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# The Role of Stress in a Pathogenesis of CHD

Taina Hintsala<sup>1</sup>, Mirka Hintsanen<sup>1,2</sup>,  
Tom Rosenström<sup>1</sup> and Liisa Keltikangas-Järvinen<sup>1</sup>

<sup>1</sup>*IBS, Unit of Personality Work and Health Psychology, University of Helsinki*

<sup>2</sup>*Helsinki Collegium for Advanced Studies, University of Helsinki  
Finland*

## 1. Introduction

Stress has been commonly seen as a risk factor of diseases of major public health relevance including Type 2 diabetes and coronary heart disease (CHD). An influence of stress in their development has been considered a “well-known fact” even to the extent that a pathogenesis of those diseases has been widely attributed to stress. Empirical evidence is, however, somewhat conflicting. Even though studies showing an association between work stress and CHD are great in number, negative findings also exist. Thus, there is no consensus on the clinical importance of work stress in a development of CHD. Consequently, work stress is currently not included in the list of established risk factors of CHD ([www.americanheart.org](http://www.americanheart.org)).

There are, however, several reasons explaining the conflicting findings, and several aspects have been omitted in stress research. Even an assessment of stress is far from unambiguity. The present paper was taken with a purpose to highlight complicated associations between different kind of stress reactions and risk factors of CHD.

This review will capitalize on the longitudinal population based birth cohort study of the *Young Finns Study*. Here, the representative, population based sample of 3596 healthy subjects from six age cohorts have been followed for 30 years and monitored in 9 study phases in order to discover the lifelong development of risk factors of coronary heart disease. From the great multidisciplinary reservoir of risk factors available in the Young Finns settings, stress is the focus of the current paper.

In this chapter we focus on different types of stress, e.g. psychological, psychosocial, physiological stress and work stress. Special issues to be highlighted here are as follows: Do the origins of stress proneness lie in childhood? Is stress vulnerability inherited?, Which is worse in regard to health: chronic or acute stress?, Does stress really have health consequences? Do genetic predispositions explain an association between stress and its health outcomes? What are the problems with statistical analyses in epidemiological studies?

## 2. Coronary heart disease

Coronary artery disease (CAD) which gradually progresses to coronary heart disease (CHD) is still the leading cause of death in industrialized countries. According to World Health

Organization cardiovascular diseases are the number one cause of death globally. In 2004, cardiovascular diseases were globally the cause of death of 29% of all deaths. Of those deaths, approximately 7.2 million were due to CHD ([www.who.int/mediacentre/factsheets/fs317/en/index.html](http://www.who.int/mediacentre/factsheets/fs317/en/index.html)). In Finland, among the working aged population, in men there were 1218 and in women 231 deaths due to CHD in 2008 (<http://www3.ktl.fi/stat/>).

Atherosclerosis is the pathogenic process that underlies most cardiovascular diseases including CHD. Recently, a non-invasive technique such as an ultrasound measure of intima-media thickness has been developed to assess early stages of atherosclerosis. Carotid artery intima-media thickness (IMT) is a marker of subclinical atherosclerosis and increased IMT has been shown to predict CHD (O'Leary & Polak 2002).

Although the inherited, even a genetic disposition to CHD has been documented, CHD is seen as a lifestyle disease. Certain lifestyle factors may contribute to the manifestation of genetic disposition, and eventually have an effect on the onset of CHD. American Heart Association lists traditional risk factors for CHD: increasing age, male sex and heredity; smoking, high blood cholesterol, high blood pressure, physical inactivity and obesity (modifiable risk factors), and stress, alcohol and diet/nutrition as other risk factors of CHD. The traditional behavioural risk factors of CHD include smoking, alcohol consumption and physical inactivity. Behavioural and personality characteristics may be seen as lifestyle factors too, because they contribute to significant choices and decisions that individuals make during their lives. A systematic review of the epidemiological literature of prospective cohort studies, that is articles between 1966-1997 identify four psychosocial or behavioural risk factors of CHD: Type A behaviour, hostility, depression, psychosocial work characteristics, and social support (Hemingway & Marmot 1999). According to a prognosis of World Health Organization stressful life events and psychosocial stress will be the most detrimental risk factors for the development of cardiovascular diseases in the near future (<http://www.who.int/en/>).

