STRESS

AND CARDIOVASCULAR DISEASE

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EUROPEAN HEART NETWORK

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ROUND UP THE USUAL SUSPECTS!

For coronary heart disease (CHD), these "suspects" are well known: tobacco smoking; dyslipidemia; high blood pressure; lack of physical activity; obesity. These are usually referred to as the "causes" of coronary heart disease. Attempts to decrease CHD morbidity and mortality often include interventions to decrease smoking; improve eating habits; control hypertension; and decrease overweight. As all these do indeed target important components in CHD pathogenesis, such attempts are usually well founded.

But *why* do some people smoke too much, ingest too much fat, sugar and salt, live sedentary lives, and overeat? Genetic factors do play a role but do not explain the present variability between and within countries in such risk factors and health outcomes. There must be some additional "causes behind the causes". Some of these ultimate causes are social determinants of health – a subject chosen by the World Health Organization for its new high-level global Commission, the Commission on Social Determinants of Health, formed in 2005. Social determinants are the conditions in which people live and work. They include, *inter alia,* poverty, social exclusion, inappropriate housing, and shortcomings in safeguarding early childhood development, unsafe employment conditions, and a lack of high-quality health systems.

The Chairperson of the WHO Commission is Professor Sir Michael Marmot, one of the six distinguished authors of the present Report. In his recent comprehensive review, Marmot demonstrates that health, more often than not, follows a social gradient. The higher our status in the pecking order, the healthier we are likely to be.

But this is not the whole story. For people above a certain threshold of material well-being, another kind of well-being becomes central. *Autonomy* – how much control we have over our life, *self-esteem*, and our opportunities for full *social engagement and participation* – all are crucial for our health, well-being and longevity.

But how do such experiences translate into health and illness? The key lies in that most important organ, our *brain*.

It follows that additional targets for interventions intended to promote health and/or prevent or cure disease do exist. Such interventions aim at our cognitive faculties, our emotions and our coping abilities, but also at our living and working conditions, in absolute and relative terms. The six authors of this report review the current evidence and make a convincing case for targeting both the "causes", and the "causes behind the causes" of CHD, and some of the mechanisms through which they operate.

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EXECUTIVE SUMMARY

For several reasons, the concept of stress has played a much more important role in ideas about cardiovascular disease (CVD) among laymen than among experts. On a theoretical level, stress is more difficult for health care practitioners to define and assess than widely accepted coronary risk factors such as physical activity, tobacco smoking, serum cholesterol and blood pressure. It is also believed to be more difficult to deal with from a societal point of view.

However, research has confirmed the importance of stress as an independent risk factor in the incidence and the course of CVD. In one large international study, for example, a population attributable risk (PAR) was calculated for all risk factors, including stress. The PAR corresponds to the proportion of myocardial infarctions that could theoretically be prevented if the risk factor could be eliminated in the population. Regardless of country, age, gender and a number of established risk factors, stress as defined in the study, either at home or at work, corresponded in men to a PAR of 40% before age 55 and 24% above 55. The corresponding numbers for women were 53% (before 55) and 31% respectively.

Some of the mechanisms by which the body responds to stress have been clarified, and studies have looked at the physiology of stress and at particular aspects of working life and overall life conditions that act as stressors. And findings in the literature suggest a number of ways in which stress levels could be reduced, contributing to a reduction in the risk of CVD as well as to general health.

This paper surveys the major studies covering several aspects of stress and cardiovascular disease. Beginning with a working definition of stress as the non-specific reaction (energy mobilisation) that arises in demanding or challenging situations, it explains how the environment acts on individuals, who respond to stressors according to their individual coping programme, influenced by their genes and their experience, and produce reactions. Stress is necessary and can be beneficial, but because the body gives priority to the “fight or flight” reaction, while energy is mobilised to deal with a stressor, normal regeneration is neglected. With long-term stress, the stress hormones, which are not harmful over short periods, may act to accelerate coronary atherosclerosis, make the heart muscle vulnerable and affect the body’s ability to regulate energy. The paper explains how these and other physical stress reactions affect the heart.

In addition to each individual’s subjective assessment of the stress he or she is experiencing, objective tests confirm the body’s reaction. For example, a simple saliva test can determine cortisol levels; excreted from the adrenal cortex, cortisol normally varies throughout the day. Excessive increases, an inability to inhibit cortisol excretion at night and and/or an inability to mobilise cortisol with constantly very low levels are indications of a body under stress. High blood pressure, low testosterone in men or low oestrogen in women (both associated with decreased regenerative activity) are other verifiable factors that are associated with an increased long-term risk of CVD.

Some of the major studies on stress in the workplace and the interventions to alleviate this stress are summarised. Two models have influenced studies. The demand/control/support model theorises that the combination of high psychological demands and low decision latitude (job strain) is dangerous to health, with effects that are worsened by a lack of social support. However, high demands with high decision latitude (active work) may be associated with psychosocial growth and improved coping. Decision latitude involves the possibility of influencing decisions in daily work and the possibility of using and developing skills. The effort/reward imbalance model posits that high effort, intrinsic or extrinsic, is associated with health risk when it is not appropriately recognised with material, social and/or psychological rewards.

Studies have produced convincing evidence that job strain is a risk factor for cardiovascular disease, independently of other risk factors. For example, a group of tax accountants, who worked as much as 70 hours per week during tax season, showed significantly higher cholesterol levels and shorter clotting time during the busy periods before deadlines. The link between job strain and CVD applies to people still actively working; after retirement the effects are diminished.

Compounding the difficulties of designing an appropriate workplace intervention are uncontrollable factors such as businesses encountering difficulties, downsizing, reorganising, merging, relocating, etc. Nonetheless, some studies can serve as examples. A recent study by the Stockholm group (Theorell et al., 2001) in a large company involved giving one group of managers compulsory psychosocial training in sessions over a period of one year; a control group did not receive training. Tests including one on serum cortisol were performed and questionnaires administered on both groups. Those whose managers received the training reflected its success in their responses to the questionnaire, and medical tests confirmed

a lower stress level in the intervention group than in the control group, where tests results remained the same. In the same way, a group of bus drivers reacted well to improvements in their routes and technological advances with lower systolic blood pressure, diastolic blood pressure, pulse rate, and stress level.

One particular workplace stressor, shift work, has been shown to be less stressful if workers start later each day ("clockwise") instead of earlier ("counterclockwise"). The "clockwise" rotation works with the human body's circadian rhythm, based on a 25-hour day.

In the industrialised countries, low social class is associated both with increased incidence of CVD and with several of the environmental risk factors that may give rise to increased prevalence of long-lasting stress. Some stressors, including poor working conditions, lack of social support and troubled family life, may contribute to stress reactions that could partly explain social inequity in cardiovascular health. Extraordinarily traumatic experiences and a high prevalence of certain negative stressful life events also disproportionately affect people in the lower social classes, according to studies. Although the Sisyphus syndrome and type A behaviour are not related to social class in the way that would be expected, hostility, defined as a "cynical" attitude to life and to one's surroundings, is more common in the lower social classes and also related to the risk of coronary heart disease early in life.

Whilst older literature on stress-related factors was dominated by studies of men, more recent studies are showing a different psychological profile for women who develop coronary heart disease at younger ages. A submissive passive coping pattern seems to be of greater importance for women than hostility and type A behaviour. Working women report much lower decision latitude at work than working men, mostly because they are less often promoted to supervisory positions, even at comparable education levels. In both managerial and blue collar positions, women and men who have the same jobs with the same level of responsibility report very similar levels of decision authority and skill discretion, so gender differences in work stress could result from the different roles the two genders still play in the workplace. According to a large-scale Swedish study, intrinsic effort (overcommitment) in combination with job strain (high demand and low control) was a good predictor of myocardial infarction in women, while extrinsic effort/reward imbalance in combination with job strain was a good predictor in men. In a follow-up study, women with overcommitment working in male-dominated jobs were at particularly high risk of belonging to the myocardial infarction group even after adjustment for other risk factors. In a further study, "control at home" and how this relates to risk of new episodes of coronary heart disease was addressed. It was found that low control predicts coronary heart disease in women but not in men. The risk is higher in women in the lower social classes, perhaps due to a lack of material and psychological resources for coping with excessive household and family demands.

Women and men also differ in respect of social support. Although a wide circle of friends decreases the risk of CVD for men, evidence indicates that for women a large social network may correspond to a high psychosocial load.

The study discusses some of the biological mechanisms of stress, including regulation of cortisol levels, heart rate variability, blood pressure, plasma fibrinogen levels, inflammatory responses and other immune system reactions, and testosterone/oestrogen levels. Regeneration after stress is crucial, and sufficient high-quality deep sleep is essential for regeneration. The paper's authors conclude that "changes in energy mobilisation and regenerative activity are two possible mechanisms behind the association between psychosocial conditions and cardiovascular disease. The evidence is good enough at this point to provide biological plausibility for the relationship between stress and heart disease."

Recommendations for dealing with stress on a personal and societal level include:

- Relaxation training
- Good sleep hygiene
- Healthy lifestyle, including physical activity, a healthy diet, avoiding excessive caffeine and alcohol, not smoking
- Reduction of type A behaviour and hostility
- Improved social support, backed by community programmes
- Improved work environment, aiming at an improved relationship between psychological demands and decision latitude/social support, by educating managers or whole organisations. Improved relationship between effort and rewards, and shift work schedules that go "clockwise", and for groups with high demands for attention or fear avoidance, avoidance of long work weeks.

INTRODUCTION

Scientific research on the relationships between stress, psychosocial factors and cardiovascular disease has been ongoing for several decades. Physicians, psychologists and psychiatrists and heart patients themselves all agree that stress plays a significant role in the incidence and course of heart disease. Determining the precise nature of that role, however, is complex as it depends on the interaction of numerous factors, both personal and societal. This paper summarises the latest research on several factors that contribute to stress in both working and private life.

