atherosclerosis and the number of narrowed vessels, a heart attack or stroke can occur.

Recent studies estimated that the behavioural risk factors explain 75% of coronary heart disease and cerebrovascular disease (1, 38, 39). Exposure to these risk factors can be changed and much effort has been put into setting up prevention strategies aimed at reducing these risk factors in order to reduce CVD risk. A positive change in the distribution of risk factors has been achieved through the reduction in the percentage of people with high cholesterol due to the increase in cholesterol reducing medication, reduction and stabilization in the percentage of smokers in the eighties and nineties and reduction in the intake of trans fatty acids since the nineties. An increased percentage of people with overweight, diabetes and a decreased consumption of fruit, vegetables and fibres are negative trends (40). This combination of positive and negative trends in the recent past makes it difficult to directly translate how this affects the incidence of CHD in the following years. The incidence of MI has not changed dramatically during 1991-2006. During the first half of the nineties the MI incidence increased, followed by a decrease in the years 1997-2000, leading to a similar incidence in 2006 as in 1991. The number of hospitalizations due to CHD increased from 1980-1995, followed by a decrease after 1995. Stroke incidence showed a slight increase up to 2004, after which a slight decrease has set in. Since 2000, the number of hospitalizations due to stroke has increased slightly. The increase in physical inactivity and overweight may have caused an increase in hypertension, which has resulted in an increased risk of stroke. In addition, more people survive a CHD due to better treatment (secondary prevention), leading to an increase in ischaemic heart disease, which in turn increases the risk of a stroke (41).

Since there has been disagreement on the extent to which traditional risk factors explain CHD, ranging from 50% to 75%, there has been a search for new potential risk factors (39, 42). The influence of stress in the development of CVD has been studied and debated extensively, where

the foundation for research on the adverse effects of stress was already set in 1930's by Selye (43). Stress can have various causes (which may originate from the work or private situation (44)), but they all have in common that exposure to stress can be modified. Reducing stress could lead to a reduction of CVD risk. However, causality is still unproven (39), and therefore, the clinical importance of stress is still not universally accepted. If the significance could be properly established, prevention aimed at reducing stress could offer additional CVD risk reduction.

Stress

The stress response is a functional response needed in order to survive and function properly. Organisms must maintain their physiological parameters (e.g. temperature, blood pressure, glucose, hormone concentrations in blood) within a certain range of values appropriate for their age, gender and species. Homeostasis is the state of equilibrium in which all the physiological parameters are within the normal range. The external environment can cause disturbances in the homeostasis so that some physiological parameters change and assume values that are above or below the normal range (45). In response to these disturbances the organism makes adjustments in its physiological process in order to bring the values of the altered parameter back into their normal range. This process in which the organism adjusts in response to the disturbances in homeostasis is called allostasis (46, 47). It involves feedback mechanisms that detect a deviation from homeostatic equilibrium and trigger the appropriate compensatory response. Environmental disturbances of homeostasis are called stressors and can be acute or chronic. Responses to acute stressors help the individual survive and re-establish homeostasis. For instance, for animals a sudden predator attack is an example of an acute stressor that threatens survival. The stress mechanism enables the body to respond quickly and adequately at the (threatening) situation, which is called the fight- flight reaction. During the fight – flight reaction, which is the first (or acute) stress response to a threatening stimulus, the physiological parameters within the body are undergoing a change needed for an adequate reaction (48). The amygdala and prefrontal cortex are areas of the brain that play a crucial role in evaluating the threat and producing a stress response that will help to cope with it. Signals from the brain activate the release of catecholamines ((nor) epinephrine) from the sympathetic adrenal medullary axis and glucocorticoid hormones (cortisol and corticosterone) from the hypothalamic pituitary adrenal (HPA) axis. This allows mobilization of energy, an increase in cardiovascular tone to facilitate energy delivery and temporarily inhibit other physiological processes such as growth, repair, digestion and reproduction. Epinephrine is especially important during the acute stress response, whereas the production of cortisol sets in after the acute response. If the threat continues, the mechanism also continues to mobilize energy to sustain the stress reaction (where the role of cortisol is crucial). After the situation has ended, the stress mechanism is shut down through hormonal feedback systems and the body can recover.

Stress can become harmful if prolonged activation of the stress mechanism leads to sustained arousal ultimately causing wear and tear of the body. Chronic arousal may be due to recurring

stress, poor adaptation to repeated stressors or the inability to inactivate allostatic responses after a stressor ends (46, 47, 49-51). For the measurement of stress, this implicates that one needs to differentiate between those with varying exposure and those with long term exposure, since this latter group is assumed to be at increased CVD risk (51, 52). However, most studies use single exposure measurements to capture chronic exposure which could severely underestimate the association between stress and health effects (52-55).

Work stress

Work stress is stress generated by exposure to work stressors. In the literature the following potential work stressors are listed: job insecurity, emotional demands, cognitive demands, psychological demands, work conflicts, bullying, work load, working hours, working overtime, role inclarity, lack of social support, lack of control, physical demands, commitment, lack of career possibilities, lack of skills discretion, mismatch between effort and appreciation, lack of fairness and relational injustice. The differentiation between an acute and chronic stress response also applies to work stressors. A new challenge, such as giving a presentation for colleagues, giving a first lecture for students or defending your thesis, may cause stress. However, if the stress response is short lasting and the person experiences personal growth by taking on such new challenges, stress is not harmful. As with 'normal' stress, work stress becomes problematic when it becomes chronic or frequently occurring so that the stress response remains elevated without having the opportunity to recover from the stress reaction.

The prevalence of work stress is estimated by measuring the potential work stressors at one point in time. The National Survey on Working Conditions is performed annually in the Netherlands and showed that 27% of the Dutch employees work overtime on a structural basis, 78% of the employees work under high time pressure, 51% experience their work as emotional demanding, 16% report unwanted behaviour by colleagues, 24% report unwanted behaviour by clients and 25% are worried about job retention (56).

Looking at the prevalence of specific job characteristics that may generate work related stress throughout Europe (in 2005): job insecurity was highest in Czech Republic (32%), Slovenia and Poland (27%) and lowest in Denmark, UK (7%) and Luxembourg (5%). In the Netherlands it was 17.8%. Working at very high speed was highest in Sweden Finland, Denmark and Slovenia (85%, 77%, 76% and 75%). It was lowest in Poland, Ireland and Bulgaria (43%, 42% and 27%). In the Netherlands, it was reported by 61% of the employees. Violence at work is reported more often in Northern European countries, in the Netherlands and the UK the prevalence of being threatened with physical violence was 10% and 12%, respectively. Incidents of harassment/ bullying were reported more often in Finland (17%), the Netherlands (12%) and Lithuania (10%), whereas in Poland, Czech Republic and Bulgaria it is reported less often (3.2%, 2.9% and 1.8%) (57). Thus, various work stressors have a high prevalence and if they indeed lead to work stress in most employees, reduction of these factors could be promising in additional reduction of CVD risk.

As mentioned above many work stressors are listed in the literature and since the start of the job stress research, there is no consensus on how work stress or work stressors are defined and operationalized (58). The consequence is that many definitions exist and that stress and stressors are operationalized in many ways. In addition, this has resulted in a long list of models trying to conceptualize work stress. This indicates the diversity of the conceptualizations and which factors are thought to be crucial. Simultaneously, it shows how difficult it is to capture the concept of work stress. Another issue is that the applicability of models (once developed in a different time period with different work stressors) into the current work environment (where other types of work stressors have become more important) may no longer be appropriate (29). To get some insight into these issues, the most used or influential models will be described below and also a description will be given of the change that has occurred in the work environment during the last twenty years.

Various work stress models

The Person-Environment Fit Model was introduced in 1973 by French, where the match between the person and the work environment is related to health (59). The employee's attitudes, skills, abilities and resources should match the demands of the job. The work environment should meet the worker's needs, knowledge and skills potential. Lack of fit (either subjective or objective) can cause problems. In the Michigan Model, introduced by Kaplan and Cobb in 1975, the theory states that environmental stressors, such as role ambiguity, conflict and work load, need to be subjectively perceived in order to lead to disease (60). Role issues and role expectations are central stressors in this model. In 1979 the Demand Control Model was introduced by Karasek. The underlying hypothesis is that the specific combination of high job demands and low decision latitude leads to job strain, which increases the risk of various stress related illnesses such as mental and physical health problems (61). In 1987 the Vitamin Model was introduced by Warr. According to the underlying theory, work characteristics have mental health effects that are analogous to the effects of vitamins in the human body. Some work characteristics have constant effects, whereas other work factors may have a curvilinear effect, where moderate levels are beneficial but may become harmful when the level is too low or too high (62). The Effort Reward Model was introduced by Siegrist in 1996 (63). The key concept is reciprocity, where effort at work should be compensated by suitable rewards and a mismatch between these two will lead to stressful experiences. Rewards are defined as money, esteem, career opportunities and security. Effort has two components: intrinsic effort (personal motivations, such as need for control and over-commitment) and extrinsic motivations or external pressure, such as work load. External demands are proposed to relate to the status of the labour market and how easily alternative employment can be found. A more recently developed model is the DISC model of de Jonge et al (64). They argue that job demands, job resources and job related strains contain cognitive, emotional and physical elements. They emphasize the importance of a match between the type of demands and

resources. For interaction to occur between demands and resources with regard to strains they need to belong to the same dimension.

Of these models, the Demand Control Model has been used most extensively in scientific research, especially in the studies that have examined the association between work stress and CVD. This model is easy to use due to its simplicity (65). Furthermore, it is claimed that it measures the objective work environment and that it is applicable to all types of jobs (66).

Change in the work environment during the last 20 years

In the EU-15 large scale socio-economic and technological changes have affected work places considerably in the recent years. The major changes concern: globalisation, an increase in employees in the service sector and technological changes (7, 57, 67). Globalisation means global integration of economies, which leads to outsourcing and possibly to an improvement in the physical working conditions within the EU-15 due to outsourcing of physical strenuous work to low wage countries. Furthermore, it increases the competition between companies (leading to increased work pressure and requiring more flexibility of the employees) and it has led to changes in the work employments (e.g. part time work, temporary contracts etc). Since 1995 the percentage of employees working in the service sector has increased with 7% whereas the percentage working in the industrial sector has decreased with 5%. This shift is accompanied by a change in exposure to occupational risk factors, where emotional demands and contact with other people becomes more important and where physical strenuous work becomes less prevalent. Technological changes have led to an increase in the use of a computer at work. During the period of 2002-2008 the percentage of employees working with a PC increased from 52% to 66%. Furthermore, manual work is replaced by computerized work, employees have to fulfil different demands and teleworking becomes more important.

All these changes are important since they reflect a shift from exposure to physical and chemical factors to psychosocial factors. Models that have been developed in a period in which working conditions are no longer comparable to those of the current work life, are probably no longer adequate to capture work related stressors that are important in inducing work stress in the current work life (29). This stresses the importance to (re)consider which work stressors are important in inducing work stress in the current work life.

Work stress and cardiovascular disease

The mechanism through which work stress exerts its effect on health may be directly through repeated activation of the neuro-endocrine response to stressors, causing deregulation of the hypothalamic pituitary adrenal axis and autonomic nervous system. These disruptions may lead to a persistent elevated blood pressure, destabilization of atherosclerotic plaques, up-regulation of cytokine expression (causing inflammation), enhancement of cortisol secretion resulting in endothelial dysfunction, insulin resistance and other metabolic as well as

hemodynamic perturbations, all heightening CVD risk (68, 69). Another proposed mechanism through which work stress exerts its effect, is indirectly through unhealthy behaviour such as a poor diet, lack of physical exercise or smoking (70). The main underlying pathway of both the direct and indirect mechanism is thought to be through the process of atherosclerosis (36, 71). Several animal studies conducted in monkeys have shown that psychosocial stress is a risk factor for atherosclerotic disease (72-76) which is supportive for the biological plausibility of the association. The number of studies, conducted in humans, that examined the association between work stress and cardiovascular disease is tremendous and various reviews have been conducted to summarize the results (29, 65, 77, 78). In studies that have examined the association between work stress and CVD, the Demand Control Model has been used most often to conceptualize work stress (29, 78). The studies have yielded conflicting results and reviewers and researchers disagree on the strength of the evidence and whether it is strong enough to confirm an association between work stress and CVD.

As described in the previous paragraphs, work stress is a difficult concept to capture, exposure to chronic work stress is hypothesized to increase CVD risk which requires a matching exposure assessment and changes in the work environment may limit the applicability of work stress models, developed in the past, to the present working conditions. All these issues probably contribute to the conflicting results and to an ongoing debate whether work stress is a risk factor for CVD or not. Specifically, with regard to the Demand Control Model various conceptual issues have been raised by various researchers and are probably contributing to these conflicting results. In addition, various methodological issues regarding the studies using the model have been raised as well. These can be subdivided into three major issues:

1 conceptual issues
2 exposure assessment
3 personal attributes which may have biasing or substantive effects.

Conceptual issues are whether the model adequately captures the most stressful aspects of the current work environment since work organization has changed the last decades (77, 79-81), whether the model is too simple and lacks comprehensiveness (54, 65, 81-84) and whether the theoretical scales of the model are indeed measuring what they intend to measure (85-87), in other words are they associated with work stress? Issues related to the exposure assessment are the use of a single exposure assessment to capture long term exposure to work stressors and what type of exposure poses the highest CVD risk. Issues related to personal attributes are whether they cause bias or whether they have substantive effects determining susceptibility to exposure and/ or susceptibility to the effects of exposure (88). Overall, these issues are undermining the strength of the current evidence on the association between work stressors and CVD. This is probably also the reason why work stress is not included in the list of established risk factors for

CVD by the American heart Association (52). If the significance of work stress could be properly established, prevention aimed at reducing work stress has major potential in reducing CVD risk. In 2011, the Dutch working population consisted of 7.13 million people and the prevalence rates of the work stressors reported by the employees were high.

This thesis aspires to contribute to improve the current evidence on work stressors and CVD by focusing on two main aims:

1 To gain insight into how various methodological and conceptual choices impact the observed association between work stressors and CVD
2 To gain insight into how to obtain a better (substantiation of the) estimate for CVD risk due to exposure to work stressors.

In order to do so, we first explored how various methodological and conceptual choices impact the observed association between work stressors and CVD in already conducted studies, by conducting a meta-regression analysis. Second, since no consensus exists on the definitions used for work stressors, work stress and (job) strain, this project started by choosing a theoretical framework, which we could use to position the various concepts. Third, we tested various hypotheses resulting from the meta- regression analysis, using data from the Maastricht Cohort Study. These hypotheses are related to the validity of the exposure assessment, the validity of the outcome assessment, estimating long term exposure and the impact of personal attributes on the association between work stressors and CVD.

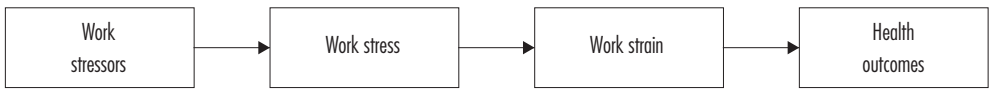
The Maastricht Cohort Study

To address the aforementioned research aims, the data of the Maastricht Cohort Study (MCS) was used. The MCS is a large prospective cohort study, which started in 1998 with the aim to study work related fatigue. The baseline population consisted of 12,140 employees and particpants were selected from various sectors and jobs. Even though the MCS was set up with a different aim, the MCS provided a unique dataset with the availability of data on a wide range of work stressors, which was annually assessed during the first three years, and data on incident myocardial infarction and stroke. Also various work strain measures were assessed, as well as personal attributes such as coping and negative affectivity. Furthermore, next to the questionnaire data on CVD we also had access to medically diagnosed CVD obtained from medical files. For a subsample of employees living in the Southern part of the Netherlands and attending hospitals in this area, case ascertainment was performed for those who indicated to have experienced a stroke or heart disease. This also enabled us to explore the issue of reporting bias of CVD.

Theoretical framework

As mentioned before, no consensus exists on the definitions used for work stressors, work stress and (job) strain. Therefore, this project started by choosing a theoretical framework, which we could use to position the various concepts. Within this project the following definitions were used: work stressors are a large number of work related environmental conditions thought to impact the health and well being of the worker (89, 90). Stress is defined as an individual state characterized by a combination of arousal and displeasure (89). Exposure to stress can result in strain (91), which can manifest as a short term health outcome that might still be reversible. If strain continues it can result in negative (irreversible) health outcomes, such as CVD. See Figure 1 for the framework. The distinction between work stressors and work stress is important from prevention point of view. It is important to explore which work stressors are contributing to work stress and in turn increase CVD risk since this offers insight into which work stressors can be targeted by prevention. Along the line, personal attributes (such as negative affectivity and coping) were also positioned within this framework.

Figure 1: Framework used to study the association between work stressors and CVD.



The following concepts, identified from the literature, were considered to be potential work stressors: emotional demands, psychological demands, physical demands, cognitive demands, lack of role clarity, lack of job security, conflicts at work, working overtime, lack of decision authority, commitment, lack of career possibilities, lack of skills discretion, lack of social support, mismatch between effort and appreciation and lack of fairness.

Within the various theoretical models, different work stressors are the focus, as sometimes already becomes clear from the name of the model. Since the Demand Control Model has been used most often to explore the association between work stress and CVD, we will elaborate in more detail about how others and how we view the separate and the combined constructs of this model. According to Karasek (61) psychological strain results from the joint effects of the demands of a working situation and the range of decision making freedom available to the worker facing those demands. The stressors place the individual in a state of stress and decision latitude is the constraint which modulates the release of stress into action. If no action can be taken the unreleased energy may manifest itself as mental strain. Others have reported that high demands and low decision latitude might be early manifestations of distress or signs of an

underlying disease (92), or that it is another way to measure social status (93). Job strain has also been considered as job stress (94). In this thesis high demands and low decision latitude are positioned under potential work stressors and job strain is positioned as a poor and incomplete measure of work stress and/or work strain. In addition, we also do not exclude the possibility that it is another way to measure social status.

Outline of this thesis

To gain more insight into how various methodological and conceptual choices impact the observed association between work stressors and CVD, a meta-regression analysis was performed. This analysis was performed to gain more insight into the question 'Which study characteristics contribute to the conflicting evidence, resulting from the studies conducted to examine the association between job strain and cardiovascular disease?' The findings are presented in chapter 2. In chapter 3, it is described how we constructed two generic exposure assessments for work stressors which have a high work strain potential in the current work life. For this study we adhered to the framework of work stressors – work stress – work strain – CVD. We focused on the ('external') validity by exploring which work stressors were associated with work strain (through the process of work stress). In chapter 4, the association between baseline exposure to work stressors, assessed with one of the two newly developed exposure assessments, and cardiovascular disease was examined. In chapter 5, we explored the stability of exposure to work stressors over time and various approaches to estimate long term exposure to work stressors, using repeated measurments. In chapter 6, the results are presented of the study 'The impact of personal attributes on the association between cumulative exposure to work stressors and cardiovascular disease' Also, within this study it is described where along the framework of work stressors to CVD these attributes exert their effect upon. In chapter 7, the findings of the research question 'Is negative affectivity related to over reporting of cardiovascular disease?' are described. In chapter 8 the main findings are discussed and recommendations are given for future research and practice.

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2

The association between study characteristics and the study outcome in the relation between job stress and cardiovascular disease: a multilevel meta-regression analysis

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Objective
Studies about job strain and cardiovascular disease (CVD) have yielded inconsistent results, which hinders making a firm conclusion about the association. Inconsistent findings may be the result of methodological differences. If the relative CVD risk is influenced by methodological differences, these differences should be explored in more detail with future research to clarify which methodological characteristics are inherent to obtain the most accurate estimate between job strain and CVD risk. By assessing how study characteristics are associated with the outcome, the first step will be made to unravel this association. Therefore the following research question will be explored: Are study characteristics associated with the size of the reported relative CVD risk?

Methods
A systematic literature search yielded 71 studies about job stress assessed with the Demand Control Model and CVD. Traditional meta-regression was extended enabling the use of correlated data to quantify heterogeneity within and between studies.

Results
Compared to studies that used the original Job Content Questionnaire (JCQ), studies in which a more deviant form of the JCQ was used yielded on average larger estimates, odds ratios were on average 43% higher. Studies conducted in the USA yielded on average 26% lower estimates than studies conducted in Scandinavian countries.

Conclusion
Several study characteristics are associated with the size of the relative CVD risk. Several of these study features are related to the validity of the exposure and outcome assessment and are inherent to obtain an accurate estimate between work stress and CVD risk. More research is needed to clarify why these study features impact the average relative CVD risk.

INTRODUCTION

Cardiovascular disease (CVD) has a high prevalence in Western countries and many risk factors for developing CVD have been identified. Besides the traditional risk factors such as hypertension, diabetes and smoking, work stress is also considered a risk factor. Work stress has most often been operationalized with the Demand Control Model (DC model) as job strain, which is the specific combination of high job demands and low decision latitude (1). Karasek hypothesized that employees who are exposed to job strain are at greatest CVD risk (2). Exposure to job strain could increase the risk for developing CVD both by wear and tear of the cardiovascular system (direct pathway), initializing atherosclerosis and ultimately leading to CVD and by an indirect pathway, namely by negatively affecting life style factors, leading to increased smoking frequency, body mass index, cholesterol etc.

The association between job strain and CVD has been investigated since the introduction of the DC model but this association is highly debated due to conflicting results since consistency in the results is one of the criteria needed to establish a causal association (3). Methodological differences between the studies might be contributing to these conflicting results and it remains unclear whether an elevated risk is only found in studies with poor methodological quality, in studies with a specific outcome or exposure assessment or only in studies with specific populations. Especially in studies where exposure and outcome are measured with self-reported data overestimated associations are expected (4).

Studies that have focused on the association between job strain and CVD risk differ amongst others in the exposure assessment. Although exposure is operationalized according to the DC Model, studies differ in whether they investigate job strain in relation to CVD, or whether they investigate demands or decision latitude separately. Some of these studies found an increased CVD risk associated with high demands (5-8) or low decision latitude (9-12), while job strain is hypothesized to be most harmful. Furthermore, exposure is most often assessed with a variety of slightly different questionnaires. Besides differences in exposure assessment (13), these studies also differ in their design, categorization of the exposure, populations and CVD assessment.

While heterogeneity in results can be considered a nuisance in scientific literature (14, 15) when the aim is to obtain a summary estimate for the effect of the risk factor of interest, some studies have recognized the potential of exploring the heterogeneity and have investigated which study characteristics are associated with the study outcome (16-24). These types of studies have not been performed yet in occupational health research, specifically not in the field of job strain and CVD research where conflicting results are prevailing and an assessment of which study characteristics are associated with the reported CVD risk would be of value.

Clarifying how study characteristics influence the CVD risk is important for future research as it could lead to insight into what causes the differences. Therefore we formulated the research question: What is the association between study characteristics and the reported effect size in studies about job strain and cardiovascular disease? By exploring this research question, we aim to assess whether there is an association between study characteristics and relative CVD risk. This in turn could lead to new hypotheses about the possible reasons for these expected differences. If these hypotheses are explored in future research this can clarify which methodological characteristics are inherent to obtain the most accurate estimate between job strain and CVD risk. For this study, we used a multilevel meta regression technique, which enables the use of multiple results from a study. This has the advantage that multiple results from a study can be used to its full potential since the within study heterogeneity is also used, additional to the between study heterogeneity.

METHODS

A literature search was performed from January to February of 2009 in the databases: Pubmed, Web of Science, PsychInfo and Embase. We used text words for exposure ("job strain", "job control", "decision latitude, "decision authority", "job demands", "job stress", "psychosocial work environment", "work stress", "occupational stress", "psychosocial risk factors", "effort reward imbalance[1]", "psychosocial work characteristics" and "job characteristics") and for CVD we used the MeSh term cardiovascular disease and the free text words: heart disease, angina pectoris, stroke, coronary events and myocardial infarction. No restrictions for language or time period were used. In addition, we checked the reference lists from two reviews (13, 25) and Web of Science was searched with 'cited reference search'. This was carried out for the studies of Kivimaki (26) and Theorell (27). Using 'cited reference search' yields a list of articles that have cited these two studies. This list of articles was screened for not yet identified studies. Dissertation abstracts and meeting abstracts were also gathered and when considered as potentially relevant, retrieval of the full text article or thesis was pursued.

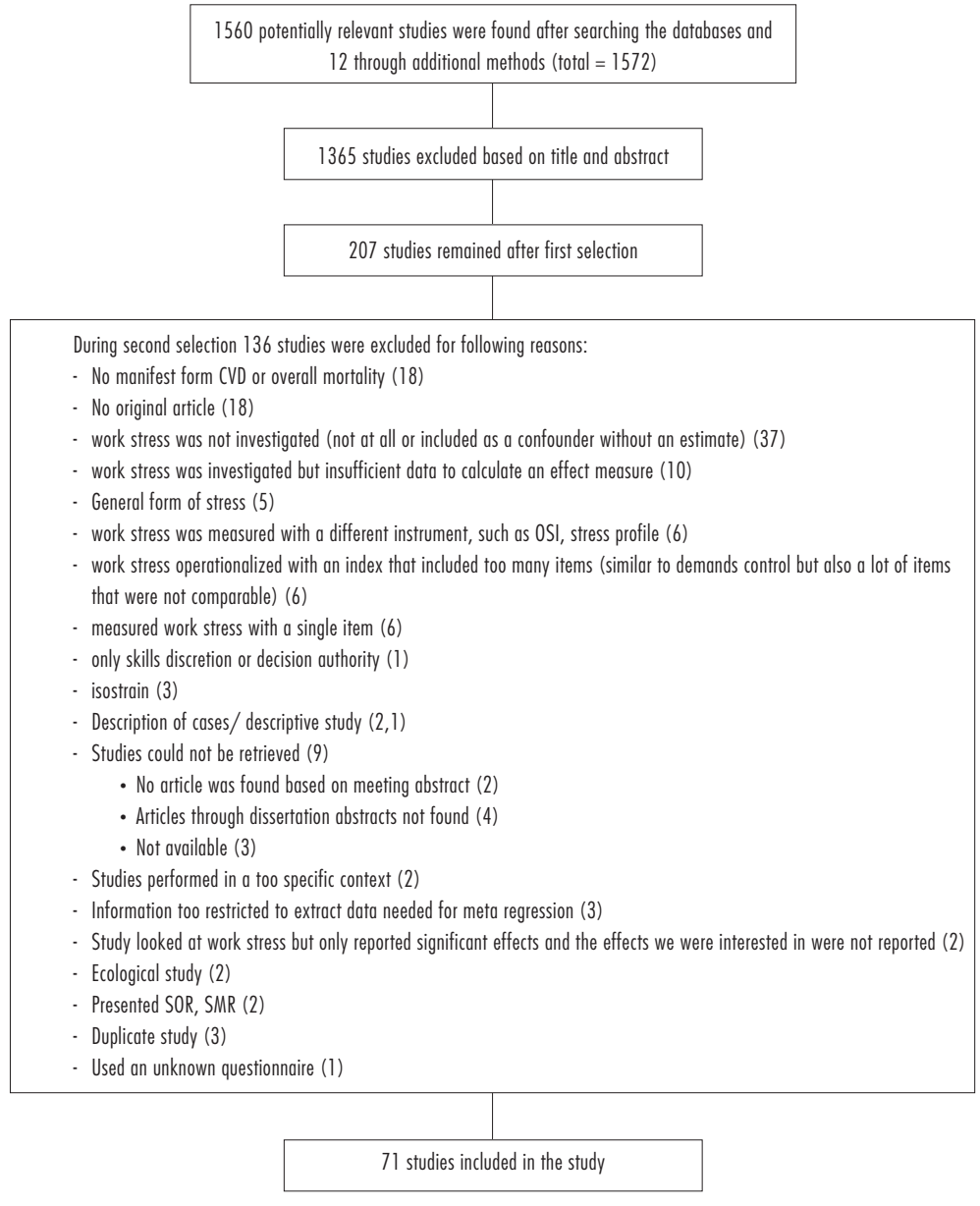
Selection of studies

Studies were eligible if they investigated the association between job strain or its components (job demands, decision latitude) and a manifest form of CVD. Furthermore, the results had to be presented as estimates of relative risks with accompanying confidence intervals. If these were not presented, at least data had to be presented which could be used to calculate a relative risk. No other inclusion criteria were used, as the aim of this study was to include heterogeneous studies.

1 Effort reward was included in the search strategy (although we do not use the results) because initially we planned to include the ERI model as well.

Studies were excluded if they did not fulfil the inclusion criteria, or for reasons as presented in Figure 1.

Figure 1: Flow chart of excluded articles.



Data extraction

Multiple studies based on the same population were included if they differed in certain study characteristics (e.g. length of follow up duration) and were considered to be correlated.

Multiple results from one study were extracted and these results were considered to be correlated. Results stratified according to gender or age groups within one study were regarded as uncorrelated. The study characteristics of which we thought to be associated with the CVD risk were extracted and categorized into groups. Within these categories one category was the reference category, see Table 1. The categorization of most of these characteristics is unambiguous, however outcome assessment, type of exposure questionnaires, adjustment for confounders in the individual studies, exposure levels and quality score need more clarification, which can be found in Appendix I. For this study, cardiovascular subgroups (stroke, myocardial infarction, ischemic heart disease, both morbidity and mortality) were grouped together, since the main underlying pathway is atherosclerosis (28).

Quality assessment of the studies

The quality of the studies was assessed by the first reviewer (KS) using the following items: selection bias, information bias, selective drop out, recall bias, valid exposure assessment, valid outcome measurement, dealing with confounders and dealing with prevalent CVD cases at baseline or gathering information about disease history in controls. The score per item ranged from 0 to 5, with 0 denoting low risk of bias and 5 meaning high risk of bias. The various items were then evaluated for their importance (based upon the judgment of the investigator) when assigning an overall score, classified as very poor, poor, moderate, high and very high quality.

STATISTICAL ANALYSIS

The model used for the analyses is an elaboration of the random-effects model described by Houwelingen et al (29), see Appendix II. In the individual studies the relative risk of CVD when exposed to job strain compared to those who are not exposed to job strain is expressed with an OR, HR or RR. In this study, the dependent variable (y) is a summary statistic of the relative risks presented in the individual studies. CVD is considered a rare disease and therefore OR's and RR's can be interpreted as being similar.

The intercept-only model is equal to the overall pooled estimate for relative CVD risk when exposed to job strain (or to one of its components, that is, low decision latitude or high job demands). To examine the influence of study features on the estimate, the model was extended to contain one or multiple study characteristics (X). The model coefficients (i.e. beta's) indicate the extent to which a study characteristic influence the estimate and give the ratio for the average relative risk in studies with a certain study characteristic relative to the average relative CVD risk

in studies with a reference study characteristic. This is expressed as the ratio of OR's (ROR), as also used in the study by Schulz et al. (30).

A ROR of > 1 indicates that studies in the referent group yield on average lower estimates and a ROR of < 1 indicates that studies in the referent group yield on average higher estimates. For example, a ROR of 1.30 means that the estimate in studies with study feature X were on average 30% higher than in studies with the reference study feature. A ROR near 1 indicates that the study feature does not impact the estimate.

The multilevel character of the model stems from the fact that we allowed a study to contribute multiple results (effects) to the analysis, resulting in two levels of heterogeneity: within study and between study. The way we accounted for such correlated data, is described in appendix II. For both effects (true and observed) a constant correlation was assumed. The SAS proc mixed procedure was used to perform the analyses using restricted maximum likelihood estimation to estimate the model parameters.

Model construction

The univariate associations, given in Table 1, were examined and used to identify the most relevant study characteristics to be associated with the outcome (based on the magnitude of the association and to a lesser extent the width of the confidence interval). These were included into the multivariate model. If study features were highly correlated (e.g. type of association measure and design), the variable that was most strongly associated with CVD risk (mainly based on the magnitude of the association and to a lesser extent the width of the confidence interval) was included. This procedure was followed for all study features, except for the study feature 'correction for confounders within a study'. For this characteristic a different procedure was followed, which is described in Appendix III.

Sub analyses

Two sub analyses were performed: one was performed in a selection of studies that used self-reported exposure and self-reported outcome. The overall pooled relative CVD risk was calculated. The second sub analysis was performed in studies that used self-reported exposure and a more objective outcome (medically diagnosed CVD). Again, the pooled relative CVD risk was calculated and the effect of study features on the relative CVD risk was examined. The results of these sub analyses were compared with the results that were based on all studies, to examine whether conducting the analyses in a specific type of studies changed the impact of study features on the relative CVD risk.

Publication bias

The presence of publication bias was examined for studies that examined the association between job strain and CVD, by means of visual inspection of the funnel plot and statistical testing with the Egger test (31).

RESULTS

The broad search strategy yielded 1560 articles, of which 71 articles remained and were included in the meta regression analysis (see Figure 1). Of these studies, 46 studies were about job strain (2, 6-8, 26, 27, 32-71), 37 studies about job demands (2, 5-8, 10, 26, 32, 33, 35, 38-40, 43, 45-47, 52-54, 56, 59-61, 63, 67, 68, 71-80) and 43 studies about decision latitude (6-10, 12, 26, 27, 32, 33, 35, 36, 38-40, 43, 45-47, 52-54, 56, 59-61, 63, 67, 68, 71, 73, 74, 76-86).

The intercept only model yielded an overall pooled relative CVD risk of 1.30 (95% CI: 1.14-1.46) for employees who were exposed to job strain compared to those who were not. The pooled relative CVD risk was 1.05 (95% CI: 0.97-1.14) for employees exposed to high or intermediate job demands and 1.14 (95% CI: 1.05-1.23) for those exposed to low or intermediate decision latitude compared to those who had high decision latitude.

Univariate associations

In Table 1 the univariate associations are given between the various study characteristics and relative CVD risk.

Good quality studies yielded similar relative CVD risk estimates as poor quality studies, ROR's were 1.07 (95% CI: 0.96-1.19), 1.02 (95% CI: 0.86-1.20) and 0.95 (95% CI: 0.80-1.12) for studies about job strain, demands and decision latitude. The ROR represents the ratio for the average relative risk in good quality studies relative to the average relative CVD risk in poor quality studies, which did not differ from each other.

Table 1: Univariate associations between study characteristics and the reported relative CVD risk.