In this chapter we introduce some recent findings about childhood and adolescent origins of stress, stress-health associations, e.g. temperament and early atherosclerosis (Hintsanen et al., 2009a), the association between chronic stress and preclinical atherosclerosis (Chumaeva et al., 2009a), and long-lasting chronic stress strengthening the physiological stress reactions in acute stress (Chumaeva et al., 2010a). Furthermore, the topic whether stress has implications for CHD risk and what are the potential mechanisms are discussed.

### 3. The Young Finns study

In the literature, The Bogalusa Heart Study and the Young Finns Study are the only population-based prospective follow-up studies that have examined cardiovascular disease and CHD risks since childhood that have collected psychological information. The collection of psychological information in the Bogalusa Heart Study continued until the end of 1980s, and since then the Young Finns Study has been collecting psychological data. Thus, the Young Finns data is worldwide quite unique and it makes possible to study psychological risk factors of CHD from childhood on.

The Young Finns Study is a multi-centre study which was carried out in five university cities in Finland which have medical schools (Helsinki, Kuopio, Oulu, Tampere and Turku), and in rural municipalities nearby (Fig. 1). The areas of Helsinki, Tampere and Turku

represented the west of the country, and the Kuopio and Oulu areas represented eastern Finland. The rural municipalities were chosen using the criteria of correspondence of industrial structure with average municipalities in the province, the age cohort being sufficiently large. The sample included an equal number of urban and rural populations in the area (Åkerblom et. al., 1991). To ensure equal and sufficiently large samples from east and west, and to include some communities in the extreme east, the sample size in Kuopio was twice that in other cities, with four instead of two rural municipalities included in the study (Åkerblom et al 1991). Two of the easternmost rural municipalities studied in the Kuopio area belonged to the province of North Karelia, where CHD morbidity and mortality among adults have been especially high (Menotti et. al., 1989). In 1980 the baseline study sample consisted of 4326 invited participants of which over 3500 children and adolescents aged from 3 to 18 participated (83.1%). The study included medical examinations and questionnaires (both self- and parent reports). These participants have had medical examinations and have filled questionnaires including demographic, socioeconomic/social and psychological information in the follow-up studies conducted in 1983, 1986, 1989, 1992, 1997, 2001, 2007 and 2011. The study design and the number of participants and the response rates at each data collection phases are outlined in Figure 2.

The participants have reported several aspects of their lives during 31 years, at several time points. These aspects include a wide range of CHD risk factors such as socioeconomic conditions, social life, health behaviour, dietary habits, environmental factors and personality.