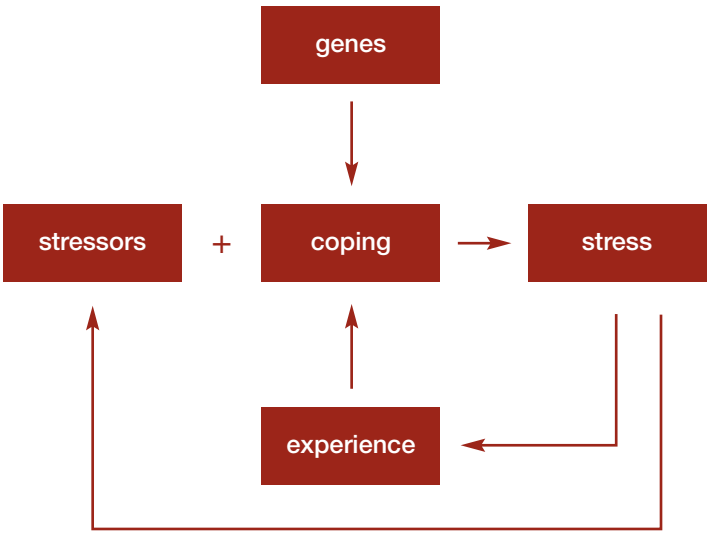
Although there is some overlap between factors studied, research is divided into the broad categories of working life, the influence of gender, private life including marital situation and social support networks, results of traumatic experiences, and the role of personality and behaviour patterns. In each instance both the evidence for the effects of stress on heart disease risk and the possibilities for reducing the risk are discussed. Then we look at research on the biological mechanisms at play. Finally, recommendations are made for reducing stress.

Stress can be an individual matter, but individuals live in a society over which their control is limited. Policy makers have an opportunity to intervene at various levels. This paper emphasises how important stress is and explains how it can be dealt with in prevention work – which is to a large extent the responsibility of regional governments, communities and personnel departments in workplaces. Close collaboration with primary care physicians, occupational physicians and other health care workers is essential.

THE STRESS CONCEPT

According to Selye (1936) stress is the non-specific reaction (energy mobilisation) that arises in demanding or challenging situations. Conditions in the environment that induce this reaction are labelled stressors. Obviously a crucial element of stress is the individual´s way of interpreting and coping with the stressor, which (according to Kagan and Levi, 1974) corresponds to the individual programme for dealing with the situation. If we follow this line of reasoning about stress, there are three levels, namely the **environment (stressors)**, which is displayed to the left in the figure below (see Figure 1), the **individual programme**, which interacts with stressors in generating stress, in the middle, and the **reactions**, in this case stress, to the right. The theory underlying this publication is that long-lasting stress reactions, if combined with other conditions, may contribute to acceleration/deceleration of processes that lead to cardiovascular disease. The pathogenesis of cardiovascular disease and how that may relate to stress will be discussed in this paper.

Figure 1. Basic underlying concepts in the stress discussion



Source: Kagan and Levi, 1974; Theorell, 1991.

When we discuss possibilities for decreasing the negative effects of stress it is very important that we differentiate between actions that we can take on the environmental stressors (for instance improving work organisation so that stress reactions occur less frequently or so that stress reactions can be dealt with more effectively in the organisation), on how the individual copes with stress (for instance teaching individuals about stress management), and on the individual reaction (for instance medication that may reduce the physiological consequences of repeated intensive stress reactions) respectively. Sometimes it is possible to act on two or three levels at the same time, but it is always important to know which level an action is addressing. The diagram also shows how the three levels are related to one another.

Our way of coping with stressors (individual programme) is a result of our gene interaction with the environment. The genes never act in isolation, and it is only when a "dangerous" gene is activated by an environmental factor that it may become dangerous. "Protective" genes may also be activated by favourable conditions. Science is only beginning to generate knowledge in this new field. As indicated in the diagram, experiences of "stress" may influence our coping pattern. This means that coping patterns are always changing. They are modelled in a continuous interaction between our genes and our external situation. The concept "experience" is used here in a broad sense. Accordingly we are not talking only about conscious experiences. For instance, we are not aware of all the stressors that we are exposed to. Despite the lack of conscious awareness of some stressors, however, the body may react to them and record its reactions.

Clinicians, both health care professionals and psychologists, generally focus on the individual programme and the reactions. The physician can help to strengthen the individual's resistance to stress (which belongs to the individual programme) by giving advice regarding diet, physical activity and sleep habits, for instance. The psychologist or psychiatrist can help the person to resist adverse conditions through educational procedures (stress management) aiming at improved coping with stress. The physician can also help the individual to reduce stress, for instance by prescribing medication such as beta blocking agents that reduce the physiological effects of arousal. The psychiatrist or psychologist, finally, can reduce reactions by efforts to teach relaxation and other methods aiming at reducing one's arousal level in stress situations.

Since clinicians are consulted by individuals, it is quite natural for them to be more interested in the individual aspects of stress than in the environment. The environmental level should primarily be addressed by politicians, public health care workers, personnel administrators and occupational health care workers, as well as business managers and leaders, but all the stress preventive work has to be done in collaboration between these groups. The reasons for this are depicted in figure 1, as will be discussed below.

Stressors and stress

Any adverse (negative) or challenging (positive) condition, physical or psychosocial, in the environment could be labelled a stressor. Selye presented his theory regarding "general adaptation syndrome" in 1936 and later started using the term "stress" when he popularised his theory. A stressor is interpreted by the individual programme as a condition that requires energy mobilisation. Energy mobilisation is a basic response triggered in all human beings in many situations. Such a response is sometimes necessary for our survival. The stress reaction is not dangerous to health per se. In fact it may be very positive. When it occurs repeatedly and intensively without periods of rest and recuperation in between, however, it may become dangerous to health. The negative stress reaction was labelled "distress" by Selye.

Our reactions, however, also influence both our programme and our environment, as indicated by the arrows. Sometimes a reaction may reduce the environmental load, but it could also increase it. And our programme is continuously adapting itself to the environment. We are different as individuals both because we have different genes and because we have different experiences.

A crucial element in the intensity and character of our way of coping with stressors is our expectations (Ursin and Eriksen, 2004). When we can actively do things that reduce danger and we are convinced that we can manage our challenges, our stress reactions will be less intensive and of a shorter duration. However, when the consequences of our coping are unpredictable (helplessness) the stress reactions will be more long lasting. Finally, when our prediction is that there will be negative outcomes regardless of what we do (hopelessness), the stress reactions will be even more long lasting and damaging.

THE STRESS CONCEPT

As discussed by Marmot in his recent book *Status Syndrome* (2004), associations and preventive actions are quite different on a collective population level than on an individual level. For instance, genetic factors are certainly important on the individual level but changes in societies may give rise to pronounced elevation of stress levels. These changes cannot be explained by sudden changes in genetic factors.

Researchers have been interested since the 1960s in all three levels in Figure 1. On the whole this paper focuses mainly on the environmental aspects and on the individual programme. Understanding the interplay between these components and how this affects reactions that could increase/decrease the risk of coronary heart disease is central to any programme aiming at stress reduction in society. The development of pharmaceutical agents such as beta-blockers has been going on since the 1960s, and these kinds of medications are becoming more and more sophisticated; they will not be discussed in detail in this paper, however, since the pharmaceutical discussion belongs to clinical cardiology.

Stress physiology

When the body mobilises energy for fight or flight, the provision of fuel for energy production will have the highest priority. This means that the concentration of glucose and fatty acids will increase. At the same time the body prepares itself in other ways, such as increased coagulation (if injury arises, bleeding should stop as soon as possible), reduced sensitivity to pain (pain from injuries should not stop muscular action) and decreased inflammation (swollen tissues should not disturb the person). If the flight or fight reaction continues for some time it also becomes evident that the body's regenerative activities are downplayed. Regeneration is the body's replacement and repairing of injured or worn out cells. This activity goes on in the gastrointestinal cells, in the skin, in the muscles (including the heart muscle), in the brain's supportive system (glia cells), in the skeleton and in the white blood cells, to mention a few examples.

When the regeneration has been inhibited for a long time – weeks, months or years – these tissues become vulnerable. In the circadian rhythm the regenerative activities have their peak during sleep, particularly during stage 4 sleep (which is the deepest sleep stage). So obviously it is very important to retain good sleep during periods of long-lasting stress. Regeneration may also be stimulated actively by physical activity and possibly also by cultural activities such as dancing or listening to music. We have insufficient knowledge regarding the effects of cultural activities, although some research results indicate that there are such protective effects.

Inhibition of regeneration is accordingly one way in which long-lasting periods of stress reactions without sufficient periods of rest may increase the risk of illness. Another way in which stress could influence the risk of illness is via direct effects of the stress hormones. These are not dangerous to health if they are active during short periods. However, if energy mobilisation goes on for very long periods with insufficient rest, the stress hormone effects on serum lipids, coagulation and inflammation will result in accelerated coronary atherosclerosis. In addition the vulnerability of the heart muscle will increase. Finally, such periods will result in an inability to regulate energy and stimulation/inhibition of stress hormones in normal ways. Examples include the regulation of cortisol excretion from the adrenal cortex. Both excessive increases with an inability to inhibit cortisol excretion at night and with an inability to mobilise cortisol with constantly very low levels have been observed. The metabolic syndrome is associated with increased cardiovascular risk. It is characterised by excessive abdominal fat, increased insulin resistance and a tendency to diabetes, high blood pressure, high cortisol levels (or inability to regulate cortisol), low testosterone (associated with decreased regenerative activity) in men and low oestrogen (also associated with decreased regenerative activity) in women.

Stress in relation to the pathogenesis of cardiovascular disease

Let us start with a few words about the pathogenesis of cardiovascular disease (not including congenital heart disease). Most of the cardiovascular disease that is of importance to public health occurs in middle and old age and can be regarded as a form of accelerated ageing. The two essential organs are the heart and the vessels, in particular the arteries. There is a massive amount of documentation showing that stiffening/narrowing of the arteries – arterio- or atherosclerosis – in the heart itself (the coronary arteries) dramatically increases the risk of developing cardiovascular disease. Narrowing of the coronary arteries is not the only decisive factor, however.

There are two manifestations of cardiovascular disease that are of particular importance. The first one is angina pectoris, which is due to a transient lack of oxygen for the work that the heart muscle is doing. The second one is myocardial infarction, which arises when the lack of oxygen becomes more long lasting and part of the heart muscle is injured due to this oxygen shortage. The part of the heart muscle that is injured is replaced by scar tissue, and if the injury is extensive this will result in persisting reduction of the functioning of the heart muscle.

So how does a lack of oxygen arise? The different coronary arteries supply different parts of the heart muscle with oxygen. When one of the arteries becomes narrowed an insufficient amount of oxygenated blood will reach the corresponding part of the heart muscle. If the vessel becomes completely and permanently blocked – which occurs if a blood clot is formed or if debris from an atherosclerotic plaque follows the blood from a more proximal to a more distal part of the coronary arteries – an infarction is inevitable. The artery may also be only partially blocked by atherosclerosis. If so the heart muscle may function well at rest and when no extraordinary demands are made upon it. During heavy physical work or emotionally upsetting conditions, however, the heart starts beating harder and faster and then the demand for oxygen increases. If this situation is long lasting a myocardial infarction may arise despite the fact that the artery is not totally blocked. When the situation is more transient there will be angina pectoris and no heart muscle injury will occur.