		Job strain				Job demands				Decision latitude			
Characteristic	Categories	N[a]	n[b]	ROR[c]	95% CI	N[a]	n[b]	RORc	95% CI	N[a]	n[b]	ROR[c]	95% CI
Design	Case control	22	10	1.06	0.79-1.40	17	8	0.89	0.72-1.11	29	8	0.89	0.93-1.38
	Cross sectional	20	7	1.08	0.79-1.49	16	6	1.05	0.86-1.28	19	7	1.02	0.87-1.20
	Nested case control	1	1	3.19	0.78-13.07	7	2	1.02	0.64-1.22	6	1	1.51	0.92-2.48
	Cohort=reference	83	17	1.00	-	84	23	1.00	-	123	26	1.00	-
Follow up duration months	12-73	11	4	0.90**	0.59-1.38	26	8	1.41*	1.12-1.80	44	9	1.04	0.86-1.28
	73-132	45	8	1.17	1.03-1.35	8	5	0.96	0.77-1.17	8	5	1.10	0.87-1.42
	NA [d]	42	8	1.06	0.84-1.36	33	12	1.00	0.85-1.19	48	13	1.09	0.92-1.30
	>134=reference	8	17	1.00	-	57	14	1.00	-	77	15	1.00	-
Gender sample	Only women	24	6	0.77	0.56-1.05	43	10	0.95	0.79-1.14	54	11	1.15	0.99-1.33
	Women and men	35	10	0.92	0.80-1.05	16	8	1.03	0.83-1.30	26	8	1.04	0.84-1.28
	Only men=reference	67	20	1.00	-	65	20	1.00	-	97	22	1.00	-

Table 1 (continued)

		Job strain				Job demands				Decision latitude			
Characteristic	Categories	N[a]	n[b]	ROR[c]	95% CI	N[a]	n[b]	RORc	95% CI	N[a]	n[b]	ROR[c]	95% CI
Maximum age limit of sample	- 65	89	26	1.12	0.80-1.55	59	23	1.15	0.97-1.39	97	27	0.92*	0.77-1.12
	> 65	10	5	1.06	0.75-1.51	26	8	0.98	0.81-1.19	23	7	0.90	0.70-1.16
	Unknown [e]	6	2	0.83	0.54-1.27	5	3	1.54	1.08-2.18	11	2	1.62	0.91-2.36
	- 56=reference	21	5	1.00	-	34	5	1.00	-	46	6	1.00	-
Sample selection	Occupation based	33	6	0.87**	0.64-1.15	42	8	1.14	0.93-1.38	49	7	0.92	0.74-1.14
	Single occupation	5	1	0.44	0.61-0.84	4	1	1.10	0.70-1.77	4	1	0.79	0.47-1.34
	NA [f]	2	1	1.09	0.57-2.12	2	1	1.44	0.93-2.25	2	1	0.88	0.53-1.43
	Population based=ref	86	27	1.00	-	76	28	1.00	-	122	31	1.00	-
Association measure	Prevalence ratio	1	1	1.21*	0.68-2.14	0	0	-	-	0	0	-	-
	Relative risk	6	2	0.55	0.42-0.72	7	3	1.20	0.93-1.54	27	6	0.94	0.79-1.12
	Hazard ratio	70	16	0.89	0.75-1.08	75	20	1.06	0.90-1.26	58	20	0.88	0.75-1.20
	Odds ratio=reference	49	18	1.00	-	42	16	1.00	-	92	16	1.00	-
Measurement of CVD	Questionnaire, doctor confirmed	6	2	1.22**	0.77-1.95	5	2	1.01	0.73-1.39	5	2	0.89	0.62-1.25
	Questionnaire, not / unknown doctor confirmed	10	3	1.35	0.88-2.14	12	5	1.11	0.91-1.35	15	6	1.05	0.87-1.25
	Combination of self reported	0	0	-	-	1	1	1.19	0.88-1.60	1	1	0.92	0.64-1.35
	Diagnostics=reference	110	30	1.00	-	106	33	1.00	-	156	35	1.00	-
Exposure level Job strain	> median vs < median			-	-			1.10*	0.99-1.21			1.18*	1.08-1.29
	High strain vs rest [g]	18	18	0.91	0.97-1.25			-	-			-	-
	High strain vs rest [h]	17	17	1.00	0.73-1.35			-	-			-	-
	High strain vs low strain [i] =ref	19	19	1.00	-			-	-			-	
Type of CVD	Only morbidity	59	22	0.94	0.80-1.10	43	18	1.07	0.86-1.34	48	18	0.97	0.83-1.14
	Morbidity and mortality	52	18	0.92	0.85-1.07	67	19	1.11	0.89-1.40	82	19	0.94	0.79-1.12
	Mortality=reference	15	5	1.00	-	14	5	1.00	-	47	8	1.00	-
CVD subgroup	Stroke	26	6	1.17	0.99-1.42	9	4	0.94	0.76-1.16	30	6	0.97	0.84-1.14
	Stroke and other CVD	16	5	1.01	0.87-1.19	28	8	1.00	0.81-1.23	38	8	0.96	0.78-1.19
	CVD without stroke=ref	84	29	1.00	-	87	29	1.00	-	109	30	1.00	-
CVD subgroup	Ischemic heart disease (IHD)	74	26	0.87	0.72-1.05	79	26	1.08	0.87-1.36	101	27	1.05	1.02-1.23
	IHD and other CVD	26	9	0.83	0.69-0.99	36	12	1.04	0.87-1.25	46	12	0.98	0.81-1.17
	CVD without IHD=ref	26	6	1.00	-	9	4	1.00	-	30	6	1.00	-
CVD subgroup	Acute myocardial infarction(AMI)	30	15	0.81	0.69-0.96	22	12	0.94	0.76-1.15	33	12	0.99	0.90-1.38
	AMI and other CVD	59	17	0.83	0.65-0.90	84	23	1.04	0.87-1.25	105	24	0.90	0.86-1.32
	CVD without AMI=ref	37	10	1.00	-	18	8	1.00	-	39	10	1.00	-

Table 1 (continued)

		Job strain				Job demands				Decision latitude			
Characteristic	Categories	N[a]	n[b]	ROR[c]	95% CI	N[a]	n[b]	RORc	95% CI	N[a]	n[b]	ROR[c]	95% CI
Type of questionnaire	Different [i]	42	14	1.63*	1.22-2.23	58	20	0.97	0.80-1.19	59	18	1.11	0.90-1.38
	JCQ-like	61	15	1.30	0.99-1.72	46	10	0.91	0.73-1.14	98	15	1.07	0.86-1.32
	Original JCQ=reference	23	7	1.00	-	20	8	1.00	-	20	8	1.00	-
Type of answer scales	Frequency [k]	38	13	1.17*	0.92-1.49	60	14	0.92*	0.79-1.07	108	18	1.13	0.95-1.34
	Strain	16	2	1.39	0.86-2.20	4	1	1.04	0.70-1.50	12	1	0.76	0.47-1.22
	Dichotomous	14	5	1.84	1.19-2.77	19	8	1.36	1.08-1.74	13	6	1.17	0.87-1.57
	Unknown [l]	8	2	2.14	1.03-4.39	4	4	0.93	0.73-1.19	7	3	1.04	0.80-1.34
	Opinion=reference	50	14	1.00	-	37	13	1.00	-	37	13	1.00	-
Type of exposure	Job Exposure Matrix (JEM)	11	6	0.89	0.68-1.16	20	8	0.81*	0.70-0.92	58	12	1.07	0.94-1.21
	Questionnaire=ref	115	30	1.00	-	104	30	1.00	-	119	30	1.00	-
Number of exposure assessments	>1	4	3	1.08	0.93-1.26	2	2	0.89	0.60-1.19	6	3	1.07	0.90-1.30
	1=reference	122	33	1.00	-	122	36	1.00	-	171	38	1.00	-
Study quality	Good	63	12	1.07	0.96-1.19	49	12	1.02	0.86-1.20	67	12	0.95	0.80-1.12
	Poor=reference	63	25	1.00	-	75	26	1.00	-	110	29	1.00	-
Publication year	<1990	10	4	1.30**	0.93-1.82	2	2	0.90	0.60-1.32	1	1	0.87*	0.52-1.49
	1990-2000	38	12	0.99	0.88-1.13	27	11	0.87	0.74-1.01	39	12	1.03	0.86-1.22
	>2000=reference	78	22	1.00	-	95	25	1.00	-	137	27	1.00	-
Country of study	West Europe (United Kingdom, Netherlands, Germany, Belgium)	19	5	0.98*	0.78-1.23	39	6	1.02*	0.84-1.23	39	6	1.04	0.84-1.30
	Japan	21	4	1.32	0.92-1.92	15	5	1.20	0.88-1.65	11	4	0.91	0.59-1.39
	USA, Hawai	15	5	0.62	0.50-0.77	11	6	0.87	0.73-1.04	15	7	0.88	0.72-1.08
	Other (Turkey, Lithuania, Czech Republic)	5	3	0.67	0.45-1.00	9	3	0.65	0.47-0.90	13	3	0.88	0.63-1.23
	Scandinavia=ref	66	18	1.00	-	50	18	1.00	-	99	20	1.00	-
Time of study	1950-1970	24	8	0.84	0.55-1.30	25	10	0.83	0.68-0.99	34	9	0.90	0.69-1.15
	1990-2000	75	22	0.91	0.61-1.36	65	21	0.98	0.82-1.17	112	25	0.91	0.28-3.03
	Unknown [m]	2	1	1.19	1.49-2.92	1	1	0.91	0.27-3.06	1	1	0.91	0.72-1.14
	1980-1989=ref	25	4	1.00	-	33	6	1.00	-	30	5	1.00	-

[a] = number of results, [b] = number of studies, [c] = ROR=ratio of the odds ratio's is expressed as the odds of CVD risk in studies with a specific characteristic relative to the odds of CVD risk in studies with a reference characteristic, [d] = case control studies and cross sectional studies, [e] = one study did not specify the age limit of the sample, [f] = multicenter study in which different samples were used: 3 centers had an occupation based sample and 3 centers had a population based sample, [g] high strain = demands above median value and decision latitude below median value versus the other three quadrants, [h] high strain = alternative formulations than based on median value, [i] high strain = demands above median value and decision latitude below median value versus low strain, [j] contains one study that uses the Karasek method (based on occupation) for assigning exposed- not exposed status, [k] 3 studies use a work organization matrix, in which the demands scale has yes-no answers scales and decision latitude scale has frequency answer scales, [l] 4 studies do not report which scales they use , [m] 4 studies did not report the time period, * P-value of the variable < 0.05, ** P-value of the variable< 0.10

Multivariate associations for job strain, job demands and decision latitude

The country in which studies were performed influenced the estimate. Studies performed in Japan yielded on average higher estimates than studies performed in Scandinavia. The ROR was 1.30 (95%CI: 0.93-1.84), which means that the estimate in Japanese studies was on average 30% higher than in Scandinavian studies, although not statistically significant. Studies performed in the USA and 'other' countries yielded on average lower estimates than Scandinavian studies (see Table 2).

The type of exposure questionnaire was associated with the estimate. Studies that used 'different' questionnaires to assess job strain yielded on average 43% higher estimates (ROR: 1.43, 95% CI: 1.07-1.92) than studies that used the original JCQ. Also the type of outcome assessment influenced the estimate, where studies that used questionnaires to assess CVD yielded on average 39% higher OR's than studies that used medically confirmed data on CVD (ROR: 1.39, 95% CI: 0.97-1.97).

For the association between job demands and CVD, again country in which the study was performed influenced the estimate. Studies performed in countries categorized as 'other' yielded an on average 43% lower estimate than studies performed in Scandinavia, see Table 7 (ROR: 0.57, 95% CI: 0.43-0.76). Also the type of exposure assessment influenced the estimate, where studies that used a JEM to assess job demands yielded an on average 19% lower estimate than studies that used questionnaires to assess job demands (ROR: 0.81, 95% CI: 0.71-0.91), see Table 2.

Table 2: Results from the multivariate model[a] for the association between study characteristics and reported relative CVD risk, according to exposure (job strain, job demands, decision latitude).

		Job strain		Job demands		Decision latitude	
Characteristic	Categories	ROR[b]	95% CI	ROR[b]	95% CI	ROR[b]	95% CI
Country of study	West Europe(UK, Netherlands, Germany, Belgium)	1.09*	0.84-1.43	0.94*	0.81-1.07		
	Japan	1.30	0.93-1.84	0.98	0.81-1.07		
	USA, Hawai	0.74	0.59-0.93	0.98	0.84-1.17		
	Other (Turkey, Lithuania, Czech republic)	0.61	0.41-0.90	0.57	0.43-0.76		
	Scandinavia = reference	1.00	-	1.00	-		
Type of questionnaire	Different	1.43**	1.07-1.92				
	JCQ-like	1.23	0.97-1.54				
	Original JCQ = reference	1.00	-				
Measurement of CVD	Questionnaire, doctor confirmed	0.76**	0.48-1.21				
	Questionnaire, not / unknown dr confirmed	1.39	0.97-1.97				
	Diagnostics = reference	1.00	-				

Table 2 (continued)

		Job strain		Job demands		Decision latitude	
Characteristic	Categories	ROR[b]	95% CI	ROR[b]	95% CI	ROR[b]	95% CI
Association measure	Prevalence ratio	1.55*	0.84-2.83				
	Relative risk	0.70	0.55-0.91				
	Hazard ratio	1.06	0.89-1.26				
	Odds ratio = reference	1.00	-				
Gender of sample	Only women	0.86**	0.70-1.04	0.95	0.89-1.20	1.17*	1.03-1.34
	Women and men	0.85	0.77-0.98	1.06	0.93-1.21	1.07	0.87-1.34
	Only men = reference	1.00	-	1.00	-	1.00	-
Age	Adjustment yes	1.23	1.08-1.42				
	Adjustment no = Reference	1.00	-				
Gender	Adjustment yes	0.87	0.77-0.98				
	Adjustment no = Reference	1.00	-				
BMI	Adjustment yes	0.89*	0.82-0.97				
	Adjustment no = Reference	1.00	-				
Age	Adjustment yes			0.87	0.72-1.04		
	Adjustment no = Reference			1.00	-		
Alcohol	Adjustment yes			1.27	1.03-1.55		
	Adjustment no = Reference			1.00	-		
SES	Adjustment yes					0.88*	0.83-0.93
	Adjustment no = Reference					1.00	-
Type of exposure	Job Exposure Matrix (JEM)			0.81*	0.71-0.91		
	Questionnaire = reference			1.00	-		
Follow up duration	12-73			1.32*	1.11-1.58		
	73-132			0.96	0.83-1.11		
	>134= reference			1.00	-		
Exposure level	> median versus < median			1.11**	1.00-1.22	1.17*	1.08-1.26
Type of answer scales	Frequency			1.04**	0.90-1.22		
	Strain			0.96	0.73-1.26		
	Dichotomous			1.30	1.09-1.54		
	Unknown			0.90	0.73-1.08		
	Opinion = reference			1.00	-		
Max age limit of sample	- 65					0.90*	0.76-1.05
	> 65					0.83	0.66-1.04
	- 56 = reference					1.00	-
Design	Case control					0.90**	0.91-1.34
	Cross sectional					0.99	0.90-1.15
	Nested case control					1.90	1.12-3.19
	Cohort = reference					1.00	-

[a] The procedure for the selection of the variables into the multivariate model is described in the methods (model selection)

[b] ROR= ratio of the odds ratio is expressed as the odds of CVD risk in studies with a specific characteristic relative to the odds of CVD risk in studies with a reference characteristic, * P-value of the variable < 0.05, ** P-value of the variable< 0.10

Statistical adjustment for potential confounders within studies was associated with the estimate. In studies that examined the association between job strain and CVD, adjustment for the following risk factors influenced the estimate: adjustment for age yielded on average a 23% higher OR than studies that did not adjust for age (ROR:1.23, 95% CI: 1.08-1.42), adjustment for gender yielded on average a 13% lower estimate (ROR: 0.87, 95% CI: 0.77-0.98), adjustment for BMI yielded on average a 11% lower estimate (ROR: 0.89, 95% CI: 0.82-0.97) than studies that did not adjust for these risk factors.

In studies that investigated the association between decision latitude and CVD, adjustment for SES yielded an on average 12% lower estimate (ROR: 0.88, 95% CI: 0.83-0.93) than studies that did not adjust for SES.

Sub analyses

Studies that used self-reported exposure and self-reported outcome yielded a pooled OR of 1.56 (95% CI: 1.36-1.78), while studies that used medically diagnosed outcomes yielded a pooled OR of 1.31 (95% CI: 1.10-1.54). The impact of the study characteristics on the relative CVD risk in the sub analysis conducted in studies that used medically diagnosed outcomes was similar to the impact of the study characteristics on the CVD risk in all studies.

Publication bias

Visual inspection of the funnel plot indicated the presence of bias, since smaller studies (less precision) showing no effects were missing. The Egger test confirmed the finding of bias (p=0.004). Results are not presented.

DISCUSSION

With this study we explored the association between study characteristics and outcome in studies that examined the association between job strain and CVD, using an extended form of meta regression. We found that several study features were associated with the relative CVD risk. The main findings which we consider worthwhile to explore in future research or which require some additional in depth discussion will be described below. Furthermore, we discuss the strengths and limitations of this study which is important for the proper interpretation of the results.

Study features that are associated with the size of the CVD risk

To our knowledge, there are no studies that have assessed the association between study features and the study outcome in the field of job strain and CVD. Kivimaki (87) performed a meta-analysis on cohort studies that explored the association between job strain and CVD and reported a pooled estimate of 1.43 (95% CI: 1.15-1.84), which is similar to the overall pooled estimate found in the present study.

In the current study, results are presented for job strain, job demands and decision latitude. In the majority of studies, job strain was analyzed as a quadrant term (the combination of having a demands score above the median and having a decision latitude score below the median) or as an alternative combination term. As has been mentioned by Mikkelsen et al (88) this type of job strain measure does not test an interaction effect between decision latitude and job demands and an effect reported in these studies may be due to an effect of only one of these two factors.

In this study, studies that used different endpoints were grouped together. The main underlying cause of myocardial infarction, angina pectoris and stroke (ischemic type) is atherosclerosis (89, 90), which is one of the hypothesized mechanism through which exposure to job strain could lead to CVD (13, 91). Furthermore, it is not uncommon for studies that have examined the association between job strain and CVD to combine several endpoints into one outcome (26, 37, 79, 85). The only point of concern might be within the group of stroke, where the pathway between hemorrhagic strokes and ischemic stroke differs. High blood pressure is more important in the former and atherosclerosis is more important in the latter (89, 90). Within the meta regression analysis only three studies (53, 69, 86) of the five (53, 57, 69, 75, 86) that focused on stroke as an endpoint, examined the effect of job strain (or one of the components) on different stroke subtypes, where results have been conflicting regarding the effect of job strain on different sub types.

In the current study no association was found between type of study design and the outcome. On forehand, a more conservative estimate for the cohort studies was expected since information bias and recall bias are thought to give an overestimation of the association and are more likely to occur in cross sectional and case control studies. However, the included cohort studies were also not free from bias. It is difficult to assess whether selective drop out had occurred during follow up and also not every cohort study had data about potential confounders and thus did not adjust for them. Furthermore, the majority of cohort studies used a single time measurement for exposure and assumed that exposure remained stable during follow up, while little is known about the variability of exposure during follow up and how this affects the reported association. Swaen et al (92), who investigated whether design was associated with a false positive finding in occupational cancer epidemiology, also did not find such an association.

In a previous review by Eller et al (13) it was already pointed out that a large variation exists in the measurements of exposure. The current study showed that lower relative CVD risks were reported in studies that used a job exposure matrix (JEM) to assess job demands than in studies that used questionnaires to assess job demands. This is consistent with previous conducted studies (32, 61, 63, 68) and findings of reviews (13). The demands scale is considered to be the most subjective component of the job strain formulation (93) and assigning exposure status based on job title does not capture the perception differences among employees in the same job. This

also raises the question whether the JCQ measures the work environment or the perceived work environment, which is crucial for prevention. The current study adds information by showing that also the type of questionnaire is related to the estimate which raises the question, what these different instruments measure? These findings underscore the importance to assess the validity of the currently used exposure measures for assessing work stressors. Since the JCQ and variations on the JCQ have never been tested whether they are indeed associated with work stress and whether they indeed assess the most important dimensions of the work environment, which are basic properties of a measure to accurately assess the psychosocial work environment. A valid exposure assessment is critical in properly establishing the relation between job strain and cardiovascular disease (4, 94). Therefore, more research is needed to determine which specific factors in the work environment (such as type of job demands (95, 96)) measure the concept of job stress most appropriately and can be used to most accurately assess the association between job stress and CVD.

In this study, country in which the study was performed was associated with the reported CVD estimate. Different job strain levels across countries could explain this. However, since in the majority of the studies exposure level was not given by absolute values, but according to categories this was not possible to examine. Only few studies (97, 98) compared the absolute values of job strain between countries and did not found a difference in exposure level. Other explanations are giving different meanings to items depending on e.g. culture (13, 95, 99) or not perceiving job strain as a risk factor.

Furthermore, in this study we also found that studies that used self-reported CVD as outcome yielded on average higher relative CVD risks than studies that used medically diagnosed outcomes. This might indicate an overestimation of the association between job strain and CVD risk as employees exposed to high job strain might confuse job strain symptoms with cardiovascular symptoms (angina pectoris). Common method bias may also be an explanation (100), where the observed association in studies that used self-reported outcome and self-reported exposure might be inflated due to bias. Negative affectivity has been suggested as a source of bias that can produce common method bias, since self-reports of individuals high in negative affectivity are likely to be biased in a negative direction, leading to over reporting of job stressors and physical symptoms. The results of the sub analysis conducted in studies that used self-reported outcome and exposure suggest such an inflated association.

No association was found between study quality and average relative CVD risk, which was against our expectations since in poor quality studies the risk of bias is more substantial than in good quality studies and we expected that most forms of bias would yield an overestimation of the estimate, thus poor quality studies were hypothesized to yield an on average higher estimate compared to good quality studies. In this study the quality assessment was performed by one

investigator, which is a disadvantage since rating of the quality is a rather subjective procedure. Especially since the overall judgment was not simply based upon counting the scored items but several items weighted more than others in the assignment of an overall score. Furthermore, studies that were rated as very good and good were grouped together, as were the moderate and poor quality studies, which decreased the contrast in quality and could have led to an underestimation of the effect of study quality on the effect estimate.

Limitations and strengths of the study

Publication bias was present in this study, which could have led to an overestimation of the pooled estimate (101, 102). However, how publication bias could have influenced the association between the study features and CVD risk is more difficult to predict, because it depends on the distribution of the study features in relation to the size of the CVD risk in the non-published studies. It is unlikely that publication bias influenced our results for the majority of study features, since this would indicate that study features in the small studies showing no effects differ systematically from study features in the larger studies and small studies that show an effect. Editors and reviewers dislike negative studies and rejection is not related to study quality (103).

Furthermore, the correlation between the multiple results from the same sample had to be modelled since these were not independent. We assumed a constant correlation for multiple results within one study and that this was the same across all studies. While a constant correlation seems plausible for some results, for other results (such as results belonging to different CVD outcomes or exposure, different follow up length) this seems less likely. Testing the possible implications of potentially violating this assumption was not feasible. However, we were able to test the impact of a change in the correlation of the between study differences. This showed that the correlation between the random effects had only a minor influence on the estimates; the direction and the magnitude of the effect remained the same.

The benefit of performing a meta-regression on correlated data is that multiple results reported by one study can be used to its full potential and the prevalence of certain study characteristics was increased. The other advantage is the availability of the within study variation for some study characteristics. These results provide the most direct/ valid estimates of the impact of the study characteristics because all the other study features in that study are held constant and a difference in effect size can therefore be assigned to that specific characteristic. Furthermore, using correlated data increased the study power.

The risk of false positive findings is present because of the multitude of study characteristics that were evaluated (104-106) and the risk of confounding is possible due to the combination of relative few studies and a multitude of study characteristics. However, the associations

presented in this study are plausible and are in line with results available from individual studies and reviews as described above. Furthermore, we were able to adjust the results for the most relevant study characteristics in the multivariate model. Also, the sub analysis performed in a selection of studies that only used medically diagnosed outcomes yielded similar estimates for the study features, as compared to the results based on all types of studies. Furthermore, using a random effects model accounts for unexplained residual heterogeneity.

In conclusion, with this study it was shown that study features are associated with the estimate. With future research it should be examined why country, type of CVD assessment, type of exposure questionnaire and gender of the sample are related to the estimate. Most of these factors seem to be related to the validity of assessing the psychosocial work environment or outcome, which probably explains why the results in this field are so conflicting. If the measures used are not measuring what we intend to measure, the estimate is influenced by other factors. These issues need to be investigated and resolved, e.g. initializing research in which the validity of measuring the psychosocial work environment is examined, which can be used to examine the association between work stress and CVD more accurately.

Appendix I: categorization of the variables

Outcome assessment was classified into three categories: questionnaires in which people were asked whether they had CVD, questionnaires in which people were asked whether they had *doctor confirmed* CVD and the use of diagnostics (review of medical dossier, hospital and death registers, diagnostic criteria).

Three types of exposure questionnaires were included: original JCQ (defined as 9 items for control and 5 items for demands and an answer category 'disagree-agree'), JCQ-like (defined as 6-15 JCQ comparable items for control, 4-7 JCQ comparable items for demands and/or a different answer category than disagree-agree) and 'different' (the number of items is different from the number of items defined under JCQ-like and/or the items were different altogether but they still needed to be comparable to what the demand control model intends to measure).

In the individual studies that explored the job strain and CVD association, adjustment for confounders was performed. Which confounders were included and the manner of adjustment differed: some studies analyzed in different steps to explore the effect of adjustment for a specific group of confounders. The reason for this are differences in the theory about whether some confounders are actually intermediates and therefore should not be included in the model, but also because of differences between studies in the (lack of) availability of data about these confounding factors. Another issue regarding these confounders is the correlation between some of these risk factors, for instance hypertension is correlated with cholesterol and BMI. For each confounder a dichotomized variable was made (yes versus no adjustment).

The exposure level for decision latitude and job demands was mostly presented as tertiles and quartiles in the published studies. To standardize these exposure categories and thereby to enhance the comparability of the various exposure levels among studies we dichotomized all these categories into two exposure levels: above and below the median value. The procedure which was used to standardize the exposure levels will be clarified by means of the two following examples: if a study presented the CVD risk for employees exposed to the fourth quartile of job demands compared to employees exposed to the first quartile, the difference between the two exposure groups was calculated by: 7/8 minus 1/8 = 6/8 = 0.75. If a study presented the CVD risk for employees exposed to the highest tertile of job demands compared to employees exposed to the lowest tertile, the difference between the two groups was calculated by: 1/6 minus 5/6=4/6=0.67. This was done for all categories; finally this new variable was divided by two.

For job strain, we used the categories as they were presented in the studies, which are (most often) conform to the theory of Karasek (2). These were grouped into three categories: high strain versus the other three quadrants (low strain, passive and active), high strain versus low strain and high strain defined as alternative formulations than based on median value.

The quality of the included studies was categorized into good (the very good and good studies) and poor (moderate, poor, very poor studies).

Appendix II: The random effects model

The model used for the analyses is given by

$$\begin{bmatrix} y_{11} \\ y_{12} \\ y_{21} \\ y_{31} \\ y_{32} \\ y_{33} \\ \dots \end{bmatrix} = \mathbf{X\beta} + \mathbf{u} + \boldsymbol{\varepsilon}$$

where y_{ij} denotes the j^{th} observed effect in the i^{th} study (e.g., study 1 provided two effects), $\mathbf{X}$ is the design matrix including the values of moderators (i.e., study characteristics), and $\boldsymbol{\beta}$ denotes the vector of regression coefficients. The vector $\mathbf{u}$ denotes random effects to model (residual) heterogeneity in the study-specific true effects. We assume that the variance-covariance matrix of $\mathbf{u}$ has a compound symmetric structure with constant variance τ^2 and ρ denoting the correlation of the true effects within the same study:

$$Var[\mathbf{u}] = \begin{bmatrix} \tau^2 & \rho\tau^2 & & & & & \\ \rho\tau^2 & \tau^2 & & & & & \\ & & \tau^2 & & & & \\ & & & \tau^2 & \rho\tau^2 & \rho\tau^2 & \\ & & & \rho\tau^2 & \tau^2 & \rho\tau^2 & \\ & & & \rho\tau^2 & \rho\tau^2 & \tau^2 & \\ & & & & & & \dots \end{bmatrix}$$

The variance-covariance matrix of the vector of sampling errors, $\boldsymbol{\varepsilon}$, is assumed to take on a structure of the form:

$$Var[\boldsymbol{\varepsilon}] = \begin{bmatrix} v_{11} & \lambda\sqrt{v_{11}}\sqrt{v_{12}} & & & & & \\ \lambda\sqrt{v_{11}}\sqrt{v_{12}} & v_{12} & & & & & \\ & & v_{21} & & & & \\ & & & v_{31} & \lambda\sqrt{v_{31}}\sqrt{v_{32}} & \lambda\sqrt{v_{31}}\sqrt{v_{33}} & \\ & & & \lambda\sqrt{v_{31}}\sqrt{v_{32}} & v_{32} & \lambda\sqrt{v_{32}}\sqrt{v_{33}} & \\ & & & \lambda\sqrt{v_{31}}\sqrt{v_{33}} & \lambda\sqrt{v_{32}}\sqrt{v_{33}} & v_{33} & \\ & & & & & & \dots \end{bmatrix}$$

where v_{ij} is the (approximately) known sampling variance of the observed effect y_{ij} and λ denotes the unknown correlation between the errors within the same study. We assume that λ is constant across all studies. For a given value of λ, $Var[\boldsymbol{\varepsilon}]$ can be computed and then τ^2, ρ, and the coefficients in $\boldsymbol{\beta}$ can be estimated with restricted maximum-likelihood estimation (assuming normality of the

distribution of **u** and **ε**) as described by van Houwelingen et al (29). We therefore estimated λ by repeatedly fitting the model above using various assumed values for λ to determine which value maximizes the restricted likelihood. Using this approach, we estimated correlations of 0.86, 0.35 and 0.55 for job strain, demands and control, respectively. The results provided in the text are those obtained using these maximum likelihood estimates for λ.

Appendix III: model construction for the study feature 'correction for confounders within a study'

The impact of studies that adjusted for possible confounders (e.g. age, BMI, SES etc.) compared to studies that did not adjust for these confounders on the reported effect size had to be assessed in such a manner that all these confounders were included simultaneously in the model. The reason for this is that these confounders are highly correlated and the issue is not whether adjustment has taken place, but rather for which ones. However, the multitude of study characteristics (confounders and factors such as design, outcome assessment etc.) restricted us to include all these variables at once in the model because over fitting of the model had to be prevented.

Thus, all the confounders were simultaneously included in one model to quantify the effect of adjusting for a specific confounder compared to not adjusting for that specific confounder, adjusted for the impact of adjusting for other confounders.

If adjustment for a specific confounder was significantly associated with the CVD risk estimate (judged on the magnitude of the association in combination with the width of the confidence interval), the other selected study features (such as country, type of questionnaire etc) were included into the model to assess whether the association between adjustment for a confounder and the CVD risk still remained after inclusion of other study features.

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3

Substantiating the concept of work strain; its implication for the assessment of work stressors

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Objective
To assess which work stressors are substantially contributing to work strain and examine their relative contribution.

Methods
We prospectively examined the association between work stressors and work strain, which was defined as employees reporting ill due to work stress. Relevant work stressors were combined into a stressor score with each stressor having its own relevance. Standardized odds ratios were calculated using logistic regression analysis and used to compare the associations obtained between already existing scales and the stressor score with work strain.

Results
The stressor score yielded a SOR of 1.89 (95% CI: 1.49-2.41) for work strain, while psychological demands (JCQ) yielded a SOR of 1.46 (95% CI: 1.09-1.88) for work strain.

Conclusions
We were able to extend and substantiate the range of relevant work stressors into a more comprehensive measure, which should be used to optimize prevention strategies.

INTRODUCTION

The association between work stress and health has been examined in the last decades by identifying workplace characteristics that may have a negative impact on health. The main assumption is that these work stressors may lead to negative health effects through the process of stress and strain (1). The most often used work stress model is the Demand Control Model (2). The combination of low decision latitude and high psychological demands, which is called job strain, has been examined in relation to many health outcomes. However, the operationalizations of these theoretical concepts have never been tested whether they are indeed associated with work stress before they were applied to examine the association between work stress and health.

Since the pathway from exposure to work stressors to health is assumed to be mediated though the process of stress and strain, the actual contribution of work stressors to work stress should be examined in order to gain more insight into which stressors have the highest stress potential. If, in turn, these stressors are associated with health we can assume with more certainty that these stressors impact health through the process of stress and strain. This is necessary because other mechanisms might be involved in the relationship from exposure to health. For example, nurses are exposed to high emotional demands but the prevalence of smoking among nurses is also high (3). When the association between emotional demands and health is examined and a positive association is found, it's difficult to entangle whether the health effect was preceded by work stress, as a consequence from exposure to high demands, or whether the health effect was a consequence of smoking itself.

An examination of the relative importance of existing stressors on work stress is relevant for four reasons. First, to consider which work conditions are currently perceived as most harmful (4-6). This is necessary since work life is under continual change and the most often used concepts were developed several decades ago. The operationalization of work stressors of the Demand Control model might no longer match the current work stressors (7). Due to the changing labor market more people are employed in health care, education, knowledge production and less people are employed in production. Thus, a reconsideration of the relative importance of stressors could lead to new insight about which stressors are relevant in enhancing health risk (7).

Secondly, the exposure to work stressors in the work place is multifarious and the use of theoretically based stress models rule out the exploration of other work stressors (7). Examining which work characteristics are substantially contributing to work stress is important to assess which stressors are most relevant and should be incorporated into a more comprehensive exposure measure.

Third, within the currently used stressor scales each item is given the same weight, which suggests that each item is equally important. However, it is probable that certain items might be more stressful than others. This should be examined and if this is the case, this should be accounted for by assigning different weights to the items.

Fourth, knowledge about which work characteristics are most harmful in contributing to work stress is a prerequisite for successful prevention strategies. Since adults spend a great deal of their day at work, successful prevention of work stressors could lead to health gain and reduction of health care costs. In 2005, in the Netherlands 16% of the employees reported work stress and the main reasons for work related absence were high work load and work related stress. Similar percentages of work stress were reported in the United Kingdom (12%), Germany and Ireland (16%), Czech Republic (17%) and France (18%). Higher levels were reported in Greece (55%) and Sweden (38%) (8). Thus, clarifying which work characteristics contribute to work stress could reduce short term consequences, such as work related absence, if prevention strategies are developed in such a manner that they are aimed at the most relevant ones.

In the occupational stress literature, many definitions for stressor, stress and strain are prevailing. To prevent misunderstanding, in this study we will adhere to the following theoretical framework consisting of the elements: work stressor – work stress – work strain (– health), where the term work stressors refers to a large number of work related environmental conditions thought to impact the health and well-being of the worker (5). Stress is defined as an individual state characterized by a combination of arousal and displeasure (9). Exposure to stress can result in strain (1), which can manifest as a short term health outcome that might still be reversible or as an irreversible health effect. The main assumption that accompanies the theoretical framework is that if the following element has occurred the preceding element was conditional for this occurrence. This means that work strain was preceded by work stress and work stress was preceded by exposure to work stressors.

In the present study we aim to substantiate the concept of work strain, within the framework of work stressor – work stress – work strain. So far no appropriate measure is available for work stress. To overcome this obstacle we used two proxy measures for work stress, which consisted of two work strain definitions. In this study the following research question will be addressed: which work characteristics are associated with work strain and what is the relative contribution of each work stressor to work strain?
In this study, an approach is used where the work strain cases are the point of reference and we will examine which work stressors are contributing to becoming a work strain case. Our expectation is that a significant difference in stressor scores should be present among employees reporting work strain and among those without work strain.

METHODS

Design

Data of the Maastricht Cohort Study (MCS) was used. The MCS is a prospective cohort study, started in 1998. Different companies and organizations were contacted to ensure that employees from different sectors and trades were included. Only companies with over 100 employees were contacted. From the 79 companies contacted, 45 agreed upon participation. Men and women between 18-65 years with an employment contract of at least 16 hours were approached. This resulted in 26,978 potential participants and resulted in 12,140 employees that participated at baseline (response rate is 45%). The attrition rates were 80%, 67% and 50% one, two years and 10 years later. The study is described elsewhere in more detail (10). For the current study, we used the measurements of work characteristics that were performed annually: May 1998 (T0=baseline), May 1999 (T3) and May 2000 (T6). For the two case definitions (see work strain I and work strain II section) we used several measurements. For work strain I, sickness absence was measured in May 1999 (T3), September 1999 (T4), May 2000 (T6), September 2000 (T7). For work strain II data of T3 was used.

Work stressors

For an overview of the work stressors, see Table 1. The answer categories of the JCQ consist of Likert scales ranging from very much agree to very much disagree. The other items have dichotomous answer scales (yes/ no).

Work strain I

Work strain I was defined as employees who reported sickness absence due to some form of work stress such as: work pressure (is too high), having physical complaints due to work pressure, being overworked, overloaded, too much stress at work. These cases were identified from phases T3, T4, T6 and T7. The non cases consisted of employees who reported sickness absence due to other reasons or did not report sickness absence at all. The non cases were included from the same phases from which the cases were identified and yielded multiple observations for the non cases.
Sickness absence was phrased as whether the employee had been absent during the previous four months. Employees were asked to report the main reason of their last sickness absence.
Work characteristics were measured at T0, T3 and T6. Work stressors at T0 were associated with work strain at T3, work characteristics at T3 were associated with work strain at T4 and T6 and work characteristics at T6 were associated with work strain at T7. See table 2 for an overview of the used measurements per phase. Employees were excluded if the start of sickness absence preceded the measurement of the stressors, if they were not working at the time of exposure measurement due to sickness or pregnancy leave or if they had two jobs.

Table 1: Overview of work characteristics: scales, items and instrument.

Work stressor scale	Items	Source
Emotional demands	Confronted with personally upsetting things	VBBA(12)
	Personally attacked or threatened	
	Upsetting work situations	
	One or more shocking events at work during the last year, e.g. accident, violent crime, sexual harassment or aggression at work	
	Getting annoyed by others	VAG(29)
Cognitive demands	Work requires continuous attention	VBBA(12)
	Work requires precision	
	Work is mentally strenuous/ requires mental effort	
	Worried about safety at work	
	Work is too simple	VAG(29)
Psychological demands	Excessive work demands	JCQ(30)
	Conflicting demands	
	Insufficient time to do work	
	Work very fast	
	Work very hard	
	Hectic job	
	Often interrupted during work	
	Job requires long and intensive concentration	
	My work pace is often suppressed by others	
Decision latitude	Keep learning new things	JCQ(30)
	Can develop skills	
	Job requires skill	
	Task variety	
	Work not repetitious	
	Job requires creativity	
	Have freedom to make decisions	
	Can choose how to perform work	
	Have a lot to say on the job	
Physical demands	Strenuous work	VBA(31)
	Work in same position	
	Uncomfortable positions during work	
	Repetitive movements	
	Lift or carry heavy weight	
Conflicts at work	Conflict with colleagues	VBBA (12)
	Conflict with supervisor	
Job security	Afraid of losing job in the near future	VBBA(12)
	Does the job offers enough security/ stability	VAG(29)
Role clarity	Clear task description	VBBA(12)
	Clear description of job responsibility	
Career possibilities	Enough possibilities for additional education	VBBA(12)
	Enough possibilities for personal development and growth.	
	Sufficient career possibilities	

Table 1 (continued)

Work stressor scale	Items	Source
Working overtime	Working overtime	Self-formulated
*Commitment**	Do you feel obligated towards the company to stay for a few more years	
Social support co worker	Coworkers take a personal interest in me	JCQ(30)
	Coworkers are friendly	
	Coworkers are helpful in getting things done	
	Coworkers are competent in doing the work	
Social support supervisor	Supervisor is concerned about the welfare of those working under him/her	JCQ(30)
	Supervisor pays attention	
	Supervisor is helpful in getting the job done	
	Supervisor is successful in getting people to work together	
Effort and appreciation	Is there a match between your income and your effort	VEIBA(32)
	Is there a match between the appreciation for your work and effort	
Fairness	Is there a match between your colleagues' effort and income	VEIBA(32)
	Is there a match between your colleagues' effort and appreciation	

*only one commitment item was included in this study, since the other items are not considered to be a stressor

Table 2: Overview of the used study phases from which the measurements for work stressors and work strain are used, for work strain I and work strain II.