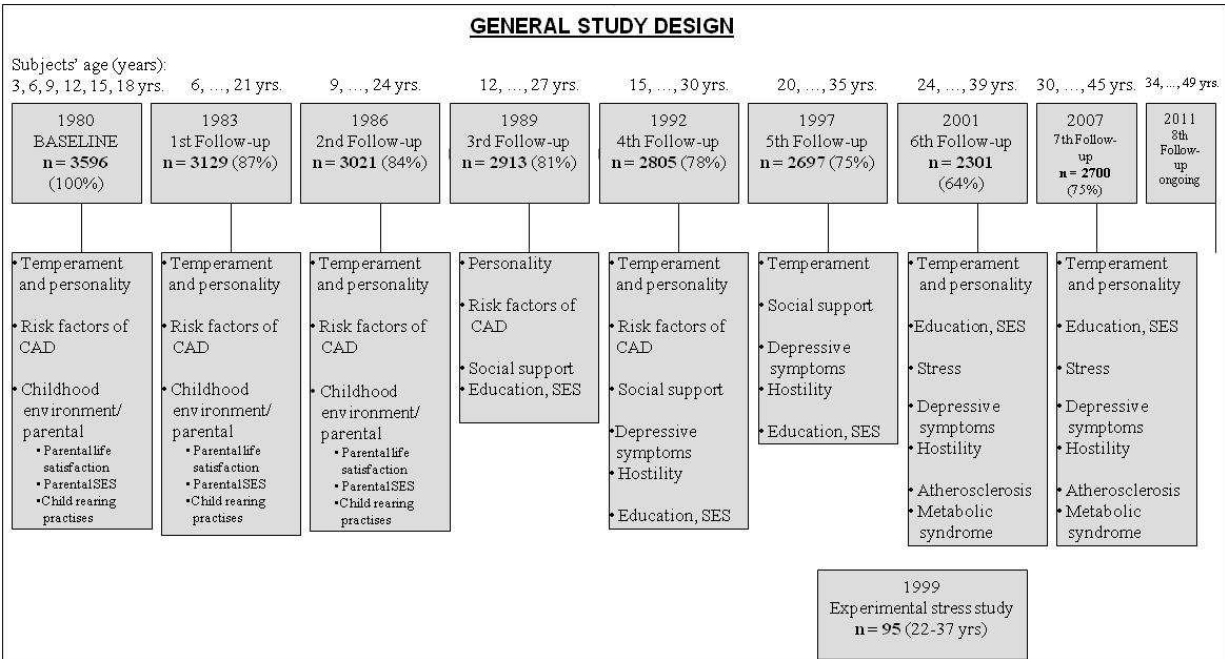


Fig. 1. The general study desing of the Young Finns Study.

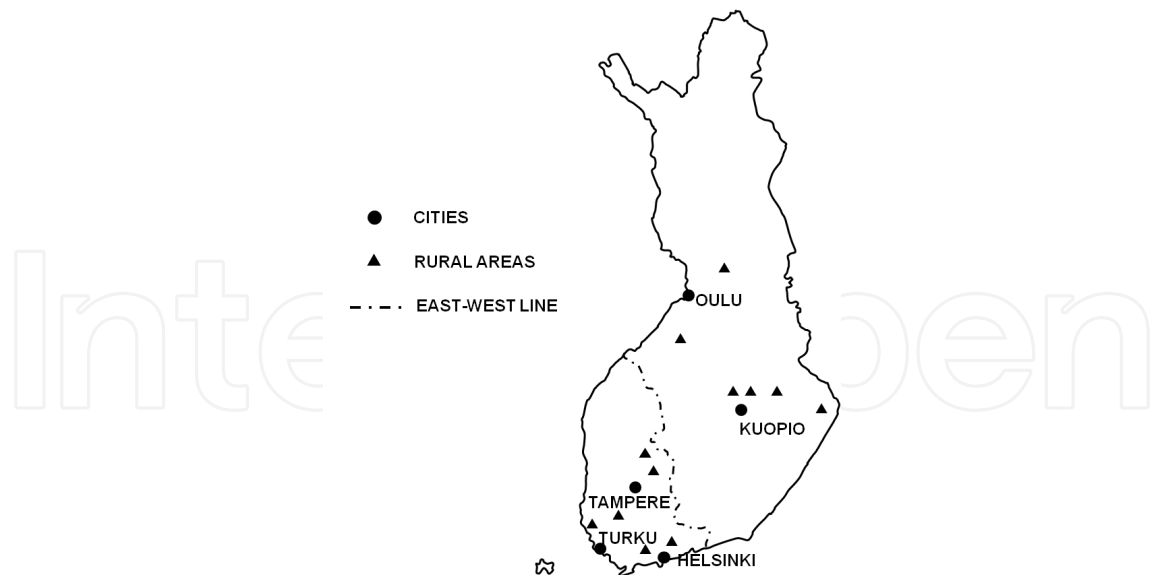


Fig. 2. The Young Finns Study: participating universities in Finland.