Spasms may also arise in the coronary vessels, although this is not common. Such a spasm may give rise to angina pectoris and – although this is very uncommon – even myocardial infarction. A coronary artery spasm is triggered by strong emotions and/or physical demands.

Coronary atherosclerosis is by far the most important condition for cardiovascular disease among middle-aged and older people. It should be pointed out, however, that at any given level of coronary atherosclerosis the risk of manifest cardiovascular disease varies. This is due mainly to two factors:

First of all, massive increases in the demand for oxygenated blood to the heart muscle may arise during tachyarrhythmias. These are episodes of very fast heart rate that may arise unexpectedly. The “speed of the heart” is completely out of proportion to the external demands but enormous demands for oxygen arise in the heart muscle. Some individuals have more of a tendency to such arrhythmias than others even long before they have developed any coronary atherosclerosis. When they are young these episodes are transient and no injury occurs to the heart muscle. However, when the person develops coronary atherosclerosis this situation changes and episodes of oxygen shortage will then give rise to symptoms – angina pectoris or myocardial infarction – during the tachyarrhythmias. Subjects who have had a myocardial infarction may have heart muscle scars that by themselves increase the risk of such episodes. The likelihood of tachyarrhythmia increases during emotionally upsetting or physically demanding situations in people with a tendency to tachyarrhythmia.

Secondly, the condition of the heart muscle itself to some extent seems to determine whether an episode of oxygen shortage will result in myocardial infarction or not. For instance, after a long period of energy mobilisation with insufficient periods of rest, the regenerative capacity of the body is low. This also affects the heart muscle, which becomes more vulnerable to oxygen shortage.

How can “stress” influence these different mechanisms? It can influence cardiovascular disease risk in several ways, summarised in Figure 2.

Coronary atherosclerosis is stimulated by tobacco smoking, high blood pressure and high concentrations of certain serum lipids (low density lipoprotein). This has been known for a long time. During the last few years it has also been established that stimulated inflammatory processes as well as increased coagulation may accelerate coronary atherosclerosis.

Tobacco smoking sometimes increases and sometimes decreases during periods of stress. There are accordingly no unanimous findings regarding the effects of stress on tobacco smoking. In some cultures tobacco smoking seems to be more associated with stress than in others. The risk of developing hypertension increases during long-lasting stress (see below). With regard to serum lipids the findings in the literature are less clear. Some lipids, such as triglycerides, are very sensitive to stress reactions, and total cholesterol has been shown to rise during periods of long-lasting stress, caused for instance by unemployment.

During the last few years the atherosclerotic process itself has been studied in relation to stress. It has been shown for instance that the blood concentration of one of the interleukins (IL-6) which is regarded as a possible important inflammatory marker of relevance to the atherosclerotic process increases during experimental stress. This increase is more long-lasting and more pronounced in persons from lower socio-economic strata than in other subjects (Brydon et al., 2004). Another mechanism related to inflammation, namely the activity of stem cells which can be transformed to endothelial cells (which form the inner surface of the arterial wall and are therefore of importance to the atherosclerotic process), is sensitive to stress (Fischer 2005, personal communication). The endothelial activity is in general sensitive to stress, and these effects last longer than those recorded with the use of more conventional measurements such as heart rate (Ghiadoni et al., 2000). Coagulation (which is closely related to inflammation) has also been shown to be of importance

to the atherosclerotic process and accordingly the fact that coagulation (for instance plasma fibrinogen) is sensitive to stress is of great importance to the link between stress and cardiovascular disease (see below).

We may thus conclude that there are several ways in which long-lasting periods of stress may influence coronary atherosclerosis. It is also important to emphasise that stress reactions could trigger the onset of excessive oxygen demands in the heart muscle. Emotional reactions resulting in increased heart activity (the heart muscle beating both harder and faster) could be important per se, but they may also be important because they increase the risk of uncontrolled excessive tachyarrhythmia (uncontrollably fast heart rate) in vulnerable individuals. Sudden physical demands or pronounced emotional reactions may also increase the risk of forming a clot, which could block a coronary artery completely. Finally, long-lasting episodes of intensive stress reactions could increase the vulnerability of the heart muscle itself (via decreased regenerative activity).

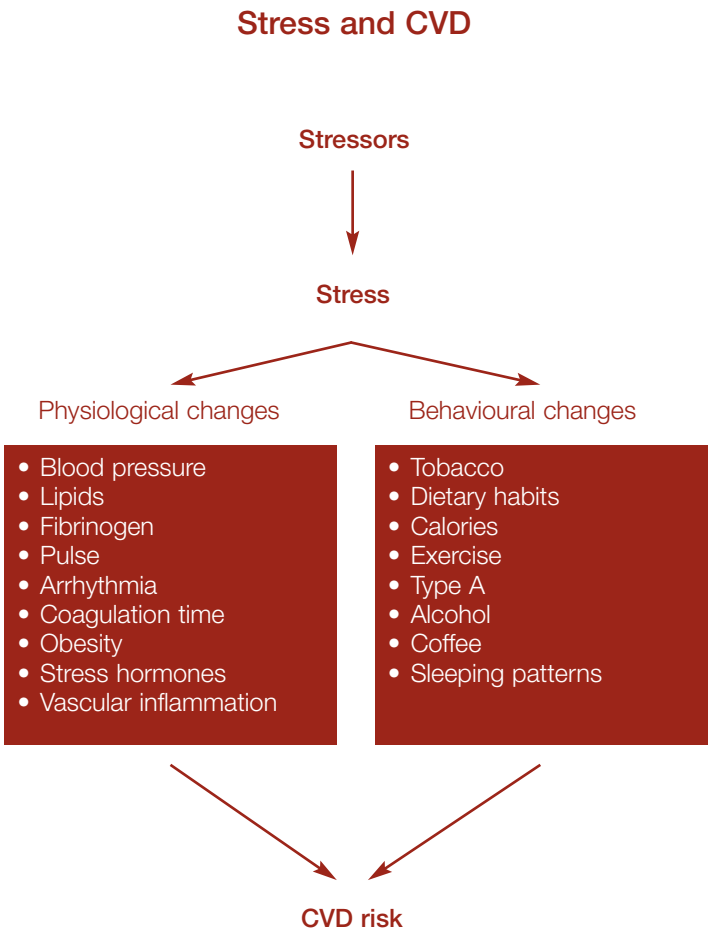
The processes that connect stressors with the risk of cardiovascular diseases follow two different pathways, as shown in figure 2. To the left in the figure a number of physiological mechanisms are indicated. These include increased blood pressure, higher levels of lipids such as LDL cholesterol, higher fibrinogen levels in the blood, higher pulse, higher level of obesity, decreased coagulation time of the blood, arrhythmia, and an increased level of stress hormones (e.g. cortisol, adrenalin). Stressors may also change the behaviour of the people exposed to them (shown to the right in the model). These behavioural changes include increased tobacco smoking, changes in dietary habits, increased intake of calories, decreased physical activity, manifestation of type A personality (hostility and anger), increased alcohol intake, higher coffee intake, and changes in sleeping habits (poor sleep quality and decreased number of hours of sleep).

It should be emphasised that the model presents a simplified picture of the possible mechanisms leading to increased CVD risk. This is due to the fact that many of the behavioural factors to the right influence the factors to the left in the model. Examples are:

- Tobacco increases fibrinogen levels in the blood, which leads to an increased risk of formation of thrombi in the arteries.
- Dietary habits influence blood lipids and obesity.
- Exercise influences blood pressure, pulse, and obesity.

Thus, the factors shown in the figure are interconnected in many different ways. From a research point of view such complicated mechanisms are difficult to study, and it is particularly difficult to evaluate the independent contribution of each single factor. From a prevention point of view the interrelatedness of all the factors can be seen as an advantage: The reduction of one of the risk factors reduces the overall risk of CVD in many different ways. In some cases the reduction of one factor even leads to reducing the risk of other diseases such as cancer or diabetes, which should be regarded as an "extra bonus" in CVD prevention.

Figure 2. Interplay between physiological and behavioural changes in relation to stress and cardiovascular disease



Stress and heart disease – how important is stress according to the patients and according to their doctors?

A recent very large international case control study (11 000 patients and 13 000 control subjects) highlighted the connection between stress and heart disease (Rosengren et al., 2004) from the point of view of patients with a recent first myocardial infarction. Subjects (both patients and control subjects) were asked two single-item questions about stress during the past 12 months at home and at work respectively. Stress was defined as feeling irritable, filled with anxiety or as having sleeping difficulties as a result of conditions at work or at home. This stress definition could of course be criticised (see above) but the word stress is vaguely defined in common language.

A population attributable risk (PAR) was calculated for all risk factors, including stress. The PAR corresponds to the proportion of myocardial infarctions that could theoretically be prevented if the risk factor could be eliminated in the population. Regardless of country, age, gender and a number of established risk factors, stress defined in this way either at home or at work corresponded in men to a PAR of 40% in the ages before 55 and 24% in the ages above 55. The corresponding numbers for women were 53% (before 55) and 31% respectively. As a comparison it could be mentioned that in men, smoking corresponds to a PAR of 52% before the age of 55 and 39% after 55. The corresponding numbers for women are 21% and 8% respectively.

The conclusion from this study is that for men self-reported stress defined in this way and assessed after a heart attack has great importance – as much as the most important accepted risk factors. Its significance is as great as that of cigarette smoking.

According to the same study only one measured risk factor attains greater importance, namely a high apoB/apoA-1 ratio. This is the ratio between the concentration of proteins carrying harmful lipids and proteins carrying protective lipids respectively.

The assessments in the Rosengren study capture a feeling of stress but do not specify what the sources of the stress could be. In relation to stress, the findings only reflect what the patients consider important – after they have experienced the onset of the infarction. This is important in its own right, however.

In another very practical approach to the question of stress and heart disease, the relevance of the general stress reaction to coronary heart disease risk has been shown indirectly by studies demonstrating that risk factors can be reduced by regular practice of relaxation over a long period of time. Whether the method for achieving relaxation is transcendental meditation, biofeedback training or other kinds of relaxation is probably unimportant. The essential component in success is a reduced degree of arousal (or stress) in everyday life situations.

The difficulty with this approach for coronary heart disease risk reduction seems to be the sustainability of the habit of practising relaxation for months and years. Various methods for this have been proposed, for instance Patel et al., 1985. It is probably important to pay attention to the psychosocial environment in the family and at work when such programmes are being planned, and therefore they should generally be combined with psychosocial interventions.