Work stressor assessment	Work strain assessment	Time line between exposure and outcome
Work strain I		
May 1998 (T0)	May 1999 (T3)	8 months*-one year
May 1999 (T3)	Sept 1999 (T4), May 2000 (T6)	1 month*-one year
May 2000 (T6)	Sept 2000 (T7)	1 month*-4 month
Work strain II		
May 1999 (T3)	May 1999 (T3)	-

* Sickness absence was phrased as whether the employee had been absent during the previous four months, therefore the time line ranges from 4 months before the work strain assessment

Work strain II

Work strain II is the combination of an affirmative answer to the GHQ item (11) 'have you been experiencing constant pressure lately' with answer categories: a bit more than usual and much more than usual in combination with an affirmative answer to the VBBA item (12) 'Do you find it difficult to relax after a working day'. Thus both questions needed to be answered affirmative by the employees. This definition was chosen to get a closer approximation of stress as an individual state of displeasure and a less progressive state of strain. The time period between exposure and outcome is assumed to be much shorter, as this definition indicates a feeling of being under pressure, which can be considered a more immediate reaction. Therefore, we chose to measure strain and stressors at the same time (T3), the population at this phase consisted of 9,655 employees. Employees were excluded if they had a missing in one of the two items used for the construction of work strain II case definition, if they were work strain II case at T0 and T3, if they were not working at the time of exposure measurement due to sickness or pregnancy leave or if they had two jobs, resulting in 8,026 employees.

Other factors

The following factors were assessed at baseline: gender, age, education level (low: primary school, lower vocational school, medium: lower secondary school, intermediate vocational school, upper secondary school, high: upper vocational school and university), having a longstanding chronic disease (yes-no), having psychological problems, such as depression, anxiety (yes- no), work hours per week (less than 16 hours, 16-25, 26-35, 36-40, more than 40), type of employment (temporary or permanent position), performing shift work (yes-no), having a supervising function (yes-no). Also life events and work family conflict were measured.

STATISTICAL ANALYSIS

The mean scores of work stressors were compared between the work strain cases and non work strain cases. The amount of missing values in the scales and individual items was low (1-4%) and therefore we decided that in case of missing values in one of the stressors, this item was left out from the analysis. All analyses were performed using the statistical package SAS 9.2.

Logistic regression analysis was used to examine the association between the work stressor scales and work strain. Unadjusted odds ratios were calculated and transformed into standardized odds ratios (SOR), making the odds ratios more comparable for variables that varied in their type of scales. Therefore, the following calculation was performed: SOR= exp (ln (OR)*sd). The SOR expresses the odds of having work strain as compared to the odds of not having work strain with the increase of one standard deviation in the stressor scale. If the risk exceeds 1, exposure to a work stressor is associated with work strain.

The backward selection procedure was used to identify which individual items from the stressor scales are associated with work strain. The rationale behind this is that all items within the existing scales have the same weight suggesting that each item is equally important. This is not necessarily true; some items might be more stressful than others. The significance level was determined at 0.05. From the selected items a work stressor score was calculated by: exponent (intercept estimate + work stressor1*beta1+ work stressor2*beta2 + work stressor3*beta3). The betas represent the weight given to each item.

The influence of other factors on the results

Gender and educational level may influence the perception of the same stressors and to which type of stressors employees are exposed in general. Therefore, we examined for work strain II whether different work stressors were selected if results were stratified on these factors and whether the relevance of the same stressors differed among the groups. This was only possible for work strain II since the power was insufficient for work strain I.

The distribution of other factors, such as chronic disease, psychological problems and trouble combining work and private life was examined among cases and non cases. In case of unequal distribution, it was examined whether this variable influenced the beta of the selected stressors and the SOR. This was examined by excluding employees with this variable from the analysis and also by inclusion of this variable into the model where the association between the work stressor score and work strain was examined.

For work strain I, employees who reported work strain II at the moment of stressor assessment were excluded. For work strain I and II, employees reporting a chronic disease at the moment of stressor assessment were excluded from the analysis.

Replication of data

For work strain I and II it was investigated whether inclusion of the univariate significant items into the model would yield the same selected items as selected with the backward selection model. For work strain I replication of the data was additionally tested by performing a backward selection in a dataset where correlated data among the non cases was circumvented by taking a random sample of 100 non cases from the same phase from which the cases were identified. This was done because in this study no adjustment was performed for the correlated data. The rationale for this choice was to increase power by including a large non case group but without adjusting for it, otherwise the gain by expanding the control group would have gone lost by adjusting for this dependence in data among the non cases.

Table 3: Characteristics of non work strain cases and work strain cases at the moment of stressor assessment (work strain I = sickness absence due to work stress, work strain II= constantly experiencing pressure and finding it difficult to relax after a working day).

	Non work strain case I Mean or number (%)	Work strain case I Mean or number (%)	Non work strain case II Mean or number (%)	Work strain case II Mean or number (%)
Total*	23744	51	7232	794
Age	42	42	41	42
Education				
Low	7162 (31)	20 (41)	2215 (32)	214 (28)
Med	7510 (32)	8 (16)	2293 (33)	263 (34)
High	8479 (37)	21 (43)	2522 (36)	301 (39)
Gender				
Female	6230 (26)	19 (37)	1873 (26)	207 (26)
Male	17482 (74)	32 (63)	5351 (74)	584 (74)
Chronic disease				
No	18202 (79)	32 (65)	5692 (80)	543 (71)
Yes	4963 (21)	17 (35)	1393 (20)	223 (29)
Psychological problems				
No	22979 (97)	45 (88)	7077 (98)	741 (93)
Yes	765 (3)	6 (12)	155 (2)	53 (7)
Working hours a week				
>40	5029 (21)	14 (27)	1486(21)	207 (26)
36-40	12298 (52)	23 (45)	3730 (52)	392 (49)
26-35	3351 (15)	8 (16)	1084 (15)	102 (13)
<26	2890 (12)	6 (12)	901 (13)	92 (12)
Shift work				
Yes	6105 (26)	13 (25)	1915 (27)	198 (25)
No	17400 (74)	38 (75)	5266 (73)	593 (75)
Supervising function				
Yes	6040 (26)	14 (27)	1801 (25)	232 (30)
No	17497 (74)	37 (73)	5376 (75)	553 (70)
Type of employment				
Temporary	433 (2)	1 (2)	110 (2)	14 (2)
Permanent	23166 (98)	49 (98)	7072 (98)	1775 (98)
Living together with partner				
Yes	14562 (87)	34 (81)	6199 (87)	685 (87)
No	2271 (13)	8 (19)	962 (13)	102 (13)
Combining of work and private life is troublesome				
Yes	2262 (10)	5 (10)	482 (7)	153 (20)
No	21141 (90)	45 (90)	6664 (93)	630 (80)
Life events				
Yes	5674 (34)	15 (36)	2136 (30)	281 (36)
No	11224 (66)	27 (64)	5065 (70)	507 (64)

Table 3 (continued)

	Non work strain case I Mean or number (%)	Work strain case I Mean or number (%)	Non work strain case II Mean or number (%)	Work strain case II Mean or number (%)
Sectors				
Civil service, education, public transport;	6051 (25)	17 (33)	1748 (24)	226 (28)
Health care;	3510 (15)	7 (14)	1062 (15)	127 (16)
(Building) industry;	11367 (48)	19 (37)	3555 (49)	341 (43)
Transport, service sector, catering industry;	2816 (12)	8 (16)	867 (12)	100 (13)

* total numbers of the categories do not add up to the total amount of cases / non cases because of missing values in that variable

RESULTS

Stressors and work strain I

In Table 3 the baseline characteristics are presented for the work strain cases and the non work strain cases. Fifty one cases were identified in this sample and 23,744 non cases. Among work strain cases more employees with low and high educational level and more women were prevalent. Also, chronic disease was reported more often by cases.

In Table 4a the mean scores, standard deviation and the range of each scale are presented for both the work strain cases and non-work strain cases. Furthermore, the standardized odds ratio (SOR) is presented, where the difference of one standard deviation in the scale represents the risk of work strain. Psychological demands, emotional demands, conflicts at work, physical demands and effort and appreciation were most strongly associated with work strain. Job strain showed a lower association with work strain, SOR: 1.27 (95% CI: 1.05-1.55), *not presented in table.*

The backward selection, conducted on the items of the scales, yielded the combined work stressor score of: -5.47+(enough time to finish the job*-0.54+conflict with supervisor*0.90+ repetitive movements*0.91). The SOR was 1.89 (95% CI: 1.49-2.40) which expresses the odds of having work strain as compared to the odds of not having work strain with the increase of one standard deviation in the stressor scale.

Table 4a: Unadjusted associations between work factors and work strain (work strain I).

Stressor scales	Scale range	Non work strain cases Mean (sd)	Work strain cases mean (sd)	SOR [A] (95% CI)
Decision latitude	24-96	72.21 (10.73)	69.92 (10.95)	0.80 (0.65-1.08)
Psychological demands	12-48	32.74 (5.56)	34.78 (5.63)	1.46 (1.09-1.88)
Social support supervisor	4-16	10.45 (2.27)	9.58 (2.69)	0.71 (0.55-0.91)
Social support colleagues	4-16	11.86 (1.53)	11.94 (1.67)	1.06 (0.80-1.39)
Cognitive demands	0-3	2.49 (0.69)	2.58 (0.61)	1.15 (0.84-1.55)
Emotional demands	0-5	1.05 (1.21)	1.56 (1.59)	1.41 (1.12-1.78)
Job security	0-2	0.27 (0.60)	0.34 (0.62)	1.11 (0.84-1.46)
Conflicts at work	0-2	0.15 (0.41)	0.33 (0.53)	1.33 (1.08-1.65)
Effort and appreciation*	0-2	0.94 (0.86)	1.21 (0.74)	1.38 (0.99-1.91)
Role clarity (responsibility and task)	0-2	0.40 (0.71)	0.54 (0.75)	1.20 (0.94-1.54)
Career possibilities	0-3	1.10 (1.15)	1.41 (1.13)	1.29 (0.98-1.67)
Do you feel obligated towards the company to stay for a few more years	0-1	0.40 (0.49)	0.29 (0.46)	0.80 (0.58-1.07)
Physical demands	0-5	1.54 (1.45)	2.11 (1.58)	1.42 (1.10-1.83)
Working overtime	0-1	0.44 (0.49)	0.51 (0.50)	1.15 (0.88-1.50)
Fairness*	0-2	0.96 (0.88)	1.22 (0.83)	1.34 (0.94-1.91)
Work stressor score I	-7.63- -4.20	-6.37 (0.64)	-5.88 (0.64)	1.89 (1.49-2.41)

[A] the SOR expresses the odds of having work strain as compared to the odds of not having work strain with the increase of one standard deviation in the stressor scale

*a higher score on effort and appreciation and fairness means a mismatch

Stressors and work strain II

In Table 3 the baseline characteristics are given for the work strain cases and the non-work strain cases. 794 cases and 7,232 non cases were identified according to this definition. Chronic disease and work family conflict were more prevalent among the cases than among the non cases.

In table 4b the mean scores, standard deviation and the range of each scale are presented for both the work strain cases and non-work strain cases. Psychological demands, cognitive demands, emotional demands and effort and appreciation were most strongly associated with work strain. Job strain showed a lower association with work strain, SOR: 1.53 (95% CI: 1.44-1.63). *Not presented in table.*

The backward selection, conducted on the items of the scales, yielded the combined work stressor score of: -3.32+(keep learning new things*0.17+freedom to make decisions*-0.22+work very hard*0.23+enough time to finish the job*-0.40+hectic job*0.42+ job offers enough security* -0.48+ working overtime*0.23+mentally strenuous*0.86+clear task description*-0.27+confronted with personally upsetting things at work *0.34+personally attacked or threatened *0.41+often annoyed by others at work*0.28+sufficient career possibilities*-0.27). The SOR was 2.91 (95% CI:

Table 4b: Unadjusted association between work factors and work strain (work strain II).

Stressor scales	Scale range	Non work strain cases Mean (sd)	Work strain cases mean (sd)	SOR [A] (95% CI)
Decision latitude	24-96	72.25 (10.52)	71.02 (11.21)	0.89 (0.81-0.96)
Psychological demands	12-48	31.94 (5.34)	35.77 (5.32)	2.04 (1.85-2.14)
Social support supervisor	4-16	10.57 (2.18)	9.85 (2.53)	0.73 (0.68-0.79)
Social support colleagues	4-16	11.88 (1.45)	11.59 (1.69)	0.81 (0.76-0.88)
Cognitive demands	0-3	2.43 (0.71)	2.74 (0.57)	1.82 (1.64-2.01)
Emotional demands	0-5	0.90 (1.10)	1.57 (1.38)	1.61 (1.50-1.72)
Job security	0-2	0.24 (0.57)	0.46 (0.73)	1.33 (1.26-1.42)
Conflicts at work	0-1	0.11 (0.35)	0.29 (0.55)	1.40 (1.31-1.50)
Effort and appreciation*	0-2	0.87 (0.86)	1.23 (0.84)	1.52 (1.39-1.68)
Role clarity (responsibility and task)	0-2	0.35 (0.67)	0.61 (0.79)	1.36 (1.29-1.46)
Career possibilities	0-3	1.05 (1.14)	1.42 (1.21)	1.35 (1.27-1.46)
Do you feel obligated towards the company to stay for a few more years	0-1	0.38 (0.48)	0.40 (0.49)	1.06 (0.98-1.14)
Physical demands	0-5	1.45 (1.41)	1.76 (1.55)	1.17 (1.14-1.31)
Working overtime yes versus no	1-0	0.41 (0.49)	0.55 (0.49)	1.32 (1.23-1.42)
Fairness*	0-2	0.89 (0.88)	1.18 (0.87)	1.38 (1.26-1.52)
Work stressor score II	-5.73-1.24	-2.78 (1.03)	-1.69 (0.95)	2.91 (2.67-3.18)

[A] the SOR expresses the odds of having work strain as compared to the odds of not having work strain with the increase of one standard deviation in the stressor scale

*a higher score on effort and appreciation and fairness means a mismatch

2.67-3.18) which expresses the odds of having work strain as compared to the odds of not having work strain with the increase of one standard deviation in the stressor scale.

Stratified results

The stratified results on gender and educational level showed that there were only minor differences in stressors that were relevant among different groups. Also the relevance of the same identified stressors did not differ substantially among different groups. The specific results are presented in Table 5.

The influence of other factors

The prevalence of chronic disease, psychological disease and trouble combining work and private life was higher among work strain cases than among the non cases. Excluding employees reporting a chronic disease in the sub analysis did not change the results: the relevance of each item in the work stressor score and also the SOR remained similar as to the results where employees with a chronic disease were not excluded. This was seen among work strain I and work strain II cases. The same was done for psychological disease and trouble combining work and private life. Only inclusion of 'trouble combining work and private life' into the model next to work stressor II influenced the SOR of work strain II slightly.

Table 5: Selected work stressors* and their relative contribution (presented as beta's from the logistic regression model) to work strain II among men and women and different educational levels.

Work stressors	Men	Women	Low educational level	Medium educational level	High educational level
Total cases / non cases	*543 /5021*	*202 /1773*	*203/ 2104*	*252 /2190*	*285 / 2427*
Opportunity to make own decisions	-0.19				
Work very hard	0.25		0.49		
Enough time to finish the job	-0.47	-0.35		-0.52	-0.49
Hectic job	0.38	0.69		0.61	0.69
Job offers enough security	-0.48		-0.53	-0.50	-0.48
Working overtime	0.32				0.58
Work is mentally strenuous	0.97	0.66	1.05	1.01	0.64
Clear task description	-0.27				-0.40
Personally attacked or threatened	0.40	0.87		0.73	
Often annoyed by others at work	0.33				
Sufficient career possibilities	-0.34		-0.57	-0.39	
Job requires learning new things		0.42			
Little freedom to decide how to perform work		0.36			
Coworkers take a personal interest in me		-0.44			
Confronted with personally upsetting things		0.54	0.57		
Little freedom to make own decisions			0.36		
Often interrupted during work			0.32		
Worried about safety			0.53		
Enough possibilities for growth and personal development					-0.46

*selected with the backward selection procedure

Around 50% of the work strain I cases reported work strain II at the moment of the stressor assessment. To examine whether the presence of work strain II influenced the reporting of the stressors these cases were excluded in a sub analysis, which reduced the number of cases from 51 to 24 cases. The relevance of the included items changed only slightly and the SOR for work strain remained similar.

Replication of the results

Inclusion of the univariate significant items into the model yielded the exact same variables as selected with the backward selection procedure for work strain II. For work strain I, the results were not replicated and including the univariate significant items into the model yielded no significant variables associated with work strain. This might be explained by the relative small number of work strain I cases. For work strain I the additional backward selection performed in the dataset in which non cases did not have multiple observations, yielded the following items: enough time to finish the job*-0.93+my supervisor pays attention*-0.44+repetitive movements *0.94). The SOR for work strain was 2.34 (95% CI: 1.68 - 3.27) for employees exposed to these items compared to employees who are not.

DISCUSSION

The aim of this study was to substantiate the concept of work strain. This study showed that many work stressors contribute to work strain, with each stressor having its own relative contribution. This indicates that work stressors should be measured in a more comprehensive way as compared to the operationalizations of work stress that are currently used. Several authors have raised concerns about the job strain model, and more specifically about the job demands scale, e.g. that it does not measure other sources of stress than the ones included (13-16). This study shows that these concerns are real, since the results of this study show that indeed other types of demands should be measured as well.

Furthermore, our study also showed that a re- evaluation of which stressors are most relevant in the current work life is necessary, since the incorporation of items from different scales such as interpersonal relations, emotional demands, role clarity, job security, psychological demands and control into one measure showed the strongest association with work stain. This indicates that in the current work life, stressors that have a high stress potential can no longer be assessed with single concepts in which each item has the same contribution, but a combination of individual items from different scales is needed in which each stressor has its own relative contribution.

Strengths and limitations of this study

One of the strengths of this study is that we adhered to a theoretical framework in which conditionality applies. In the framework of stressor – stress – strain – health, the occurrence of work strain is preceded by work stress and work stress is preceded by exposure to work stressors. This is in contrast to starting from the point of work stressors, where this conditionality does not apply; work stressors *may* lead to work stress and work stress *may* lead to work strain and work stressors *may* lead to health effects. Furthermore, as noted by Kasl (17), the impact of work stressors is much better to pinpoint if transitions between more adjacent steps in a development schema is studied, which we did in this study, than between more distal steps

Furthermore, in this study we had access to a large heterogeneous population and the availability of a multitude of work stressors. This enabled us to examine which work stressors can be identified as general work stressors. The composition of the sample determines which stressors are prevalent in this population (and also the relevance), as it depends for instance on the type of jobs that are included. Among work strain cases I, more employees with lower and higher educational level were present. In the work strain II sample, the gender and educational level stratified results showed that there were only minor differences in stressors that were relevant among different groups. Also the relevance of the same identified stressors did not differ substantially among different groups. This suggests that the impact of work stressors on work strain can be generalized to a broad working population.

However, with regard to prevention, to optimize a prevention strategy a new assessment to

prioritize work stressors in that particular company will be most successful, since among different groups/ jobs there are subtle differences in the prevalence and relevance of work stressors. This is in line with the recommendations made by Hurrell et al (18).

This study also has several limitations, such as the limited power in the work strain I sample that led to an unstable model. A more stable model was the aim and therefore multiple results from the non cases were included, without adjusting for the correlation. Replication of the results in the sample where multiple observations among the non cases was prevented yielded similar results; from the initially three selected items, two were replicated. This supports the reproducibility of the results despite the small case group.
Other limitations of this study are associated with the difficulty of exploring the validity of the assessment of work stressors without a gold standard for measuring work stress. Ideally, a study is warranted in which work stressors are associated with work stress. Instead, we used a design in which we explored the association between work stressors and work strain since no appropriate measure was available for work stress. We used two work strain definitions. Work strain I was defined as employees who reported work stress as the main reason for their sickness absence. As mentioned before, for work strain to occur exposure to work stress was conditional and thus employees who reported sickness absence due to work stress must have been exposed to work stress (ors). A limitation of this first definition is that the time line between exposure and strain varied between one month to one year. With a longer in-between period the association might be underestimated because the exposure to work stressors might have changed. On the other hand, strength of this definition is that stressors were measured before sickness absence due to work stress occurred. Also, we examined the issue of reporting bias, since fifty percent of the work strain I cases experienced work strain II at the moment that work stressors were measured. Excluding these employees from the analyses showed only minor impact on the relevance of the stressors. Even though the restricted power hinders proper interpretation, our finding is in accordance with the findings of Waldenstrom et al (19). They showed that the presence of psychological distress does not influence the reporting of stressors.
The issue of reporting bias may be even more important in work strain II. This definition was chosen to get a closer approximation of stress as an individual state of displeasure. Therefore work strain II and work stressors were measured at the same time. When outcome and exposure are measured at the same time, it is difficult to entangle whether stressors preceded work strain or the presence of work strain influenced the perception and the reporting of stressors. Since work stressor II yielded a higher SOR for work strain II than work stressor I for work strain I this could indicate bias, where the relevance of each stressor contributing to work strain is overestimated. We think bias is limited and did not influence our results since the presence of psychological distress does not necessarily influence reporting of the stressors (19) and we have examined other factors that could have influenced the reporting of the stressor, such as the presence of chronic disease, which did not have a major impact on the relevance of each

stressor. Besides, in this study we used two case definitions and both definitions led to the same conclusion: the work stressor score showed the highest association with work strain.

Furthermore, even though a multitude of work stressors were measured in the MCS, the availability of data on relational injustice (20), managerial leadership (21) and work place bullying (22) might have yielded a different selection of work stressors.

The majority of studies that have examined the association between the psychosocial work environment and strain or health outcomes have used predefined theoretical concepts that focus on one or two dimensions of the work environment. This limits the comparison of our study with others. We did find a study by Dai et al (23) in which they investigated whether combining stressors from the ERI and Job strain models was more predictive of job burnout, which they confirmed. This study differs from ours in examining the association between stressors from the ERI and Job strain model with a more distal step in the pathway, namely burnout. Whereas in our study we examined which work stressors were associated with a more proximal step in the pathway, namely work strain. Since this is the presumed pathway through which work stressors affect health, the next step for us, is to relate the work stressor measures to a health outcome.

The identified stressors in this study have been examined by others in relation to health and these studies found that low possibilities for development, low role clarity (24), high demands (16), job insecurity (25), working overtime (26), emotional demands (27) and interpersonal conflicts (28) are associated with a variety of adverse health effects. Within this study, several items from these scales were identified to be associated with work strain, which provides support for the finding that these stressors lead to ill health through work strain.

In conclusion, we were able to assess a wide variety of work stressors and its contribution to work strain and combined these into one measure. These measures were more strongly related to work strain than the most often used concepts.
For future research we recommend to use a more comprehensive exposure assessment since combining work stressors into one measure will assess the psychosocial work environment more adequately and will yield a more accurate association between the psychosocial work environment and health, where the pathway is mediated through work stress, since all these stressors are jointly contributing and each is relevant. Furthermore, each stressor has its own contribution to work strain. This means that different stressors should be given different weights, which is ignored in the currently most often used concepts where each item within a scale has the same weight.

For the development of prevention strategies, the focus should be on stressors from different dimensions in the work environment. If prevention strategies are aimed at the most relevant stressors that are causing work strain, prevention will be more successful in reducing strain.

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4

The prospective relationship between work stressors and cardiovascular disease, using a comprehensive work stressor measure for exposure assessment

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Objective
The currently used instruments which measure the psychosocial work environment have been criticized. We analyzed the association between work stressors and cardiovascular disease, using the Maastricht Cohort Study Work Stressor Score (MCS-WSS), a comprehensive measure which has been associated with work strain.

Methods
At baseline 11,489 employees of the Maastricht Cohort Study were participating. This prospective cohort study started in 1998 in the Netherlands and includes a heterogeneous population of employees. The psychosocial work environment, cardiovascular risk factors and the occurrence of cardiovascular disease were measured with questionnaires at various time points during follow up, the last follow up was in 2008. For a subsample of employees, CVD extracted from medical records was available. The MCS-WSS consists of items from emotional demands, psychological demands, role clarity, career possibilities, working overtime, job insecurity, cognitive demands, skills discretion and decision authority. Each item has its own contribution in inducing work strain, represented by its own weighting factor. The association between a high exposure to work stressors at baseline and cardiovascular morbidity was assessed with Cox regression analyses. Analyses were adjusted for age, gender, educational level, smoking, body mass index, alcohol consumption and leisure physical activity.

Results
During a median follow up of 49 months, 309 employees developed incident cardiovascular disease. Overall, no significant associations were found between a high exposure to work stressors at baseline and cardiovascular morbidity.

Conclusions
The results of this study indicate that a single high exposure to work stressors has no considerable impact on cardiovascular disease.

INTRODUCTION

Work stress has been examined for its association with cardiovascular disease (CVD) since several decades, where the majority of studies have used the Demand Control model (1). However, conflicting findings are prevailing (2-4) which has resulted in questions concerning the strength of the evidence. Methodological and conceptual issues are related to the validity of the demands (5, 6) and decision latitude scales (7, 8), whether the model adequately captures the most stressful aspects of the current work environment since work organization has changed during the last decades (3, 9-11), the lack of comprehensiveness of the model (4, 11-15) and no differentiation in the relative contribution of each work characteristic in inducing work stress, while it is probable that certain work stressors contribute more to work stress than others. These issues can hinder a proper evaluation of the psychosocial work environment and, in turn, can hinder the establishment of an accurate association between work stressors and CVD. Both are needed to establish whether the psychosocial work environment poses a real risk for the development of CVD and the magnitude of the association between work stress (ors) and CVD.

In the present study, we will use one of the two work stressor measures (the Maastricht Cohort Study Work Stressor Score (MCS-WSS)) which was previously developed with the aim to improve the validity of the measurement of the current psychosocial work environment (16) by dealing with the aforementioned issues. The MCS-WSS is innovative due to the approach used to construct this measure. To prevent misunderstanding on the definitions used, we define work stressors as a large number of work related environmental conditions thought to impact the health and well-being of the worker (17). Stress is defined as an individual state characterized by a combination of arousal and displeasure (18). Exposure to stress can result in strain (19), which can manifest as a short term (reversible) health outcome or as an irreversible health effect.
The MCS-WSS includes work stressors that have been identified from a wide range of work characteristics and actually have been tested for their association with work strain in a heterogeneous sample of employees. The usual approach to construct a new measure in this field is the use of confirmatory factor analysis (CFA), which is used to measure a concept, which you cannot measure directly (e.g. stress). We think that this concept consist of various components. Although CFA tests a hypothesized structure for a set of variables, it does not necessarily mean that the structure is true. Thus, by examining which work stressors are most associated with work strain and including these work stressors into a measure, we are more certain that we actually measure what we wish to measure (and thereby increasing the validity of the measure), namely work stressors that have shown a relation with work strain in the current work life. Moreover, the resulting measure showed a stronger association with work strain as compared to job strain (16). It also showed that inclusion of work stressors from various dimensions is needed to capture the multifarious nature of work stress / work strain. Last, each work stressor has its own potential in inducing work strain since each included item

into the measure showed a different association with work strain. Therefore, each work stressor has its own weighting factor within this measure.

Due to these properties of the measure we believe we have a valid measure to assess the current psychosocial work environment. The next step, which is the main aim of this study, is to examine whether the psychosocial work environment, assessed with the MCS-WSS, is associated with CVD. The secondary aim is to compare the results obtained within the Maastricht Cohort Study population with the results obtained in other studies. For this purpose, we also include the job demands and decision latitude scales of the JCQ. To include similar elements (work stressors) of the framework within this study, we will not include job strain.
Within this study self-reported CVD and medically confirmed CVD are used as outcome measures. The use of self-reported MI and stroke has shown good agreement with objectively obtained data (20), but the use of both self-reported work stressors and self-reported CVD has been criticized since it is assumed to yield spurious findings (21).

METHODS

Participants and design
Data from the prospective Maastricht Cohort Study (MCS) was used, which started in 1998 (22). Different companies and organizations with over 100 employees were contacted to ensure that employees from different sectors and trades were included. From the 79 companies contacted, 45 agreed upon participation. Men and women between 18-65 years with an employment contract of at least 16 hours per week were approached. The study was approved by the Medical and Ethical Committee of the AZM/Maastricht University (MEC08-4-032.4). All participants gave written informed consent for participation. The study protocol ensures the privacy and anonymity for all study participants, for questionnaire data as well as for data on morbidity and cause-specific mortality which is only available on an anonymous level to the researchers. The privacy of participants is established and enlisted with the Dutch Data protection Authority in Den Haag under number m1332237.
From the 26,978 potential participants, 12,140 employees participated at baseline (45%). The response during follow up was 80% (May 1999), 67% (May 2000), 62% (January 2001), 46% (May 2002), relative to the baseline population. In October 2008, questionnaires were sent out to those who responded to the questionnaire of January 2001. This resulted in a response of 50% relative to the baseline population.
Employees who were lost to follow at the last measurement (October 2008) did not differ in their baseline median work stressor score from those who remained in the cohort. Employees who were willing to participate were compared with employees who declined to participate at baseline. A non-response analysis among a subsample of the non-responders showed that a higher percentage

of respondents worked more than 40 hours per week (20 versus 12%), which might be indicative of a higher prevalence of stress. General health did not differ among the two groups. (23)

Cardiovascular morbidity
At baseline (May 1998) self-reported CVD was assessed with the items 'Do you have a long-standing disease?' If yes, employees could check the following two items from a list of diseases: 'heart disease, myocardial infarction (MI) or high blood pressure' and '(consequences of a) stroke'. Based on these items employees with prevalent CVD were excluded. In the follow-up questionnaire of May 1999, CVD was assessed in the same way as at baseline. The follow up questionnaires of May 2000, January 2001, May 2002 and October 2008 contain different items to assess CVD and to calculate the time until event: May 2000 (Have you ever experienced a MI? If yes: <1 year, 1-2 years, > 2 years ago); January 2001 (Have you experienced a MI in the last 8 months?); May 2002 (Have you ever experienced a MI? If yes: < half year, half year- 1 year, > 1 year ago) and October 2008 (Have you experienced a MI in the past? If yes:< 1 year, 1-2 year, 2-5 years, > 5 years ago). For stroke, information about the time of occurrence was only obtained with the questionnaire from 2008 and January 2001.

We also collected data from medical records for employees who were residing in the southern part of the Netherlands and attend the hospitals located in this area, N=6,103 employees. Employees were traced back in the medical records who gave an affirmative answer to the items 'Do you have a long-lasting disease?' in combination with checking one of the following two items from a list of diseases: 'heart disease, myocardial infarction (MI) or high blood pressure' and '(consequences of a) stroke', which was assessed in 1998 or those who gave an affirmative answer to the questions 'do you have a heart disease' or 'have you ever experienced a stroke', which was assessed in 2008. Those with a medically confirmed CVD before 1998 were excluded from the analyses (exclusion of 93 prevalent cases, resulting in n= 6,010). An incident cardiovascular event was defined as stroke, a percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), myocardial infarction or (un)stable angina pectoris.

Work characteristics
The job characteristics included into the Maastricht Cohort Study Work Stressor Score (MCS-WSS) were assessed at baseline with a questionnaire. The MCS-WSS consists of the following items with each item having its own weighting factor: keep learning new things*0.17+freedom to make decisions*-0.22+work very hard*0.23+enough time to finish the job*-0.40+hectic job*0.42+ job offers enough security*-0.48+ working overtime*0.23+mentally strenuous*0.86+clear task description*-0.27+confronted with personally upsetting things at work*0.34+personally attacked or threatened *0.41+often annoyed by others at work*0.28+sufficient career possibilities*-0.27. The total score is the sum of all items where the answer category is multiplied by the weighting factor. All items have yes- no answer scales, except for keep learning new things, freedom to make

decisions, work very hard, enough time to finish the job and hectic job which have a likert scale ranging from 1- 4. The description of the construction of the measure is described elsewhere (16). The underlying assumption of this measure is that a high score on this measure represents simultaneous exposure to various work stressors and is more likely to elicit a stress response than a low score on this measure. The categorization into high and low exposure was based upon the median value of the baseline distribution of MCS-WSS. Decision latitude and psychological job demands were measured with the Job Content Questionnaire (24), consisting of 9 items for decision latitude (6 items for skills discretion and 3 items for decision authority) and 9 items for job demands. The classification of high demands and low decision latitude was made upon the median value of the scales. We also categorized the MCS-WSS, job demands and decision latitude into quartiles to enhance exposure contrast, to examine whether this would impact the resulting association. Also, we examined the association obtained when the continuous score (of MCS-WSS, job demands, decision latitude) was used.

Potential confounders

Baseline confounders were assessed using questionnaires: age (continuous), gender, educational level (low: primary school, lower vocational school, medium: lower secondary school, intermediate vocational school, upper secondary school, high: upper vocational school and university), smoking was inventoried as 'Do you smoke daily?' (yes-no), alcohol consumption was inventoried as 'How many glasses of alcohol do you drink weekly?' (none, 1-14 glasses, 15-21 glasses, > 22 glasses), physical activity was inventoried as 'How often do you perform leisure physical activity of a minimum of half an hour per week?' (never or once a week, 2-7 times a week, more than 7 times), body mass index (BMI) was calculated from the items 'weight' and 'length' (16-20, 20-25, 25-30, >30 kg/m^2).

STATISTICAL ANALYSIS

Analyses were performed with SAS 9.2. Cox regression analysis was used to examine the association between baseline work stressor scores, job demands, decision latitude and incident CVD. Models were adjusted for age and gender, age, gender and educational level and fully adjusted with also inclusion of smoking, BMI, alcohol consumption and leisure physical activity. Workers with missing values in the work stressor variables or confounders were excluded from the analyses (the percentage missings was 8%, 3% and 1% respectively for MCS-WSS, job demands and decision latitude and 1% for gender, age, smoking, leisure physical activity and alcohol consumption and 2% for BMI and educational level).

The proportional hazard assumption was visually evaluated by inspection of the –ln (-ln S (t)) survivor curves for every work stressor variable and by testing an interaction of each work stressor variable with the log of time in the multivariable model. None of the statistical tests (interaction with the log

function of time) were significant and no strong departures from parallelism were seen in the log negative log plots, although a slight decreasing hazard ratio (HR) was seen with longer follow up.

In the follow-up questionnaires T6 (May 2000), T8 (January 2001), T9 (May 2002) and MCS2 (October 2008), employees were asked whether they had experienced a myocardial infarction in the past, with the exact period specified in categories between two consecutive follow-up measurements of the cohort. This was used to calculate the time until event. E.g. employees who indicated to experience a MI at Oct 2008 could choose from the following time periods: < 1 year ago, 1-2 years ago, 2-5 years ago, and > 5 years ago. For the first category, the event could have occurred somewhere between October 2008 and October 2007. The midpoint was chosen to assign the time of event, which was April 2008. For the second category, the event could have occurred somewhere between October 2007 and October 2006. The midpoint was chosen to assign the time of event, which was April 2007 and so on. For the last category, the event could have occurred somewhere between October 2003 and May 2002 which was the follow up questionnaire preceding the one of October 2008. Again, the midpoint was chosen to assign the time of event. For the items where no information was available about the time of occurrence, the time of event was equal to the time of reporting the event.

For those with medically confirmed CVD, the time of event was the date of diagnosis. Survival time was considered censored if employees did not develop manifest CVD at the end of the study, if they developed a type of cardiovascular disease where atherosclerosis is not the main underlying pathway or if they were lost to follow up.

Statistical interaction was tested for age, gender and educational level by including an interaction term in the model and by examining the results stratified on gender, age (above and below 50) and educational level (low-medium-high). It was examined whether the p-value of the interaction term was significant and whether the stratified HR's differed significantly from each other and from the overall HR for the association between work stressors and CVD.

To assess whether an overestimated association between work stressors and CVD would result due to using self-report data, we assessed the association within a subsample of employees for whom both self-reported and medically diagnosed CVD was available.

RESULTS

After excluding employees with prevalent stroke, heart disease or hypertension 11,489 employees remained. The baseline characteristics of these employees are given in Table 1. During a median follow up of 49 months (minimum of 1 month and maximum of 126 months), 309 events (cardiovascular disease morbidity) occurred: 152 myocardial infarctions, 143 strokes and 14 employees developed both stroke and MI.

Table 1: Baseline characteristics of the 11,489 employees participating in the Maastricht Cohort Study without prevalent CVD.

Variables	Number (%)	Variables	Number (%)
Mean age in years (sd)	41 (9)	*Weekly working hours*	
Gender		>40	2288 (20%)
Male	8326 (72%)	36-40	6090 (53%)
Female	3143 (27%)	26-35	1694 (15%)
Educational level		16-25	1137 (10%)
Low	2196 (19%)	<16	190 (2%)
Medium	5045 (44%)	*Supervising function*	
High	3900 (34%)	Yes	2750 (24%)
BMI (kg/m2)		No	8643 (75%)
< 20	601 (5%)	*Sectors*	
20-25	5868 (51%)	Health care	1762 (15%)
25-30	4114 (36%)	Industry	5550 (48%)
>30	716 (6%)	Education- governmentpublic transport	2772 (24%)
Smoking		Service- transportation-catering	1405 (12%)
Yes	3159 (28%)	*Number of years working*	
No	8253 (72%)	< 5 years	770 (7%)
Alcohol consumption (glasses per week)		5-10	1556 (14%)
0	3078 (27%)	11-20	4025 (35%)
1 -14	7067 (62%)	>20	5105 (44%)
Physical activity, number of times per week			
< 1	3781 (33%)		
2 -7	6850 (60%)		
> 7	786 (7%)		

Work stressors and cardiovascular morbidity

Table 2 shows that there is no association between a high work stressor score, high demands, low decision latitude and cardiovascular morbidity. Examining the association using quartiles or the continuous score gave similar results, *results not presented*. Tables 3 and 4 show no association between a high MCS-WSS, high job demands, low decision and CVD. Analyses were performed within the subsample that had both self-reported CVD and medically confirmed CVD. *We also examined the association with cardiovascular death and even though the numbers of events was low (66 events), overall, the results were similar as to those based on cardiovascular morbidity (self-reported and medically confirmed), results not presented.*

No interaction effects were observed between the continuous work stressor score and gender, educational level or age and CVD risk, *results not presented*.