#### 4. Stress

The purpose of this chapter is to highlight complicated associations between different kind of stress reactions and risk factors of CHD. Generally the term stress refers to experiences of endangering one's physical or psychological wellbeing. Physiological stress refers to bodily adaptation processes and the maintenance of body's balance (McEwen 1998; Selye 1973). Selye (1973) defined stress as a function of elevated corticosteroid levels and used the term stress to refer to the effects of any agent that threatens the homeostasis of the organism. McEwen and Stellar introduced (1993) the term allostasis which refers to the body's ability to achieve stability. The allostatic load is assumed to be caused by frequent stress, lack of adaptation to repeated stress, and inability to shut down the allostatic response when the stress is over and inadequate response or dysfunction of the stress systems (McEwen 1998).

In the behavioural sciences, stress refers to a mental experience of distress caused by the evaluation of the imbalance between available personal resources (individual appraisals of stressful encounters) and environmental demands (e.g. stressful life events). Thus, psychological stress can be defined as a discrepancy between personal capacities and environmental demands (Lazarus & Folkman 1984). Somatic stress symptoms are related to both physiological and psychological stress (Lazarus & Folkman 1984; Lovallo 1997). The different types of stressors are likely to elicit divergent stress reactions. The multifaceted nature of stress and various sources of stress must also be taken into account. It is important to define the stress precisely in epidemiological studies. Consequently, stress has been determined here in terms of stressful life events, experience of chronic stress, experimentally induced mental and physiological stress reactions and work stress.

##### 4.1 Work stress

European Foundation for the improvement of living and working conditions (2007) reports that work stress is affecting more than 40 million individuals across the European Union, and is among the most often reported cause of illness by employees. Work stress has been



suggested to increase the CHD risk via several different pathways and mechanisms. Therefore it is important to focus also on psychosocial characteristics at work in regard to cardiovascular health. The work stress models that are presented here have been used extensively in studies of occupational and cardiovascular health (Belkic et. al., 2004; van Vegchel et. al., 2005).

Theories of work stress focus on various aspects in the work environment. Contemporary models on work stress include factors that are long-term harmful stressors at work. There are several work stress models, but the scientifically most tested concepts include The Job Demands-Job control Model (Karasek & Theorell 1990) and the Effort-Reward Imbalance (ERI) model (Siegrist et. al., 2004). More recently organisational justice has been hypothesized to form an important source of stress at work (Elovainio et. al., 2010; Kivimäki et. al., 2005).

The two-dimensional Job Demands-Job Control model involves work-related aspects of job demands and job control. Job demands refer to time pressures and an excessive work load, and job control involves employees' decision latitude and opportunities to use social, organisational and personal resources in their work. The model proposes that employees who have high job demands together with low job control are suffering from job strain, and if prolonged, have increased risk of stress-related diseases. The ERI model of work stress is based on social exchange theory and it has broadened the view from proximal work aspects into descriptive and evaluative information on job demands, i.e. efforts, and more distant aspects of work, i.e. rewards. Efforts denote quantitative and qualitative load, and increase in total load at work. Rewards refer to financial reward, esteem reward, reward related to promotion aspects and job security (Siegrist et al 2004).

Research on the psychosocial health determinants has recently extended the focus also to organizational justice, that is, social relations, decision making and managerial procedures at work (Colquitt 2001; Kivimäki et. al., 2005). Organizational justice can be defined as "the extent to which employees are treated with justice at their workplace" (Colquitt 2001; Moorman 1991). Organisational justice includes four components: 1) procedural justice, 2) interpersonal justice, 3) informational justice and (4) distributive justice. Procedural justice refers to being able to express your views and feelings during organisational procedures, perceiving that they have been consistently applied. Interpersonal justice denotes aspects of supervisors' behaviour, i.e. have they treated the person with respect and dignity. Informational justice consists of communicating and giving details about the decisions. Distributive justice refers to the perception of whether outcomes at work reflect the effort one has put into work and whether the outcome is appropriate.