Depression and heart disease

Among cardiologists, opinions about the importance of stress in relation to cardiovascular disease are more divided. During recent years, however, there has been a growing consensus that depression is an important risk factor in relation to cardiovascular disease. A comprehensive meta-analysis recently provided strong evidence for the association between depression and the risk of cardiovascular disease (Rugulies, 2002). There is both evidence showing that depression is common after the onset of heart disease and evidence showing that depression increases the risk of developing myocardial infarction and of dying from an infarction when heart disease has become apparent. Up to 20% of patients have an episode of major depression within a few weeks of suffering a myocardial infarction, and a further 25% experience elevated levels of depressive symptoms. Depressive symptoms following acute myocardial infarction are associated with increased morbidity and impairment in quality of life.

Relevant concepts in stress prevention in relation to cardiovascular disease

Table 1 shows concepts that have been explored scientifically in relation to stress and heart disease. The concepts have been organised into the three levels described in Figure 1.

Table 1. Concepts examined scientifically in relation to stress and coronary heart disease

Environment	Individual programme	Mental reactions
Low social class	Sisyphus syndrome	Stress
Bad work environment	Type A behaviour	Chronic fatigue syndrome
Lack of social support	Hostility	Burnout
Family load and conflict	Overcommitment	Vital exhaustion
Traumatic experiences*		Depression
Stressful life events		

* Refers to extraordinarily stressful experiences which most people do not ever encounter in their lives, such as rape or natural disaster

Social class is a concept that has been discussed extensively (see Marmot, 2004) in relation to heart disease risk. From several points of view it could be regarded as an overriding concept, but it does not cover all aspects of the relevant stressors. There is unanimous agreement among researchers that in industrialised countries low social class is associated both with increased prevalence and incidence of coronary heart disease and with several of the environmental risk factors that may give rise to increased prevalence of long-lasting stress. Some of the stressors listed in the table are more common in the lower social classes; these stressors may contribute to stress reactions that could partly explain social inequity in cardiovascular health. Examples of such stressors are poor working conditions (see Marmot et al., 1999), lack of social support (see Berkman and Glass, 2000) and troubled family life (Orth-Gomér et al., 2000).

The other groups of stressors mentioned in the table, extraordinarily traumatic experiences (see Sondergaard, 2002) and a high prevalence of certain negative stressful life events (see Moller et al., 2005, Rosengren et al., 1993) have been examined in only a few epidemiological studies in relation to social class (see Dohrenwend and Dohrenwend, 1974; Brown, 1973). These studies have indicated a clear relationship between low social class and a high prevalence of negative life events. Sisyphus syndrome (a never ending comfortless extreme struggle, see Wolf, 1969) and type A behaviour, which could be defined as a never-ending "excessive effort to overcome insurmountable obstacles" (see Friedman and Rosenman, 1959) are not related to social class in the way that would be expected. Hostility on the other hand – perhaps the most basic component of type A behaviour – is a "cynical" attitude to life and to one's surroundings (Williams, 2003). This attitude is more common in the lower social classes and also related to the risk of coronary heart disease early in life.

Chronic fatigue syndrome (Cleary, 2000), burnout (Maslach et al., 2001), vital exhaustion (Appels, 2004) and depression are examples of disorders to which intensive periods of "stress" without periods of recuperation may contribute. Vital exhaustion has been specifically related in prospective studies to the development of coronary heart disease episodes (Appels, 2004; Prescott et al., 2003). Of these disorders, depression is more common in the lower social classes (Brown and Harris, 1978; Stansfeld et al., 1999) whereas the relationship between chronic fatigue syndrome, burnout and vital exhaustion on the one hand and social class on the other hand is not clear.

STRESS IN THE WORKPLACE

Two models for describing adverse/beneficial work

When we discuss stress with the aim of determining how to reduce it, is important that we define factors that we can influence by means of organisational efforts. The workplace is one major area for intervention, so we will begin with a survey of recent research on the aspects and characteristics of work that can cause stress.

Two models have been particularly influential for describing stressors in workplaces, namely the demand/control/support and the effort/reward imbalance models. Among the precursors of these models is the person-environment fit model (Kahn et al., 1964). In addition researchers have constructed practical questionnaires for identifying a large number of stressors in workplaces (Hurrell et al., 1998; Cooper et al., 1976). One of the broadest instruments (including many factors and properly validated) is the General Nordic questionnaire for psychological and social factors at work (Lindström et al, 2000). These are very useful in intervention work. Here we focus mainly on the demand/control/support and effort/reward imbalance models because they have been more extensively tested in relation to cardiovascular outcomes and mechanisms than the other models.

The demand/control/support model was introduced by Karasek (1979) and further developed by Karasek and Theorell (1990). The support dimension was tested and discussed in more detail for the first time by Johnson and Hall (1990). According to this theory, the combination of high psychological demands and low decision latitude (job strain) is particularly dangerous to health, and the effects may be worsened by a lack of social support. On the other hand high demands with high decision latitude (active work) may be associated with psychosocial growth and improved coping. Decision latitude has two components, decision authority (possibility of influencing decisions in daily work) and skill discretion (possibility of using and developing skills).

The effort/reward imbalance model was introduced by Siegrist (1996). It states that high effort is associated with health risk when it is not rewarded adequately. Reciprocity is the key concept. Effort has both intrinsic and extrinsic aspects. The main component of intrinsic effort is “overcommitment”. The extrinsic aspect is similar to psychological demands in the demand/control model. Rewards have three components, which are referred to as material (monetary), social (for instance promotion possibility), and psychological (self esteem). When extrinsic effort is not matched by sufficient reward (sum of the three dimensions) there is an increased risk of illness. Intrinsic effort serves as an interacting variable (Siegrist et al., 2004).

There is a growing body of research showing that both the demand/control and effort/reward constructs are related to the risk of heart disease. Reviews including both models have been published (Schnall et al., 2000; Hemingway and Marmot, 1999; Marmot et al., 1999). The evidence for demand/control was summarised more recently by Belkic et al. (2004) who made a methodological analysis of sources of error and strengths in published studies. The conclusion was that there is convincing evidence that job strain is a risk factor for cardiovascular disease.

Loss of decision latitude has been shown to be associated with an increased risk of developing a myocardial infarction (Theorell et al., 1998) or new episodes of cardiovascular disease (Bosma et al., 1997).

There have been prospective studies with negative findings, however (Reed, 1989; Eaker et al., 2004). The participants in these studies have been relatively old. This means that a large proportion of them have retired during the follow-up period. It has been shown in previous research that the effect of exposure to job strain diminishes after retirement. A prospective European study (Kornitzer et al. 2006) with a five-year follow-up on 20 435 middle-aged men previously free from coronary heart disease has recently been performed. One hundred eighty of these men had myocardial infarctions during follow-up. After adjustment for age only there was clearly an excess risk of myocardial infarction in the job strain group (Odds ratio 1.53 with 95% confidence limits 1.00 to 2.35) but not in the active or passive groups. After adjustment for smoking and systolic blood pressure the odds ratio decreased to 1.47 with 95% confidence limits 0.96 to 2.25. The decision latitude component did not contribute much to this association however.

There is no evidence from studies in recent years that the demand/control model shows a decreased ability to predict new heart disease episodes in men.

Two studies of cardiovascular disease, the prospective Whitehall II study (Bosma et al., 1998) and the Stockholm SHEEP study (Peter et al., 2004) used the two models together, and the findings indicated that they predict coronary heart disease episodes independently of one another. In the Whitehall II study the decision authority component of the demand/control model and the effort/reward imbalance model both made independent predictions of new episodes of heart disease among previously healthy state employees. In Stockholm, SHEEP, a large population based case control study of first myocardial infarctions, studied self-rated job strain as well as the intrinsic and proxy measures of the extrinsic parts of the effort/reward model as separate variables. The results were different for men and women. For men a combination of job strain and imbalance between extrinsic effort and reward was the best predictor of myocardial infarction status. In women the intrinsic part of the effort/reward model (overcommitment) had the same role as the extrinsic one in men – a combination of overcommitment and job strain was the best predictor of coronary heart disease episodes.

Psychological assessment of working conditions: the subjectivity factor

Critics argue that "subjectivity bias" may explain most of the associations observed between the psychosocial work environment and coronary heart disease (Wainwright and Calnan, 2002; Mc Leod and Davey Smith, 2003). A number of psychological dimensions that could possibly influence the subject's description of his/her working conditions have been recorded and used in analyses. These include hostility, including a cynical and suspicious attitude to the environment, and negative affectivity, which is a propensity to evaluate everything negatively, both the environment and one's own health. Both hostility and negative affectivity could potentially create spurious relationships. Even after controlling for these factors that could falsify the results of the study, there were clearly significant relationships remaining between working conditions and the risk of developing new cardiovascular disease episodes (myocardial infarction and angina pectoris) during follow-up (Bosma et al., 1998a).

More detailed observations of working conditions have also been tried, and this seems to be a very fruitful area of research. Greiner et al. (2004), in their studies of bus drivers in San Francisco, have been able to show that objectively recorded adverse conditions in the working day of the bus driver are much more clearly related to blood pressure elevation than are self-reports. Recent German research by Rau (2001) has indicated that the relationships between objective working conditions and cardiovascular disease risk may be even clearer than the ones between self-reported conditions and risk.

Other factors influencing work conditions

Theoretically there is a possibility that adverse material childhood circumstances (infections, nutrition, drinking water, etc.) could explain the relationship between psychosocial work conditions and coronary heart disease (see for instance Wainwright and Calnan, 2001). Life course research is beginning to address these kinds of questions. Several findings speak against the interpretation that material childhood conditions could explain it all. First, social class in general does not entirely explain away the association between job conditions and ill health. Indeed, in studies in which associations have been explored in different social strata the relationship between job strain and heart disease, for instance, has been much stronger in blue collar workers than in white collar workers (Hallqvist et al., 1998). This indicates that bad job conditions are not simply a "passive" part of a bad social situation – they probably have effects of their own.

Hintsanen et al. (2004) have shown that job strain is associated with increased early signs of atherosclerosis in young adult men and women even after adjustment for other risk factors. The same group of researchers, in their study of a cohort of employees, made similar observations with regard to prospective relationships between work stress and risk of death from cardiovascular disease later in life. Both job strain and effort/reward imbalance remained significant predictors even after adjustment for a number of childhood factors (Brunner et al., 2004).