Table 2: Association between work stressors, assessed with the MCS-work stressor score, job demands and decision latitude with incident cardiovascular morbidity in a population of 11,489 employees in which 309 events occurred.

Exposure	Total number/ events	Crude HR*	95% CI**	Total number/ events	HR[A]	95% CI	Total number/ events	HR[B]	95% CI	Total number/ events	HR[C]	95% CI
High work stressor score	10620/286	1.02	0.81-1.29	10595/284	1.00	0.78-1.26	10309/279	1.01	0.79-1.28	10077/271	0.93	0.73-1.19
Low work stressor score		1.00	-		1.00	-		1.00	-		1.00	-
High job demands	11141/299	1.02	0.99-1.06	11107/ 297	1.03	0.99-1.07	10786/ 292	1.04	0.99-1.08	10532/ 282	1.04	0.99-1.08
Low job demands		1.00	-		1.00	-		1.00	-		1.00	-
Low decision latitude	11346/305	1.10	1.06-1.15	11317/ 303	1.10	1.06-1.15	10988/ 298	1.06	1.02-1.10	10717/ 287	1.06	1.01-1.10
High decision latitude		1.00	-		1.00	-		1.00	-		1.00	-

* HR = hazard ratio; ** 95% CI= confidence interval; [A] adjusted for age, gender; [B] age, gender, educational level; [C] age, gender, educational level, smoking, BMI, leisure physical activity, alcohol consumption

Table 3: Association between work stressors, assessed with the MCS-work stressor score , job demands and decision latitude with incident cardiovascular morbidity in a *subsample of employees, N=5,750,* in which 176 self-reported incident CVD events occurred.

Exposure	Total number/ events	Crude HR*	95% CI**	Total number/ events	HR[A]	95% CI	Total number/ events	HR[B]	95% CI	Total number/ events	HR[C]	95% CI
High work stressor score	5275/ 162	1.01	0.74-1.38	5259/ 160	0.94	0.69-1.28	5092/ 157	0.94	0.68-1.28	4968/151	0.88	0.64-1.21
Low work stressor score		1.00	-		1.00	-		1.00	-		1.00	-
High job demands	5567/ 173	1.01	0.74-1.36	5546/ 171	0.91	0.67-1.23	5352/ 168	0.89	0.66-1.21	5213/ 161	0.90	0.66-1.23
Low job demands		1.00	-		1.00	-		1.00	-		1.00	-
Low decision latitude	5668/ 174	0.91	0.68-1.23	5649/ 172	1.06	0.79-1.43	5453/ 169	0.96	0.70-1.31	5307/ 162	0.95	0.69-1.31
High decision latitude		1.00	-		1.00	-		1.00	-		1.00	-

* HR = hazard ratio; ** 95% CI= confidence interval; [A] adjusted for age, gender; [B] age, gender, educational level; [C] age, gender, educational level, smoking, BMI, leisure physical activity, alcohol consumption

Table 4: Association between work stressors, assessed with the MCS-work stressor score , job demands and decision latitude with incident cardiovascular morbidity in a *subsample of employees, N=6,010*, in which 119 medically confirmed incident CVD events occurred.

Exposure	Total number/ events	Crude HR*	95% CI**	Total number/ events	HR[A]	95% CI	Total number/ events	HR[B]	95% CI	Total number/ events	HR[C]	95% CI
High work stressor score	5512/ 104	0.95	0.65-1.40	5497/ 104	0.90	0.61-1.33	5296/ 99	0.88	0.60-1.31	5191/ 98	0.84	0.51-1.26
Low work stressor score		1.00	-		1.00	-		1.00	-		1.00	-
High job demands	5818/ 112	0.92	0.64-1.34	5798/ 112	0.89	0.61-1.29	5596/ 109	0.89	0.61-1.30	5451/ 105	0.81	0.59-1.28
Low job demands		1.00	-		1.00	-		1.00	-		1.00	-
Low decision latitude	5922/ 116	1.01	0.69-1.47	5904/ 116	1.22	0.85-1.78	5700/ 112	1.17	0.80-1.74	5547/ 108	1.17	0.78-1.74
High decision latitude		1.00	-		1.00	-		1.00	-		1.00	-

* HR = hazard ratio; ** 95% CI= confidence interval; A adjusted for age, gender; B age, gender, educational level; C age, gender, educational level, smoking, BMI, leisure physical activity, alcohol consumption

DISCUSSION

In this study, the association between the psychosocial work environment and cardiovascular disease was examined in a heterogeneous population of employees, using a comprehensive work stressor measure to assess exposure. No association was found between a high work stressor score and cardiovascular disease. Also, no association was found between low decision latitude and high demands and CVD.

For comparison with other studies the JCQ was included as well. Studies investigating the association between job demands, decision latitude and CVD have yielded mixed findings (11, 25-34) (6, 25, 26, 30, 32-35). In the current study, we did not find an association between job demands, decision latitude and CVD. One of the reasons for not finding an association might be related to the population. The level of work stressors might have been too low to have a major impact on CVD risk or the Dutch employees differ in their perception of work stressors compared to employees from other countries. There are also various methodological explanations for the non-significant findings in this study. First, using a single exposure assessment of work stressors might be inappropriate to capture long term exposure to work stressors. Exposure status might have changed during follow up (36) and could have diluted the association between work stressors and CVD. Second, employees who cannot cope with work stressors might already have changed jobs, leaving the ones who can cope adequately with work stressors in a stressful job (healthy worker effect). Third, selection bias could have occurred, however we believe it is unlikely since those who did not want to participate did not differ regarding their general health compared to those who were willing to participate. Fourth, the merit of a heterogeneous sample to extrapolate the results to a large variety of jobs might also be a shortcoming, since only a small proportion has extreme values of exposure, which limits the statistical power to detect an association (13). Furthermore, from the analyses, where the outcome was self-reported CVD, prevalent CVD cases were excluded based on the item 'do you have a heart disease, myocardial infarction or high blood pressure'. This is one item and we could not differentiate between those with manifest disease and those with only elevated blood pressure. If hypertension is part of the pathway, excluding employees with hypertension could have led to an underestimation of the association. However, studies that have adjusted for hypertension have not shown a strong attenuation of the association after inclusion of this risk factor into the model (37). The same applies to cholesterol and diabetes (3, 37, 38), which were not measured at baseline and not corrected for in the analyses. Inclusion of the other factors into the model (smoking, body mass index, leisure physical activity and alcohol consumption) also did not reduce the association much. This suggests that these factors are also not strong confounders within this sample. An alternative explanation is the use of questionnaires to measure the confounders which has been criticized for its validity, especially the assessment of body mass index is known to suffer from under reporting (39-41). Misclassification of these confounders may result in residual confounding. However, within

this study no association has been observed between work stressors and CVD to begin with. Adjusting for educational level, which was used a marker for socio- economic status, is unlikely to have resulted in overcorrection since exposure to work stressors was not related to educational level and inclusion into the model did not reduce the association.

This study also has merits. The first one is that we had CVD data from self-report and from medical records. Incident CVD (MI and stroke) was assessed with self-report data. The medically confirmed diagnoses were obtained by tracing individuals back in the medical records who reported to have experienced a heart disease or stroke. Medically confirmed CVD consisted of the diagnoses stroke, a percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), myocardial infarction or (un)stable angina pectoris. Therefore, data from the medical files and from the questionnaires used to define an event are not directly comparable to assess consistency between the two. Studies that have examined the validity of self-reported MI and stroke have reported sensitivity values of 82%-92% for MI (20, 42, 43) and 70-98% for stroke (20, 42-45). Specificity ranges between 85%-98% for MI (20, 42, 43) and above 97% for stroke (20, 42-45). This indicates that when self-reported CVD is used, a number of the reported events are false negatives and false positives. This is specifically a concern when there is an underlying factor that causes employees to over report work stressors and CVD, yielding trivial findings (18). In the current study, the associations between work stressors and self-reported CVD were not systematically higher than the association obtained with medically confirmed CVD. This indicates that the association between work stressors and self-reported cardiovascular morbidity is unbiased (18). Secondly, the use of a comprehensive work stressor measure improved the validity of the assessment of the current psychosocial work environment. However, this measure was also constructed within the MCS and requires validation in a different population. Using a comprehensive measure to assess the psychosocial work environment reduces the risk of (residual) confounding due to other work stressors since the most important ones are incorporated into this measure (4). The measure comprises various work stressors which together are strongly associated with work strain and where each work stressor has its own contribution in inducing work strain. The next step was to examine whether these work stressors, captured with the measure, would show an association with CVD. This is considered a strength, since the aim is to examine whether work stress is related to CVD. With the measure we aim to capture the multifarious nature of work stress in which various work stressors have their own contribution.
Third, despite the attrition rate of 50% at the end of a follow up period of 10 years and employees with incident cardiovascular disease may have gone undetected, we believe that selective attrition bias is limited because employees who were lost to follow up did not differ from the ones who were still participating with regard to baseline median work stressor scores. Besides, follow up was complete for cardiovascular mortality which gave similar results as obtained with self-reported CVD.

In conclusion, no significant association was found between work stressors and CVD. This indicates that a single high exposure to work stressors does not have a considerable impact on CVD. The results of this study should be confirmed by studies where repeated measurements of work stressors are used to assess *long term* exposure to work stressors more accurately.

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5

Different approaches to estimate exposure to work stressors, using repeated measurements, and the association with cardiovascular disease

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Objective
To explore the stability of exposure to work stressors over time and to examine the impact of different approaches of estimating exposure on the cardiovascular disease (CVD) risk estimation.

Methods
The Maastricht Cohort Study-Work Stressor Score (MCS-WSS) was used to assess work stressors at three consecutive time points among 6,154 employees participating in the MCS. Incident CVD was assessed with questionnaires. Five approaches were used to estimate exposure as: e.g. cumulative exposure above a cut-off point, total exposure and average exposure.

Results
The correlation between the work stressor scores assessed at the first and third time point was 0.58. Employees with a stable exposure above the highest quartile had a fully adjusted Hazard Ratio of 1.58 (95% CI: 0.93-2.72).

Conclusions
Employees with a stable exposure above the highest quartile score during a minimum of two years might have the highest relative CVD risk.

INTRODUCTION

Many studies have examined the association between work stress (ors) and cardiovascular disease (CVD), where work stress has been conceptualized with the Demand Control Model (1). These studies have yielded mixed evidence regarding the association (2-4). Several conceptual and methodological issues have been raised regarding the Demand Control model and also regarding the studies that have been conducted to examine this association (2-7), which might clarify the conflicting results.

To deal with several conceptual issues regarding the model, we will use one of the two work stressor measures which we have previously developed with the aim to improve the assessment of the current psychosocial work environment (8).

One of the methodological issues that may contribute to the conflicting results is the use of a baseline measurement of work stress (ors) within longitudinal studies. Long term (chronic) exposure to work stressors, rather than short term exposure, is expected to have detrimental effects on the cardiovascular system (9, 10). Baseline measurements have been regarded as constant over time and are used as indicators of long term exposure (11). However, the use of a single exposure measurement is likely to be a poor estimate of long term exposure since change in exposure can occur due to job change or due to change within a job (6, 11). Periodical fluctuations within job characteristics may contribute to across time variation (e.g. deadlines, overwork, quota's), but also external change may lead to changes within work related stressors. For instance, job turnover or layoffs may cause change in co-workers or supervisors which may change the interpersonal relationships or the work load. Besides these objective changes, change can also occur within the perception of the job characteristics due to changes within an individual (for instance development of new (coping) skills) (11, 12). In addition, the measurement of work stressors is subject to error (12) and can contribute to across time variation.

For employees with stable exposure, a single time measurement may provide an accurate estimate of long term exposure (13). However, if exposure fluctuates during follow up, the use of a single measurement leads to non-differential misclassification of long term exposure and will bias the association towards the null (6, 9, 11, 14). Repeated measurements covering a certain time period enable us to better differentiate between employees with long term exposure (stable exposure) and those with changing exposure. The expectation is that employees with long term exposure will show an increased CVD risk, while those with changing exposure will not, due to possibilities to recover from exposure. The underlying assumption is that exposure during that certain time period is a better indicator of exposure before and after that period, and therefore is a better indicator of long term exposure.

Various studies have explored the stability of exposure to work related stressors over time and have shown that even during a relatively short time period change can occur. Two studies (13, 14) have reported a moderate temporal stability for job strain, job demands and job control over a period of three years. Other studies have also reported moderate stability over a four and five

year follow up (11, 15). In one study (16) even substantial change within a one year period was reported. The authors of that study argue for the inclusion of information concerning change on job control and job demands when the longitudinal effects on health are examined since forty percent of the across time variation was unaccounted for, after correction for measurement error. If in these cases only the baseline measurement would have been used to estimate long term exposure, the estimated long term exposure would suffer from non-differential misclassification. If exposure to work related stressors varies over time, insight is required into how long term exposure should be estimated with the use of repeated measurements. In this way repeated measurements enable us to explore whether different types of long term exposure are related to different estimates of CVD risk. This could lead to more insight into what type of exposure is needed to cause harm. Is cumulative exposure to work stressors above a certain cut off value needed or is the total dose of exposure or average exposure during working life of importance? This is important because besides the assumption that chronic exposure is required we lack knowledge about the type of chronic exposure that is required to increase CVD risk.

Comparison of the results based upon analyses incorporating repeated exposure measurements with the results based upon analyses incorporating a single exposure assessment can give more insight into the impact of misclassification of long term stable exposure on the CVD risk estimate. Kivimaki et al (13) showed that the use of a single exposure measurement underestimates the status of long term work stress as a CHD risk factor.

In this study, data from the prospective Maastricht Cohort Study (MCS) is used to examine 1) the stability of exposure to work stressors over time and 2) the influence of different approaches to estimate long term exposure to work stressors on the size of the association obtained between exposure and cardiovascular disease, using data from three time points covering a two year period.

METHODS

Data of the prospective Maastricht Cohort Study (MCS) was used, which started in the Netherlands in 1998 to study fatigue (17). Different companies and organizations with over 100 employees were contacted to ensure that employees from different sectors and trades were included. From the 79 companies contacted, 45 agreed upon participation. Men and women between 18-65 years with an employment contract of at least 16 hours per week were approached. From the 26,978 potential participants, 12,140 employees participated at baseline (response rate 45%). Questionnaires were sent out at baseline and during follow up to collect data. The response rates during follow up were 80% (May 1999), 67% (May 2000), 62% (January 2001), 46% (May 2002) and 50% (October 2008) relative to the baseline population.

Exposure

Exposure to work stressors was measured with the Maastricht Cohort Study Work Stressor Score (MCS-WSS), which consists of the following items: keep learning new things, freedom to make decisions, work very hard, enough time to finish the job, hectic job, job offers enough security, working overtime, mentally strenuous, clear task description, confronted with personally upsetting things at work, personally attacked or threatened, often annoyed by others at work, sufficient career possibilities. Within the algorithm the items have different weighting factors, which depend on the answer scales. This is described in detail elsewhere (8).

The work stressor score was assessed on three occasions (T1=May 1998, T2=May 1999, T3=May 2000) and were used to estimate long term exposure to work stressors and were captured into a single measure. Four approaches were used to create different exposure types: cumulative exposure above a cut off value, total exposure, average exposure and single exposure, see Table 1. For these four approaches employees were selected with complete data on the MCS-WSS

Table 1: Different approaches to estimate different types of long term exposure.

Approach	Type of long term exposure estimated	Definition	Categorized as/range
Approach 1	Cumulative exposure above median value*	*Number of times with a score above the median value:*	NA**/0-3
		Work stressor score T1 > median +	
		Work stressor score T2 > median +	
		Work stressor score T3 > median	
	Cumulative exposure above highest quartile*	*Number of times with a score above the highest quartile:*	NA/0-3
		Work stressor score T1 > highest quartile +	
		Work stressor score T2 > highest quartile+	
		Work stressor score T3 > highest quartile	
Approach 2	Total dose, divided into quartiles	*Sum of continuous score over three measurements:*	Quartiles/
		Work stressor score T1 +	Q1= -6.87-0.20
		Work stressor score T2 +	Q2=0.20-2.23;
		Work stressor score T3	Q3=2.23-4.29;
			Q4=4.29-13.66
Approach 3	Average score, divided into quartiles	*Average exposure of the continuous score over*	Quartiles/
		three measurements:	1= -2.29 - 0.056
		Work stressor score T1+	2= 0.056 – 0.73
		Work stressor score T2+	3= 0.73-1.42
		Work stressor score T3 / 3	4=1.42-4.55
Approach 4	Single exposure, divided into quartiles*	*Exposure was estimated using single measurements*	Quartiles/
		from three separate time points	1= -2.28-0.01
		Work stressor score T1	2= 0.01- 0.81
		Work stressor score T2	3= 0.81-1.60
		Work stressor score T3	4= 1.60- 4.61

* the distribution of the work stressor score at baseline was used. Median= 0.81 and quartiles: -2.28-0.01; 0.01-0.81; 0.81-1.60; 1.60-4.61; **NA=not applicable

at three time points, which led to the exclusion of 5,558 employees who had missing values. Employees also had to be free of prevalent CVD before and during 1998-2000, which led to the exclusion of 428 employees with prevalent CVD. Employees had to remain free of CVD during the period in which exposure was assessed since the occurrence of CVD could influence the reporting of work stressors. This resulted in 6,154 employees.

A fifth approach was used to model exposure as a time varying exposure, as described by Ake et al (18). For this approach employees with prevalent CVD, as reported in May 1998, were excluded (n= 651). Employees were also excluded if all three exposure assessments were missing (n=340); otherwise missing values were substituted by means of last observation carried forward. This resulted in a population of 11,149. For this approach we used data in counting process format, which may contain more than one record per subject. For any subject with multiple records in the dataset each such record represents one interval for that subject. Each record is of the form (T1, T2, I.), where T1 represents the time at which the interval started, T2 the time at which the interval ended and I is an indicator variable showing the status of the interval. The indicator I could take one value: 1 to indicate an event at T2, 0 to indicate censoring at T2 or 50 to indicate change in the time dependent variable. For example an individual did not have an event during a three year observation period and had a time varying work stress exposure, he was exposed to work stress during the first year and third year but not during the second year. This individual has three records whose intervals correspond to the exit status codes (change in work stress). The corresponding entry, exit, status and exposure to work stress of the three intervals would be 0-12, status= 50, work stress=1; 12-24, status=50, work stress=0; and 24-36, status=0 and work stress=1. The accompanying SAS syntax is proc phreg; model (entry, exit)*status (0, 50)= work stress; run;

Outcome

Cardiovascular disease (myocardial infarction (MI) and stroke) was assessed with questionnaires. Items that were used to assess CVD and to calculate time until event were assessed in the following way: May 2000 (Have you ever experienced a MI? If yes: < 1 year ago, 1-2 years ago, >2 years ago); January 2001 (Have you experienced a MI in the last 8 months?); May 2002 (Have you ever experienced a MI? If yes: < six months ago, six months- 1 year ago, > 1 year ago) and October 2008 (Have you experienced a myocardial infarction (MI) in the past? If yes:< 1 year ago, 1-2 years ago, 2-5 years ago, > 5 years ago). For stroke, information about the time of occurrence was only obtained with the questionnaire from 2008 and January 2001. Employees who reported to have experienced a MI or stroke before 2000, who are being treated by a general practitioner or specialist for their heart or who had undergone heart surgery were excluded.

Potential confounders

Gender, age and educational level (classified as low: primary school, lower vocational school, medium: lower secondary school, intermediate vocational school, upper secondary school, high:

upper vocational school and university) were assessed in May 1998. The following confounders were measured in May 2000: Smoking was inventoried as 'Do you smoke daily?' (yes-no), alcohol consumption was inventoried as 'How many glasses of alcohol do you drink weekly?' (none, 1-14 glasses, 15-21 glasses, > 22 glasses), physical activity was inventoried as 'How often do you perform leisure physical activity of a minimum of half an hour per week?' (never or once a week, 2-7 times a week, more than 7 times), body mass index (BMI) was calculated from the items 'weight' and 'length' (classified as: 16-20, 20-25, 25-30, >30 kg/m^2), high blood pressure was inventoried as 'Have you ever been diagnosed with an elevated blood pressure?' (yes/ no), negative affectivity (NA) was assessed with the Positive and Negative Affect Schedule (19). It consists of 20 items and the answer scale ranges from: not at all, a bit, average, to a considerable extent, to a large extent. The sum score of the negative affectivity subscale was dichotomized into high/ low using the 75^{th} percentile which was 22 in this sample. NA is a trait which reflects stable and pervasive individual differences in mood and self-concept characterized by a general disposition to experience a variety of aversive emotional states. It has also been described as a general tendency to report distress, discomfort, and dissatisfaction over time and across situations, even in absence of any overt or objective source of stress. High NA individuals tend to dwell on the negative side of themselves and the world (20). NA may inflate the association between self-reported work stressors and self-reported health outcomes (21, 22). Therefore, we examine whether adjustment for NA leads to a substantial reduction of the association between self-reported work stressors and CVD.

STATISTICAL ANALYSIS

All analyses were performed using SAS 9.2. The theoretical range of the work stressor score, as determined in the sample in which the measure was constructed, was -5.73-1.24 (8). For the cumulative exposure and the single exposure measurement, the median and quartile values of the distribution of the work stressors score at baseline was used. The baseline work stressor score showed a relatively normal distribution: mean=0.83, median=0.81, standard deviation (SD) =1.12, actual range:- 2.28 - 4.61, skewness=0.20, value of the highest quartile > 1.60. The total dose was normally distributed with mean=2.22, median=2.20, SD= 2.87, actual range= -6.87 -13.66, skewness=0.12, values of the quartiles: -6.87-0.20; 0.20-2.23; 2.23-4.29; 4.29- 13.66. The average work stressor score was normally distributed with mean=0.74, median=0.73, SD=0.95, actual range= -2.29- 4.55, skewness=0.12.

To examine the pattern of exposure above and below the median value on the MCS- WSS (0.81) over time, we examined the percentage of employees who were categorized as exposed in May 1998 and remained exposed at the subsequent two measurements later. The same was done for exposure above and below the highest quartile value on the MCS- WSS (>1.60). In addition we used the continuous work stressor score to calculate the correlation coefficients between the

three time points, to examine the correlation of the MCS-WSS over two years.

The proportional hazard assumption was examined by visual inspection of the log negative log curves and by testing an interaction of the MCS-WSS with log of time in the multivariable model. There were indications for a violation of the assumption for the single exposure estimate from the third time point, where visual inspection showed a slight decreasing risk after 40 months and the time dependent variable for exposure almost reached significance (p=0.06). For the other exposure estimates inclusion of an interaction term with time was non-significant and visual inspection indicated a small departure from parallelism.

Cox regression analysis was used to assess the association between exposure to work stressors and CVD, using the several approaches to estimate long term exposure. Also the modeling of the time varying nature was performed within the proc phreg procedure. Confounders with missing values were excluded from the analyses. Models were adjusted for age, gender (I), adding educational level (II), adding BMI, physical activity, smoking, hypertension, alcohol consumption (IV) and adding negative affectivity (V). Survival time was censored if employees did not develop CVD at the end of the study (2008) or if they were lost to follow up.

The exposure estimates used in approaches 1 to 4 were also included as continuous scores since categorizing of the exposure variable leads to loss of power (23).

For the single exposure we used data from three separate time points. The association between single exposure (using T3, T2, T1) and CVD was calculated among employees who had complete data on the work stressor score at three consecutive time points. The baseline for T3 was May 2000, the baseline for T2 was May 1999 and for T1 it was May 1998. Incident CVD was assessed after baseline and adjustment for the corresponding baseline confounders was performed. Within the analyses using T1 and T2 as baseline, no correction was performed for hypertension and NA since these were not assessed at T1 or T2.

We examined the possibility of bias due to 1) selection bias as a result of the initial response rate of 45% by using data from a non-response analysis (24) and 2) bias due to the selection of employees with complete data on the work stressor score at three time points. The included and excluded employees were compared with regard to baseline work stressor scores, CVD risk factors and all-cause mortality. 3) Selective loss to follow up was examined, to assess whether the drop outs differed from those who remained in the cohort.

RESULTS

The participation rate at baseline was 45% and selection bias could have occurred if employees with high exposure to work stressors and a higher CVD risk did not want to participate. A non-response analysis among a subsample of the non-responders revealed that the prevalence of working more than 40 hours per week was higher among the respondents than among the non-respondents (20 versus 12%), which might be an indication of a higher prevalence of work stress,

but there were no differences regarding general health since the majority rated their health as good or excellent (24).

Employees with complete data on the work stressor score at three points did not differ from the employees with incomplete data regarding baseline mean work stressor score, mean age, gender and BMI. Among the excluded employees low educational level and smoking was more prevalent (24 versus 17%; 32% versus 24%) than among those with complete data. The percentage of deaths was also higher among the excluded employees (2.7% versus 1.7%).

With regard to selective loss to follow up, the percentage of deaths was significantly higher among those lost to follow up at the end of the study (4% versus 0.5 %). With regard to the baseline work stressor score, employees who were lost to follow at the last measurement

Table 2: Characteristics of the employees (assessed in May 2000) with complete data on the work stressor score at three consecutive time points, N=6,154.

Characteristic	Number (%)
Mean age, years (SD)	43 (8)
*Gender **	
Male	4488 (73%)
Female	1662 (27%)
*Educational level**	
Low	995 (16%)
Medium	2662 (43%)
High	2377 (39%)
Missing	120 (2%)
Smoking	
Yes	1377 (22%)
No	4729 (77%)
Missing	48 (0.8%)
Body Mass Index, kg/m²	
16-20	246 (4%)
21-25	2982 (48%)
26-30	2398 (39%)
>30	460 (8%)
missing	68 (1.1%)
Physical activity, times per/ week	
never	2209 (36%)
2-7	3597 (58%)
> 7	327 (5%)
missing	21 (0.3%)
Negative affectivity	
> 22	1309 (21%)
< 22	4570 (74%)
Missing	275 (4.4%)
High blood pressure	
Yes	1191 (19%)
No	4914 (80%)
Missing	49 (0.8%)
More than one job, yes	246 (4%)
Temporary contract, yes	104 (2%)
Flexible contract, yes	47 (1%)
Supervising function, yes	1634 (27%)
Shift work, yes	1481 (24%)
*Sector***	
Health care	931 (15%)
Industrial	2925 (47%)
Education	1594 (26%)
Service	704 (11%)
*Number of years working ***	
>10 years	5022 (82%)
5-10 years	769 (13%)
< 6 years	357 (6%)
*Number of years in current position with current employer***	
>10 years	1937 (31%)
6-10 years	1175 (19%)
1-5 years	2433 (40%)
< 1 year	598 (10%)

* assessed in May 1998, these factors are assumed to be (relatively) stable over time

**were not measured at a later time point than 1998

(October 2008) did not differ from those who remained in the cohort.
During a median follow up time of 102 months (minimum of 1 month and maximum of 102 months) 165 cardiovascular events were observed among the 6,154 employees in the first four approaches and 308 events were observed among the 11,149 employees in the fifth approach with a median follow up time of 49 months (minimum of 1 month and maximum of 126 months). The characteristics of the sample are shown in Table 2. 73% of the sample was men, medium and high educational level were more prevalent than low educational level (43%, 39%, 16%) and 39% was overweight (BMI 26-30). The majority of the employees (47%) had been working in the industrial sector and 82% of the employees had been working for 10 years or more.

Stability of exposure to work stressors over time

Table 3 shows that 72% and 54% of the employees who were originally classified as exposed in May 1998 (score above the median) remained exposed at the two consecutive time points later. When this was examined for employees where exposure status was assigned on a score above the highest quartile, only 33% of the employees classified as exposed in May 1998 remained exposed at the subsequent two measurements. *Results are not presented.*
The correlation coefficients for the repeated measurements of the work stressor scores between T1-T2, T1-T3 and T2-T3 were 0.65, 0.58 and 0.67, respectively. A correlation of 0.65 means that the measures of T1-T2 share 42% of their variance (0.65*0.65*100) and 58% is unaccounted for. The measures of T1-T3 share 34% of their variance and the measures of T2- T3 share 45% of their variance.
After the exclusion of employees who reported a job change (26%) or change of employer (6%) during this two year period, the correlation between the work stressor scores at T1-T2, T1-T3 and T2-T3 changed to 0.68, 0.64 and 0.71. Among the employees who reported change of job or change of employer, the correlation between the work stressor score at T1-T2, T1-T3 and T2-T3 were 0.53, 0.44 and 0.54.

Table 3: Pattern of exposure above and below the median value (median=0.81) over time.

Exposure status in May 1998	Exposure status in May 1999	Exposure status in May 2000
1=3145	1=2251(72%)	1=1697 (54%)
		0=429
	0=923	1=378
		0=505
0=3009	1=726	1=389
		0=337
	0=2419 (80%)	1=388
		0=2031 (67%)

1=exposed, 0=non-exposed

Table 4: The hazard ratio of cardiovascular disease by the number of times that employees scored above the median value (0.81), in the Maastricht Cohort Study, 2000-2008.

Number of times exposed above the median	N (events)	HR[a]	95% CI	HR[b]	95% CI	HR[c]	95% CI	HR[d]	95% CI	HR[e]	95% CI
0	2031 (46)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
1x	1230 (35)	1.23	0.79-1.91	1.34	0.87-2.08	1.38	0.88-2.15	1.46	0.93-2.29	1.46	0.91-2.33
2x	1196 (38)	1.39	0.91-2.14	1.44	0.93-2.20	1.50	0.97-2.31	1.53	0.99-2.37	1.55	0.98-2.44
3x	1697 (26)	1.23	0.81-1.84	1.20	0.80-1.81	1.22	0.81-1.86	1.26	0.83-1.92	1.21	0.77-1.89

Abbreviations: N, number; HR, Hazard Ratio; CI, confidence interval
[a] unadjusted; [b] adjusted for age, gender; [c] adjusted for age, gender, educational level; [d] adjusted for age, gender, educational level, alcohol consumption, smoking, BMI, physical activity, hypertension; [e] adjusted for age, gender, educational level, alcohol consumption, smoking, BMI, physical activity, hypertension, negative affectivity

The association between the different approaches to estimate exposure to work stressors and CVD

Table 4 presents the results for the cumulative exposure of the number of times that employees scored above the median on the MCS-WSS. Employees with a stable exposure above the median value had a fully adjusted HR of 1.21 (95% CI: 0.77-1.89) as compared to those with a stable exposure below the median value. Number of times exposed above the median value included as a continuous variable yielded an adjusted HR of 1.07 (95% CI: 0.93-1.22).
Table 5 presents the results for the cumulative exposure of the number of times that employees scored above the highest quartile on the MCS-WSS. Employees who scored three times in the upper quartile score of the MCS- WSS during two years had an adjusted HR of 1.66 (95% CI: 0.98-2.80), when NA was included into the model the HR reduced to 1.58 (95% CI: 0.93-2.72). Number of times exposed above the highest quartile included as a continuous variable yielded an adjusted HR of 1.15 (95% CI: 0.98-1.35).

Table 5: The hazard ratio of cardiovascular disease by the number of times that employees scored above the highest quartile value (> 1.60), in the Maastricht Cohort Study, 2000-2008.

Number of times exposed above the highest quartile	N (events)	HR[a]	95% CI	HR[b]	95% CI	HR[c]	95% CI	HR[d]	95% CI	HR[e]	95% CI
0	3768 (89)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
1x	1174 (35)	1.30	0.88-1.93	1.35	0.92-2.00	1.32	0.88-1.96	1.30	0.87-1.94	1.37	0.91-2.03
2x	712 (23)	1.39	0.88-2.20	1.38	0.88-2.19	1.35	0.84-2.15	1.33	0.83-2.13	1.18	0.72-1.92
3x	494 (17)	1.53	0.91-2.57	1.51	0.90-2.54	1.51	0.90-2.54	1.66	0.98-2.80	1.58	0.93-2.72

Abbreviations: N, number; HR, Hazard Ratio; CI, confidence interval
[a] unadjusted; [b] adjusted for age, gender; [c] adjusted for age, gender, educational level; [d] adjusted for age, gender, educational level, alcohol consumption, smoking, BMI, physical activity, hypertension; [e] adjusted for age, gender, educational level, alcohol consumption, smoking, BMI, physical activity, hypertension, negative affectivity

Table 6 presents the results for total exposure during two years. Employees with the highest quartile total exposure had a fully adjusted HR of 1.22 (95% CI: 0.77-1.95) as compared to employees with the lowest quartile dose. Total exposure included as a continuous variable yielded an adjusted HR of 1.04 (95% CI: 0.99-1.10).

Table 6: The hazard ratio of cardiovascular disease by the quartiles of total exposure, in the Maastricht Cohort Study, 2000-2008.

Quartiles of total exposure	N (events)	HR[a]	95% CI	HR[b]	95% CI	HR[c]	95% CI	HR[d]	95% CI	HR[e]	95% CI
1st quartile	1556 (42)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
2nd quartile	1543 (32)	0.77	0.48-1.21	0.77	0.50-1.23	0.83	0.52-1.31	0.90	0.56-1.44	0.97	0.59-1.58
3rd quartile	1551 (45)	1.07	0.70-1.62	1.08	0.71-1.65	1.18	0.77-1.80	1.27	0.82-1.95	1.35	0.86-2.12
4th quartile	1503 (46)	1.17	0.77-1.77	1.16	0.77-1.77	1.19	0.77-1.82	1.25	0.81-1.93	1.22	0.77-1.95

Abbreviations: N, number; HR, Hazard Ratio; CI, confidence interval
[a] unadjusted; [b] adjusted for age, gender; [c] adjusted for age, gender, educational level; [d] adjusted for age, gender, educational level, alcohol consumption, smoking, BMI, physical activity, hypertension; [e] adjusted for age, gender, educational level, alcohol consumption, smoking, BMI, physical activity, hypertension, negative affectivity

Table 7 presents the results for the average MCS-WSS exposure. Employees in the upper quartile of the average MCS-WSS had a fully adjusted HR of 1.26 (95% CI: 0.79-2.01) compared to employees in the lowest quartile of the MCS-WSS. Average exposure included as a continuous variable yielded a fully adjusted HR of 1.14 (95% CI: 0.96-1.35).

Table 7: The hazard ratio of cardiovascular disease by the quartiles of average exposure in the Maastricht Cohort Study, 2000-2008.

Average exposure	N (events)	HR[a]	95% CI	HR[b]	95% CI	HR[c]	95% CI	HR[d]	95% CI	HR[e]	95% CI
1st quartile	1534 (41)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
2nd quartile	1538 (32)	0.78	0.49-1.23	0.78	0.49-1.25	0.84	0.53-1.33	0.93	0.58-1.48	1.00	0.62-1.64
3rd quartile	1542 (44)	1.06	0.70-1.63	1.09	0.71-1.66	1.17	0.76-1.81	1.23	0.80-1.91	1.32	0.84-2.08
4th quartile	1540 (48)	1.19	0.79-1.82	1.19	0.78-1.81	1.22	0.80-1.87	1.28	0.83-1.98	1.26	0.79-2.01

Abbreviations: N, number; HR, Hazard Ratio; CI, confidence interval
[a] unadjusted; [b] adjusted for age, gender; [c] adjusted for age, gender, educational level; [d] adjusted for age, gender, educational level, alcohol consumption, smoking, BMI, physical activity, hypertension; [e] adjusted for age, gender, educational level, alcohol consumption, smoking, BMI, physical activity, hypertension, negative affectivity

Table 8 presents the results for exposure assessed with a single measurement from three different time points. The fully adjusted HR was 1.93 (95% CI: 1.25-3.00) when the T3 single measurement was used. The exposure assessed at T3 violated the proportional hazard assumption. Partitioning the time axis at 40 months showed that only an association was found in the first forty months. The single exposure assessments from T2 and T1 showed no association with CVD and no time varying effect.
The fifth approach, where exposure was modelled as a time varying exposure, yielded an unadjusted HR of 1.28 (95% CI: 1.02-1.60). We adjusted for confounders, measured in May 1998. This yielded an age and gender adjusted HR of 1.26 (1.00-1.59), additional adjustment for educational level yielded a HR of 1.29 (1.02-1.63) and inclusion of smoking, BMI, physical activity yielded a HR of 1.21 (0.95-1.54). No adjustment was performed for hypertension and negative affectivity since these variables were assessed in May 2000.

Table 8: The hazard ratio of cardiovascular disease by quartiles of exposure in the Maastricht Cohort Study, 2000-2008, where single exposure assessments from three time points were used (T3, T2, T1).