## **5. Do the origins of stress-proneness lie in childhood?**

It may be suggested that origins of one's stress proneness lie in childhood. This has not been studied a lot in humans, but rationale for this suggestion has been derived from animal studies. Several studies conducted on rats and nonhuman primates have shown that lack of nurturing behavior does affect the stress systems of the pups so that pups that have received less nurturing develop altered physiological stress responsiveness and show increased behavioral stress reactivity in adulthood (Caldji et. al., 1998; Coplan et. al., 1996; Ladd et. al., 1996; Liu et. al., 1997).

The effect of maternal care to the development of offspring stress responsiveness has been examined with various research designs. For example, by handling the pups it is possible to

increase the nurturing behaviors performed by the mother such as licking and grooming, and this makes it possible to compare pups that have received high nurturing by the mother and pups who have received normal care (Liu et al 1997). Studies have also used maternal separation for instant by comparing the physiological stress responsiveness of pups that have not been separated and pups that have been separated from their mother for varying periods of time (Stanton et. al., 1988). However, this kind of design might be suspected to reflect effects of food deprivation rather than deprivation of maternal nurturing. To examine whether this is the case, a study by Stanton, Gutierrez and Levine (1988) specifically examined whether increased stress responsiveness is related to lack of maternal nurturing or to lack of nutrition offered by the lactating mother. Their results showed that the association was partly dependent on the age of the examined rat pups so that in younger ages (12 and 16 days of age), lack of maternal nurturing increased stress reactivity, whereas when the pups grew somewhat older (20 days of age), the lack of maternal nurturing as well as the lack of nutrition increased stress reactivity assessed as elevated corticoid levels in response to novelty situation (Stanton et al 1988). Based on these results, it seems that maternal nurturing has an independent effect that cannot be explained by food deprivation.

Still other design was used by Coplan and colleagues (1996) who compared offspring of mother monkeys (bonnet macaques) who had differing conditions in which they foraged for food. One group of mothers foraged in uncertain conditions (the amount of needed foraging varied) whereas the other group foraged in predictable conditions (the amount of needed foraging was either constantly low or constantly high) (Coplan et al 1996). As it has been shown that unpredictable need for foraging lowers the amount of grooming the mother directs towards the monkey infants (Rosenblum & Paus 1984), comparing different foraging groups allows to compare the effects of higher and lower maternal nurturing behaviors.

In general, the studies conducted on animals that have examined effects of maternal nurturing to the stress responsiveness of the infants in their adulthood, have shown that those infants who have received less nurturing from their mothers show various alterations in their hypothalamic-pituitary-adrenal (HPA) -axis functioning later in life (Caldji et al 1998; Coplan et al 1996; Liu et al 1997). For instance, in response to acute stressors, offspring have shown changed physiological stress reactivity measured with plasma levels of adrenocorticotrophin hormone (ACTH), levels of corticosterone, glucocorticoid feedback sensitivity, and levels of hypothalamic corticotrophin-releasing hormone messenger RNA (Liu et al 1997). Furthermore, stable increases in corticotrophin releasing factor (CRF) in the cerebrospinal fluid have been found in grown up offspring of less nurturing mothers (Coplan et al 1996). Also changes in behaviour are observable, and offspring of less nurturing mothers show higher rates of behaviours reflecting stress (e.g. fearfulness) (Caldji et al 1998).

There are also several other findings that show that changes in stress reactivity in response to lower maternal nurturing can be found also in humans. For instance, Repetti, Taylor and Seeman (2002) have reviewed the literature and concluded that childhood unsupportive family relations (e.g. high rate of conflicts in the family and low nurturing) affect physiological stress responsiveness of HPA-axis functioning and sympathetic-adrenomedullary (SAM) functioning as well as emotion regulation and coping with stress. However, long-term prospective studies are rare.