If low decision latitude and lack of reward constitute parts of the explanation of social inequality in health, they represent conditions that could be the focus of interventions. For several reasons the health effects of such interventions are difficult to evaluate. One of the main reasons is that in a constantly changing market, precisely those worksites which are

participating in an intervention may be subject to mergers, outsourcing or other major structural changes. Such changes may make it impossible to interpret the process. However, particularly in the Scandinavian setting, evaluations of the health effects of organisational changes aiming at improved worker participation have been made (for a summary, see Wahlstedt, 2001). The effort/reward imbalance model has been the basis of an intervention for bus drivers (Kompier et al., 2000).

Organisational interventions in workplaces aiming at decreased heart disease risk

It is hard to know what the action should be in preventive programmes. There are, however, other research findings that could help us in this. For instance, in Danish and Swedish studies (Olsen and Sondergaard-Kristensen, 1988; Karasek and Theorell, 1990) it has been shown that a more specific adverse job condition, job strain (see below), which is a combination of high demands and low degree of control, is associated with a population attributable risk (PAR) of approximately 10% for men below 55 years of age and for working women. If among working men below age 55 those 25% who report the worst conditions from the job strain point of view obtain improved working conditions (so that they have at least as good conditions as the remaining 75%) the incidence of new myocardial infarctions would be reduced by approximately 10%. This proportion was calculated after adjustment for other risk factors.

Recently the Stockholm group (Theorell et al., 2001) performed an intervention study aiming at improved psychosocial knowledge in managers. The theory behind this intervention was built upon both the demand/control/support and the effort/reward imbalance models. The managers in an insurance company had mandatory psychosocial education once every second week (half an hour lecture and 90 minutes group discussion) for a whole year. The education programme comprised all relevant aspects of psychosocial working conditions, such as the role of demand, decision latitude, support and effort/reward imbalance. Their employees were examined before, after six months and after a whole year with regard to psychosocial work conditions and serum cortisol (when they arrived at the office in the morning).

Employees in another comparable part of the same organisation (whose managers were not subjected to the psychosocial training) were followed at the same intervals (130 subjects in each group). While cortisol remained unchanged in the comparison group, the employees in the intervention group had a substantial significant decrease in serum cortisol during the follow-up year. There was also a more favourable development of the serum concentration of the liver enzyme gamma glutamyl transferase, and in female participants there was also a more favourable development of serum triglyceride concentration in the experimental group than in the control group – both possible consequences of the improved cortisol concentration. Psychosocial questionnaire data from the same groups of employees indicated that the development of decision authority was more favourable in the intervention group than in the control group, while demands and work pace developed in the same way in the two groups. These results indicate that managers could be one target group in psychosocial worksite interventions and that improvement of decision authority for employees may be a crucial variable.

Improved manager knowledge may not necessarily be the only possible strategy, however. In a psychosocial intervention programme in Sweden (Orth-Gomér et al., 1994) a similar strategy was used which involved all the employees in workplaces. Compared to the control group the intervention group showed improved decision authority and improved lipoprotein patterns (which are associated with decreased cardiovascular risk).

It is sometimes claimed that inference on causal mechanisms has to be built on randomised controlled trials. Such a fundamentalist view of research on causal mechanisms is hardly fruitful. Many established causal mechanisms connecting risk factors and diseases have never been examined with randomised trials. Examples are the associations between smoking and lung cancer and between sleeping position and cot death among babies. Nobody would suggest that we should wait for randomised trials in these fields instead of applying our knowledge in practical prevention interventions.

When it comes to intervention studies in the field of stress at work and CVD there are many obstacles and barriers that prevent researcher from applying the ideal randomised intervention trial.

- The researcher does not have the power to reduce or change exposures at the worksite.
- Randomisation is usually not possible and rarely desirable from an ethical point of view.
- The potential number of participants is usually too small and the follow-up time too short to obtain the necessary statistical power if CVD cases are the endpoints.
- In most cases many unforeseen factors influence the course of events and tend to overshadow the significance of the factors being studied.

Facing these challenges intervention researchers have turned to one or more of the following solutions:

- Use of *intermediate endpoints* instead of "hard endpoints" such as hospitalisations or mortality. Such intermediate endpoints are blood pressure, cholesterol level, CVD risk score, carotid artery wall diameter or other established CVD risk factors.
- Use of *non-randomised control groups* such as workers at similar workplaces with the same social status.
- Use of *"natural experiments"* where potential risk factors are changed as a result of company decisions or the enforcement of new laws.

Such intervention studies usually elucidate two important issues:

- The *causality issue*: does the "pill" have the desired effect?
- The *feasibility issue*: Does the patient take the "pill"? These issues are equally important. It does not help that the pill has an effect if the patient does not take it. And it does not help that the patient takes the pill if it has no effect (Kristensen, 2005).

A few examples of CVD intervention studies will be described below.

In a classical study Friedman et al. studied cholesterol and blood clotting among tax accountants. This was a natural experiment where the time before deadline for the accounts was considered as the "exposed period". The accountants served as their own control group. During the busy periods the accountants worked as much as 70 hours per week and they also experienced conflicting demands from the clients. The study showed significantly higher cholesterol levels and shorter clotting time during the busy periods before deadlines. These two factors were seen as indicators of increased risk of CVD during the busy periods.

Orth-Gomér studied the association between shift work and risk of CVD by following two groups of Stockholm policemen. One group started to work according to a "clockwise" rotation system schedule, while the other group worked according to the usual "counter-clockwise" system. Under a clockwise system the policemen started a bit later every day, which is more in accordance with biological rhythms since the spontaneous circadian period has been shown to be approximately 25 hours. After four weeks of work the two groups switched schedules. The analyses showed that triglycerides, systolic blood pressure, serum glucose, and serum uric acid levels were lower during clockwise rotation. Self-rated health, length of sleep and quality of sleep were also better during the clockwise rotation period. Thus, the study pointed at the clockwise system as the healthiest from a CVD point of view. Furthermore, the study also demonstrated that the system was acceptable and feasible.

In another Swedish intervention study Johansson et al. followed CVD risk factors in a group of bus drivers where improvements were introduced concerning work stressors. Bus drivers from similar routes were studied as the control group. On the intervention bus routes physical changes were made in the streets and technological improvements were introduced in relation to passenger service. The follow-up study showed that drivers in the intervention group experienced fewer hassles at work than before the intervention. In the drivers in the intervention group the systolic blood pressure, the diastolic blood pressure, the pulse rate, and the stress level went down. The study confirmed that it was possible to reduce the level of job hassles among bus drivers, and that this reduction resulted in reduced CVD risk factor levels. The study is very relevant since bus drivers are known as one of the high risk groups with regard to CVD.

In a Norwegian study Erikssen et al. followed a group of 225 workers at a ferro-alloy plant. During the first years of follow-up the blood pressure was constant over time. Then the average level of systolic blood pressure increased by approximately 15 mmHg, the diastolic blood pressure by about 10 mmHg, and the pulse rate by 7 bpm. Further analyses showed that the only likely explanation of this rather dramatic increase in average blood pressure was the continuous rumours about

a possible factory closure. Since the plant was the only large worksite in the geographic area, the closure would have a dramatic impact on the lives of the employees and their families. This study shows the dramatic impact of an "invisible" stressor connected with a low level of control and predictability. In this natural experiment there was no control group, but the researchers found it very unlikely that the average increase in blood pressure in such a large group of workers could happen by chance.

In a Danish study of an actual closure of a shipyard, Iversen et al. chose the workers in a similar shipyard as the control group. The incidence of hospitalisations due to CVD was followed for the two groups in the national hospitalisation registry. The analyses showed that the relative risk among the workers in the closed shipyard was 0.80 during the two years before closure, 1.04 during the period of closure, and 1.60 during the two years after closure. For ischemic heart disease alone the relative risk was 2.60 during the years after closure. Thus, the study suggests that a factory closure connected with low control, low predictability and a low level of rewards results in a marked increased risk of CVD.

These and other interventions in the field of psychosocial factors at work demonstrate that it is possible to carry out intervention studies in this field, although it is nearly impossible to apply the strict model of the randomised controlled trial (Kristensen, 2000). The number of intervention studies is increasing steadily and so is the quality of these studies. This is a very promising field of research because it deals with the two equally important topics of aetiology and feasibility.

Specific working conditions

Shift work

Shift work defined as constant rotation between day and night work has been shown to be associated with an increased risk of myocardial infarction (for a review see Boggild and Knutsson, 1999). It has also been shown that improved shift work schedules (going from "counterclockwise" to "clockwise") may decrease the risk of coronary heart disease (Orth-Gomér, 1983).

Long working hours

Despite the intuitive idea that long working hours could increase coronary heart disease there is relatively sparse scientific evidence confirming this. Studies (Hinkle et al., 1968) in the 1960s and 1970s showed that extremely long working weeks (more than 60 hours per week) were associated with an increased risk of developing myocardial infarctions or dying of coronary heart disease at a young age.

Few studies concerning long working hours have been published during recent years. However, a Japanese study (Sokejima and Kagamimori, 1998) of white collar workers showed that both short (below regular work hours per week) and long work weeks were associated with elevated risk. Another very recent Japanese case-control study (Fukuoka et al., 2005) showed very clearly that patients reported longer working hours than control subjects. An epidemiological study of a large Swedish cohort was based upon imputations: in national surveys specified occupations were shown to have a large proportion of subjects with working weeks exceeding 50 hours per week. These occupations were compared with other occupations with regard to incidence of hospitalisation for myocardial infarction. This study (Alfredsson et al., 1985) showed different results for women and men. For women the expected relationship was found – a higher incidence of heart disease in the occupations with long working hours. In men the opposite was found, however – those assigned (mainly moderately) long working hours were associated with a lowered incidence. In this study no adjustments were made for biological risk factors or for social class. The findings are therefore difficult to interpret. Still, they point to the importance of context in relation to working hours. In addition there may be threshold effects. This could mean for instance that in men a working week of at least 60 hours per week is required before an increased cardiovascular disease risk occurs while in women 50 hours per week may be sufficient.

Long working hours *per se* may not increase risk. However, in certain occupations – for instance among professional drivers, (see Belkic et al., 1994), with a high degree of attention and fear avoidance – long working hours may increase risk.

In studies published earlier it was difficult to differentiate the effects of long working hours from the effects of high psychological demands in general. During the 1970s unexpected results were obtained during the long-term follow-up of two Belgian cohorts, both composed of middle-aged males working in Brussels, one in a private bank and the other in a semi-public savings bank. At five and ten years follow-up respectively – with higher incidence in the private bank – a significant difference in the incidence of new hard

coronary events was observed; these differences could not be explained by differences in classic coronary risk factors (Kornitzer et al., 1975; Kornitzer et al., 1979). A retrospective ecological study was started in those retired at the ten-year follow-up survey. They were given a specially constructed questionnaire concerning their job content with questions on perceived psychological demands, decision latitude and social support at work as well as on financial problems. A computed weighted job stress score was significantly higher in those retired from the private bank as compared to those from the semi-public savings bank (Kittel et al., 1980).