Single time exposure	N (events)	HR[a]	95% CI	HR[b]	95% CI	HR[c]	95% CI	HR[d**]	95% CI	HR[e]	95% CI
T3 #											
1st quartile	1695 (43)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
2nd quartile	1604 (33)	0.78	0.49-1.23	0.83	0.53-1.31	0.89	0.56-1.41	0.96	0.60-1.53	1.00	0.62-1.61
3rd quartile	1524 (34)	0.87	0.55-1.36	0.87	0.56-1.37	0.88	0.55-1.39	0.95	0.60-1.51	0.97	0.60-1.57
4th quartile	1328 (55)	1.67	1.12-2.49	1.69	1.13-2.52	1.81	1.21-2.70	1.93	1.28-2.91	1.93	1.25-3.00
*T2 **											
1st quartile	1766 (65)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
2nd quartile	1705 (54)	0.84	0.59-1.21	0.84	0.58-1.20	0.89	0.62-1.28	0.91	0.63-1.31	1.01	0.68-1.47
3rd quartile	1652 (53)	0.86	0.60-1.24	0.86	0.60-1.24	0.90	0.62-1.31	0.88	0.61-1.28	0.93	0.63-1.38
4th quartile	1370 (53)	1.06	0.74-1.52	1.06	0.74-1.53	1.09	0.76-1.58	1.06	0.73-1.54	1.09	0.74-1.63
*T1 **											
1st quartile	1626 (62)	1.00	-	1.00	-	1.00	-	1.00	-	1.00	-
2nd quartile	1684 (62)	0.97	0.68-1.38	1.00	0.70-1.42	1.04	0.73-1.49	1.08	0.75-1.54	0.99	0.68-1.43
3rd quartile	1597 (58)	0.96	0.67-1.37	0.95	0.66-1.36	1.04	0.72-1.49	1.01	0.70-1.46	0.93	0.64-1.35
4th quartile	1596 (63)	1.05	0.74-1.48	1.05	0.74-1.49	1.04	0.73-1.49	1.03	0.72-1.47	0.91	0.62-1.33

Abbreviations: N, number; HR, Hazard Ratio; CI, confidence interval; [a] unadjusted; [b] adjusted for age, gender
[c] adjusted for age, gender, educational level; [d] adjusted for age, gender, educational level, alcohol consumption, smoking, BMI, physical activity, hypertension; [e] adjusted for age, gender, educational level, alcohol consumption, smoking, BMI, physical activity, hypertension, negative affectivity, # violation of the PH assumption only a significant association was observed within first forty months of follow up; * no violation of the PH assumption was observed, ** for T1 and T2 model d was adjusted for age, gender, educational level, smoking, BMI, physical activity. NOTE: total number of employees and events differ in T1 and T2 from T3, see methods

DISCUSSION

This study examined whether exposure to work stressors varied over time and whether different approaches to estimate exposure influenced the size of the association between exposure to work stressors and cardiovascular disease.

A moderate temporal stability of work stressors was found over a two year period. Two methods were used to examine stability of exposure over time: the fluctuation in exposure status based on a score above/ below median (and highest quartile) and the correlation between two time points was calculated. By calculating the correlation between two time points misclassification due to dichotomization is circumvented. A moderate stability over time is in line with findings reported by other studies that examined across time variation over a period of one to five years (11, 13-16). Most of these studies, except for the study of de Lange (16) did not correct for measurement error. The consequence is that if across time variation is used as an indicator of actual change, actual change is overestimated (12). This was observed in the study of de Lange, where the unaccounted variation decreased from 62% to 42% after correction for measurement error. This is still a substantial across time variation where other sources are likely to contribute to the across time variation. Within our study we examined whether exclusion of employees reporting job change or employer change would reduce the variation. This showed only little reduction in variation, which is in line with the findings of Kayaba et al. (11). Other plausible contributors to the across time variation within our study are change in perception or change that occurs within a job or change due to measurement error (12). In addition, it seems plausible that certain items included in the work stressor score are more prone to change than other items.

The results obtained from the repeated measurements, as compared to the results obtained from the single measurements, yielded stronger estimates for the association between work stressors and CVD. Even though the differences were not statistically significant, we consider them as meaningful differences. This suggests that using repeated measurements reduces the amount of non-differential misclassification which is more prevalent when a single measurement is used as an indicator of long term exposure. One of the single measurements, the T3 measurement, did yield a strong association between work stressors and CVD, especially within the first forty months after exposure. We believe that it may have been a finding by chance. In a previous study we did not find an association between baseline exposure to work stressors and CVD (25). Also the single measurements of T1 and T2 showed no association (and no time varying association).

We used several approaches to estimate different types of exposure to work stressors using repeated measurements to examine whether different types of exposure would yield different estimates of CVD risk. The rationale to examine different types of exposure was to explore whether a certain level of exposure, a minimum duration of exposure or a certain type of exposure is needed to increase CVD risk (most) since it seems implausible that each form of exposure initiates a stress response. Even though the different approaches did not yield

significantly different hazard ratios, the differences in the size of the HR's might indicate meaningful differences where employees with stable exposure above the highest quartile during two years might have the strongest CVD risk. A high work stressor score at three consecutive time points might suggest a constant high level of sustained biological arousal since exposure during two years might be a better indicator of exposure before and after this two year period, and therefore is a better indicator of long term exposure. This is in line with the mechanism where chronic exposure leads to allostatic load, causing wear and tear of the cardiovascular system (10, 26) through atherosclerosis (10, 27, 28), which needs years to develop. High total exposure and high average exposure might result from peak exposure periods in combination with lower exposure periods. This enables employees to recover from high exposure to work stressors, which therefore does not result in a significantly increased CVD risk. Not finding a significant association or a less strong association among employees with a stable exposure above the median value and modelling the time varying nature might be because the level of exposure was too low to elicit a stress response. The work stressor measure consists of various items that have dichotomous or likert answer categories which does not capture intensity. A high work stressor score (e.g. above the highest quartile value as compared to above the median value) indicates that employees are exposed to many stressors simultaneously, which is more likely to elicit a stress response. Another explanation is that dichotomization yields non-differential exposure misclassification and is considered to yield an underestimated association between exposure and outcome. This might also be an explanation for not finding a significant association for those in the middle exposure groups of cumulative exposure above a cut off value (those categorized as once or twice exposed). The inconsistency over time may be due to small variation around the cut off value or due to regression to the mean in case of categorizing employees as exposed above the highest quartile value. Therefore, the results of the methods used are most reliable for comparing those employees with consistent scores (those with a stable exposure above/ below a cut off value).

One of the hypotheses within this field is that work stress leads to increased BMI, smoking and hypertension which in turn increase CVD risk (2, 3, 6). Among the highest exposure groups, inclusion of these factors slightly increased the HR, which was against the expected direction. Although the HR increased we do not consider this as a meaningful increase since the imprecision and the width of the confidence intervals also increased. Besides, the inclusion of each covariate separately did not attenuate the association strongly, indicating that the included covariates are not strong confounders or mediating factors. With regard to negative affectivity, adjustment only slightly decreased the association in the highest exposure groups. Therefore, in this study, the effect of NA on the association can be considered as limited.

To our knowledge, only a few other studies have estimated chronic exposure to work stress (ors), using repeated measurements, and have examined the association with CVD. Kivimaki et al examined whether several composite measures for exposure would improve the prediction

of CVD (13). The mean, maximum and baseline adjusted change scores did not improve the prediction of CVD. To compare these results with our findings is difficult because of differences in the sample, the number of repeated measurements and the interval between the measurements, different exposure assessments and information on measurement error.

Strengths and limitations of this study

The strengths include its prospective design and the availability of three measurements to estimate long term exposure, which is a better indicator of long term exposure than exposure estimated with a single measurement. Of course, more repeated measurements over time would be valuable to examine whether using three measurements with a one year interval covering a two year period is indeed a good indicator of long term exposure. If a two year period of exposure is not a good indicator of exposure in the following years, the resulting association for stable exposure and CVD as presented in this study is an underestimation of the actual association. The MCS-WSS has been developed within the heterogeneous sample of the MCS. We expect that the results can be extrapolated to a broad group of employees in other countries where the work environment and circumstances are similar to those in the Netherlands. Ideally the work stressor measures should be validated in another sample and examined for its association with CVD. Furthermore, the MCS-WSS is a comprehensive measure which captures the multifarious nature of the work environment, with each work stressor having its own weight (with regard to its work stress potential) and which has been associated with work strain in the current labor market (8). This study also has limitations. The complete case analyses and the high attrition during follow up could have yielded biased estimates if missing values in the work stressor score or reasons for drop out were related to (stable) exposure to work stressors as well as to a higher CVD risk. To examine whether bias occurred, the underlying mechanism of missingness was assessed (29, 30). The percentage of death was higher among the employees with missing values in the work stressor score than among the included employees (2.7% versus 1.7%). This was also seen for the employees who were lost to follow up at the end of the study compared to those still participating (4% versus 0.5%). This could be an indication that those excluded also more often developed CVD, which is not captured with questionnaires. An underestimation of the actual association would have been yielded if missingness is also related to stable exposure to work stressors. It is unlikely that the association would be biased if lost to follow up or missingness is unrelated to stable exposure. In addition, the complete case analyses (29, 30) resulted in a loss of power and might be an explanation for the non-significant findings. The number of events in the various exposure groups was rather small and also, the categorization of the exposure estimates led to a loss of power (23). When the different exposure estimates were included as continuous variables, all results reached almost significance. Another explanation for the low number of incident events might be related to relatively young age within the study population, the mean age was 43 years and 23% of the sample was 50 years or older. Another limitation is that no distinction could be made between the proportion of actual change and change due to measurement error (12) since

we had no information about the amount of measurement error in the work stressor measure. Furthermore, reporting bias due to high negative affectivity might result in an overestimated association when work stressors and CVD are assessed with questionnaires (2, 31, 32). In this study, correction for NA did not strongly attenuate the association and therefore is thought to be of minor influence. Last, self-reported MI and stroke was not validated in this sample. Studies that have examined the validity of self-reported MI have reported values for sensitivity ranging between 82% to 92% (33-35) and values for specificity between 85% and 98% for MI (33-35). With regard to stroke, studies have reported values for sensitivity ranging between 70%-98% and values for specificity above 97% (33-37). If in this study the percentage of false negatives was relatively high this could also explain the low number of events.

In conclusion, exposure to work stressors varied over time and employees with a stable exposure above the highest quartile during two years might have the strongest CVD risk. Replication of the results by future studies with more power is required to confirm our findings with more certainty.

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6

The impact of personal attributes on the association between cumulative exposure to work stressors and cardiovascular disease

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Objective

To examine the impact of personal attributes (coping and negative affectivity) on the association between cumulative exposure to work stressors and cardiovascular disease (CVD).

Methods

6,154 employees from the Maastricht Cohort Study (MCS) were selected who had complete data on the MCS work stressor score (MCS-WSS) at three consecutive time points during 1998-2000 and free of CVD during the exposure assessment period. CVD was assessed from 2000 until 2008 with questionnaires. Cumulative exposure to work stressors was calculated as the frequency of exposure in the upper quartile of the MCS-WSS and consisted of the categories: none, once, twice or thrice exposed. Cox regression analyses were used to examine the direct effect of personal attributes on CVD incidence and the intermediating, confounding and moderating effect on the association between cumulative exposure to work stressors and CVD. Logistic regression was used to examine the influence of personal attributes on the odds of high cumulative exposure (thrice exposed).

Results

High NA was significantly associated with high cumulative exposure to work stressors. There was no significant evidence supporting an intermediating, confounding or moderating effect of NA or coping on the association between cumulative exposure to work stressors and CVD.

Conclusion

The association between cumulative exposure to work stressors and CVD is not confounded or intermediated by NA or coping. High NA showed a direct effect on high cumulative exposure to work stressors. However, it should be examined whether high NA individuals experience more often a high level of work stressors or are actually exposed more often to a high level of work stressors.

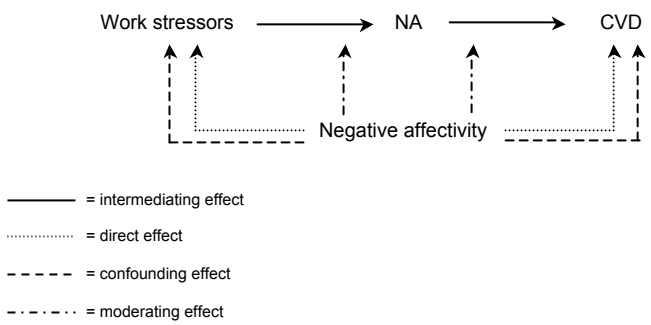
INTRODUCTION

The association between the psychosocial work environment and cardiovascular disease (CVD) has been examined for several decades. So far, individual differences have mostly been disregarded in the majority of these studies, while individual differences in personal attributes, such as coping and negative affectivity, might give more insight into why employees differ in their susceptibility to exposure to work stressors (1-5), in their susceptibility to develop CVD and in their susceptibility to the effect of work stressors on CVD incidence (6-9).

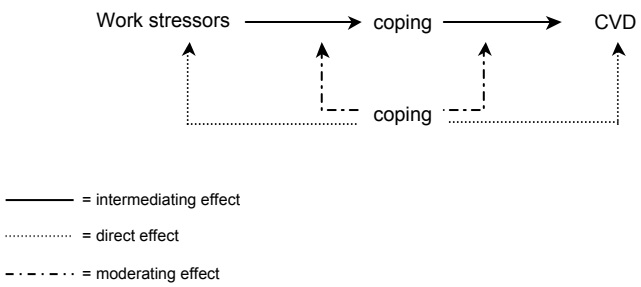
Negative affectivity (NA) is a pervasive disposition where those high in NA have the tendency to negatively appraise themselves, others and the world in general and to experience chronically high levels of distress (10). NA may have various effects on exposure to work stressors, on CVD incidence and on the association between work stressors and CVD (3). A direct effect of high NA on work stressors may result from the fact that high NA individuals tend to perceive high levels of work stressors as compared to those without high NA (3). Since primary appraisal determines whether the work environment will be perceived as stressful (11), NA can influence the number and type of situations perceived as stressful (12). High NA individuals may also create their own stressors as a result of their own behaviour, where the negative view of others and themselves has a self-fulfilling prophecy (3). NA has also been reported to be an independent risk factor for poor health (6, 8, 9, 13, 14). Furthermore, individuals high in NA may be hyper responsive to objective stressors resulting in an exaggerated response (3) or may choose less effective coping styles. Furthermore, when the appropriate style is chosen, the effectiveness might be less than among individuals low in NA (15-17), then NA is expected to exert a moderating effect on the association between work stressors and CVD. High NA has also been suggested to result from exposure to high levels of work stressors (3) which in turn increases CVD incidence. Besides these effects, NA might have a biasing effect (18, 19), where high NA individuals exhibit a complaining tendency and are not actually exposed to a higher level of work stressors or strains/ health outcomes than those without high NA. *Overview A.1 shows the pathways where NA may act upon.*

Another personal attribute that may have various effects on exposure to work stressors, on CVD incidence and on the association between work stressors and CVD, is coping style. It has been positioned as a mediator where the causal impact of the work stressors on CVD works via coping (4, 20, 21). Coping has been suggested to have a direct effect on CVD incidence; specifically among those with avoidance and palliative coping where stress alleviation is obtained through increased smoking frequency, alcohol consumption or unhealthy food consumption, which are all known risk factors for CVD. Another proposed mechanism of coping on CVD incidence is that coping moderates the association between the effects of stress on outcomes (4, 11) because how one copes with a stressful event determines how and whether the situation is resolved and the health consequences of the stress exposure (22). *Overview A.2 shows the pathways where coping may act upon*.

Overview A.1: Pathways within the model of (perceived) work stressors – CVD where negative affectivity can moderate, intermediate or confound the association between work stressors and CVD or have a direct effect on work stressors and/ or CVD.



Overview A.2: Pathways within the model of work stressors – CVD where coping can moderate or intermediate the association between work stressors and CVD or have a direct effect on work stressors and/ or CVD.



Studies that have examined the impact of personal attributes, such as NA and coping, on the association between work stressors and CVD are scarce (23, 24). More research is needed to reveal whether personal attributes are substantial contributors to the association between exposure to work stressors and CVD. If so, including personal attributes in research on work stressors and CVD may contribute to a better prediction of long term stress outcomes, such as CVD, where the effects of chronic stress on health accumulate over the long term (25). Therefore, the main focus of this study is to explore the impact of personal attributes, negative affectivity and coping, in the process from exposure to work stressors to the development of CVD. As described above, various effects are hypothesized, which will be examined with the following four secondary research questions:

1 Does coping or NA have a direct effect on CVD incidence?
2 Does coping or NA have a direct effect on high cumulative exposure to work stressors?

3 Does coping or NA intermediate or confound the association between cumulative exposure to work stressors and CVD?
4 Does coping or NA have a moderating effect on the association between cumulative exposure to work stressors and CVD?

Recently, we have developed a work stressor measure to assess exposure to work stressors, which will be used in this study (26). Furthermore, we will specifically focus on cumulative exposure to work stressors since chronic stress is probably more influenced by enduring personality attributes (27). In this study, cumulative exposure to work stressors is used as risk factor (research questions 3 and 4) and as endpoint (research question 2).

METHODS

Study population

Data of the prospective Maastricht Cohort Study (MCS) was used, which started in 1998 in the Netherlands (28). Different companies and organizations were contacted to ensure that employees from different sectors and trades were included. Only companies with over 100 employees were contacted. From the 79 companies contacted, 45 agreed upon participation. Men and women between 18 and 65 years with an employment contract of at least 16 hours per week were approached. This resulted in 26,978 potential participants of which 12,140 participated at baseline (response rate 45%). The response rates during follow-up were 80% (May 1999), 67% (May 2000), 62% (January 2001), 46% (May 2002) and 50% (October 2008) relative to the baseline population. All data used for this study was collected with questionnaires. For the current study, employees were selected without missing values in the work stressor score at three consecutive time points (excluding N= 5,558) and those without CVD during 1998-2000 (excluding N= 428), resulting in N=6,154.

Work stressors

Exposure to work stressors was measured with the Maastricht Cohort Study Work Stressor Score (MCS-WSS), which consists of the following items: keep learning new things, freedom to make decisions, work very hard, enough time to finish the job, hectic job, job offers enough security, working overtime, mentally strenuous, clear task description, confronted with personally upsetting things at work, personally attacked or threatened, often annoyed by others at work and sufficient career possibilities. Within the algorithm the items have different weighting factors, which depend on the answer scales. This is described in detail elsewhere (26).

For this study, cumulative exposure to work stressors was calculated as the frequency of exposure in the upper quartile (>1.60) of the MCS-WSS at three subsequent time points (May 1998, May 1999 and May 2000), as used in a previous study (29). The MCS-WSS is normally distributed and has a score range of -2.28 - 4.61. Four groups of cumulative exposure to work

stressors were created: none, once, twice or thrice exposed. The four categories were used for studying cumulative exposure to work stressors as independent risk factor. For studying cumulative exposure to work stressors as endpoint we will specifically examine the association between personal attributes and cumulative exposure consisting of three times exposed (which will be defined as *high* cumulative exposure) as compared to those with no cumulative exposure.

Negative affectivity

Negative affectivity was measured with the PANAS (30) in May 2000. The PANAS consist of two subscales, each consisting of 10 items and the answer scale ranges from: not at all, a bit, average, to a considerable extent and to a large extent. Negative affectivity has a right skew distribution with a score range from 10 to 48, with a median of 16, mean of 17.98, skewness=1.11. The values of the percentiles are 38 (95^{th}), 22 (75^{th}), 16 (50^{th}), 13 (25^{th}) and 10 (5^{th}).

Coping

Coping was measured with the 15 item Utrecht Coping List (31) in May 1999. The UCL measures four coping styles: avoidance coping is measured with three items, active coping with five items, social support seeking behaviour with five items and palliative coping with two items. The answer categories range from seldom/ never, sometimes, often, to very often. A high score on social support seeking and active coping is considered protective, whereas a high score on palliative and avoidance coping is considered harmful. All coping variables were relatively normally distributed with a score range of 3-12 (avoidance), 4-16 (active), 5-20 (social support seeking) and 2-8 (palliative).

Confounders

Gender, age and educational level (classified as low: primary school and lower vocational school, medium: lower secondary school, intermediate vocational school and upper secondary school, high: upper vocational school and university) were assessed in May 1998. The following confounders were measured in May 2000: Smoking was inventoried as 'Do you smoke daily?' (yes-no), alcohol consumption was inventoried as 'How many glasses of alcohol do you drink weekly?' (0, 1-14 glasses, 15-21 glasses, > 22 glasses), physical activity was inventoried as 'How often do you perform leisure physical activity of a minimum of half an hour per week?' (0-1 times a week, 2-7 times a week, >7 times), body mass index (BMI) was calculated from the items 'weight' and 'length' (classified as: 16-20, 20-25, 25-30, >30 kg/m^2) and high blood pressure was inventoried as 'Have you ever been diagnosed with an elevated blood pressure?' (yes/ no).

Cardiovascular disease

Incident CVD was defined as the first event occurring after the baseline (May 2000) and consisted of myocardial infarction (MI) or stroke. The reason to pool stroke and MI into one CVD measure was to increase power. This decision was carefully considered and thought to be justified since atherosclerosis is the main underlying mechanism for stroke and MI (32, 33) and work stress (ors) are thought to increase CVD incidence through the process of atherosclerosis (34). Furthermore, stroke and MI have mostly similar risk factors. CVD was assessed with questionnaires during the follow-up period with the following items: January 2001 (Have you experienced a MI in the last 8 months?); May 2002 (Have you experienced a MI? If yes: < six months ago, six months - 1 year ago, > 1 year ago) and October 2008 (Have you experienced a MI in the past? If yes:< 1 year, 1-2 year, 2-5 year, > 5 years ago). For stroke, information about the time of occurrence was only obtained with the questionnaires from 2008 and January 2001. Employees with prevalent CVD at baseline (May 2000) were excluded from the analyses (559 employees of which 114 had MI, 49 had stroke and the other 396 had undergone heart surgery or received treatment for their heart by a general practitioner or specialist).

Assessment of CVD incidence time

Time to the event was estimated by using the time period specified in the answer categories of the items used to assess CVD, as described in the paragraph above. E.g. employees who indicated to experience a MI at Oct 2008 could choose from the following time periods: < 1 year ago, 1-2 years ago, 2-5 years ago, and > 5 years ago. For the first category, the event could have occurred somewhere between October 2008 and October 2007. The midpoint was chosen to assign the time of event, which was April 2008. The same procedure applied to the second and third categories. For the last category, the event could have occurred somewhere between October 2003 and May 2002 which was the follow up questionnaire preceding the one of October 2008. Again, the midpoint was chosen to assign the time of event. For the items where no information was available about the time of occurrence, the time of event was equal to the time of reporting the event. This resulted in 14 categories of time with a distribution of events sufficient to perform Cox regression analysis.

STATISTICAL ANALYSIS

SAS® 9.2 (SAS Institute Inc.) was used to perform the statistical analyses.

As it is uncertain whether a linear relationship exists between NA or coping and CVD or work stressors or whether a certain cut off score is needed, in the current study they will be examined both ways. To differentiate between those with a harmful or protective attribute in the analyses, the sum scores of the NA and coping scales were dichotomized using the 75^{th} percentile, which

were 22 (NA), 7 (avoidance), 5 (palliative), 13 (active) and 12 (social support seeking). For the descriptive statistics, coping was categorized into three groups: 1st quartile, 2nd and 3rd quartiles and the 4th quartile. The results of the analyses for personal attributes as continuous variables are presented in the tables, whereas the results of the analyses examining personal attributes as categorical variables are described in the text.

Direct effect of personal attributes on CVD incidence

To examine whether personal attributes show an association with CVD, we first explored whether the distribution of coping and NA significantly differed among those with and without incident CVD. Frequency tables were generated and the Chi square test was performed. To examine whether personal attributes show an independent association with CVD, Cox regression analyses were performed. The proportional hazard (PH) assumption was evaluated by visual inspection of the log minus log plots and by testing the interaction of the main variables with the logarithm of time. The PH assumption was justified.

The analyses were adjusted for age, gender and educational level and additionally adjusted for hypertension, smoking, BMI, alcohol consumption and leisure physical activity, where the latter four factors are hypothesized to intermediate the association between high NA, avoidance coping, palliative coping and CVD. Due to power restrictions BMI, alcohol consumption and leisure physical activity were collapsed into two categories (>25 versus < 25, 0 versus > 1 glass per week and 0 versus > 2 times per week). In addition, we examined the influence of each factor separately on the association by including it in the model next to the personal attribute, instead of including them as one group into the model.

Direct effect of personal attributes on high cumulative exposure to work stressors

To examine whether the personal attributes show an association with high cumulative exposure to work stressors, we first explored whether the distribution of personal attributes significantly differed among those categorized as none, once, twice and thrice exposed to work stressors. Frequency tables were generated and the Chi square test was performed.

To examine whether personal attributes show an independent association with high cumulative exposure (those three times exposed), logistic regression analyses were performed. The analyses were adjusted for age, gender and educational level. Subsequent correction was performed for NA (as a continuous variable) since avoidance and palliative coping styles are more common among those with high NA or neuroticism, while social support seeking behaviour and active coping are less common (16, 35).

Intermediating or confounding effect of personal attributes on the association between cumulative exposure to work stressors and CVD

The personal attributes were evaluated upon having a confounding or intermediating effect on the association between cumulative exposure to work stressors and CVD by controlling for the

separate personal attributes next to age and gender. No additional confounder correction was performed due to limited power.

Moderating effect of personal attributes on the association between cumulative exposure to work stressors and CVD

Interaction between cumulative exposure to work stressors and the personal attributes was tested by introducing a product term into the Cox model. In addition, results were stratified on the presence/ absence of the personal attributes to explore a potential pattern because establishing statistical interaction requires sufficient power. No confounder correction was performed due to the restricted power.

Additional analysis

Coping styles may differ according to gender which can be attributed to gender differences in socialization (36-38), where certain coping styles are more relevant among men while other coping styles are more relevant among women. Of the 6154 employees, 1661 (27%) were females, among which 22 events occurred. Due to limited power, results could not be stratified. Therefore, the results were replicated for male employees only, to examine whether this would affect the results.

Assessment of bias

Selective loss to follow up was examined by comparing those lost to follow up in 2008 with those who remained in the cohort regarding their median work stressor score, coping, NA and covariates measured in 2000. Bias due to complete case analysis was examined by comparing those with missings with those with complete data on the work stressor score at three time points regarding their median work stressor score and covariates measured in 1998.

RESULTS

During a median follow up time of 102 months (minimum of 1 month and maximum of 102 months) 165 incident events occurred. Of the 165 events, 73 were strokes and 88 were MI's. 4 persons reported both a stroke and MI.

Direct effect of personal attributes on CVD incidence

Table 1 shows that the personal attributes showed a similar distribution among those who developed CVD and those who did not develop CVD.

Table 2 shows the age, gender and educational level adjusted HR for CVD incidence for those with a high cumulative exposure to work stressors (those three times exposed) of 1.51 (95% CI:0.90-2.54). NA and coping did not show an association with CVD. Correction for smoking,

BMI, alcohol consumption and leisure physical activity did not strongly attenuate the association between high NA, avoidance coping, palliative coping and CVD, indicating that the association is not intermediated by lifestyle factors.

Personal attributes examined as categorical variables generated somewhat different results for high NA: high NA (≥23) showed a tendency towards a significant association with CVD; the age, gender and educational level adjusted HR was 1.32 (95% CI: 0.92-1.88). None of the coping styles were significantly associated with CVD.

Table 1: Distribution of personal attributes and demographic factors among employees with cumulative exposure to work stressors (0x, 1x, 2x and 3x exposed) and employees with CVD and those without CVD.

	Cumulative exposure to work stressors					Incident CVD		
	0x Number (%)	1x	2x	3x	X^2 *	yes	no	X^2
Total / events	3773/ 90	1174/ 35	712/23	494 /17		165	5989	
% High negative affectivity (22-48)	536 (15)	312 (29)	241 (37)	220 (48)	<0.0001	43 (28)	1266 (23)	0.15
% Avoidance coping								
Low (3)	253 (7)	87 (7)	53 (8)	31 (6)	<0.0001	17 (10)	407 (7)	0.18
Medium (4-6)	2619 (70)	761 (66)	434(61)	288(59)		103 (62)	3999(67)	
High (7-12)	878 (23)	313 (27)	220 (31)	171 (35)		45 (27)	1537(26)	
% Active coping								
Low (4-10)	768 (20)	257 (22)	129 (18)	97 (20)	0.0003	31 (19)	1220 (21)	0.88
Medium (11-12)	1648 (44)	449 (39)	292 (41)	178 (36)		70 (43)	2497 (42)	
High (13-16)	1332 (36)	454 (39)	286(40)	216 (44)		63 (38)	2225 (37)	
% Social support seeking behaviour								
Low (5-8)	683 (18)	208 (18)	131 (19)	104 (21)	<0.0001	41 (25)	1085 (18)	0.08
Medium (9-11)	1745 (47)	468 (40)	295 (42)	192 (39)		71 (43)	2629(44)	
High (12-20)	1305 (35)	485 (42)	280 (40)	195 (40)		53 (32)	2212 (37)	
% Palliative coping								
Low (2)	327 (9)	76 (7)	52 (7)	49 (10)	0.002	19 (12)	485 (8)	0.21
Medium (3-4)	2293 (61)	707 (61)	406 (57)	267 (55)		90 (55)	3583 (60)	
High (5-8)	1131 (30)	385 (33)	251 (35)	171 (35)		54 (33)	1884 (32)	
% Educational level								
Low	604 (16)	199 (17)	114 (16)	78 (16)	0.71	36 (22)	959 (16)	0.002
Medium	1661 (45)	502 (44)	295 (43)	204 (42)		83 (51)	2579 (44)	
High	1435 (39)	453 (39)	284 (41)	205 (42)		43 (27)	2334 (40)	
% Male gender	2726 (72)	841 (72)	534 (75)	386 (78)	0.02	143 (87)	4345 (73)	<0.0001
Mean age (SD)	43 (9)	43 (8)	44 (8)	44 (8)		48 (7)	43 (8)	
Smoking								
Yes	802 (21)	275 (24)	194 (27)	106 (22)	0.004	72 (44)	1305 (22)	<0.0001
No	2940 (79)	892 (76)	513 (73)	384 (78)		91 (56)	4638 (78)	

Table 1 (continued)

	Cumulative exposure to work stressors					Incident CVD		
	0x Number (%)	1x	2x	3x	X2 *	yes	no	X^2
BMI								
16-20	147 (4)	54 (7)	25 (4)	20 (4)	0.02	2 (1)	244 (4)	0.002
20-25	1908 (51)	530 (46)	322 (46)	221 (46)		63 (38)	2919 (49)	
25-30	1418 (38)	478 (41)	298 (42)	204 (42)		86 (52)	2312 (39)	
>30	260 (7)	99 (9)	61 (9)	40 (8)		13 (8)	447 (8)	
Alcohol consumption, glasses p/week								
none	965 (26)	313 (27)	181 (25)	127 (26)	0.98	52 (32)	1534 (26)	0.06
1-14	2378 (63)	731 (62)	448 (63)	317 (65)		88 (53)	3786 (63)	
15-21	328 (9)	102 (9)	65 (9)	36 (7)		20 (12)	511 (9)	
>22	88 (2)	24 (2)	17 (2)	11 (2)		5 (3)	135 (2)	
Leisure physical activity (number of times per week)								
Never	1281 (34)	441 (38)	287 (40)	200 (41)	0.003	60 (36)	2149 (36)	0.82
2-7	2281 (61)	660 (56)	387 (55)	269 (55)		98 (59)	3499 (59)	
>7	198 (5)	70 (6)	35 (5)	24 (5)		7 (4)	320 (5)	
Hypertension								
Yes	699 (19)	215 (19)	164 (23)	113 (23)	0.006	54 (33)	1137 (19)	<0.0001
No	3047 (81)	947 (81)	544 (77)	376 (77)		111 (67)	4803 (81)	

* X^2= p-value obtained with chi square test

Table 2: Crude and adjusted associations between cumulative exposure to work stressors, personal attributes and cardiovascular disease, obtained with Cox regression analysis among N=6,154 employees.

Exposure	N/events in crude model	Crude HR	95% CI	HR*	95% CI	HR**	95% CI
0x > Q3 = reference	6154/165	1.00	1.00	1.00	1.00	1.00	1.00
1x > Q3#		1.29	0.87-1.91	1.30	0.88-1.93	1.26	0.84-1.88
2x > Q3		1.38	0.87-2.18	1.33	0.84-2.12	1.30	0.81-2.08
3x > Q3		1.51	0.90-2.54	1.50	0.89-2.52	1.61	0.95-2.71
NA (10-48)	5879/158	1.01	0.99-1.04	1.02	0.99-1.04	1.02	0.99-1.04
Avoidance coping (3-12)	6108/165	0.96	0.86-1.06	0.96	0.87-1.06	0.98	0.89-1.09
Active coping (4-16)	6106/164	1.02	0.94-1.10	1.04	0.96-1.12	1.04	0.96-1.12
Social support seeking behaviour (5-20)	6091/165	0.89	0.84-0.95	0.93	0.87-0.99	0.94	0.88-1.01
Palliative coping (2-8)	6115/163	1.00	0.88-1.15	1.02	0.88-1.17	1.02	0.89-1.18

Q3= score in the upper quartile of the work stressor score; * adjusted for age, gender and educational level;
**also adjusted for smoking, body mass index (> 25 versus < 25), leisure physical activity (> 1 versus never), alcohol consumption (> 1 versus none) and hypertension

Direct effect of personal attributes on high cumulative exposure to work stressors (those three times exposed)

Table 1 shows that high NA and high avoidance coping were more prevalent among those with high cumulative exposure to work stressors (those 3 times exposed) as compared to those with no cumulative exposure.

Table 3 shows that NA was positively associated with high cumulative exposure, yielding an age, gender and educational level adjusted OR of 1.14 (95% CI: 1.12-1.15). The initial association between avoidance coping and high cumulative exposure to work stressors reduced substantially towards the null after inclusion of NA in the model and was no longer significant. The initial association between active coping and high cumulative exposure to work stressors increased after inclusion of NA in the model from 1.04 (95% CI: 0.99-1.09) to 1.15 (95% CI: 1.09-1.22).

Personal attributes examined as categorical variables yielded similar results for high NA (≥ 23) and high active coping (≥13), but it yielded a somewhat different picture for high avoidance (≥7) and high social support seeking behaviour (≥12). High avoidance (≥7) yielded an age, gender and educational level adjusted OR of 1.79 (95% CI: 1.46-2.19) which reduced to 1.25 (95% CI: 0.99-1.56) after NA correction. High social support seeking behaviour (≥12) yielded an age, gender and educational level adjusted OR of 1.31 (95% CI: 1.07-1.61) which slightly reduced to 1.25 (95% CI: 1.00-1.56) after NA correction.

Intermediating or confounding effect of personal attributes on the association between cumulative exposure to work stressors and CVD

Table 4 presents the associations between cumulative exposure to work stressors and CVD, when controlling separately for the personal attributes. None of them significantly decreased the association. Controlling for personal attributes as categorical variables generated similar results.

Table 3: The odds of high cumulative exposure to work stressors (consisting of 3 times exposed) with the increase of one unit on the personal attribute scale, as compared to the odds of no cumulative exposure to work stressors, obtained with logistic regression analysis among 4,268 employees.

Personal attribute	N/events in crude model	Crude OR	95% CI	OR*	95% CI	OR**	95% CI
NA (10-48)	3600/474	1.12	1.11-1.14	1.14	1.12-1.15	-	
Avoidance coping (3-12)	3748/491	1.16	1.09-1.23	1.17	1.10-1.24	1.01	0.95-1.08
Active coping (4-16)	3750/490	1.05	1.00-1.10	1.04	0.99-1.09	1.15	1.09-1.22
Social support seeking (5-20)	3733/491	1.02	0.98-1.05	1.03	0.99-1.07	1.02	0.99-1.07
Palliative coping (2-8)	3751/487	1.07	0.98-1.17	1.08	0.99-1.18	1.00	0.91-1.10

*adjusted for age, gender and educational level; ** adjusted for negative affectivity

Table 4: The age and gender adjusted associations between cumulative exposure to work stressors and CVD, separately adjusted for personal attributes to assess confounding and / or intermediating effect.

	N/ events in model with personal attribute	Age and gender adjusted HR*	95% CI**
0x>Q3 = reference		1.00	
1x > Q3#		1.34	0.91-1.98
2x > Q3		1.37	0.87-2.17
3x > Q3		1.50	0.89-2.52
Adjusted for NA (10-48)	5871/158	1.00	
		1.37	0.92-2.05
		1.25	0.77-2.05
		1.48	0.86-2.56
Adjusted for Avoidance coping (3-12)	6100/165	1.00	
		1.35	0.91-1.99
		1.39	0.88-2.21
		1.52	0.90-2.55
Adjusted for Active coping (4-16)	6098/164	1.00	
		1.35	0.92-2.00
		1.38	0.87-2.18
		1.50	0.89-2.52
Adjusted for Social support seeking behaviour (5-20)	6083/165	1.00	
		1.36	0.92-2.01
		1.39	0.89-2.21
		1.52	0.91-2.56
Adjusted for Palliative coping (2-8)	6107/163	1.00	
		1.37	0.93-2.03
		1.40	0.88-2.21
		1.53	0.91-2.58

Q3= score in the upper quartile of the work stressor score; *HR= hazard ratio; **95% CI= 95% confidence interval

Moderating effect of personal attributes on the association between cumulative exposure to work stressors and CVD

None of the product terms between cumulative exposure to work stressors and personal attributes (as continuous variables) reached significance, see Table 5. The stratified results showed that high NA Individuals (≥23) had a HR of 2.41 (95% CI: 1.02-5.67) when exposed to high cumulative exposure to work stressors while low NA (≤ 22) individuals had a HR of 1.23 (95% CI: 0.57-2.68).

Additional analyses

The sensitivity analyses restricted to men yielded, in general, similar results as the results based on the sample where women were included. Results are not presented.

Table 5: The association between cumulative exposure to work stressors (once, twice, thrice exposed as compared to those with no cumulative exposure) and CVD, stratified on presence and absence of personal attributes.