## 6. Is stress vulnerability inherited?

Temperament refers to biologically rooted, partly inherited, relatively stable individual differences in reactivity to stimuli (Cloninger et. al., 1993; Gray 1991; Lewis & Haviland 1993; Strelau 1998). The inheritance of stress refers here to an innate temperament. Rationale is as follows: temperament a) has a biological basis, b) is highly inherited, and c) explains what one experiences as a stress and partly determines what the health consequences are. The common assumption in several temperament theories is that temperament plays important role in moderating stress (Strelau 1998). Temperament traits are closely related to emotions that have been suggested to be a possible source of stress-related individual differences (Lovallo 1997). Temperament is considered to be an important determinant in what one identifies as a stressor, a state of stress, in how one copes with stress and therefore also the physiological consequences of stress (Strelau 1998). Temperament may explain a perception of stress and may predispose to negative emotional stress reactions.

## 7. Acute stress vs. chronic stress

Acute stress refers to a very short-time stress that can both be positive (eustress) and more distressing experience such as daily hassles or stressful encounters in day-to-day life. Chronic stress is the type of stress that is ongoing for a longer period of time and often feels unmanageable. Both acute and chronic stress may be detrimental to health (Lovallo 1997). It is not clear which is more detrimental to health, acute or chronic stress. What is likely that they may have different effects on health.

Acute stress is a normal adaptive reaction to threat of the sympathetic-adrenal-medullary axis (SAM) releasing catecholamines and the hypothalamic-pituitary-adrenal (HPA) axis secretion of glucocorticoids (Sapolsky et. al., 2000). Even though acute stress reaction is adaptive and necessary, it may have detrimental influences on cardiac health. Acute stress may trigger cardiac events or lead to sudden death (Culic 2007; Hemingway et. al., 2001).

Chronic stress is likely to influence the autonomic nervous system function, and may alter the endocrine system and the immune system function. If a person is exposed to chronic stress, the SAM and HPA axis are continuously over-activated or in imbalance, and overcompensation or collapse of these systems may leave the individual susceptible to stress-related diseases (Korte et. al., 2005). Prolonged secretion of epinephrine, norepinephrine and cortisol, i.e. primary stress mediators, may affect the stress system so that their ability to protect the organism is compromised and instead starting to damage the brain and the body (McEwen 2008). The secondary outcomes of the wear and tear condition processes are the metabolic parameters such as insulin, cholesterol, triglycerides which may reach sub-clinical level at this stage of stress. The final stage of stress may include the wear and tear of the body, i.e. allostatic exhaustion (McEwen 1998; 2008).

## 8. Work stress

Several epidemiological studies have shown the association between work stress and CHD risk (Belkic et al 2004; Kivimäki et. al., 2006; van Vegchel et al 2005). Job strain has been suggested to be a risk factor for CHD and cardiac events (Belkic et al 2004; Kivimäki et. al., 2002; Kivimäki et. al., 2006). A review of 45 empirical studies on effort-reward imbalance



between 1986-2003 reports that the extrinsic effort-reward hypothesis (high effort combined with low rewards increase disease risk) has shown a good explanatory power for the incidence of CHD (van Vegchel et al 2005).

Previous studies report lower levels of organisational justice to be associated with lower wellbeing, higher self reported morbidity, higher medically certified absence from work, and increased mental health problems (Elovainio et. al., 2000; Elovainio et. al., 2001; Kivimäki et. al., 2003; Kivimäki et. al., 2005). Injustice at work has been related to impaired cardiovascular regulation among women (Elovainio et. al., 2006b), and cardiovascular mortality (Elovainio et al 2006b). Low organizational justice has been reported to be a risk to the health of employees (Elovainio et. al., 2006a). Furthermore, it has been reported that employees who experience high organisational justice at work had lower risk of incident CHD than those with low or an intermediate level of justice (Kivimäki et. al., 2005).

When studying work stress-CHD risk associations, it is important to examine the role of third variables such as pre-employment origins of work stress. We have examined the childhood origins of work stress which is a novel perspective in work stress research. Furthermore, it is also important to extend work stress research towards taking individual differences and genetic influences into account.