This job stress score showed important correlations with the type A behaviour pattern and socio-professional level. The same job stress questionnaire was then administered at the baseline survey of the Belgian Interuniversity Research on Nutrition and Health Study (BIRNH Study) in 2257 middle-aged working males (Kornitzer and Bara, 1989). After ten years of follow-up the job stress questionnaire was found to be an independent predictor of cardiovascular mortality with a relative risk (RR) of 1.23 adjusted for age, systolic blood pressure, smoking, blood cholesterol and education level (Kittel et al., 1998).

In a more recent study, cases of first myocardial infarctions were compared to matched population control subjects. In addition the myocardial infarction cases were interviewed in detail about possible triggering factors during the 24 hours and the week preceding the myocardial infarction respectively. The disease-free periods preceding the onset were used in these latter comparisons (Moller et al., 2005). It was found that increased responsibility and conflicts at work (similar to the findings in the prospective study) were more common in the case group than in the control subject group. Financial problems were also reported much more often in the case group.

All these findings were made in both men and women, and adjustment for other risk factors made very little difference. According to these self-reports, triggers during the week preceding myocardial infarction were “deadlines at work” and “praise from boss” (trying to push the patient to work more?), and during the 24 hours before the onset the trigger was work pressure due to deadline. Accordingly both in prospective and in cross-sectional studies work changes related to responsibility, work load and relationships seemed to be important.

Although the triggers (both week and day preceding) were potentially important, they did not have great value from the public health perspective since despite the statistical relationship very few myocardial infarctions occur in relation to such events. Still these relationships point at important theoretical associations – which could be used in preventive work.

Downsizing and reorganisation in modern working life

With the advent of economic globalisation in combination with progress in information technology, competition between companies and pressure towards an increase in the return on investment have been growing over the past two decades. As a consequence, work pressure increased considerably in several private sectors of national economies, but also in public sectors, due to financial cuts in public expenditures (Eurostat 2004). Finnish studies have shown that pronounced downsizing among employees in a municipality (follow-up of 7.5 years) is associated with a doubled risk of cardiovascular death (Vahtera et al., 2004). Such sweeping changes in working life are also associated with privatisation of parts of the public sector. A study of Whitehall II participants (civil servants in London) during the late 1980s and early 1990s showed that those who were threatened by or went through privatisation (with resulting threats to job security) had subsequent deterioration in cardiovascular risk patterns with increasing body mass index and increasing blood pressure (Ferrie et al., 1998). This could not be explained by changes in health-related behaviours and accordingly physiological reactions related to long-lasting stress could have contributed to this health change.

Governments particularly in Sweden, Norway and The Netherlands have been worried about rising and very expensive long-term sick leave rates during the late 1990s and early 2000s. In relation to cardiovascular disease the consequences of these processes have been of particular interest. In the Whitehall II studies civil servants without initial signs of heart disease but with other symptoms of ill health at the start of this period were followed (Kivimäki et al., 2005). In this group, civil servants who had not had sick leave episodes during follow-up (“sickness presenteeism” or working while ill) had a doubled risk of developing myocardial infarctions compared to comparably “sick” civil servants with at least one or several sick leave episodes during this period – after adjustment for other risk factors. Thus sickness presenteeism may be associated with increased cardiovascular risk during periods of reorganisation.

Sweden is an interesting case in this context. During the 1990s Sweden went through a pronounced financial crisis which resulted in markedly increased unemployment rates. Some economic recovery took place during the latter part of the decade, at the expense of increasing demands and decreasing decision authority, most pronounced in the public sector of employment (Theorell, 2004). In the period from 1997 to 2001, a sharp increase in long-term sick leave was observed, particularly among women in the public sector (Westerlund et al., 2004). The biennial national Swedish Work Environment survey offered an opportunity to analyse the impact of expanding and shrinking organisations on sickness absence and hospital admissions in a prospective design. Long-term (≥ 90 days) medically certified sickness absence and hospital admissions for specified diagnoses during 1997 to 1999 were related to changes in number of staff in the organisations' workforce in previous years (1991 to 1996). As expected, downsizing was associated with elevated long-term sick leave. A moderate increase in number of staff was associated with an improvement in staff health. Repeated rapid large expansion of the number of staff members during several years, on the other hand, was associated with increased long-term sick leave and hospitalisation. Such a rapid expansion may cause chaotic conditions with many stressors. In the public sector such a rapid and pronounced increase in number of staff may be due to the closing of a hospital or a health care centre with the staff in this unit subsequently being placed in adjacent centres.

While the findings on long-term sick leave in relation to rapid expansion were most pronounced for women in the public sector, the findings for hospitalisation for cardiovascular disease were significant only in the private sector women (Westerlund et al., 2005). A further Swedish study analysed the association of expanding or shrinking organisations with "absenteeism" or "presenteeism" in a group of employees who were at risk of developing cardiovascular disease (Theorell et al., 2003). Subjects were 5720 employees aged 18 to 65 in the WOLF study (a prospective study of biological and psychosocial cardiovascular risk factors in working men and women in the Stockholm area during the years 1992-1995). From a medical examination a cardiovascular risk score was calculated for each participant. The WOLF study base was linked to national registers of economic and administrative activities in worksites. Worksites with downsizing (at least 8% decrease from one year to the next), stable number of staff (changes less than 8% decrease or 8% increase) and expansion (> 8% increase) were identified. Sick leave spells lasting for at least 15 days during the calendar year following the downsizing/expansion were identified through individual linkage with the national insurance register. Interestingly, among women it was found that sickness absence during the year following downsizing was decreased compared to the group of women employed in stable worksites. This may again reflect some pressure towards "sickness presenteeism", because the trend was particularly pronounced among women with an elevated cardiovascular risk score (Theorell et al., 2003). All these findings illustrate the importance of including structural changes of labour market and work, in particular downsizing and continued rapid expansion, in research on work stress and health. They also illustrate that cardiovascular disease shows a somewhat different pattern than many other health changes. Taken together the findings illustrate that excessive sickness presenteeism could be particularly dangerous to cardiovascular health, at least among women.

That employees with stable working conditions (defined by managers in the respective worksites) have fewer risk factors for cardiovascular disease than employees with more unstable conditions was shown in an epidemiological study in Sweden (Westerlund et al., 2004).

LIFE CONDITIONS

Unemployment

Tsai et al. (2004) recently published a large prospective study of the association between involuntary unemployment and cardiovascular mortality in Taiwan in 2001-2002. Adjustments were made for gender, age, income, firm size and urbanisation that could give rise to spurious associations. It was shown that involuntarily unemployed men in 2001 had a significantly elevated cardiovascular mortality in 2001 and 2002. Kim et al. (2004) showed that cardiovascular mortality increased very rapidly after the recent economic crisis in Korea with a marked rise in unemployment rates. Henriksson et al. (2003) published a study from southern Sweden based upon an examination of a cohort of 1430 men who were followed for six years ending in 1997, when the participants were 43 years old. During the beginning of this period the unemployment rates rose dramatically. The study showed that risk factors for cardiovascular disease were clearly increased with unemployment at the start but not in the middle or late 1990s when the unemployment rate was high. How can these diverging findings be understood?

That the experience of unemployment is a strong stressor has been shown in longitudinal studies (see for instance Brenner and Levi, 1987; Cobb, 1974). Accordingly elevated serum cortisol, serum lipids and blood pressure have been observed particularly after job loss. The discussion (see Janlert 1997) regarding the association between job loss and cardiovascular disease risk has dealt with the fact that on the one hand subjects with cardiovascular risk due to excessive tobacco smoking or low physical activity may run a greater risk of becoming unemployed than others, and on the other hand the experience of unemployment in itself may lead both to long-lasting stress reactions and adverse changes in personal habits that may increase risk. Although these different paths may be difficult to disentangle there is agreement that both processes may exist together. The intensity that the unemployment experience may have depends upon the time period and upon the societal context. The two Asian studies may illustrate that in countries with very little societal support to the unemployed the unemployment experience may be a very strong stressor. However, in countries with functioning social protection the unemployment experience may be a weaker stressor.

Marital load and conflict

A few studies have found that a close confiding marital relationship may protect against coronary heart disease. The first one was a cohort study in Israel (Medalie et al., 1973). Marital conflicts were studied in relation to the risk of developing new episodes of cardiovascular disease in a cohort of women who had suffered a myocardial infarction or severe angina pectoris at the start. Such conflicts predicted new episodes of heart disease independently of other risk factors (Orth-Gomér et al., 2000). A recent follow-up also indicated that the progression of coronary atherosclerosis was more pronounced in this group than in other groups (Orth-Gomér et al., 2005). A combination of marital conflict and job strain was a particularly strong predictor of atherosclerosis progression (submitted 2005).

It is obvious that the quality of the marriage could be of great importance to risk and that this could be a target for interventions.

Lack of social support

The importance of social support has been studied for many years in relation to coronary heart disease. In general a large social network (many family members, colleagues and friends) will mean good social support (see Berkman and Glass, 2000). There are different aspects of social support. There is potential support at work and outside work, and support may be emotional as well as instrumental. In the former category there is emotional support in crisis situations but also emotional support in the daily round of life. In the latter category there are more material aspects of support including access to information that we may need. It has been pointed out that a large social network may play a different role for men versus women, however. Among men a large social network is mostly beneficial, whereas for women a large social network may correspond to a high psychosocial load.

It has been suspected for a long time that social cohesiveness is associated with a low risk of developing coronary heart disease (see for instance Marmot, 2004; Berkman and Glass, 2000; Orth-Gomér and Johnson, 1987). This idea has also been subjected to intervention studies (Schneiderman et al., 2004). These interventions have not been directed so much at the social support itself but rather at the individual's own ability to obtain social support. In addition they have been of rather low intensity and the findings have not been conclusive. In one of them (ENRICHD), a large American multi-centre study, patients who had suffered a first myocardial infarction were approached with a programme for improved social support. Follow-up data did not show any

significant effects of the programme on the outcome measures, and surprisingly the effects were different for men and women. Whereas some beneficial effects were observed for white men there were no effects for female patients. This may be an illustration of possible gender differences in the meaning of social support.

On a societal level there is an indication that a cohesive society protects against coronary heart disease. In a series of studies, Marmot et al. showed that Japanese men who migrated to Hawaii or California were less likely to adopt the high American incidence of coronary heart disease if they were able to keep the cohesive Japanese social patterns (Marmot and Syme, 1976).