Personal characteristic	N/ events	HR (95% CI) when once exposed compared to zero times exposed	N/ events	HR (95% CI) when twice exposed compared to zero times exposed	N/ events	HR (95% CI when thrice exposed compared to zero times exposed	p-value
-	1174/35	1.29 (0.87-1.91)	712/32	1.38 (0.87-2.18)	494/17	1.51 (0.90-2.54)	
Negative affectivity							
High (23-48)	312/11	1.78 (0.77-4.11)	241/11	2.26 (0.98-5.22)	220/10	2.41 (1.02-5.67)	0.20
Low (10-22)	770/23	1.25 (0.78-2.00)	415/10	1.02 (0.53-1.97)	235/7	1.23 (0.57-2.68)	
Avoidance coping							
High (7-12)	313/7	0.89 (0.38-2.07)	220/9	1.58 (0.74-3.41)	171/5	1.24 (0.47-3.24)	0.09
Medium and low (3-6)	848/28	1.46 (0.94-2.26)	487/14	1.25 (0.70-2.23)	319/12	1.64 (0.89-3.04)	
Social support seeking							
High (12-20)	485/10	0.88 (0.43-1.79)	280/6	0.89 (0.37-2.13)	195/6	1.32 (0.55-3.15)	0.42
Medium and low (5-11)	676/25	1.59 (0.99-2.53)	426/17	1.71 (0.99-2.93)	296/11	1.62 (0.86-3.10)	
Active coping							
High (13-20)	454/11	1.07 (0.54-2.11)	286/11	1.65 (0.83-3.27)	216/9	1.80 (0.86-3.76)	0.48
Medium and low (4-12)	706/24	1.45 (0.90-2.34)	421/12	1.22 (0.65-2.27)	269/8	1.31 (0.62-2.74)	
Palliative coping							
High (5-8)	385/11	1.24 (0.62-2.51)	251/12	2.07 (1.05-4.09)	171/4	1.04 (0.36-2.95)	0.30
Medium and low (2-4)	783/24	1.35 (0.84-2.17)	458/11	1.04 (0.55-1.98)	316/13	1.83 (1.00-3.33)	

N= total number; HR= hazard ratio; 95% CI= 95% confidence interval

Assessment of bias

Among respondents who were lost to follow up as compared to those who remained in the cohort, the percentage of smokers and low educational level was higher (25% versus 21% and 19% versus 15%, respectively) and the percentage of high educational level and leisure physical activity was lower (36% versus 42% and 61% versus 66%). No differences were observed with regard to the median work stressor score, NA, coping, hypertension and BMI> 25.

Employees with incomplete data on the work stressor score at three time points had a higher percentage of BMI> 25, smokers and low educational level (45% versus 41%, 32% versus 23% and 24% versus 16%, respectively). Furthermore, they had a lower percentage of high educational level (29% versus 39%).

DISCUSSION

This study examined the various hypothesized effects of NA and coping on CVD incidence, on high cumulative exposure to work stressors, as well as on the association between cumulative exposure to work stressors and cardiovascular disease.

The association between high cumulative exposure to work stressors and CVD was non-significant but elevated. The age, gender and educational level adjusted HR was 1.51 (95% CI: 0.90-2.54), which increased to 1.66 (95% CI: 0.98-2.80) after correction for BMI, smoking, hypertension and physical activity. Due to the restricted power and the debate on whether or not to include these factors since they could be intermediates we consider the HR of 1.51 as a better estimate of the true association, which we consider meaningful and relevant. Since the confidence intervals encompass unity we cannot exclude the possibility of a chance finding, however we consider the restricted power as a more likely explanation for the imprecise estimate. Furthermore, finding a non-significant but elevated association for those with high cumulative exposure to work stressors is plausible since being classified as exposed during three time points covering a two year period approximates long term exposure best.

There is no consensus about whether NA and coping should be examined as continuous or categorical variables, which can also be seen in the numerous studies using both methods (8, 9, 13, 14, 23, 24). Using a continuous variable suggests that a linear effect on CVD incidence or on high cumulative exposure to work stressors can be expected. Using a categorical variable suggest that a cut off score is needed, above which an effect is expected, which in turn is also related to distinguish properly between individuals with and without the positive or negative personal attribute. The findings that an elevated but non-significant association is found between high NA (≥23) as a categorical variable and CVD and between high avoidance (≥7) and high cumulative exposure to work stressors provide support for the latter hypothesis.

Adjusting the association between high avoidance (≥7) and high cumulative exposure to work stressors for NA strongly reduced the association to no longer significant, but the association remained elevated. This could indicate an independent association, where NA contributes to the strength of the association but does not entirely explain it.

NA showed a consistent strong significant association with high cumulative exposure to work stressors. This is in line with the results of other studies (1, 2, 39). Several explanations are plausible: high NA individuals perceive the work environment more stressful than those without high NA, they may create their own stressors or that they end up in jobs with adverse working conditions (3). What remains unclear is whether high NA individuals are actually more often exposed to a high level of work stressors over a prolonged period or that they merely perceive more often a high level of work stressors. One study provides evidence that a substantial proportion of the reported exposure reflects the actual exposure (40). Furthermore, since exposure was measured before NA we cannot rule out that the association might be the result of reversed causation, where high cumulative exposure to work stressors has led to high NA (41).

Inclusion of NA into the model did not strongly attenuate the association between cumulative exposure to work stressors and CVD and therefore does not support the hypothesis that NA has a biasing or an intermediating effect on this association. For NA to has a substantial confounding effect, NA must show a strong association with work stressors as well as with CVD (42).

This study has provided indications that NA might has a moderating effect, since stratifying the results on high (≥23) and low NA (≤22) individuals seem to indicate that those with high NA exposed to high cumulative exposure had a higher CVD incidence than those without high NA and a similar exposure. Although a plausible explanation is that employees with high NA have an exaggerated response or prolonged response (3), a chance finding cannot be ruled out since the differences were not statistically significant.

High active coping (>13) and high social support seeking behaviour (≥12) were associated with high cumulative exposure to work stressors. These findings are counterintuitive and might be explained by the fact that the situational context was not taken into account. This might also clarify why overall no clear moderating or direct effects were observed for coping on the association between work stressors and CVD, on high cumulative exposure to work stressors and on CVD incidence. The rationale to examine coping as a personality trait was that if one wishes to establish that ineffective coping contributes to health problems that it is unlikely that only situational specific coping strategies play a role. For coping to influence the development of health problems, there must be some commonality in type of coping strategies (21). However, others have argued to take the situational context into account (4, 16, 43, 44). Although the situational context may be relevant to take into account to assess moderating effects, the power did not allow us to examine it.

This study has various strengths and limitations. The first strength concerns the validity of the exposure assessment. The MCS-WSS has been shown to be associated with work strain and captures the most important work stressors in the current work environment (26). Second, repeated measurements of work stressors were used, which is a better indicator of long term exposure than a baseline assessment which is used in the majority of other studies. Third, self-reported CVD has shown good agreement with medically confirmed stroke and myocardial infarction (45-49) and can be considered a valid outcome measure. In addition, the results of this study do not support the hypothesis that negative affectivity is a nuisance variable inflating the association when self-report measures are used to assess exposure and outcome.

One concern regards the 50% loss to follow up over a period of 8 years and the potential bias that could have occurred due to the exclusion of employees with incomplete data on the work stressor score. For bias to occur, loss to follow up has to be related to NA, coping, work stressors and CVD. Even though the two groups did not differ in the percentage of high NA, high avoidance or high palliative coping, selective loss to follow up cannot be ruled out since it could have occurred before coping and NA were first measured. Furthermore, among those lost to follow up smoking and low educational level were more prevalent, which are known risk factors for CVD and could be an indication that CVD incidence was higher among those lost to follow up. The same pattern

with regard to covariates was seen for those who were excluded due to missings in their work stressor scores as compared to those with complete data. Thus, if bias occurred in this sample, it probably led to an underestimation of the results. Another limitation was the restricted power to examine effect modification properly, and which might explain why certain results did not reach significance. Another concern is that the assessment of hypertension with self-report could have suffered from reporting bias. No objective data was available to validate the hypertension item, therefore the risk of misclassification and residual confounding cannot be excluded.

In conclusion, no evidence was found for the hypotheses that the association between cumulative exposure to work stressors and CVD is confounded or intermediated by NA or coping. High NA showed a direct effect on high cumulative exposure to work stressors. Future research should examine whether high NA individuals experience more often a high level of work stressors or are actually more often exposed to a high level of work stressors.

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7

Negative affectivity does not lead to over reporting of cardiovascular disease

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Objective
Negative affectivity (NA) is a personal attribute which has been implicated as a potential source of over reporting of cardiovascular disease (CVD). The aim of this study was to examine whether the percentage of objectively confirmed CVD positive among those reporting CVD is lower among individuals with high NA as compared to those with low NA.

Methods
Case ascertainment was performed for employees of the Maastricht Cohort Study residing in the southern part of the Netherlands and who reported a heart disease or stroke in the follow up questionnaire of 2008. The percentage of objectively confirmed CVD positive was calculated (positive predictive value) for those with low and high NA. The PPV is a useful measure to assess the percentage of false positives.

Results
The PPV of self-reported heart disease was 59% for high NA individuals and 58% for low NA individuals. The PPV of self-reported stroke was 61% for high NA individuals and 33% for low NA individuals.

Conclusion
No evidence was found for negative affectivity as a source of over reporting of heart disease or stroke. Results should be replicated by futures studies to confirm our findings and to examine the impact of NA on the reporting of other CVD subtypes.

INTRODUCTION

Many epidemiological studies rely on questionnaires to assess cardiovascular disease (CVD). Various studies have indicated moderate to good validity for self-reported CVD as compared to medically confirmed CVD (1-5). In general, it seems that self-reports of well-defined and easy to diagnose CVD conditions have a higher positive predictive value as compared to complex and less clear defined conditions (4, 6). In addition, respondent characteristics, such as age, education (4), sex, comorbidities and personality traits (1) may influence the reporting of CVD. The influence of respondent characteristics may be of greater importance for a disease with low agreement as compared to a disease with high agreement (2).

One of the personality traits which has been considered to lead to *over* reporting of health outcomes is negative affectivity (NA) (7-9). In 1984 Watson and Clark introduced the concept of NA as a pervasive disposition where individuals high in NA have the tendency to negatively appraise themselves, other people and the world in general and to experience chronically high levels of distress (10). It can be considered as the disposition to respond negatively to questionnaires, leading to over reporting of self-reported disease (7). Especially in studies that examined the association between self-reported work stressors and self-reported health outcomes, such as CVD, NA is often discussed as a biasing factor (7-9).

A prerequisite for bias to occur in studies is that negative affectivity has to lead to over reporting of the risk factor and CVD. Although it is known that NA and work stressors are positively associated (11, 12) as well as NA and CVD (9, 13), these associations can be real and not merely the result of reporting bias (12). However, studies that have examined the association between work stressors and CVD are considered biased due to NA if only self-report is used to assess exposure and outcome (7, 9, 14). To disentangle whether NA leads to over reporting of work stressors and CVD, both objective and self-report data are needed on work stressors and on CVD (15). In the Maastricht Cohort Study (MCS), work stressors were measured with self-report and no objective data are available. For a subsample of the MCS both objective and self-report data are available on CVD and this provided us the opportunity to examine whether negative affectivity leads to over reporting of CVD.

The primary aim of this study is to examine whether the percentage of objectively confirmed CVD among those reporting CVD is lower among individuals with high NA than among those with low NA. The positive predictive value (PPV) is a useful measure to assess whether NA leads to over reporting, since it shows the percentage of false positives. To examine whether NA has a different impact on the PPV of different CVD subtypes we differentiated between heart disease and stroke. It is expected that the PPV of self-reported heart disease will be lower among high NA individuals than among low NA individuals, than the PPV of a more specified CVD type, such as stroke. Heart disease is not a specified condition, but it encompasses well-defined, less clear defined and complex CVD conditions. It is expected that, if NA reflects a negative reporting tendency, a higher percentage of the reported heart disease will not be objectively confirmed.

METHODS

Study population

Data of the prospective Maastricht Cohort Study (MCS) was used, which started in May 1998 to study work related fatigue (16). At baseline 12,140 employees participated (response rate 45%). After baseline several follow up questionnaires were sent out to assess (amongst others) cardiovascular disease. The response rates during follow-up were 80% (May 1999), 67% (May 2000), 62% (January 2001), 46% (May 2002) and 50% (October 2008), relative to the baseline population.

For the current study, a subsample of the MCS population was used. Due to study constraints, case ascertainment was only performed for employees residing in the southern part of the province Limburg in the Netherlands, who gave an affirmative answer to the items assessing heart disease and stroke in October 2008. In October 2008, 454 and 130 employees reported a heart disease and stroke, respectively. Excluding the study participants who did not reside in the Southern part of the province Limburg in the Netherlands, resulted in 255 individuals reporting heart disease and 76 individuals reporting stroke.

Negative affectivity

In May 2000, negative affectivity (NA) was measured with the Positive and Negative Affect Schedule (PANAS) (17). The scale consists of two subscales (NA and positive affect (PA)) each consisting of 10 items and the answer scale ranges from: not at all, a bit, average, to a considerable extent, to a large extent. The sum score of the negative affectivity subscale was calculated and ranged between 10 to 40. A score above the 75th percentile (22) was used to classify individuals as having high NA.

Cardiovascular disease

The follow up questionnaire of 2008 was used to identify employees with heart disease and/ or stroke. The heart disease item was phrased as 'Do you have a one of the following diseases?' From a list of diseases they could check the box 'heart disease' with the following four answer categories: no I have not experienced a heart disease, I have experienced a heart disease and I have received treatment for it in the past but no longer at this moment, I have experienced a heart disease and I receive treatment for it at this moment and I have experienced a heart disease and I have never received any treatment. The stroke item was inventoried as 'Have you ever experienced a stroke?'

Respondent characteristics

Age, gender, diabetes and hypertension were assessed in 2008. Diabetes was inventoried as 'Do you have a one of the following diseases?' From a list of diseases they could check the box 'diabetes type II'. Hypertension was inventoried as 'Have you ever been diagnosed with elevated

blood pressure?' Educational level was inventoried in 1998 as 'What is the highest educational level that you have obtained?' The answer categories were classified as low: primary school, lower vocational school, medium: lower secondary school, intermediate vocational school, upper secondary school, high: upper vocational school and university.

Medical record review

In 2012 case ascertainment was performed for employees reporting to have experienced a stroke and/or heart disease in the questionnaire of 2008. In the southern part of Limburg three major hospitals are located, which were visited by two medically certified personnel who coded the disease status using the information from the medical records. The specific diagnosis and date of diagnosis was extracted from the files and coded. During the case ascertainment, information about NA was unknown to the persons who coded the medical records.

Categorization of the extracted diagnoses into objectively confirmed heart disease

The diagnoses which were extracted and the diagnoses which were included into the group 'objectively confirmed heart disease positive' where the heart disease- item was used for case ascertainment are listed in Table 1. The group 'objectively confirmed positive' consists of categories 2 and 5 (these categories include diagnoses such as myocardial infarction (MI), unstable angina, angina pectoris or coronary atherosclerosis which required an intervention such as percutaneous intervention (PCI), coronary bypass grafting (CABG), placing stents and atrium fibrillation, deep vein thrombosis (DVT), supra-ventricular tachycardia, mitral insufficiency, aorta aneurysm, aorta valve insufficiency, valve stenosis). These categories were chosen because diagnosis is made on objective data.

Table 1: Diagnoses extracted from the medical files and the diagnoses included in the group 'objectively confirmed heart disease*.

Categories	N (%)	Diagnoses
1	6 (3%)	Cerebrovascular accident (CVA)
2	91 (48%)	Acute myocardial infarction (AMI), unstable angina, angina pectoris or coronary atherosclerosis which required an intervention such as percutaneous coronary intervention (PCI),coronary artery bypass grafting (CABG), placing stents
3	14 (7%)	Angina pectoris without additional information
4	10 (5%)	Coronary atherosclerosis
5	46 (24%)	Rest group of manifest heart disease, such as: atrium fibrillation, deep vein thrombosis (DVT), supra-ventricular tachycardia, mitral insufficiency, aorta aneurysm, aorta valve insufficiency, valve stenosis
6	20 (11%)	Atypical complaints, performing of diagnostic tests without information on the test results, chest pain, heart palpitations
7	3 (2%)	Transient Ischemic Attack (TIA)
Total	190	

*objectively confirmed included categories: 2 and 5

In Table 2 it is listed which diagnoses were extracted and the diagnoses which were included into the group 'objectively confirmed stroke positive' where the stroke- item was used for case ascertainment. In this case we only included CVA. We did not include TIA's since diagnosis is mainly based on the reporting of the patient and the consequences are transient.
Those who did not have medical record registration and those with CVD conditions that were not objectively confirmed were classified as 'objectively confirmed negative'.

Table 2: Diagnoses extracted from the medical files and the diagnoses included in the group 'objectively confirmed stroke*.

Categories	N (%)	Diagnoses
1	34 (41%)	Cerebrovascular accident (CVA)
2	2 (4%)	Acute myocardial infarction (AMI)
3	0	Angina pectoris
4	2 (4%)	A. Carotid stenosis
5	3 (4%)	Atrium fibrillation, carotid problems, liquor hypotensic syndrome
6	3 (4%)	Suspected of minor stroke or CVA, atypical complaints such as pain on the chest
7	11 (14%)	Transient Ischemic Attack (TIA)
Total	55	

*objectively confirmed included category 1

STATISTICAL ANALYSIS

Descriptive statistics are given for the heart disease sample as well as for the stroke sample. The respondent characteristics are compared among those with high NA and low NA to examine whether potential differences in PPV can be explained by these characteristics. Hypertension and diabetes were included as 'comorbidities'. The differences between high NA and low NA employees in the categorical characteristics were tested for significance using the Chi-square test. We also included the missing NA group into the descriptive statistics as a separate group to examine whether those with missing NA values differed from those without missing values.
The positive predictive value (PPV) was calculated, overall and stratified on high NA and low NA. This was done separately for each CVD item, leading to two overall analyses. All analyses were performed using SAS, version 9.2. The difference between the proportions of objectively confirmed positive among those with high NA and those with low NA was tested for significance, using the Chi-square test. Employees with missing data on the NA scale were excluded from the analyses.
Case ascertainment was performed for those who reported heart disease and stroke in 2008. Selective attrition bias may be a concern if those high in NA have a higher tendency to drop out

during follow up than those low in NA. Therefore, it was examined whether those high in NA had a higher dropout rate as compared to those low in NA.

Sensitivity analyses
These analyses were performed to assess whether inclusion of heart conditions that are not objectively confirmed, such as atypical complaints e.g. chest pain, into the medically confirmed heart disease group would reduce the difference in the PPV of self-reported CVD between high NA and low NA individuals.
From validity studies it is known that agreement has been good or reasonable for well- defined outcomes with clear diagnostic criteria, while it has been low for conditions with less clear criteria (18). It was expected that the inclusion of vaguely defined conditions, where symptoms are the main component and reporting bias due to NA would be more prevalent, would increase the percentage of medically confirmed cases among high NA individuals, while it would not affect the percentage among low NA individuals. Thus the difference between low and high NA would become smaller.
For stroke, it was examined whether inclusion of TIA's into the objectively confirmed group would reduce the difference in the PPV of self-reported stroke between high NA and low NA individuals

RESULTS

The characteristics of the heart disease sample are presented in Table 3. The characteristics stratified on high NA and low NA show that among high NA individuals the prevalence of 65 years and older and high educational level was lower, whereas the prevalence of hypertension and diabetes was higher. These differences were not statistically significant, except for diabetes.
Table 4 shows that of the 255 individuals, 190 were traced back in the medical files (75%). The PPV of self-reported heart disease was 54%. It also shows that the PPV of self-reported heart disease did not differ, depending on NA level: the PPV was 59% among individuals high in NA and 58% among individuals low in NA (p-value=0.93).
The characteristics of the stroke sample are presented in Table 5. The characteristics stratified on high NA and low NA show that among high NA individuals the prevalence of male gender, high educational level and diabetes was higher, whereas hypertension was lower.
Table 6 shows that of the 76 individuals, 54 were traced back in the medical files (71%). The PPV of self-reported stroke was 45%. It also shows that the PPV was 61% among high NA individuals and 33% among low NA individuals, which is a significant difference (p-value=0.04).
We examined whether those who were still participating in 2008 differed in their NA score from those who were no longer participating in 2008. No difference was found in the percentage of high NA (23% versus 25%). Also no difference was found in the median score between the two groups (18.39 versus 17.85).

Table 3: Characteristics of the sample reporting heart disease.

Characteristic	Number (%)	Low NA**	High NA	*P*-value #	*NA=missing*
Total	*255*	*129*	*68*		**58**
Mean age (SD)	57.9 (7)	57.7 (7)	58.2 (6)		57.9 (9)
Age group					
> 65 years	38 (15%)	20 (16%)	5 (7%)	0.11	13 (23%)
< 65 years	215 (84%)	109 (84%)	62 (93%)		44 (77%)
Gender					
Male	207 (81%)	107 (84%)	56 (84%)	0.99	44 (75%)
Female	46 (18%)	21 (16%)	11 (16%)		14 (24%)
Educational level					
Low	73 (29%)	35 (28%)	17 (27%)	0.09	21 (38%)
Medium	128 (50%)	59 (47%)	38 (60%)		31 (56%)
High	43 (17%)	32 (25%)	8 (13%)		3 (5%)
Diabetes					
Yes	39 (14%)	16 (14%)	14 (24%)	0.04	9 (16%)
No	186 (73%)	95 (86%)	45 (76%)		46 (84%)
Hypertension					
Yes	152 (60%)	74 (58%)	44 (66%)	0.29	34 (59%)
No	101 (40%)	54 (42%)	23 (34%)		24 (41%)

*SD=standard deviation; **NA=negative affectivity;# P-value = obtained with chi-square test

Table 4: The positive predictive value of self-reported heart disease, also according to high and low NA.

		Objectively confirmed -	Objectively confirmed +	Total
Self-reported heart disease	Total	118 (46%)	137 (54%)	255
	High NA*	28 (41%)	40 (59%)	68
	Low NA	54 (42%)	75 (58%)	129
	Missing NA	36 (62%)	22 (38%)	58

*NA= negative affectivity

Results of the sensitivity analyses

Including not objectively confirmed diagnoses into the medically confirmed diagnoses for heart disease and stroke led to an increase in the PPV of self-reported heart disease and stroke (71% and 59% respectively). It did not substantially impact the difference in PPV between high NA and low NA individuals. The statistical difference between high NA and low NA was p=0.51 and p=0.01 for self-reported heart disease and stroke, respectively. See Appendix.

Table 5: Characteristics of the sample reporting stroke.

Characteristic	Number (%)	Low NA**	High NA	*P*-value #	*NA=missing*
Total	*76*	*36 (47%)*	*23 (30%)*		17 (22%)
Mean age (SD)	55.9 (7.46)	56 (8)	57 (6)		54 (9)
Age group					
> 65 years	8 (11%)	4 (11%)	3 (13%)	0.85	1 (6%)
< 65 years	67 (88%)	31 (89%)	20 (87%)		16 (94%)
Gender					
Male	56 (74%)	26 (72%)	18 (90%)	0.12	12 (71%)
Female	17 (22%)	10 (28%)	2 (10%)		5 (29%)
Educational level					
Low	17 (22%)	8 (24%)	6 (26%)	0.79	3 (18%)
Medium	37 (49%)	17 (50%)	9 (39%)		11 (65%)
High	20 (26%)	9 (26%)	8 (35%)		3 (18%)
Diabetes					
Yes	10 (13%)	3 (10%)	4 (19%)	0.28	3 (19%)
No	58 (76%)	28 (90%)	17 (91%)		13 (81%)
Hypertension					
Yes	41 (54%)	22 (61%)	12 (52%)	0.49	7 (41%)
No	35 (46%)	14 (39%)	11 (48%)		10 (59%)

*SD=standard deviation; **NA=negative affectivity;# P-value= obtained with chi-square test

Table 6: The positive predictive value of self-reported stroke, also according to high and low NA.

		Objectively confirmed -	Objectively confirmed +	Total
Self-reported stroke	Total	42 (55%)	34 (45%)	76
	High NA*	9 (39%)	14 (61%)	23
	Low NA	24 (67%)	12 (33%)	36
	Missing	9 (53%)	8 (47%)	17

*NA= negative affectivity

DISCUSSION

This is, to our knowledge, the first study that examined whether high negative affectivity leads to over reporting of CVD. This was done by exploring whether the PPV of self-reported CVD was lower among high NA individuals than among low NA individuals. Overall, for heart disease no significant differences in PPV were found depending on NA level.

The PPV of self-reported CVD was related to the type of self-reported CVD (heart disease or stroke). The PPV did not differ between high and low NA individuals with regard to self-reported heart disease. Whereas, the PPV for self-reported stroke was 28% lower among individuals low in NA than among those high in NA. This is in the opposite direction of what is expected if NA would cause over reporting. This could be due to the relative small numbers included in the analysis. Another explanation could be the relatively high percentage of hypertension among those with low NA. In the Netherlands, patients with hypertension (especially those with medical treatment) are closely monitored by the general practitioner to prevent CVD and are educated about hypertension being a risk factor for stroke (19). This, and the frequent contact with the health care system, might contribute to an increased awareness or confusion about having stroke (2, 4). However, literature on the influence of respondent characteristics and the presence of comorbidities that are thought to influence the reporting of CVD is mixed (1, 2, 4). Studies have shown that the absence of comorbidities are associated with higher agreement (4), whereas others have shown that the presence of hypertension was related to a significantly greater PPV (1). This makes it difficult to assess whether the presence of hypertension among low NA individuals caused this finding.

Another explanation might be reversed causation, where stroke impacts negative affectivity, as assessed with the PANAS. Negative affectivity has been positioned as a pervasive disposition, where those high in NA report more negative affect across time and regardless the situation (10). However, within the literature on personality traits there is no consensus on whether personality traits are fixed or whether they can change (20-23). Transition periods which are stressful, undesirable and unpredictable, such as experiencing a stroke, are thought to change personalities (20). However, studies that examined the stability over the life course resulted in mixed evidence (20-23) and studies that have examined the impact of a stressful transition are scarce. Unfortunately we do not have repeated measurements on NA to examine whether those who experienced a stroke changed in their NA score to gain more insight into this finding. However, the fact remains that high NA did not lead to over reporting of CVD which was the main research question of this study.

Whether the finding that NA does not lead to over reporting of CVD can be extrapolated to other studies using self-reported CVD probably depends on the proportion of different CVD subtypes making up the total CVD. The diagnosis angina pectoris is often based on only symptom reporting (8). High NA individuals are more likely to report distress and discomfort (10) and might mix these feelings up with angina complaints. In addition, high NA individuals have a higher prevalence

of doctor visits (24). This could lead to over reporting of angina pectoris, where a part of the conditions are not objectively established. Within this study the percentage of angina pectoris was 22% of the total. This represents unstable angina, (un)angina requiring intervention and angina pectoris without additional information. This former group (where objective evidence is lacking) was only 7% of the subsample. Thus, if one uses the item 'heart disease' one should consider the relative contribution of each subtype to the total.

In addition, this study was conducted within a sample of employees. We are not sure whether the results of this study can be extrapolated to a general population (which is a mixture of working and non-working individuals).

Limitations and strengths of the methods used

The PPV in this study is low for heart disease and stroke as compared to PPV's reported in other studies for MI and stroke (2-5). This could be related to misclassification of employees who did report CVD but could not be traced back in the medical records as 'objectively confirmed negative'. Case ascertainment was conducted in three major hospitals (including an academic medical centre where more specialist care is available) located in the area where the employees, who reported heart disease or stroke, resided. In the Netherlands, it is common that patients visit a hospital closest to their home address, except when it is a complex condition and more specialist care is required. Therefore, we believe that the three hospitals cover the majority of the study population and it is unlikely to explain the low PPV. Even more importantly, if patients would attend a hospital outside this area and were misclassified, it is unlikely that this would be related to NA status. Second, medical records were used as the gold standard. Although they are not free of errors or omissions (18) and the process of chart abstraction is subject to inaccuracy, we believe that if we failed to trace patients back in the medical files or made some mistakes in the coding or extracting information from the files, this could have led to the low PPV. However, it is unlikely to be related to NA status and should not impact the PPV of self-reported CVD stratified on NA level. A plausible explanation for the low PPV's in this study might be the low percentage of participants of 65 years and older. The posterior probability of a disease rises with increasing prevalence and the prevalence of stroke and heart disease is known to rise with age.

A third concern is when high NA individuals show a higher dropout rate during follow up than low NA individuals. This could mean that they dropped out before CVD could be assessed in 2008 which could lead to an underestimation of NA as a source of over reporting. No indications were found for selective drop out since those who dropped out and those who remained in the cohort in 2008 did not differ in their NA score assessed in 2000. A fourth concern is that 23% of the employees in the heart disease sample had missing values in NA. The worst case scenario would be that those with missings in NA are actually employees with high NA. If we would consider them as high NA, the original no difference in PPV among those with high and low NA would change into a 10% difference in favour of those with low NA. This would match the idea that NA leads to over reporting. For the stroke sample, the worst case scenario would merely reduce the

difference from 30% to 20% but still in favour of those with high NA. However, no indications are available that among employees with missing values in NA, high NA is more prevalent than low NA. The missings in NA could be due to organisational issues regarding the setup of the cohort study: employees who indicated in 1998 that they would retire in the next two years were lost to follow up in 2000 (in which NA was assessed). In 2008 the retired employees were notified and asked to participate again because information regarding retirement was assessed. The relatively high percentage of > 65 years in the missing NA group is supportive of this explanation. Furthermore, the number of cases, especially when stratified on NA, was rather small. Therefore, the findings of this study should be replicated by studies with more power, where the findings are less influenced by small numbers.

Strength of this study was that the people who searched the medical records were unaware of the NA score of the individuals reporting CVD. Therefore it is unlikely that the effort to trace individuals back in the medical records is influenced by the NA score of the individuals. In addition, NA was assessed with the PANAS, which is a validated scale.

In conclusion, the findings of this study do not support the idea that negative affectivity results in over reporting of CVD status. Since NA did not lead to over reporting of heart disease or stroke, NA as a source of common method bias when both exposure and CVD are measured with self-report is unlikely. More research is needed to confirm these results and to examine in more detail whether NA impacts the PPV of self-reported CVD, according to different CVD types (in particular angina pectoris).

APPENDIX

Table 1: The positive predictive value of self-reported heart disease, also according to high and low NA, where categories 2, 3, 4, 5 and 6 were included.

		Medically confirmed -	Medically confirmed +	Total
Self-reported CVD	Total	74 (29%)	181 (71%)	255
	High NA*	17 (25%)	51 (75%)	68
	Low NA	38 (29%)	91 (71%)	129
	Missing NA	19 (33%)	39 (67%)	58

*NA= negative affectivity

Table 2: The positive predictive value of self-reported stroke, also according to high and low NA, where also the category 7 was included.

		Medically confirmed -	Medically confirmed +	Total
Self-reported stroke	Total	31 (41%)	45 (59%)	76
	High NA*	5 (22%)	18 (78%)	23
	Low NA	20 (56%)	16 (44%)	36
	Missing	6 (35%)	11 (64%)	17

*NA= negative affectivity

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8

General discussion

In this thesis the association between the psychosocial work environment and CVD is addressed from a methodological viewpoint. The two aims of this thesis were, first, to gain more insight into how various methodological and conceptual choices impact the size of the obtained association between work stressors and CVD and, second, to obtain a better estimate for CVD risk when exposed to work stressors. This will give more insight into which methodological and conceptual issues are contributing to the conflicting evidence. This is relevant since these issues hinder a firm conclusion about a causal association between work stress and CVD and the establishment of exposure to work stressors as a risk factor for CVD. In this chapter the main findings are discussed and methodological considerations are described. In addition, recommendations for future research and practice will be given.

Main findings

To examine whether methodological and conceptual issues impact the size of the reported association between work stress (ors) and CVD in already conducted studies, a meta-regression analysis was performed. This study showed that several study characteristics impact the size of the reported estimate of CVD risk. The most important study characteristics were type of questionnaire used to assess exposure, type of outcome assessment and country in which the study is performed.

To obtain a better estimate for the association between work stress and CVD a valid exposure assessment is a prerequisite. Two work stressor measures were constructed using the conceptual framework consisting of work stressors- work stress- work strain, as introduced in the introduction of this thesis. This framework was used to position the various elements and to examine which work stressors were most associated with work strain. Conditionality applied to the framework, thus those who developed work strain must have been exposed to work stress and those with work stress must have been exposed to work stressors. Since there is no appropriate measure for work stress, we examined which work stressors were most associated with work strain and included them into the work stressor measure. The process of identifying which work stressors were most associated with work strain was repeated separately for two different work strain definitions and resulted in two work stressor measures. This was done to increase confidence in the robustness of our findings. The two work stressor measures include work stressors from various work dimensions, such as emotional demands, job insecurity, role clarity and job demands with each item having a different weighting factor indicating its potential to induce work strain. Both work stressor measures showed the strongest association with work strain, as compared to already existing scales, such as job demands, job strain and emotional demands. This study showed that work strain is a complex concept and multifarious of nature where each work stressor has its own contribution to work strain.

When the association between baseline work stressors and CVD was examined, using one of the two work stressor measures (the MCS-work stressor score) no association was found. The association was examined using different CVD measures: cardiovascular mortality, self-reported

myocardial infarction (MI) and stroke and objectively confirmed CVD, extracted from medical records. The size of the association did not depend on the type of CVD measure that was used.
Indications were found that exposure to work stressors varied over time. It was estimated that around 8% of the employees in the MCS had a stable exposure to a high level of work stressors (a score in the upper quartile of the MCS- work stressor score) during two years. This could explain why no association was found when a single exposure assessment was used to measure long term exposure. In the study where repeated measurements were used, a nearly significant association was found between stable exposure to a high level of work stressors during a two year period and CVD (HR: 1.51, 95% CI: 0.91-2.54), while no association was observed when a single exposure assessment was used. This underscores the importance of using repeated measurements to better approximate long term exposure. The association between other estimates of exposure (total exposure, average exposure and cumulative exposure above the median value) and CVD were also non-significant but the magnitude of the association was much smaller as well.
Furthermore, this thesis showed that although negative affectivity is significantly associated with self-reported work stressors and nearly significantly associated with self-reported CVD, it is unlikely to have yielded trivial associations since it did not lead to over reporting of CVD.
This thesis shows that conceptual and methodological issues impact the size of the association obtained between work stressors and CVD. Exposure to work stressors, in order to capture work stress, should be measured with a comprehensive measure and repeated measurements should be performed during a minimum of two years to capture stable exposure. This is a better indicator of long term exposure as compared to a single exposure assessment. Stable exposure to a high level of work stressors during a two year period showed a nearly significant association with CVD (HR: 1.51, 95% CI: 0.91-2.54), corrected for age, gender and educational level, which is considered to be meaningful and clinically relevant. Although, we cannot exclude with certainty that this is a finding by chance since the confidence interval encompass unity, a likely explanation for the non-significant finding is the limited power of the study.

Methodological considerations

A useful starting point to examine the literature within a research field is to conduct a review, meta-analysis or meta-regression analysis. A systematic review is a literature review focusing on a research question that tries to identify, appraise, select and synthesize all high quality research evidence relevant to the research question. Part of the systematic review is a meta-analysis with which results across studies are combined into a summary estimate of the effect size. A meta-analysis also attempts to gain greater objectivity, generalizability and precision by including all the available evidence that examines a certain issue (1). A prerequisite for performing a meta-analysis is the absence of heterogeneity. The presence of heterogeneity indicates variation in true effect sizes underlying the different studies (2), which may be due to clinical and methodological diversity (1). This hinders the use of a summary estimate since generalizability might be restricted

(3). A meta-regression analysis is useful to gain insight into the sources of heterogeneity. This was the main reason for us to conduct a meta-regression analysis as a starting point.
We conducted a meta-regression analysis on observational studies that examined the association between job strain and CVD. The findings indicated that results from studies performed in different countries or studies that used different JCQ questionnaires should not be pooled. Various authors have expressed their concerns about the variation in exposure assessments and addressed the difficulty of comparing results of studies conducted in different countries due to cultural differences (4, 5). This was based on their observation of the various studies included in their review. The added value of performing a meta- regression is that by using a multivariate model, differences in effect sizes can be assigned with more certainty to a certain study characteristic, since correction is performed for other study characteristics that impact the reported effect size. Furthermore, these findings would be completely ignored if one would perform a meta-analysis; the pooled estimate would be used to indicate CVD risk across different countries as well across populations where different JCQ questionnaires are used. This is what occurred in the meta analysis conducted by Kivimaki et al (6). The differences in estimated CVD risk depending on country or type of questionnaire should be further examined. Especially the latter finding is important, because if the same construct is measured with somewhat different questionnaires but yields very different estimates, this might be an indication of poor validity. More recently, a meta-analysis was performed on individual participant data from 13 different cohort studies from published and unpublished studies that examined the association between job strain and CHD to answer the question whether work stress is a risk factor for CVD (7). Before the meta analysis was performed, it was first explored whether the alternative versions of the JCQ used in the different cohort studies were comparable to the complete version by assessing the agreement, sensitivity and specificity, where the complete version of Karasek was used as the gold standard (8). Based on this study it was concluded that partial job demand, job control and job strain indices assess the same underlying concepts as the complete survey instrument. However, it can be questioned whether the JCQ should be used as gold standard while it is uncertain whether the full version of the JCQ measures work stress or whether it is a proxy measure for low socio-economic status or something else. Therefore, the results of this meta-analysis should be interpreted cautiously and should not be used to draw conclusions concerning the association between work stress and CVD.
A disadvantage of a meta- (regression) analysis is the risk of bias, especially when observational studies are included. Therefore, meta-regression should be used as an exploratory tool to generate new hypotheses, which should always be tested in individual studies (9, 10). The internal validity of a well conducted single study is higher than the internal validity of a meta-regression which heavily depends on the included studies and their characteristics. For example, the results of the meta- regression analyses indicated that studies using self-reported CVD yielded on average higher estimates for CVD risk than studies using objectively confirmed CVD, which could be indicative of a spurious finding (11). However, the findings of the individual studies of this thesis

examining this issue in more detail do not support this hypothesis, at least not for the studies conducted in the MCS. An explanation could be that the prevalence of not objectively confirmed angina pectoris was rather low within the Maastricht Cohort Study population (subsample). If several of the included studies in the meta-regression used angina pectoris as the main outcome or if the percentage of angina pectoris was substantial relative to the other CVD subtypes, this could clarify why studies using self-reported CVD as outcome yielded on average higher estimates for CVD risk. Thus, the type of CVD disease could have confounded the observed association between type of CVD measure and estimated CVD risk.