Traumatic experiences and negative life events

Although among laypeople there is a common idea that negative life events may play a role in the development of coronary heart disease, there are relatively few published studies on this theme. In particular there are very few prospective studies. Li et al. (2002) performed a large scale study of parents who lost a child. They showed that the loss of a child does increase the risk of developing a myocardial infarction. However, this seems to occur with some delay since the risk did not become obvious until several years had passed.

Theorell et al. (1975) performed a prospective study with a two-year follow-up of a large cohort of middle-aged building construction workers. A high life event score (Holmes and Rahe, 1967) was not associated with risk, but one particular life event related to work, increased responsibility, was associated with an elevated one-year risk of myocardial infarction. In the two-year follow-up a cluster of events that included changes in responsibility and conflicts at work was associated with increased risk (Theorell and Floderus Myrhed, 1977).

Most of the prospective studies in this field deal with specific events such as death of spouse and retirement as triggers of myocardial infarction. The findings in this research have not been unequivocal. It seems likely that the health risk associated with such events is modified by a number of psychological and social factors. Lack of control and marked social threats in life events may be important aspects.

There is, however, evidence that acute stressors and negative emotional states may act as triggers of myocardial infarction (Strike and Steptoe, 2005). In these cases, psychological factors do not ‘cause’ heart disease, but instead precipitate major cardiac events in individuals who already have underlying coronary artery disease. Evidence has emerged from studies of the effects of natural disasters such as earthquakes, and interviews with survivors of myocardial infarction. Emotional stress and emotions such as anger appear to be particularly relevant (Moller et al., 1999). A heightened tendency to stress-induced activation of blood platelets may be responsible for emotional triggering in susceptible individuals (Strike et al., 2006).

Individual traits – personality and behaviour patterns

Sisyphus syndrome and type A behaviour pattern are two individual traits that have been explored extensively in research on coronary heart disease. Although they are related, the most extensively studied of the two is the type A behaviour pattern. The central characteristic was initially described as a propensity to manage insurmountable obstacles. Psychological research showed that this pattern, which was initially based upon clinical observations of young male victims of myocardial infarction, had three basic components, namely “high drive” (a high tempo), “impatience and hostility” and finally “obsession with work”. Several questionnaires were constructed but the most effective instrument for predictions was a structured interview (for a review see Matthews and Haynes, 1986). After several prospective studies had presented negative findings (Kittel et al., 1986; Ragland and Brand, 1988) the interest in type A behaviour was attenuated. Type A behaviour research, however, had introduced programmes for the reduction of type A behaviour (Thoresen and Powell, 1992; Burell and Granlund, 2002; Sundin et al., 2003) and it was shown that these programmes were effective in one way or the other in secondary prevention. This means that educational programmes were successful in reducing type A behaviour in patients with coronary heart disease and that this may have contributed to a reduced incidence of new coronary heart disease episodes during follow-up.

In the epidemiological studies it was found that the hostility component was more important than the other type A components. Several prospective studies showed a relationship between a high degree of hostility and subsequent risk of developing a myocardial infarction, including in secondary prevention (Boyle et al., 2004). In addition hostility was shown to be related to social class in the expected way (more hostility in the lower social classes) and it was also shown to be related to several physiological parameters of relevance to coronary heart disease (for a review see Williams, 2003). In addition it was shown that educational programmes aiming at reducing hostility were successful.

THE INFLUENCE OF GENDER

Most of the older literature on stress-related factors and coronary heart disease was dominated by studies of men. For instance, type A behaviour and hostility are concepts that were constructed mainly on the basis of young male victims of coronary heart disease. It has been shown that the psychological profile of women who develop coronary heart disease at younger ages is different from the corresponding profile of men (Hällström et al., 1986; Orth-Gomér, 1998). According to these researchers a submissive passive coping pattern seems to be of greater importance for women than hostility and type A behaviour. Although this is very speculative since the number of published studies in this field is small, more outgoing aggressive coping behaviours seem to be relevant for men's coronary heart disease while a more inwardly-directed behaviour seems more relevant for coronary heart disease in women.

It has been known for a long time that working women report much lower decision latitude at work than working men. Most of this difference seems to be due to the fact that women are less often promoted to become supervisors and managers than men (Karasek and Theorell, 1990; Hall, 1990). Women and men who have the same jobs with the same level of responsibility report very similar levels of decision authority and skill discretion. This seems to be true both for managers and for blue collar workers (see Bernin and Theorell, 2001; Theorell, 1991). The finding that men in general tend to report higher levels of decision latitude at work than women has been repeated in many studies and seems to be as relevant in European working life today as it was in the 1980s and 1990s. The same observation is also relevant for two of the reward dimensions, material rewards (salaries) and career opportunities: Women have lower salaries and poorer career opportunities than men even at comparable education levels. This points to a gender perspective that could be fruitful in future intervention efforts.

Energy has also been devoted to an improved understanding of the role of gender in the associations between the life conditions in working ages in relation to health. For instance, in the example described above the demand/control and the effort/reward models were combined in the predictions of myocardial infarction cases in the SHEEP study. Intrinsic effort (overcommitment) in combination with job strain (high demand and low control) was a good predictor in women, while extrinsic effort/reward imbalance in combination with job strain was a good predictor in men (Peter et al., 2003).

This study was followed up by a study based upon the analytical model proposed by Hall (1990). This model addresses the effects of the working climate induced by male and female dominance respectively. Subjects working in occupations with male and female dominance, respectively, were examined with regard to the prevalence of myocardial infarction, and interactions with the components of the effort/reward imbalance were explored. Women with overcommitment working in male-dominated jobs were at particularly high risk of belonging to the myocardial infarction group even after adjustment for other risk factors (2.7 (1.1-6.5)). This points to the potential importance of gender segregation and the role that female overcommitment may play in male-dominated jobs (Peter et al., 2005).

An interesting new line of research has been introduced by Chandola et al. (2004), who studied "control at home" and how this relates to risk of new episodes of coronary heart disease in the Whitehall II study. After adjustments it was found that low control predicts coronary heart disease in women but not in men. Furthermore, the results indicated that perceived lack of control at home mediates part of the relationship between low social position and coronary heart disease in women, and that part of this could be due to a lack of material and psychological resources for coping with excessive household and family demands in women belonging to the lower social classes.

Another difference between women and men in relation to coronary heart disease risk is discussed briefly in the section on social support below. Although a wide circle of friends decreases risk for men, evidence indicates that the significance of this factor is different for women.

BIOLOGICAL MECHANISMS OF STRESS

Cortisol

How can the two models, the effort/reward imbalance model and the demand/control/support model, be linked biologically to heart disease risk and other health risks? Long-lasting excessive energy mobilisation without periods of relaxation has been related to disturbances in the regulation of energy mobilisation (Mc Ewen, 1998). Energy mobilisation also inhibits regeneration (Theorell and Hasselhorn, 2002).

Energy mobilisation is reflected in such parameters as blood pressure elevation and elevation of catecholamine, cortisol and thyroid hormone excretion. Both cortisol and catecholamines can also be assessed in urine. In addition cortisol can be assessed in saliva (Kirschbaum and Hellhammer, 1999). Saliva cortisol is easily collected, which makes it possible to record circadian rhythms. In general energy mobilisation corresponds to high serum concentrations of these hormones. During normal conditions the morning cortisol levels are much higher than the evening levels. The assessment of circadian rhythm in different states of long-lasting stress has shown that not only repeated peaks reflect responses to demands for arousal. Disturbed regulation of cortisol levels can also arise during long-lasting periods of adverse psychosocial conditions. Inability to down-regulate (high levels in the evening and night) as well as inability to respond (low flat curves) have been observed in subjects with stress-related disorders (Rosmond and Bjorntorp, 2000; Cleary, 2000).

There is a rapidly growing literature which relates both the demand/control/support model and the effort/reward imbalance model to cortisol regulation. Steptoe et al. (2004) have studied variations in saliva cortisol over the day in relation to overcommitment and the external part of the effort/reward model. The study, which was based upon contrasting samples from the Whitehall II study, showed that men who had high scores on the overcommitment scale had on average 22% higher saliva cortisol concentrations than men who had low scores.

Comparisons between these groups also showed that the rise in saliva cortisol concentration from awakening to half an hour later was higher in overcommitted than in non-overcommitted men. No such findings were made in women. The external part of the effort/reward score was not related to saliva cortisol levels in men or in women.

Steptoe et al. (2000) have also shown that teachers (men or women) with job strain have higher saliva cortisol levels at 8.00 and 8.30 in the morning than other teachers.

These associations were particularly strong in subjects who reported a high level of “anger out”, a tendency to react with openly expressed anger in stressful situations. A study of Japanese female health care workers (Fujiwara et al., 2004) showed more elevated urinary catecholamine output in those with self-reported job strain than in others. Saliva cortisol levels, on the other hand, were consistently lower in the job strain group than in the others.

Studies of cortisol regulation in subjects with job strain and imbalance between effort and reward have not shown a consistent picture. However, disturbed regulation has been observed in several studies. Whether elevation or depression of cortisol levels arises may vary between samples, and depend on type of job, gender and duration of exposure. In subjects who have retained their capacity to regulate energy, the excretion of cortisol is high particularly in the morning when the job situation is stressful (because of high demands, high commitment or lack of control). Later in the day, however, these subjects are able to lower their cortisol excretion. Patients with long-lasting severe depression are sometimes unable to down-regulate cortisol excretion in the evening – they accordingly seem to have “too high” levels at night. Finally, when the stressful conditions have lasted for a long time (months) and more severe psychiatric symptoms are found (anxiety syndromes, sleep disturbance and mild depression) the levels are likely to be lower than average, particularly in the morning (Alderling et al., 2004). This could be regarded as a form of physiological exhaustion. During such conditions serum lipids are likely to be elevated and anabolism indicators, namely testosterone (in men) and oestrogen levels (in women), are likely to be depressed (Rosmond et al., 2004). Whether or not these different kinds of regulatory disturbances are related to one another sequentially is not known, however.

Heart rate variability due to job stress

Heart rate variability is a relatively new concept. It builds upon the fact that the heart rate varies due to many biological processes that have “rhythms” of their own. For instance breathing affects heart rate variations. When we inhale our heart rate increases, and when we exhale our heart rate decreases. These variations are less pronounced when we become old and when we are exposed to a situation that evokes a stress response. For instance the parasympathetic system (which is the “slowing-down” system) also has a “rhythm” (peaks and troughs in activity) of its own that is mostly faster than our breathing rate. Advanced computer programmes can sort out such rhythms and this means

that they can give us information about the level of activity in the parasympathetic system. In general a high rate of activity in all the systems that create such variation is an indicator of good health. Collins et al. (2004) have followed spontaneous variations in job strain and control in subjects with jobs "low" and "high" in job strain, respectively. Their dependent variable was variations in heart rate. The findings on heart rate variability indicated that there were associations between job strain and/or lack of control on the one hand and decreased parasympathetic activity on the other hand.

Another "new" principle is to record how fast the heart muscle contracts during a beat. Vrijkotte et al. (2004) found a significant association between the pre-ejection fraction (velocity of contraction – an index of sympathetic drive in the heart) and overcommitment in a study of 67 white collar workers who were followed during two work days and one non-work day. In summary there is evidence that job strain, lack of control and overcommitment are associated with high levels of energy mobilisation and inhibition of the "slowing-down" system.

Blood pressure

Blood pressure regulation has been studied extensively in relation to decision latitude and job strain. The study of working men in New York City (Landsbergis et al., 2003) has shown consistent relationships between a high "life exposure" to job strain and high systolic blood pressure during continuous blood pressure recordings in prospective analyses. The researchers also found strong cross-sectional associations between job strain and both systolic and diastolic blood pressure (Schnall et al., 2000).

Similar results were found in a Swedish study of working men when borderline hypertensives were examined with continuous blood pressure recordings and job strain measurements inferred from other sources (Theorell et al., 1991) and these findings were later confirmed in more detailed analyses (Rau et al., 2001). Rau (2001) has also studied blood pressure during work activities in relation to job strain using very detailed information regarding job conditions; these studies have confirmed that in white collar workers there is an independent contribution of more objectively assessed job strain to blood pressure level.

In the Whitehall II study a relationship was found between low job control and high ambulatory blood pressure, although demands had no effect (Steptoe and Willemsen, 2004).

For many years it was believed that there is no relationship between blood pressure measured in the conventional way (in the doctor's office) and job strain described as a stable job characteristic. Two prospective population studies have recently shown that job strain does predict incident hypertension even when other factors have been adjusted. The first one was the CARDIA study in the USA (Markovitz et al., 2004) which followed 3200 employed initially healthy normotensive subjects aged 20 to 32 from 1987-1988 for eight years. Subjects who had had increased job strain were more likely than others to have developed hypertension. The other study is a Canadian population study (Brisson et al., 2004) with similar findings.

Other mechanisms

The evidence is growing that psychosocial factors may contribute to elevated plasma fibrinogen, an indicator of inflammatory activity and increased coagulation (for a review see Theorell, 2002). Accordingly, adverse long-lasting psychosocial conditions may induce bodily states that increase the vulnerability to illness. Enhanced coagulation and increased inflammatory activity could both be regarded as phenomena that accompany energy mobilisation. There has been increasing attention during recent years to the immunological system and its role in the atherosclerosis process.

The immune system has been studied both in epidemiological and in experimental examinations.

Inflammatory responses have become increasingly important in atherosclerosis research and in addition there seems to be a strong link between stress and the immune system. Accordingly the immune system is relevant both to stress and to coronary heart disease. During recent years both experimental and epidemiological research points to the importance of this link.

The serum concentration of gamma globulin G (which is a crude indicator of immune activity) was followed in employees who had spontaneous variations in job strain. The results showed that the concentration increased with increasing job strain but also that this phenomenon was limited almost entirely to subjects who had poor social support in their general life situation (Theorell et al., 1990).

Interleukin 6 concentration in serum has been studied in relation to the demand/control model in a Swedish epidemiological study (Theorell et al., 2000). Low decision latitude was associated with high serum IL-6 in men but not in women. Low job control has also been associated with impaired vascular endothelial function in the Whitehall II study (Hemingway et al., 2003). Another analysis from the Whitehall study has demonstrated that individuals exposed to work stress (high demands and low decision latitude coupled with low social support at work) are more than twice as likely than others to develop the metabolic syndrome over a 14 year follow-up period (Chandola et al., 2006).

Regenerative activity: protection against stress

Regenerative activity, one of the most important protective forces against stress, is reflected in the serum concentration of testosterone (men), oestrogen (women) and their joint precursor DHEA-S. A longitudinal study of variations in job strain in men showed that periods of high job strain were associated with lowered serum concentration of testosterone (Theorell et al., 1991). Hansen et al. (2003) studied metabolic and endocrinological concomitants of repetitive work (sewing machine operators) which were shown to be associated with increased glycated haemoglobin (HbA1c), which is an indicator of long-term energy mobilising, and with lowered DHEA-S as well as free testosterone. A one-year follow-up study in the late 1990s in Sweden (Hertting and Theorell, 2003) showed that female health care staff members had a lowered serum concentration of oestradiol (the female counterpart of male testosterone and also an indicator of anabolic/regenerative activity) after having experienced the latest episode of downsizing (which occurred after several years of repeated episodes of downsizing). The evidence on regeneration is, however, much weaker than that on energy mobilisation.

A factor that is of great importance to regeneration is sleep. During deep sleep the growth hormone concentration in the blood is generally very high as an indication of high anabolic activity, and the serum testosterone concentration in men is lowered after disturbed sleep. Disturbed sleep has been shown to be associated with an elevated risk of developing coronary heart disease episodes and also with the progression of coronary atherosclerosis (Leineweber et al., 2003; Leineweber et al., 2004). Burnout is associated not only with marked disturbances of sleep but also with elevated serum lipids and other components of the metabolic syndrome (Söderström et al., 2004, Ekstedt et al., 2004, Grossi et al., 2003). Studies have shown that reduction of sleep to only four hours per night results in severe (reversible) disturbances in insulin resistance (Gonzalez-Ortiz et al., 2000). Accordingly reduced sleep may result both in excessive energy mobilisation and reduced anabolism. There is also a relationship with job strain since a longitudinal study (Theorell et al., 1988) showed that increasing job strain was followed by increasing sleep disturbance.

Accordingly, changes in energy mobilisation and regenerative activity are two possible mechanisms behind the association between psychosocial conditions and cardiovascular disease. The evidence is good enough at this point to provide biological plausibility for the relationship between stress and heart disease.

REDUCING RISK CAUSED BY STRESS

The concept of stress has played a much more important role in ideas about cardiovascular disease among laymen than among experts. There are several reasons for this. On a theoretical level, stress is more difficult for health care practitioners to define and assess than widely accepted coronary risk factors such as physical activity, tobacco smoking, serum cholesterol and blood pressure. It is also believed to be more difficult to deal with from a societal point of view. Stress is often believed to be difficult to address on a practical level as well – which is in fact even more important since preventive work directed towards adverse forms of stress is not primarily the responsibility of physicians or health care providers. The result is that often physicians feel that they cannot do anything about the patient's stress and therefore avoid the subject altogether. In particular the primary care physician cannot easily influence the patient's working conditions.

In order to tackle stress as a risk factor, health care professionals will need to modify their approach to put more emphasis on this aspect of treatment. Helping patients recognise the stress they experience, reducing it where possible and coping better where stress cannot be reduced, is the primary contribution that physicians can make. However, since stressors come from the broader environment as well, effectively dealing with stress also requires the cooperation of human resources managers in companies and policy makers in government.

With regard to individual level protective interventions it is obvious that the findings in the literature suggest a number of ways in which stress levels could be reduced, contributing to a reduction in the risk of CVD as well as to general health.

Relaxation training

There are several studies which point to the potential of relaxation training in the reduction of coronary heart disease risk factors (Patel et al., 1985). Methods for achieving relaxation include transcendental meditation, biofeedback training or other kinds of relaxation, but the actual method used is unimportant; the significant factor is a reduced degree of arousal (or stress) in everyday life situations. For the maximum effectiveness, the relaxation method should become a lifelong habit. It might be most effective combined with psychosocial intervention.

Sleep hygiene

Awareness of the importance of sleep is of great potential importance. Good health requires both enough sleep and enough deep sleep for the body to regenerate, particularly when the person is under stress. Relatively simple pieces of advice in this field could have quite substantial effects on the tolerance to stress. Such advice could be related to room temperature, activities preceding sleep, ingestion of coffee etc.

Lifestyle

A number of pieces of advice relating to lifestyle are important in stress prevention, although these will not be discussed in detail here. Physical activity, diet with adequate intake of calories and vitamins, avoidance of extensive ingestion of coffee and alcohol etc. are examples. Policies that make it easier for individuals to exercise regularly and eat a healthy diet are called for.

Reduction of type A behaviour and hostility

These are usually programmes that subjects with manifest coronary heart disease are motivated to follow. The programmes are mostly organised in groups at regular intervals – every week or every other week – and could last for many months. Such programmes are often difficult to introduce in groups without illness. But they could be introduced in special groups that are motivated for other reasons.

Improved social support

Although no controlled intervention studies have shown clear effects, there is substantial support for the importance of social support in stress prevention (Berkman and Glass, 2000). This could be an important goal for communities. It should be borne in mind that the definition and the significance of social support may be different for women than for men.

Improved work environment

Interventions should aim at an improved relationship between psychological demands on the one hand and decision latitude and social support on the other hand. This could be achieved in several ways, for instance via education of managers or through programmes aiming at the whole organisation (for instance Participation Activation Research, see Bond and Bunce, 2001 and Kristensen, 2005). They should also aim at an improved relationship between effort and reward (see Kompier et al., 2000). Finally shift work schedules could often be improved (from "counterclockwise" to "clockwise"), and for groups with high demands for attention or fear avoidance, long work weeks should be avoided (Belkic et al., 1994).

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MISSION STATEMENT

The European Heart Network is a Brussels-based alliance of heart foundations and other concerned non-governmental organisations throughout Europe committed to the prevention of cardiovascular disease in 26 countries across Europe.

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French Federation of Cardiology
Georgian Heart Foundation
German Heart Foundation
Heart to Heart League, Slovakia
Hellenic Heart Foundation, Greece
Hungarian Heart Foundation
Icelandic Association of Heart Patients
Icelandic Heart Association
Irish Heart Foundation
Italian Association against Thrombosis (ALT)
Italian Heart Foundation
Lithuanian Heart Association
National Heart Forum, UK
Netherlands Heart Foundation
Northern Ireland Chest, Heart and Stroke, UK
Norwegian Association of Heart and Lung Patients (LHL)
Norwegian National Health Association, Council on Cardiovascular Diseases
Portuguese Heart Foundation
Slovenian Heart Foundation
Spanish Heart Foundation
Swedish Heart Lung Foundation
Swiss Heart Foundation
Turkish Heart Foundation