Strength of our meta-regression analysis was the use of within-study differences by including multiple results of one study. This makes our approach different from the existing meta-regression analysis where only one result per study is included. Limitations of our meta-regression analysis were the limited power to use a model selection method to examine which study characteristics independently influence the size of the reported estimate and the potential of data dredging by examining too many study characteristics due to too much heterogeneity. A recommendation for future studies is to restrict the amount of heterogeneity in the included studies. The choice to include studies could be based on various study characteristics that are hypothesized to have the most important effect on the reported effect size.

Exposure to work stressors

In this thesis, the Maastricht Cohort Study-Work Stressor Score (MCS-WSS) was used to measure exposure to work stressors with a high work strain potential in a heterogeneous group of employees working in the current work life and to examine the association with CVD. Below, first, the development of the work stressor score will be discussed where the focus will be on whether the measure captures the concept of work stress. Second, more methodological issues regarding exposure assessment will be discussed with specific focus on the duration, the level and intensity of exposure.

Development of the measure (to assess the concept work stress)

For this project, originally two work stressor measures were developed (as described in Chapter 2) for which we adhered to the framework of work stressor – work stress – work strain. This framework was used to position various elements as described in the introduction. Conditionality applied to the framework, thus those with work strain must have been exposed to work stress and those with work stress must have been exposed to work stressors. Two work strain definitions were used as an external reference point to examine which work stressors were most associated with work strain. Ideally, work stress would be the most appropriate reference point. However, work strain was used instead since a gold standard for work stress is unavailable. To increase confidence in the robustness of our findings, two work strain definitions were used to construct two work stressor measures. The process of identifying which work stressors were most associated with work strain was repeated separately for each work strain definition. The

first work strain definition was defined as ‘having experienced constant pressure lately’ (GHQ) and ‘having difficulty to relax after work’ (NFR). The other work strain definition consisted of employees who reported sickness absence due to work related stress. The work stressors that showed the strongest association with work strain were identified from a long list of work stressors, which were measured in the Maastricht Cohort Study. The following work stressors were examined for their work strain potential: emotional demands, cognitive demands, psychological demands, conflicts at work, job insecurity, lack of role clarity, lack of career possibilities, working overtime, lack of decision authority, skills discretion, commitment, lack of fairness, mismatch between effort and appreciation and lack of social support. The work stressors which showed the strongest association with work strain were included into the measure.

Although the difference in work strain definitions and sample size led to the identification of different work stressors, the measures had in common that both measures included items from different dimensions, each item had its own contribution to work strain and each measure showed a stronger association with work strain than job strain and other existing scales. Therefore, we can reason that the findings are quite robust and support our argument to use a more comprehensive measure to measure work stressors that have been associated with work strain preceded by work stress. Not using a comprehensive measure encompasses the risk of measuring only part of the stressors that are implicated in work stress (5) and that the association between work stress and CVD will be underestimated.

Another concern is the uncertainty of what exactly is measured when a measure is used that has not been tested for its work strain potential and that the obtained association with CVD might not reflect the association between work stress and CVD. To ensure that work stressors with a high work strain potential are measured, a suitable approach was used to construct a more valid measure where the ‘external’ validity was the focus (by using an external reference point) instead of the ‘internal’ validity (by examining the internal consistency of the separate scales). By using such an approach, our measure is different from any other measure that is based on a model, where the approach used to ensure validity is confirmatory factor analysis, which focuses on the internal validity (expressed as the internal consistency). The internal validity concerns whether the different items measure the same underlying construct. For example, do the items of the psychological demands scale and the items of the job decision latitude scale measure demands and control? However, whether job demands and job control are related to work stress is not tested. Because this latter step is missing, it is uncertain whether these concepts capture work stressors that induce work stress. Therefore, the approach used to construct the measure can be considered a major strength.

With regard to combining work stressors in a measure, in two other studies the Demand Control model and the Effort Reward Imbalance model were combined in order to improve the prediction of CVD and burn out (12, 13). The rationale of the researchers was probably similar as to ours; to improve risk prediction by capturing the elements of work stress more accurately. However, our study is more valid in the sense that we combine various work stressors into one measure

that have been tested for their association with work strain. We assume that this will improve the estimation of CVD risk. In the two studies it was examined whether the outcome prediction improved and the researchers assumed that this occurred through the process of work stress and work strain.

In our approach to develop the measure, self-reported items were used to identify employees with work strain and to assess exposure to work stressors. For the construction of the MCS- WSS it was examined which work stressors were associated with work strain; both were measured with self-report and at the same moment. This could have led to an association that suffers from common method bias (CMB). The four major sources of CMB are common rater effects (e.g. social desirability, mood state), item characteristic effects (e.g. item ambiguity, common scale formats, item social desirability), item context effects (e.g. item embeddedness, context induced mood) and measurement context effects (exposure and outcome measured at the same point, using the same medium to measure exposure and outcome) (14). Common rater effects and measurement context effects could be a problem, since negative affectivity (NA) could cause a spurious association between work strain and work stressors. Those high in NA are expected to respond negatively on each item and thus each item would be associated with work strain. This would hinder the selection of specific items that are most associated with work strain. Since specific items were identified, the influence of NA is thought to be of minor influence.

To prevent reporting bias, researchers have argued to use more objective measures for the assessment of work stressors and work stress (15, 16). An example of an objective measure is the physiological measurement of the effects of work stress in the body such as elevated blood pressure, increased heart rate and increased levels of hormones such as cortisol and adrenaline. However, the use of physiological measurements has various disadvantages: 1) quantifying stress with one physiological measure is impossible since individuals differ in their physiological reaction to a stressful situation: certain individuals will exhibit a rise in the cortisol level; others will exhibit a rise in blood pressure, 2) these measures can vary between and within individuals and complicates associating these parameters with work stress, 3) the measures are also determined by other non-stress related factors such as gender, hereditary, weight, age, diet, medication use, smoking, physical activity, and 4) it can be questioned whether these measures are a good reflection of the stress condition in the brain, which is being reported (17). Because of these limitations, van Doornen et al argue that these measures should be used as a mediator of health effects, where employees with strong physiological reactions to the work place should be compared with employees with low physiological reactions (17). Those with the strongest physiological reactions are the ones at increased disease risk, which is not necessarily correlated to reporting of the work environment. This is valuable for answering the question whether stress is related to disease, but it does not clarify which factors in the work environment contribute to stress, which is necessary information for prevention.

Although nearly all domains of work stressors were measured in the MCS, information was missing on managerial leadership (18), relational injustice (19), discrimination and work place

bullying (20). The unavailability of these work stressors means that they could not be examined for their work strain potential and therefore could not be included into the work stressor measure. The consequence is that our measure may still be an underestimation of work strain in the current work life, since inclusion of any missed relevant work stressors would only increase the association with work strain further. For the studies in which we examined the association between work stress and CVD; the resulting associations may also be underestimated. However, looking at the items included they seem to cover the majority of the most important work domains of the current work environment.

After the development phase, we chose to proceed with one of the two measures, the MCS-Work Stressor Score, because it was constructed in a sample with sufficient number of cases yielding a stable model used to identify the relevant work stressors that were included into the measure and the MCS-WSS was not associated with educational level. This reduces the risk of residual confounding due to socio-economic status (SES) in the studies we conducted. Job strain (and especially the job control component) has been considered as a measure of low socio economic status (21). The observed association between job strain and CVD can be the result of residual confounding (22), since it is difficult to disentangle which part of the association is explained by SES and which part by the work environment since SES a difficult concept to capture and to sufficiently adjust for it.

Thus, by using work strain as a reference point to identify which work stressors are associated with work strain (through the process of work stress), we have constructed a measure which captures the concept of work stress more appropriately than any other already existing scale. The measure showed the strongest association with work strain as compared to other existing scales and it matches the idea that work stress is multifarious of nature. Furthermore, the inclusion of items from emotional demands, job insecurity and role clarity shows the importance of these work stressors in inducing work strain in the current work life and that they cannot be left out when work stress is being measured. Overall, with this approach we developed a measure which full fills criterion validity and face validity. In our approach we adhered to a framework where conditionality applied, which yielded a measure consisting of work stressors that have been tested for their work strain potential in order to capture the concept of work stress. However, when we examine the association between work stressors and CVD, this conditionality does not apply and therefore we refer to the association between work stressors and CVD, instead of referring to the association between work stress and CVD. Although it is this latter what we aim to assess. Thus, work stressors are being measured to assess the association between work stress and CVD, although work stress is not actually measured.

Assessment of exposure to work stressors

As described in the introduction, chronic work stress is hypothesized to increase CVD risk (23, 24). This has implications for the exposure assessment, since it should capture chronic exposure. However, most studies in this field use a single exposure assessment, relate it to incident CVD

and assume that exposure remains stable during follow up (25). Within this thesis we have indications that self-reported exposure to work stressors varies over time. In addition, we have shown the importance of repeated measurements to estimate the association between work stressors and CVD risk more accurately. Those with a stable exposure above the highest quartile score on the MCS- WSS during two years have the highest CVD risk. The results where those with stable exposure are compared to those with no exposure are unlikely to have suffered from misclassification and regression to the mean, while this is more probable for the 'changing' exposure groups. Therefore we cannot conclude with certainty that the middle exposure groups (employees who are once or twice exposed during a two year period) are not at increased risk, since the estimated risk might be an underestimation of the actual risk.

To measure change, one requires measures with high reliability to differentiate between measurement error and change (26, 27). We do not know anything about the reliability of the MCS-WSS. A high reliability means that if a measure is administered on two different occasions to the same sample under identical circumstances little variation in outcome is expected. The amount of time between the two measures is critical. If too little time is elapsed memory can contribute to a high correlation since the participant remembers the answers that he gave at the previous survey, whereas if too much time is elapsed real changes can have occurred and the correlation is no longer an adequate representation of random measurement error (27). Using the repeated measurements with a one year interval as a test-retest is probably inappropriate since it is no longer certain which part reflects measurement error and which part reflects actual change. For continued use of the MCS-WSS within the MCS (but also in other studies) we strongly recommend to perform a test – retest of the measure to assess the amount of measurement error. Incorporating a margin for change due to measurement error would refine the classification of exposure status as well as assessing change over time and thereby reducing misclassification. This would yield a more accurate estimate for the association between work stressors and CVD, obtained for the middle exposure groups. Among employees classified as having a stable exposure in the upper quartile of the work stressor score during a two year period, change *within* the upper quartile is missed but we can question whether this is an important change? The advantage of using a rather high cut off value to assess stable exposure is that a high cut off value is more likely to capture the true exposed employees. The reference group consisted of employees who never scored above the highest quartile value during two years and were classified as employees with a stable non exposure. Within this group major changes could have occurred from the lowest score possible to just below the 75th percentile. However, if we assume that a minimum level (or threshold value) of exposure is needed (28) than exposure below this cut off point can be considered as unimportant. If this assumption is unjustified, change within this group could have led to an underestimation of the association as presented in the study.

Intensity of exposure

The items and answer scales of the questionnaires used to identify the work stressors related to work strain do not capture frequency or intensity (28). The unavailability of frequency is not a major concern since the repeated measurements, as used in various studies in this thesis, offer the opportunity to gain insight into the duration of exposure.

Information about intensity could be used as an indicator of the magnitude of the resulting stress response besides the assumption that exposure above a high cut off value is more likely to elicit a stress response than a score at a lower level. It could provide data to explore the issue of intensity and how this is implicated in the pathway from exposure to work stressors to the development of CVD. This could especially be important for examining whether different work stressors with different intensity (lead to differences in the magnitude of the stress reaction) act as triggering factors of CVD among employees with subclinical disease (29). The issue of intensity in relation to triggering effects is probably of less importance for employees free of subclinical disease (23). However, for these employees information about intensity could provide insight into the question whether those with chronic exposure to high intensity work stressors develop CVD in a shorter time period than employees with chronic exposure to lower intensity work stressors.

Assessment of cardiovascular disease

Within the majority of the studies included in this thesis we defined incident CVD as stroke and myocardial infarction (MI). Prevalent CVD included more CVD subtypes, which was related to the broadly defined CVD items in the questionnaire: under treatment by a GP or specialist for their heart, undergone heart surgery, ever had a heart disease. The reason to pool stroke and MI into one incident CVD measure was to increase power. This decision was carefully considered and thought to be justified since atherosclerosis is the main underlying mechanism for stroke and MI (5) and because the sub types share common risk factors (30). Moreover, work stress (ors) are thought to increase CVD risk through the process of atherosclerosis (31). For the more broadly defined CVD items it is uncertain whether it concerns a CVD subtype where atherosclerosis is the main underlying mechanism, therefore these items were not used to identify incident cases. Furthermore, MI and stroke are the most common subtypes and are responsible for the majority of incident events (32). In the study described in Chapter 4, where the association between baseline work stressors and CVD was examined, the power was sufficient to test whether our decision to pool these subtypes together was justified. This was examined by exploring whether stratification on CVD subgroups would reveal substantial differences in CVD risk among those exposed to work stressors. This was not observed. This is in line with the findings of a recent study conducted by Slopen et al (33) where job strain was examined for its association with incident CVD among female employees. CVD consisted of MI, ischemic stroke and coronary revascularization (coronary arterial bypass grafting and percutaneous coronary angiography). The overall association and the association stratified on

CVD subtype did not differ (meaningfully nor statistically) from each other or from the overall CVD group.

For the majority of studies performed in this thesis we had to rely on self-reported data to assess CVD. It is important to assess whether self-report is suitable to exclude prevalent cases and to identify incident cases. Baseline CVD cases should be excluded otherwise recurrent CVD would be mixed up with incident events. Also, the presence of CVD could have led to changes in the work environment or in the perception of the same work characteristics.

Various researchers conclude that exclusion of prevalent CVD using self-report is suitable due to the low percentage of false negatives (34, 35), which indicates that the number of true events that is missed is very low. The positive predictive value of self-reported CVD is lower. This could lead to the exclusion of employees who do not actually have MI or stroke. If the false positives have a different association with exposure to work stressors than the true positives, bias is likely to occur. For example, if the false positives mix up hypertension with manifest disease, it is likely that the exclusion of these individuals underestimate the true association, since hypertension is considered to be a potential intermediating factor between exposure to work stressors and CVD (5, 28). Overall, it can be concluded that in our studies the exclusion of baseline CVD cases was rather strict, minimizing the risk of missing a true case, whereas the possibility of an underestimated association is more likely due to the exclusion of false positives.

Self-reported stroke and MI might be less suitable to assess incident events of stroke and MI (34, 35), due to the high percentage of false positives. The positive predictive value of self-reported heart disease and stroke was around 50%, as reported in Chapter 7. This means that the other 50% of self-reported heart disease and stroke was not objectively confirmed. Reporting bias is especially a concern when employees reporting a false positive event also tend to over report exposure to work stressors. This could lead to an overestimation of the association between work stressors and CVD. Negative affectivity (NA) has been mentioned as a potential cause of reporting bias of CVD (11, 36, 37). To examine whether NA leads to reporting bias, we examined the percentage of medically confirmed heart disease and stroke among those reporting heart disease and stroke stratified on high NA and low NA. The reporting of CVD seems to be independent of NA status. However, more research is needed to clarify which factors contribute to the low positive predictive value of self-reported heart disease, myocardial infarction and stroke and whether these factors are also similarly related to the reporting of work stressors.

Time window

The time window in the included studies was on average 10 years for cardiovascular morbidity and 12 years for cardiovascular mortality (Chapter 4) and 8 years for cardiovascular morbidity where the first two years were not considered as follow up since they represented the extended exposure period (Chapters 5 and 6). We adhered to the hypothesis that work stressors exert their effect on the cardiovascular system through the process of atherosclerosis (38, 39). This requires a long follow up duration from the start of the exposure to the occurrence of incident manifest

CVD. Within the MCS, the follow up duration to capture incident CVD cases is probably long enough, especially considering the fact that 80% of the baseline sample had been working for more than 10 years. However, the start (or baseline) of the study is not equal to the start of the exposure and a long follow up duration has implications for the exposure assessment.

Change of jobs (and thus change in work stressors) is likely to occur during follow up. Within the MCS, 26% of the MCS employees reported job change during a two year period. This indicates that job change is prevalent and change in exposure to work stressors is likely to occur. Furthermore, it can be reasoned that if job insecurity and the number of flexible contracts are increasing (even further) in the future, this will increase the percentage of job change among employees and change in exposure to work stressors. Therefore, repeated measurements are relevant in order to differentiate between employees with changing and stable exposure to work stressors. In our studies, a two year period was used to differentiate between those with changing and stable exposure. If this two year time period is a good indicator of future (and also past) exposure it has no major consequence for the association between work stressors and CVD, as reported in the studies. However, if this two year period is a poor indicator of future and past exposure, the association will reflect an underestimated association, and repeated measurements covering a longer period are required.

In the studies described in Chapter 5 and 6, 165 incident CVD events occurred during the entire range of the follow up duration (circa 47% of the events occurred within 32 months after 2000, 30% of the events occurred between 32 and 60 months and 23% of the events occurred 60 months after 2000). This might complicate the interpretation of the results, since the exposure assessment during 1998-2000, consisting of self-reported work stressors, could have been influenced by subclinical CVD. For subclinical disease to influence the reporting of work stressors, employees have to experience complaints during their work performance. Then, it could have led to an overestimated association between work stressors and CVD. We cannot exclude the possibility that subclinical CVD influenced the reporting of work stressors in a number of patients, however this a potential concern in all cohort studies. A possible solution to prevent reporting bias due to subclinical disease is to exclude the events that occurred during the first five years of follow up (37). However this requires a sample with a sufficient number of events. Furthermore, if physical effort or stress evokes symptoms, this is more indicative of more severe or advanced subclinical disease, where incident CVD is expected to occur within a shorter follow up, than it is indicative of very mild (or no) subclinical disease where physical effort and stress probably do not evoke symptoms. We believe that the number of employees with severe subclinical disease was restricted since in the two studies where we measured exposure to work stressors during two years (Chapter 5 and 6) employees who developed CVD during the two year exposure assessment were excluded, which probably led to the exclusion of employees with most severe subclinical disease (40). Within the study where baseline exposure to work stressors was related to incident CVD (Chapter 4) prevalent CVD cases were excluded based on an item which also led to the exclusion of prevalent hypertension cases. This also limits the possibility of a large

number of subclinical CVD patients at baseline, since hypertension is assumed to increase risk of atherosclerosis and CVD. This probably also led to a conservative estimate of the association between work stressors and CVD.

Precision, strength of the evidence and confounding

Looking at the precision and the strength of the evidence it favours a causal association; a HR of 1.66 (95% CI: 0.98-2.80), corrected for age, gender, educational level, BMI, physical activity smoking and hypertension, and is considered to be meaningful. However, the confidence interval encompasses unity and does not reach statistical significance. Therefore, we cannot exclude with certainty that this is a finding by chance. A likely explanation is the limited power of the study, especially since the confidence limits nearly reach significance. Correction for smoking, BMI, hypertension and physical activity attenuated the association in the opposite direction than which was expected based on their assumed effect on the association between work stressors and CVD. Residual confounding due to inaccuracy of the measurement of the included confounders could explain this finding. However, for the strongest confounders (smoking, age, educational level and gender) the validity of self-report is expected to be relatively high. The validity of smoking where one differentiates between smokers and non-smokers is good (41). No studies are available on age, gender and educational level but since it concerns factual data it is less likely to suffer from reporting bias (42). Correction for these factors yielded a HR of 1.51 (95% CI: 0.90-2.54). The unmeasured confounders (cholesterol, diabetes) and the included confounders that are more likely to have suffered from reporting bias (body mass index, hypertension, and physical activity) (43-45) are also considered to be potential intermediates and then they should not be corrected for. In addition, other studies that have measured these factors (5) with objective measures (where reporting bias is no issue) and adjusted for them in the analyses also did not reported a major attenuation on the association. This suggests that the factors are no strong confounders or intermediates. Not accounting for the time varying effect of confounders might be another explanation for not finding a substantial effect on the association when they are corrected for. If the impact of a predictor on the hazard changes during follow up, the PH- model may produce biased results (46). On the other hand, if the variables change over time (due to exposure to work stressors), for example smoking frequency increases or cholesterol level increases, this might be indicative of an intermediating effect and correction should not be performed. Thus, if BMI, cholesterol, hypertension and smoking are intermediates it is expected that the values change (increase) with continuation of exposure over time. Therefore, the association of 1.51 (95% CI: 0.90-2.54) probably approximates the actual association best and is considered meaningful but probably non-significant due to restricted power of the study.

Another potential confounding factor is negative affectivity. It has been considered as a potential cause of common method bias (47), meaning that high NA individuals over report work stressors and self-reported disease, causing an inflated association (48). It is considered a serious threat of validity in studies using a single method (self-report) to assess both exposure and outcome.

Various solutions have been recommended to prevent or adjust for common method bias (14). In one study we statistically adjusted for NA, which did not substantially reduce the association. However statistically controlling for reporting bias has been criticized (49). In another study it was examined whether high NA was associated with over reporting of CVD, using both objective and self-reported data on CVD. High NA was not associated with over reporting of CVD, making NA less likely to be the underlying cause of the observed associations in the studies conducted within the MCS.

Non work related factors that could trigger a stress response may have confounded the association between work stressors and CVD (16). It is likely that factors outside the work negatively influence the functioning of the employee at work and contribute to work stress. Our assumption with regard to the MCS-work stressor score is that a high score (e.g. above the highest quartile) means simultaneous exposure to various work stressors. This is more likely to elicit stress than a low(er) score. By not correcting for other stress related factors (such as work family conflict, financial stress, relationship stress etc) it could have led to an overestimation of the obtained association between work stressors and CVD.

Dose response relationship

The presence of a dose response relationship would strengthen the evidence supporting a causal relationship. An increase in the effect with an increase in the level of exposure means that a linear relationship exists between exposure and outcome. If a threshold value exists, for instance as in the case for BMI in relation to CVD, no dose response relationship will be detected (26). Looking at the age, gender and educational level adjusted HR's for total and average exposure, as presented in Chapter 5, there seems to be an increase in CVD risk with increasing level of exposure. However, the magnitude of the estimates was rather small and non-significant. An explanation for not finding a clear or significant dose response relationship for the level of exposure is that the impact of the factor time is unclear. It is unknown whether those in the upper quartile of the total exposure represent employees with high exposure at three consecutive times or represent a mix of exposures (high- low) during the two year period, with a period of low exposure enabling the employees to recover from the stress response. Another explanation is that a certain level of exposure (threshold value) is needed to induce work stress (28), leading to the bodily response which is needed to increase CVD risk. Our results indicate that a cut off value of the highest quartile value on the MCS-WSS is needed to increase CVD risk, which also has to continue over time.

As argued above, detecting a dose response relationship is also related to the duration of exposure to work stressors, where a longer duration of exposure is expected to increase CVD risk. This also matches the hypothesis that chronic exposure is required to increase CVD risk (23, 24). To examine this in detail, more repeated measurements on work stressors should become available, covering a longer period than two years. Examining this issue in more detail could provide extra evidence for the existence of a causal association between exposure to work stressors and CVD and more insight into the mechanism where duration and level are taken

into account. Preferably, future research could focus on the level of exposure according to an increasing level of duration. For example, the level of exposure could be examined among those with a stable exposure.

A comparison with the results of other studies

The majority of studies examined the association between work stress and CVD with the Demand Control Model. The comparison of our results with studies using the Demand Control model is hindered by various factors (as described in the introduction and Chapter 3). The most important one is that the components of the model have never been tested for their work stress potential among employees (in the current work environment) and therefore it is uncertain what the model measures (21, 42, 50). Researchers have positioned job strain as work stress (51), distress (42) and even as another measure for low socio-economic position (21). What complicates the matter, is that job strain is analysed as a combination variable (high demands and low decision latitude) in the majority of the studies and an effect reported in these studies may be due to an effect of only one of these two factors (52), where decision latitude is known to follow a social gradient and is more prevalent among those with low SES. This may result in an effect where confounding is likely (11, 28).

Studies that examined the association between specific work stressors, that are included in our work stressor measure, and CVD have yielded mixed evidence for job insecurity (33, 53, 54), more consistent evidence for working overtime (55) and one study reported a positive longitudinal association between hectic work and CVD (56). In addition, most studies show an association between effort reward imbalance (where job promotion is part of the rewards scale) and CVD (57), although the exact contribution of job promotion is unclear. To our knowledge there are no studies that examined the association between emotional demands, cognitive demands, task clarity and CVD, which are the other work stressors included into the measure. It remains difficult to compare the results of these studies with the results presented in this thesis since methodological and conceptual issues remain, such as the stability of the work stressor over time, the differences in operationalization of the work stressors and the multifarious nature of work stress, which is not captured when focusing on one work stressor. Studies performed in the future using our measure will provide the opportunity to compare results across studies and to assess the consistency of results.

External validity

The external validity concerns whether the results as presented in the studies are generalizable to other individuals, settings or time periods.

The MCS comprises a heterogeneous group of employees, working in a wide variety of jobs (such as nurses, assembly workers, cleaners, physicians, etc) in different sectors (industrial sector, health care sector, service sector). The MCS-work stressor score was developed and tested for its association with CVD in the MCS population during the period of 1998-2008. Besides the wide

variety of jobs in the MCS, 74% of the sample was male and the majority of the sample was in the age range of 25 until 65 (mean age was 41 years) and educational level (low, medium and high) was almost evenly distributed, with one third of each. Gender, educational level, age but also occupation can determine to which type of work related stressors employees are exposed and the prevalence of specific work stressors in a subgroup. In addition, exposure to similar work related stressors might be more relevant (represented by its weighting factor) in one group than in the other. When the measure was constructed, it was explored whether different work related stressors emerged as most important work strain inducing factors and whether similar work related stressors were assigned different weighting factors when the results were stratified on gender and educational level. Despite several differences there was also overlap. Because of the aim to construct a generic measure we chose to proceed with the measure which was constructed in the total sample. The generic measure comprises items from amongst others emotional demands, physical demands, psychological demands, role clarity, career possibilities and decision authority, which seems to cover the most important work domains across different jobs. This indicates that the generic measure can be used to measure work stressors in a broad population when used for research purposes. Moreover, we were able to show an association between long term exposure to work stressors and CVD. This indicates that if one would use a more specific measure (job specific or gender specific) the observed association between work stressors and CVD will probably become stronger.

The measure was developed and tested for its association with CVD in a Dutch setting. The results are probably generalizable to other countries with a similar economic and social context as in the Netherlands. As differences in gender and occupation determine the prevalence of certain types of work related stressors, differences in work related stressors also exist between countries. The meta regression showed that the size of the estimated association between job strain and CVD differed between countries and various explanations were given for this finding. Another explanation for the differences in risk estimates between countries could be due to that fact that the used measure captures the included elements in one country better than in the other.

The work stressor measure was developed in the late 90's, early 2000 and it captures work stressors from various work dimensions. As mentioned in the introduction, the work environment has changed during the last 20 years, for example, a major change concerned the shift in jobs from the industrial sector to the service sector (58). Due to this shift more employees interact with students, clients or patients. The increase in the prevalence of emotional demands and its association with work strain has most likely resulted in the selection of this type of work stressor into the measure. Thus, the generalizability to other time periods depends on changes in work related exposure. Therefore, the emergence of new psychosocial risk factors should be monitored and examined for its work strain potential to ensure a measure that captures the most important work related stressors.

From a research point of view, a standardized generic measure to assess work stressors across different populations which must be applicable to different types of occupations is preferred.

This is a requirement if one wishes to compare results from various studies to assess whether there is consistency in the evidence. However, item bias or differential items functioning (DIF) might hinder direct comparison of results of studies that are conducted in different countries (59) or in different populations regarding occupations, educational level, age and gender (60, 61). Item bias means that the same items might be interpreted differently in different countries or in different populations, which might also be related to differences in conceptual reference frames (59). Item bias might result from methodological or substantial problems. Methodological problems resulting in item bias are instrument errors due to vaguely and unclearly defined questions. Substantial problems are due to the fact that different items relate in different ways to certain exogenous variables. E.g. different occupational groups might be exposed to very different work environment conditions. It is also probable that persons employed in different occupations perceive the question differently and that the content of a certain item means something different. This latter is related to vaguely defined items, but it is questionable whether it is possible to construct items that are perceived in a similar way by employees of various socio-economic backgrounds (60). Specific jobs have specific work related stressors and certain stressors that are important in one job are not important in another job. In this case, using a generic measure will always lead to an underestimation of the true association between work stress and CVD. If DIF threatens the validity due to assigning different meanings to an item depending on the subgroup to which the respondent belongs, it is uncertain how it will affect the results.

The characteristics of a sample determine which work related stressors are prevalent and which ones will be selected as most important in inducing work strain. However, a representative sample is not a prerequisite for examining whether exposure to work stressors is a risk factor for CVD. Important, for addressing etiological questions is the contrast between exposure groups, which has to be high. Within the study population, a wide range of jobs and sectors are represented, which means that different types of work related stressors are included. By including employees working in different types of jobs, contrast in exposure is probably also ensured. The characteristics of the sample determine whether the results can be extrapolated to other individuals with different characteristics. Educational level, age and gender are considered to be potential effect modifiers (28, 62-65). In addition, we considered coping and NA as potential effect modifiers as well. The plausibility that the effect differs among certain subgroups is related to a higher susceptibility due to having fewer resources for coping or having less efficacious coping resources (66-70) or a higher vulnerability to the effects of exposure (e.g. with increasing age (28) or prolonged response (71)). This thesis does not support the hypothesis that age, gender, educational level, coping or NA have moderating effects, which might reflect the absence of such effects. Other explanations are the low power in the studies and the fact that we have explored some of the interaction effects between baseline work stressors and CVD (this applies to age, gender and educational level), whereas an interaction effect might only become apparent among employees with prolonged exposure.

In summary, it can be concluded that the results regarding the association between work stressors and CVD can probably be extrapolated to a heterogeneous group of employees, working in countries with similar conditions as in the Netherlands. However, future research should first validate the work stressor measure to examine whether the results can be replicated. If the results can be replicated, it should also be examined whether different work stressors (with different weighting factors) emerge when the measure is validated in different samples and/or different settings and whether stronger or different effects will be found when subgroup specific measures are tested for their association with CVD. By performing subgroup analyses also more insight will be gained about potential interaction effects. This could offer additional information for prevention, which could be targeted at those most susceptible.

Implications for future research and practice

This thesis has shown that stable exposure to a high level of work stressors during a two year period, assessed with a comprehensive measure, is a risk factor for CVD. Based on the findings as presented in this thesis, our recommendations for future research are: to use repeated measurements of exposure covering a minimum period of two year, although repeated measurements covering a longer time period would be valuable to assess whether a two year period is sufficient to estimate long term exposure or whether more measurements are required; to perform a test-retest to differentiate between error and actual change; to use a comprehensive measure; to validate our measure in a different sample and to use self-report data if objective data is unavailable to measure work stressors and stroke and MI, since NA does not cause inflated associations. Replication of our results is required. Therefore, it is important that other researchers in this field will use the comprehensive work stressor measure. For this reason some recommendations for the validation of the work stressor measure will be given below.

Validation of the work stressor measure

Validation of the work stressor measure should be performed in a heterogeneous sample within a similar social and economic context as in the Netherlands. Replication of our studies is needed to examine whether in a different heterogeneous population the same set of work stressors emerge as most important in leading to work strain (through the process of work stress); whether the selected work stressors have similar weighting factors as they have in our work stressor measure; whether work stressors, assessed using the work stressors measure, are associated with CVD and whether a similar identified cut off value is associated with highest CVD risk. A proper work stress or work strain definition should be considered to examine which work stressors are associated with work stress or work strain. Ideally work stress or work strain should be defined on the basis of items that link stress to work. A prospective design with shorter time intervals could be considered for assessing the association between work stressors and work strain. A cross sectional design is required for assessing the association between work stressors and work stress since work stress is a relatively acute response to exposure to work stressors. For work stress,

objective measures could be considered, such as physiological measurements. However the link between the stress measure and work stressors should be ensured. Furthermore, repeated measurements remain crucial since long term exposure is assumed to impact health, whereas acute responses are only thought to impact health if they are frequently occurring. Data should preferably be available for all types of work related stressors to examine which work stressors are most important. Furthermore, we recommend a large study population with a sufficient number of work stress or work strain cases, to enable the backward selection performed on all work stressors.

For setting up adequate prevention strategies and guidelines how to monitor those at increased risk, various issues need to be resolved. Within this thesis we could not elucidate whether the actual work environment can pose a real threat and increase CVD risk or whether the perception of the work environment by the individual is a necessity to cause stress and increase CVD risk. Below, the results that are indicative of the impact of the individual in the process from exposure to outcome will be summarized. This is followed by recommendations for future research on how to examine whether the person or the environment or a combination of the two should be targeted by prevention and how to gain more insight into the potential effect modifying effects of personal attributes.

Person or work environment

In Chapter 6 it was shown that high negative affectivity (NA) was significantly associated with stable exposure to a high level of work stressors. What remains unclear is whether it concerns a causal association and what the cause was and what the effect was. Also it remains unclear whether the measured exposure reflects actual exposure or the perceived exposure where those with high NA merely perceive more often a high level of exposure than actually being more often exposed to a high level of work stressors. Also, indications were found that high NA might be an effect modifier since those high in NA had a higher CVD risk than those low in NA when exposed to a similar level of work stressors. This could indicate that NA is not merely a complaining tendency. However, the differences were not statistically significant and could be a chance finding.

The literature supports the plausibility of the hypothesis that NA (and other personal attributes) could be crucial in unravelling the association between work stressors and CVD and the mechanism behind it. The tendency of experiencing greater levels of distress and to negatively view the world and themselves (47) could lead to difficulties in letting go or unwind from work (72), leading to a prolonged response that hinders recuperation. Prolonged cardiovascular response may occur with exposure to chronic or repeated exposure to stressors or as a result of cognitive or emotional processes that sustain cardiovascular arousal (72). Stress related thoughts and emotions are not limited to those occasions when a stressor is physically present. For most people, the time spent in the moment when a stressor is actually present is relatively short as compared to the time in anticipation of future stressors and recovery from past stressors,

including the repeated cognitive representation (72). Furthermore, personal attributes could lead to differences in reporting tendency where some exaggerate, deny or simply are not able to perceive all stimuli in the work environment consciously (73) which may be related to why employees who are exposed to a similar work environment perceive it very differently (15, 73).

To clarify whether the work environment is harmful by itself data on 'objective' work stressors and perceived work stressors are required. A suitable design for examining this issue could be an extension of the study conducted by Persson et al (42). They examined whether the Job Content Questionnaire is able to measure the work environment objectively and hypothesized that if that would be the case employees in identical jobs would have identical scores on the JCQ. If there would be substantial variation in the scores this would be indicative that perception of the work environment determines the score, rather than the work environment itself.

To examine whether variation can be attributed to personal attributes, those with average scores and those with substantial variation (those with on average higher and lower scores) should be compared for differences in personal attributes and for differences in CVD risk. In this case the average score is used as a proxy for an objective score of the work environment since it is not influenced by an individual's cognitive and emotional processing (15), whereas the deviation from the average score represents the perception of the work environment. To limit the variation due to actual differences within jobs, the average score can be estimated within a work unit (74) instead of estimating the average score within a job. A work unit can be defined as a group of employees with reference to a specified manager or head of a unit (74).

The resulting information could be helpful for setting up guidelines regarding monitoring and prevention. If personal attributes are crucial in experiencing work stress and if employees with specific personal attributes are more susceptible to the effects of work stressors, monitoring and prevention should focus on identifying employees with these attributes, rather than focusing on the specific work stressors. If it is exposure to work stressors that increases CVD risk, rather than personal attributes, it should be considered how to optimize intervention strategies to reduce exposure to work stressors. If work stressors need to be reduced, one of the most important considerations is to refine the generic work stressor measure into a more sector or job specific measure to ensure that the most relevant work stressors within a certain job or sector are identified and reduced.

The impact of reduction of exposure to work stressors on CVD reduction

Reduction of long term exposure to a high level of work stressors could make a contribution to CVD reduction since stable exposure during a two year period to a high level of work stressors is prevalent (8%) and the magnitude of the association is substantial; a HR of 1.51 (95% CI: 0.90-2.54). The attributable risk (AR) or risk difference is the difference between the incidence rates in exposed and non-exposed groups. It reflects the absolute risk of the exposure or the excess risk of the outcome (CVD) in the exposed group as compared to the non-exposed group. The absolute risk of CVD among those with long term exposure to a high level of work stressors is

34%. The population attributable risk (PAR) estimates the proportion of disease in the study population that is attributable to the exposure. The PAR in the MCS population is estimated to be 4%, which implicates that 4% of CVD in the MCS is due to long term exposure to a high level of work stressors.

In comparison to cholesterol, hypertension and smoking, which are the three most important modifiable risk factors that explain 75% of CVD (75), the prevalence of long term exposure to work stressors and the magnitude of the effect are lower. Within the MCS population the prevalence of smoking and hypertension were 22% and 19%. The HR of CVD was 2.99 (95% CI: 2.19-4.07) for smoking and the HR of CVD was 2.01 (95% CI: 1.45-2.78) for hypertension. This corresponds to a working population attributable fraction of 30% for smoking and 16% for hypertension. We can reason that a PAR of 4% is relatively low in comparison to the PAR's for smoking and hypertension. However, long term exposure to a high level of work stressors is involuntary, which is in contrast to smoking. Furthermore, for other work related exposures, such as chemical exposures, a PAR of 4% is unacceptable. The minimum level of exposure to a certain substance or chemical at work during ones working life should not endanger the health of the employee and their offspring. For instance, for chemicals with cancer inducing properties, the exposure is prohibited to exceed an extra risk of 10^{-4} per year. The Arbo Council sets the target level at 10^{-6} per year per chemical (76). If exposure cannot be prevented it is common practice to protect employees against exposure, for instance by means of personal protection equipment. Within the MCS subsample 3% of the employees developed incident CVD (165/6154) during a period of 8 years of which 4% (7 cases) is attributable to stable exposure to a high level of work stressors, measured during two years (8% of the subsample). Translating this to the entire working population in the Netherlands, which was around 7 million in 2011; this would affect around 900 employees per year. This is more than what is accepted for exposure to chemicals in the work setting. Exposure should be prevented or employees should be better equipped against (the harmful effects of) exposure to work stressors.

Final conclusion

This thesis has provided firm evidence that long term exposure to a high level of work stressors is associated with CVD. To assess this association accurately, repeated measurements are needed, as well as a comprehensive measure consisting of various work stressors with each having its own relevance in inducing work strain which have been tested for its association with work strain. In addition, when objective data on CVD is lacking, the association between work stressors and CVD can be measured with self-report since NA does not lead to over reporting of CVD. Long term exposure to work stressors should be acknowledged as a risk factor for CVD by cardiologists and prevention strategies need to be developed to reduce CVD risk due to exposure to work stressors.

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Summary

Cardiovascular disease (CVD) constitutes a major public health problem in the world and affects many people. It is related to high mortality and the consequences of the disease are long-lasting. The consequences of CVD are considerable for both the society and the individual, in terms of economic costs and well-being. CVD is a disease with a multi factorial aetiology and since 1945 epidemiological research has established several individual risk factors for CVD. These risk factors can be divided into non-modifiable and modifiable risk factors. The modifiable risk factors explain the majority of the CVD events and offer opportunity to reduce CVD risk by targeting prevention strategies at these risk factors. The potential role of work stress in the development of CVD has been studied and debated extensively. Exposure to work stress can be short-lasting or long-lasting. However, for work stress to have harmful effects on the cardiovascular system it has to be long-lasting. Work stressors are defined as factors in the work environment that can negatively impact the health through the process of stress. Since they are highly prevalent and modifiable, prevention aimed at reducing work stressors could lead to CVD risk reduction. However, the clinical significance of work stress as a risk factor for CVD is still not established after decades of research. This is due to the conflicting evidence in this research field. This hinders making a firm conclusion about whether work stress is risk factor for CVD, hindering prevention.

Several issues are most likely to be contributing to the conflicting evidence. Work stress is a difficult concept to capture and has resulted in the development of various models trying to capture the concept. The most often used model in research assessing the association between work stress and CVD, is the Demand Control Model. This model positions work stress (job strain) as the result of high psychological demands and low decision latitude. De validity of the model (and the accompanying instrument) is examined by means of assessing the internal consistency of the two components of the model (psychological demands and decision latitude). The internal consistency is assessed by examining whether the items of the psychological demands measure psychological demands. The same is done for decision latitude. What is missing is the evidence that these two components actually lead to work stress. This questions the applicability of the model, since it is uncertain whether the model captures the essence of work stress. A methodological issue is that in the majority of studies that examined the association between work stress and CVD, exposure to work stress is measured with a single measurement. It is assumed that exposure remains stable during follow up. This is a crucial assumption since exposure to work stressors is thought to be harmful when it is chronic or frequently occurring. Another issue is the impact of personal attributes on the susceptibility to exposure to work stressors, to the effects of exposure to work stressors and to CVD. These issues require clarification and could ultimately lead to the establishment of the clinical significance of work stress. This in turn could lead to the development and implementation of prevention activities aimed at the reduction of work stress and thereby CVD risk.

The aim of the studies as presented in this thesis was to examine the association between the psychosocial work environment and CVD, from a methodological viewpoint. This was achieved

by examining whether 1) various methodological and conceptual choices impact the size of the obtained association between work stressors and CVD and whether 2) a better estimate for CVD risk when exposed to work stressors can be obtained when dealing with certain conceptual and methodological issues. These questions were addressed by means of three approaches: the first approach was to conduct a meta regression analysis to examine the existing evidence, as found in the literature, on the association between job strain and CVD in order to examine which study factors may contribute to the conflicting findings (**Chapter 2**). The second approach consisted of choosing a theoretical framework which was specifically important for the positioning of the concepts 'work stressors, work stress, work strain' and was used as a guideline in the study in which the work stressor measures were constructed (**Chapter 3**). The third approach was to test the various hypotheses in individual studies using data from the Maastricht Cohort Study (MCS) (**Chapter 3-7**).

To examine which study factors influence the size of the obtained association and thereby contribute to the conflicting findings, a meta regression analysis was conducted, using the existing evidence on the association between work stress and CVD (**Chapter 2**). The innovative of this meta regression was the use of within study variation in addition to the use of between study variation. The findings of the meta regression were used to generate new hypotheses about why certain study characteristics influence the reported CVD risk. The results of the meta regression analysis showed that various methodological and conceptual issues are related to the size of the reported CVD risk estimate. The main findings were: that studies in which a more deviant form of the JCQ was used to measure job strain yielded on average 43% higher odds ratios than studies in which the original Job Content Questionnaire (JCQ) was used, the relative odds ratio (ROR) was 1.43, 95% CI: 1.07-1.92. Studies conducted in the USA yielded on average 26% lower estimates for CVD risk than studies conducted in Scandinavian countries, ROR= 0.74, 95% CI:0.59-0.93. Studies using self-report to assess CVD yielded on average 39% higher OR's than studies using medically confirmed CVD, ROR=1.39, 95% CI: 0.97-1.97.

The finding of the meta regression analysis that the type of questionnaire used to assess job strain was associated with the size of the reported CVD risk formed the basis for the first study that was conducted using data from the Maastricht Cohort Study (MCS) (**Chapter 3**). Two work stressor measures were developed. In this study we adhered to the framework of work stressor – work stress – work strain. Two work strain definitions were used as an external reference point. The first work strain definition (work strain I) consisted of employees who reported sickness absence due to work related stress. The other work strain (work strain II) definition was defined as 'having experienced constant pressure lately' (General Health Questionnaire) and 'having difficulty to relax after work' (Need for Recovery). These definitions were used to examine which work stressors were most associated with work strain, identified from a long list of work stressors, which were measured in the Maastricht Cohort Study. Ideally, work stress would be

the most appropriate reference point. Since there is no appropriate measure for work stress, work strain was used instead. To increase confidence in the robustness of our findings, two work strain definitions were used to construct two work stressor measures. The process of identifying which work stressors were most associated with work strain was repeated for each work strain definition. The two newly developed measures showed the strongest association with work strain, as compared to the existing scales, indicating that the new measures are more validly measuring work stressors that have been associated with work strain. The standardized odds ratio (SOR) for work strain was 1.89 (95% CI: 1.49-2.40) for employees with a standard deviation increase on the work stressor score I scale. The SOR for work strain was 2.91 (95% CI: 2.67-3.18) for employees with a standard deviation increase on the work stressor score II scale. The measures include work stressors from various concepts (such as emotional demands, cognitive demands, role clarity, overtime work, job insecurity) and therefore capture the multifarious nature of work stress. In addition, each stressor has its relative contribution to work strain and the included work stressors in the measure have been tested for their work strain potential in the current work environment. By using work strain as a reference point in a framework where conditionality applied this ensures that work stressors with a high work strain potential, preceded by work stress, are captured with the work stressor measure.
Although we aim to measure work stress, in the studies where we examined the association with CVD we examined the association between *work stressors* and CVD since the conditionality that applied in the study as described in Chapter 3 did not apply to the other studies. Within the studies following Chapter 3 we chose to proceed with work stressor score II, which was constructed using the work strain II definition, which will be called the Maastricht Cohort Study – Work Stressor Score (MCS-WSS) from now on.

The next step was to examine the MCS-WSS for its predictive validity with regard to CVD. Within the MCS, cardiovascular morbidity was assessed using self-report data. Self-reported CVD has been criticized for its validity. A specific concern is that if a factor leads to over reporting of *both* cardiovascular disease and work stressors, trivial associations are likely to result. The meta regression showed that studies using self-reported CVD as outcome yielded on average higher estimates of CVD risk as compared to studies using medically confirmed or other objective data to assess CVD. This seems supportive of the trivial association hypothesis. In **Chapter 4** the association between work stressors, assessed with the MCS-WSS, and CVD was examined. No association was found between work stressors and CVD. For this study various sources were available for the assessment of CVD: self-reported CVD, medically confirmed CVD obtained from medical records and cardiovascular mortality obtained from death certificates. The association based on self-reported CVD gave similar results as the associations based on medically confirmed CVD (hazard ratio (HR): 0.94, 95% CI: 0.68-1.28 versus HR: 0.88, 95% CI: 0.60-1.31) and cardiovascular mortality (HR: 1.20, 95% CI: 0.74-1.96). The finding that the association between self-reported work stressors and CVD did not differ depending on the method of CVD

assessment, argues against the reasoning that using self-report to assess both work stressors and CVD yields an over estimated association.

A plausible explanation for not finding an association between work stressors and cardiovascular disease, as reported in the study as described in Chapter 4, is the use of a single measurement of work stressors. A single exposure measurement is only an appropriate indicator of long term exposure if exposure remains stable during one's working life. If exposure varies, misclassification results and biases the association towards the null. In **Chapter 5** it was examined whether exposure to work stressors varied over time and whether using repeated measurements would yield a stronger estimate for CVD risk than using a single measurement. In addition, we examined whether a specific type of exposure is most harmful. It was shown that exposure to work stressors varied over time (only 8% of the sample showed a stable exposure above the highest quartile value) and that repeated measurements are needed to obtain a better indicator of long term exposure. We estimated exposure in various ways: total exposure, average exposure, cumulative exposure above a cut off value, single exposure and exposure modelled as as a time varying exposure. Stable exposure to a high level of work stressors showed a relevant and nearly significant association with CVD (HR: 1.51, 95% CI: 0.91-2.54 adjusted for age, gender and educational level). Cumulative exposure above the median value, high total exposure, high average exposure and high single exposure yielded HR's of 1.20 (95% CI: 0.80-1.81), 1.19 (95% CI: 0.77-1.82), 1.22 (95% CI:0.80-1.87) and 1.04 (95% CI: 0.74-1.49) respectively. This suggests that stable exposure to a high level of work stressors during a two year period is a better indicator of long term exposure than the other exposure estimates and that a minimum level of exposure is required to cause harm.

Personal attributes, such as negative affectivity (NA) and coping might be important when the association between work stressors and CVD is examined. They may influence exposure to work stressors, the risk of CVD, mediate the response or may act as moderators. Personal attributes can have substantive effects or biasing effects. The majority of the existing studies disregards personal attributes. The main underlying assumption of the Demand Control model is that it measures the objective work environment and therefore personal attributes do not need to be considered. However, if the work environment is measured with questionnaires one cannot differentiate between which part of the response reflects the actual work environment and which part reflects the perception of the work environment. We examined the association between cumulative exposure to work stressors and CVD and the impact of personal attributes on this association (**Chapter 6**). Those with high NA had a significant increased odds of high cumulative exposure to work stressors (OR: 5.52, 95% CI: 4.48-6.61, corrected for age, gender and educational level). Those high in NA also showed a nearly significantly association with CVD (HR: 1.31, 95%CI: 0.92-1.88, corrected for age, gender and educational level). NA had no confounding or mediating effect on the association between work stressors and CVD, since inclusion into the

model did not reduce the association substantially. Besides, those with high NA might be more susceptible to the effects of stable exposure to a high level of work stressors, since the HR was higher among those with high NA than among those with low NA (HR: 2.41, 95%CI: 1.02-5.67 versus 1.24 (95% CI: 0.47-3.24).

To examine negative affectivity as a source of over reporting of CVD in further detail we performed a study in which it was examined whether negative affectivity leads to over reporting of CVD (**Chapter 7**). No study has ever examined whether among high NA individuals the percentage of false positives of stroke and heart disease is higher than the percentage of false positives among low NA individuals. This would provide very strong evidence for NA as a source of over reporting CVD. Therefore, we examined the positive predictive value of self-reported heart disease and stroke. The reference test was diagnosis based on objective data, obtained from medical records. If NA would lead to over reporting, high NA individuals would report a heart disease or stroke more often while it is not objectively established. The PPV for self-reported heart disease was 59% for high NA individuals and 58% for low NA individuals, which was a non-significant difference. The PPV of self-reported stroke differed significantly between high NA individuals and low NA individuals (61% versus 33%), although it was against the expected direction. Thus, the level of false positives was not significantly higher among those with high NA than among those with low NA. This suggests that high NA is not related to over reporting of CVD in the MCS.

In the general discussion (**Chapter 8**) the main findings are described and discussed. Furthermore, suggestions are given for future research and practice. The results as presented in this thesis show that various methodological and conceptual issues influence the estimated CVD risk. Exposure to work stressors should be measured with a comprehensive measure, incorporating various work stressors with different weighting factors that have been tested for its association with work strain in the current work life. The testing of which work factors are associated with work strain through the process of work stress, ensures than one is measuring work stressors with a high work strain potential preceded by work stress. Furthermore, exposure varied over time which underscores the importance of repeated measurements to differentiate between those with stable and changing exposure. Using a single measurement will lead to misclassification in case of varying exposure and will bias the association towards the null. Stable exposure above the highest quartile, during two years, showed a strong nearly significant association with CVD. Therefore, exposure should be measured over an extended period since stable exposure above the highest quartile is a better indicator of long term exposure than a single exposure assessment. Furthermore, the results of the studies conducted in the MCS, where exposure and outcome are measured with self-report, do not represent trivial associations where NA explains the underlying association. For this to occur NA has to lead to over reporting of work stressors and CVD and this latter was not the case. It is desirable that future studies with sufficient power replicate our studies to examine the consistency in evidence and to exclude the possibility of a chance finding as reported in our

studies. If so, long term exposure to work stressors should be acknowledged as an established risk factor. Future research should clarify whether the person, the environment itself or the interaction between the two is important in inducing work stress and CVD. This could be used for setting up monitoring and prevention guidelines. Furthermore, awareness should be increased among cardiologists that work stress is a risk factor. In addition to giving advice on reduction of smoking, healthy diet and exercise, awareness should be increased about the harmful effects of work stress. The studies, as described in this thesis, emphasize the importance of work stress in relation to CVD risk. Reduction of exposure to work stressors has great potential to reduce CVD risk in the working population.

Samenvatting

Hart- en vaatziekten (HVZ) komen vaak voor en zijn gerelateerd aan een hoge mortaliteit. De gevolgen zijn langdurig en hebben tevens een grote impact op de maatschappij en op het individu, in termen van kosten en welzijn. Sinds 1945 zijn er verschillende individuele risicofactoren vastgesteld, die kunnen worden onderverdeeld in modificeerbare en niet modificeerbare factoren. De risicofactoren die te modificeren zijn, verklaren het grootste deel van de HVZ. Door preventie-activiteiten te richten op deze risicofactoren is het mogelijk om het aantal HVZ terug te dringen. De bijdrage van werkstress aan het ontstaan van HVZ wordt al vele jaren bestudeerd en bediscussieerd. Werkstress kan zowel kortstondig als langdurig aanwezig zijn. Om schadelijke effecten uit te oefenen op het hart- en vaatstelsel wordt verondersteld dat werkstress langdurig aanwezig moet zijn. Werkstressoren zijn factoren in het werk die de gezondheid negatief kunnen beïnvloeden door middel van stress. Aangezien werkstressoren vaak voorkomen en te modificeren zijn, kan preventie gericht op reductie van werkstressoren leiden tot een reductie van het HVZ risico. Echter, de klinische significantie van werkstress in relatie tot HVZ is na tientallen jaren van onderzoek nog steeds niet met zekerheid vastgesteld. Dit is toe te schrijven aan de tegenstrijdige resultaten in het onderzoeksveld. Dit maakt het moeilijk om een harde conclusie te trekken en staat preventie in de weg.

Er zijn een aantal zaken die hoogstwaarschijnlijk bijdragen aan de tegenstrijdige resultaten. Werkstress is een lastig concept om te meten. Verschillende theoretische modellen zijn ontwikkeld in de loop der jaren om het concept in kaart te brengen. Het meest gebruikte model in onderzoek naar werkstress en HVZ, is het Demand Control Model. Dit model positioneert werkstress (job strain) als het resultaat van hoge psychologische eisen in combinatie met lage controle. De validiteit van het model (en het bijbehorend meetinstrument) wordt beoordeeld door te onderzoeken of de interne consistentie van de afzonderlijke componenten van het model (psychologische eisen en controle) hoog is. Er wordt dan beoordeeld of de verschillende items van psychologische eisen daadwerkelijk psychologische eisen meten en hetzelfde wordt gedaan voor controle. Wat ontbreekt, is het bewijs dat deze twee componenten samen tot werkstress leiden. Doordat het onzeker is of het model de essentie van werkstress goed in kaart brengt, zijn er kritische kanttekeningen te plaatsen bij de bruikbaarheid van het model. Een methodologisch probleem is dat in het merendeel van de studies die het verband tussen werkstress en HVZ hebben onderzocht, blootstelling aan werkstress wordt gemeten met een eenmalige meting. Er wordt aangenomen dat de blootstelling stabiel blijft gedurende de follow up. Dit is een cruciale aanname, want de hypothese is dat werkstress alleen schadelijk is wanneer deze chronisch is of zeer frequent terugkeert. Een ander punt is de bijdrage van persoonlijke kenmerken aan het verband tussen werkstress en HVZ. Het is onvoldoende onderzocht of persoonlijke kenmerken de vatbaarheid voor de blootstelling aan werkstressoren, voor de effecten van de blootstelling aan werkstressoren en/ of voor HVZ beïnvloeden. Deze zaken vragen om opheldering en kunnen er toe leiden dat de klinische significantie van werkstress met meer zekerheid kan worden vastgesteld. Vervolgens kunnen er structureel preventie-activiteiten worden ontwikkeld en ingevoerd, gericht

op het verminderen van werkstress, die kunnen leiden tot een reductie van het HVZ risico.
Het doel van het onderzoek, zoals beschreven in dit proefschrift, was het onderzoeken van het verband tussen de psychosociale werkomgeving en HVZ, vanuit een methodologisch perspectief. Dit is gedaan door te onderzoeken of 1) verschillende methodologische en conceptuele keuzes de grootte van het verband tussen werkstress en HVZ beïnvloeden en 2) of er een betere schatting van het HVZ risico bij blootstelling aan werkstressoren kan worden verkregen als men een aantal methodologische en conceptuele problemen aanpakt. Voor het onderzoeken van deze vragen zijn drie verschillende methoden gebruikt: de eerste aanpak was het uitvoeren van een metaregressie analyse om inzicht te verkrijgen in welke studiekenmerken bijdragen aan de tegenstrijdige resultaten. Hiervoor werd een analyse uitgevoerd op al bestaande onderzoeksresultaten (**Hoofdstuk 2**). De tweede aanpak bestond uit het kiezen van een theoretisch kader welke belangrijk was voor het positioneren van de verschillende concepten (werkstressoren, werkstress en "werkstrain"). Tevens werd het kader gebruikt als richtlijn/ rode draad in o.a. de studie waarin de twee werkstressormaten ontwikkeld zijn (**Hoofdstuk 3**). De derde aanpak bestond uit het testen van de verschillende hypothesen in studies waarbij gebruik werd gemaakt van de MCS data (**Hoofdstukken 3-7**).

Om te onderzoeken of studiekenmerken van invloed zijn op de grootte van het geschatte verband tussen werkstress en HVZ en daarmee bijdragen aan de tegenstrijdige resultaten, werd een metaregressie analyse uitgevoerd op reeds uitgevoerde studies die het verband tussen job strain en HVZ hebben onderzocht, zoals beschikbaar in de literatuur. Het vernieuwende aan deze metaregressie was dat zowel de tussen studie variantie als ook de binnen studie variantie is meegenomen. De bevindingen van deze studie werden gebruikt om nieuwe hypothesen te genereren over waarom bepaalde studiekenmerken van invloed zijn op de grootte van het gerapporteerde HVZ risico. De resultaten van deze studie lieten zien dat verschillende methodologische en conceptuele zaken samenhangen met de grootte van de gerapporteerde HVZ risico schatting. De belangrijkste bevindingen waren: studies waarin gebruik werd gemaakt van een ander type vragenlijst om job strain te meten dan de originele Job Content Questionnaire (JCQ) leverden een gemiddeld 43% hogere odds ratio op dan studies waarin gebruik werd gemaakt van de originele JCQ om job strain te meten: de relatieve odds ratio (ROR) was 1.43, 95% betrouwbaarheid interval (BI): 1.07-1.92. Studies die zijn uitgevoerd in de USA leverden gemiddeld 26% hogere schattingen op voor het HVZ risico dan studies die zijn uitgevoerd in Scandinavische landen, de ROR was 0.74, 95% BI:0.59-0.93. Studies waarin gebruik werd gemaakt van vragenlijsten om HVZ te meten leverden gemiddeld 39% hogere odds ratios op dan studies waarin gebruikt werd gemaakt van medisch vastgestelde HVZ, ROR=1.39, 95%BI: 0.97-1.97.

De bevinding dat de type vragenlijst die werd gebruikt om job strain te meten van invloed was op de grootte van het gerapporteerde HVZ risico, vormde de basis voor de eerste studie waarbij gebruik werd gemaakt van de Maastricht Cohort Studie (MCS) data om de hypothese te testen of

het concept werkstress breder gemeten moet worden dan hoe het tot nu toe wordt gemeten in de al uitgevoerde studies (**Hoofdstuk 3**).
Er werden twee nieuwe werkstressormaten ontwikkeld. In deze studie werd gehandeld volgens het theoretisch kader van werkstressor – werkstress – "werkstrain". Twee "werkstrain" definities werden gekozen om te dienen als extern referentiepunt. De eerste definitie ("werkstrain" I) bestond uit werknemers die zich ziek meldden vanwege (de gevolgen van) werkgerelateerde stress. De tweede definitie ("werkstrain" II) werd gedefinieerd als 'het ervaren van constante druk de laatste tijd' en 'het moeilijk vinden om te ontspannen na het werk'. Deze definities werden gebruikt om te onderzoeken welke werkstressoren het meest samenhangen met "werkstrain" (voorafgegaan door werkstress), geïdentificeerd uit een lange lijst van werkstressoren gemeten in de MCS. Idealiter gezien zou werkstress het meest geschikte externe referentiepunt geweest. Echter, er is geen geschikte maat voor het meten van werkstress en daarom werd "werkstrain" als alternatief gekozen. Om het vertrouwen in onze bevindingen te verhogen werden er twee "werkstrain" definities gekozen, die hebben geleid tot twee werkstressormaten. Het proces waarmee werkstressoren werden geïdentificeerd die het meest samenhangen met "werkstrain" werd herhaald, voor elke "werkstrain" definitie afzonderlijk. De twee nieuwe werkstressormaten lieten het sterkste verband zien met "werkstrain" in vergelijking met de al bestaande schalen. Dit lijkt erop te wijzen dat de nieuwe werkstressormaten meer valide werkstressoren die een verband lieten zien met "werkstrain" meten dan de al bestaande maten. De gestandaardiseerde odds ratio (SOR) voor "werkstrain" was 1.89 (95% BI: 1.49-2.40) voor werknemers met een toename van 1 standaard deviatie op de schaal van werkstressormaat I. De SOR voor "werkstrain" was 2.91 (95%BI: 2.67-3.18) voor werknemers met een toename van 1 standaard deviatie op de schaal van werkstressormaat II. De maten omvatten verschillende werkstressoren afkomstig uit verschillende concepten (o.a. emotionele eisen, cognitieve eisen, rolonduidelijkheid, overwerk, baanonzekerheid) en tonen de veelomvattendheid van het concept werkstress aan. Daarnaast heeft elke werkstressor zijn eigen bijdrage aan "werkstrain" en bovendien hebben we getoetst welke werkstressoren het grootste "werkstrain" potentieel hebben in de huidige werkomgeving. Door gebruik te maken van een extern referentiepunt binnen een theoretisch kader waarbinnen voorwaardelijkheid van toepassing is, is men er meer zeker van dat werkstressoren zijn opgenomen in de maat die een hoog "werkstrain" potentieel hebben, voorafgegaan door werkstress.
Met deze maat proberen we werkstress te meten, maar in de studies waar de associatie met HVZ werd onderzocht, onderzochten we echter het verband tussen werkstressoren en HVZ omdat de voorwaardelijkheid in de studie beschreven in hoofdstuk 3 niet van toepassing was in de andere studies. In de studies die volgen op hoofdstuk 3 hebben we ervoor gekozen om verder te gaan met één van de twee werkstressor maten, namelijk de werkstressor maat II. Deze zal verder de Maastricht Cohort Studie Werkstressor Score (MCS-WSS) worden genoemd.

De volgende stap was het onderzoeken van de voorspellende validiteit van de MCS-WSS in relatie tot HVZ. In de MCS worden HVZ gemeten met vragenlijsten. Het gebruik van vragenlijsten wordt

bekritiseerd, omdat het gevaar bestaat dat de validiteit in het geding komt als een onderliggende variabele leidt tot zowel overrapportage van HVZ als overrapportage van werkstressoren. Dit suggereert een verband waarbij echter de onderliggende variabele het werkelijke verband veroorzaakt. De metaregressie liet zien dat studies waarin gebruik werd gemaakt van vragenlijsten om HVZ te meten gemiddeld hogere schattingen van het HVZ risico opleverden dan studies waarin gebruik werd gemaakt van meer objectieve data om HVZ vast te stellen. Dit lijkt het bezwaar te ondersteunen om vragenlijsten te gebruiken, waarmee zowel de expositie als de uitkomst wordt gemeten.

In **hoofdstuk 4** is het verband tussen werkstressoren, gemeten met de MCS-WSS, en HVZ onderzocht. Er werd geen verband gevonden tussen werkstressoren en HVZ. Voor deze studie waren verschillende bronnen beschikbaar voor het vaststellen van HVZ: HVZ gemeten met vragenlijsten, medisch vastgestelde HVZ en overlijden ten gevolge van HVZ. Het gevonden verband tussen werkstressoren en gerapporteerde HVZ was vergelijkbaar met het verband gevonden tussen werkstressoren en medisch vastgestelde HVZ (HR: 0.94, 95% CI: 0.68-1.28 versus HR: 0.88, 95% CI: 0.60-1.31) en het verband tussen werkstressoren en overlijden ten gevolge van HVZ (HR: 1.20, 95% CI: 0.74-1.96). Dit laat zien dat het verband tussen werkstressoren en HVZ niet afhankelijk is van hoe HVZ wordt gemeten en dat het gebruik van vragenlijsten om zowel werkstressoren als HVZ te meten niet tot een overschatting leidt van het verband in de MCS.

Een waarschijnlijke verklaring voor het niet vinden van een verband tussen werkstressoren en HVZ, zoals beschreven in de studie in hoofdstuk 4, is het gebruik van een eenmalige meting van werkstressoren. Een eenmalige meting is alleen geschikt als indicator voor langdurige blootstelling als blootstelling hetzelfde blijft tijdens iemands carrière. Als blootstelling varieert, leidt dit tot misclassificatie en een onderschatting van het verband tussen werkstressoren en HVZ. In **hoofdstuk 5** hebben we onderzocht of de blootstelling aan werkstressoren fluctueert over de tijd heen en of herhaalde metingen een hogere schatting van het HVZ risico op zou leveren dan een eenmalige meting. Daarnaast hebben we onderzocht of een bepaald type blootstelling het meest schadelijk is. Deze studie liet zien dat blootstelling aan werkstressoren fluctueerde (slechts 8% van de onderzoekspopulatie had een stabiele blootstelling boven het hoogste kwartiel op de werkstressor maat) en dat herhaalde metingen nodig zijn om een betere inschatting te maken van langdurige blootstelling. Langdurige blootstelling werd geschat op verschillende manieren: totale blootstelling, gemiddelde blootstelling, cumulatieve blootstelling boven een bepaalde waarde, eenmalige blootstelling en blootstelling gemodelleerd als een tijdsafhankelijke variabele. Stabiele blootstelling aan een hoge score op de werkstressormaat liet een bijna significante associatie zien met HVZ (HR: 1.51, 95% BI: 0.91-2.54 gecorrigeerd voor leeftijd, geslacht en opleidingsniveau). Cumulatieve blootstelling boven de mediane waarde, hoge totale blootstelling, hoge gemiddelde blootstelling en een hoge eenmalige meting leverden de volgende hazard ratios: 1.20 (95% CI: 0.80-1.81), 1.19 (95% CI:0.77-1.82), 1.22 (95% CI:0.80-1.87) en 1.04 (95% CI: 0.741.49). Deze resultaten lijken erop te wijzen dat stabiele blootstelling

aan een hoge score op de MCS-WSS gedurende twee jaar een betere indicator is voor langdurige blootstelling dan de andere maten voor blootstelling en dat er een minimum niveau van blootstelling nodig is om schade uit te oefenen op het hart en vaatstelsel.

Persoonlijke kenmerken zoals negatieve affectiviteit (NA) en coping kunnen van belang zijn bij het onderzoeken van het verband tussen werkstressoren en HVZ. Ze hebben mogelijk invloed op de blootstelling aan werkstressoren, het risico op HVZ, op de stress respons of kunnen het verband wijzigen. Daarnaast kunnen ze werkelijke effecten of verstorende effecten hebben op het verband. De meeste bestaande studies hebben persoonlijke kenmerken buiten beschouwing gelaten bij het onderzoeken van de relatie tussen werkstressoren en HVZ. De belangrijkste aanname van het Demand Control model is dat het de objectieve omgeving meet waardoor persoonlijke kenmerken buiten beschouwing gelaten kunnen worden. Als de werkomgeving wordt gemeten met vragenlijsten kan men echter niet differentiëren tussen welk deel van het antwoord op een vraag een reflectie is van de echte werkomgeving en welk deel een reflectie is van de perceptie van de werkomgeving. Wij onderzochten het verband tussen de cumulatieve blootstelling aan werkstressoren en HVZ en de invloed van persoonlijke kenmerken op deze associatie (**hoofdstuk 6**). Werknemers met een hoge NA hadden een significant verhoogd risico op langdurige cumulatieve blootstelling aan werkstressoren (OR: 5.52, 95% BI: 4.48-6.61, gecorrigeerd voor leeftijd, geslacht en opleidingsniveau). Werknemers met een hoge NA hadden een bijna significante associatie met HVZ (HR:1.31, 95%BI: 0.92-1.88, gecorrigeerd voor leeftijd, geslacht en opleidingsniveau). Negatieve affectiviteit had geen verstorend of mediërend effect op het verband tussen NA en HVZ, omdat inclusie van NA in het model het verband niet substantieel verminderde. Daarnaast is er nog een indicatie dat werknemers met hoge NA meer vatbaar zijn voor de effecten van langdurige hoge blootstelling aan werkstressoren in vergelijking met werknemers die laag scoorden op NA (HR: 2.41, 95%BI: 1.02-5.67 versus HR: 1.24, 95% BI: 0.47-3.24).

Om te onderzoeken of NA een bron van overrapportage van HVZ is en dus tot bias kan leiden als zowel werkstressoren als HVZ met vragenlijsten worden gemeten, is een studie uitgevoerd waarin onderzocht is of NA tot overrapportage van HVZ leidt (**hoofdstuk 7**). Tot nu toe heeft geen enkele studie onderzocht of het percentage vals positieven voor beroerte en hartziekte hoger is bij werknemers met hoge NA dan het percentage vals positieven voor beroerte en hartziekte bij werknemers met lage NA. Wij onderzochten de positief voorspellende waarde van gerapporteerde hartaandoeningen en beroertes. De referentietest was een diagnose gebaseerd op objectieve data, verkregen uit medische dossiers. Als NA tot overrapportage leidt, betekent dit dat individuen met hoge NA vaker een hartaandoening of beroerte rapporteren terwijl het niet objectief is vastgesteld. De positief voorspellende waarde voor gerapporteerde hartaandoeningen was 59% voor individuen met hoge NA en 58% voor individuen met lage NA. De positief voorspellende waarde voor zelf gerapporteerde beroerte verschilde significant tussen werknemers met hoge en lage NA (61% versus 33%). Dit was echter tegen de verwachte richting

in. Concluderend kunnen we stellen dat het aantal vals positieven niet hoger is voor werknemers met hoge NA dan voor werknemers met lage NA. Dit lijkt erop te wijzen dat hoge NA niet tot overrapportage leidt van HVZ in de MCS.

In de algemene discussie (**hoofdstuk 8**) worden de belangrijkste bevindingen beschreven en bediscussieerd. Tevens worden er suggesties gegeven voor toekomstig onderzoek en voor de praktijk. De resultaten van dit proefschrift laten zien dat verschillende methodologische en conceptuele zaken het geschatte HVZ risico beïnvloeden. Blootstelling aan werkstressoren moet worden gemeten met een veelomvattende maat waarin verschillende soorten werkstressoren zijn opgenomen, die elk een eigen bijdrage hebben en die tevens getoetst zijn op hun verband met “werkstrain” in de huidige werkomgeving. Door te toetsten welke factoren daadwerkelijk een verband hebben met “werkstrain”, middels werkstress, kan men met meer zekerheid stellen dat werkstressoren worden gemeten die een verband hebben laten zien met werkstress. Daarnaast varieerde de blootstelling aan werkstressoren over de tijd, wat pleit voor het belang van herhaalde metingen om te kunnen differentiëren tussen werknemers met langdurige en wisselende blootstelling. Dit is belangrijk omdat chronische blootstelling schadelijk is en dus ook deze vorm van blootstelling wil relateren aan HVZ. Het gebruik van een eenmalige meting leidt namelijk tot misclassificatie bij wisselende blootstelling en leidt tot een onderschatting van het verband. Stabiele hoge blootstelling aan werkstressoren, tijdens twee jaar, liet een bijna significante associatie zien met HVZ. Blootstelling zou daarom over een langere periode gemeten moeten worden, omdat een stabiele blootstelling tijdens twee jaar een betere indicator is voor langdurige blootstelling dan een eenmalige meting. De resultaten van de studies die uitgevoerd zijn in de MCS is, waar werkstressoren en HVZ met vragenlijsten zijn gemeten, zijn niet toe te schrijven zijn aan een verstorend effect van NA. Dit kan namelijk pas gebeuren indien NA zowel tot overrapportage leidt van werkstressoren als van HVZ en dit laatste hebben we kunnen uitsluiten. Het is wenselijk dat toekomstige studies met voldoende power onze studies repliceren om te zien of onderzoeksresultaten afkomstig uit verschillende onderzoekspopulaties consistent zijn en om toevalsbevindingen uit te sluiten. Indien dit het geval is moet langdurige blootstelling aan werkstressoren als een risicofactor voor HVZ worden erkend. Toekomstig onderzoek moet zich ook richten op het ophelderen van de vraag of de persoon, de omgeving of de interactie belangrijk is in het opwekken van werkstress. Dit is belangrijk voor het opzetten van preventie strategieën en richtlijnen hoe te monitoren wie risico lopen. Daarnaast dient werkstress ook onder de aandacht van cardiologen worden gebracht, zodat zij naast adviezen over roken, beweging en dieet, ook inzicht kunnen geven in de schadelijke gevolgen van werkstress.
De studies, zoals beschreven in dit proefschrift, onderstrepen het belang van de bijdrage van werkstress aan HVZ en het belang van het verminderen van de blootstelling aan werkstressoren om het HVZ risico te verlagen in de werkende populatie.

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About the author

Karolina Szerencsi was born on February the 14th, 1980 in Culemborg, the Netherlands. She completed secondary school (Atheneum) at the Koningin Wilhelmina College in Culemborg in 1998. In 1999 she started the study Physical Therapy in Eindhoven. In 2003 she finished the study and started to work as a physical therapist. In 2005 she started the study Biomedical Sciences in Nijmegen, where she chose the master Epidemiology in combination with the minor Occupation, Environment and Health. During her master, she fulfilled a 3 month internship at the department of Epidemiology and Biostatistics in Nijmegen and a 5 month internship at the Integraal Kankercentrum Zuid in Eindhoven, which resulted in the master thesis 'Cancer patients with cardiovascular disease have survival rates comparable to cancer patients within the age-cohort of 10 years older without cardiovascular morbidity'. From October 2008 until January 2013 she worked as a PhD student at the department of Epidemiology in Maastricht on the research project 'work stress and cardiovascular disease', which resulted in the present thesis. In January 2013 her contract got extended with 8 months and during this period she has been working on various proposals.