## **9. Does stress have implications for CHD risk and what are the potential mechanisms?**

Showing the causal link between stress and the outcome requires evidence and knowledge about the potential mechanisms. The research of the Young Finns Study provides epidemiological and experimental evidence on the importance of stress in early atherosclerosis and in the pathogenesis of CHD, and also shows that the associations between stress and cardiovascular risk are complicated.

Stress may influence health via several different pathways, i.e. alterations in autonomic nervous system, neuroendocrine activity, immune system functions, behavioral and cognitive functions (Lovallo 1997). Prolonged stress may alter the function of autonomic nervous system, neuroendocrine functions and inflammation systems (McEwen 1998; Sapolsky 1996; Sapolsky et al 2000), and it may affect individuals' health-behaviour in terms of increased smoking and alcohol consumption, and decreased physical activity, and may increase anxiety, depression and psychological distress and include alterations in memory functions and attention (Hemingway & Marmot 1999; Lovallo 1997). Being exposed to chronic stress may lead to different types of health problems such as mental disorders, vital exhaustion, burnout and increase of CHD disease risk via several different pathways (Lovallo 1997).

### **9.1 Epidemiological evidence**

The findings presented in this chapter are mainly from the Young Finns study (YFS) and they focus on early atherosclerosis. The results of a smaller sample of men describe the associations between psychological factors and hormonal variables and Insulin resistance syndrome risk factors.

In the YFS, an association between job strain and IMT has been documented among men aged 32.3 years on average (Hintsanen et. al., 2005). This implies that among men job strain

may be linked to atherosclerosis in its early non-symptomatic stages. A recent longitudinal study on the association between job strain and IMT reports that large decreases in job strain from 2001 to 2007 in men was associated with slower progression of IMT and decreases in both job control and demands (a change towards passive jobs) were associated with greater IMT progression (Rosenström et al., 2011). These results imply that temporal changes in job demands and control are linked with IMT.

Our research has focused in three temperament theories: Gray's neurobiological model of temperament, Cloninger's psychobiological theory of temperament, and the EAS theory of temperament by Buss and Plomin. Gray's temperamental model assumes three fundamental systems with independent neurobiological mechanisms in the mammalian central nervous system (CNS): the behavioral inhibition system (BIS), the behavioral approach system (BAS) and the fight/flight system (FFS). The BIS is activated by aversive stimuli and is assumed to cause behavioral inhibition, and increase in attention levels and negative affects. The BAS is primarily activated by appetitive stimuli causing approach behavior and positive affects. There are individual differences in the sensitivity or functioning strength of these systems. Thus, some individuals are more prone to react to incentives and to experience positive affects, that is BAS sensitive, while some are fixed to threats in the environment and more likely to experience negative affects than others (Corr 2008; Gray 1991).

Cloninger's psychobiological theory of temperament, measured by temperament and character inventory (TCI) includes three genetically independent dimensions of temperament: novelty seeking (NS), harm avoidance (HA) and reward dependence (RD) (Cloninger et al 1993). Persistence (P) was added to the model a little bit later (Cloninger et al 1993). Novelty seeking, linked with dopaminergic activity, refers to tendency to respond strongly to novelty. High novelty seeking is characterized by exploratory behaviors, impulsivity, excitability and disorderliness. Harm avoidance, related to serotonergic activity, denotes that high harm avoidant persons are cautious, fearful, inhibited and prone to anxiety and fatigue. Reward dependence, associated with noradrenalin activity, refers to sensitivity to social cues, empathy and sentimentality. Persistence is a tendency to act persistently regardless of weariness and frustration, and high persistence is characterized by perseverance.

The emotionality-activity-sociability (EAS) theory of temperament focuses on broad temperament traits that are likely to be present in majority of situations (Buss & Plomin 1984). The temperament traits are negative emotionality, sociability and activity. Negative emotionality is characterized by tendency to get upset easily and equals to stress sensitivity. Sociability is a preference to be in a company of other people. Activity refers to the tempo of physical actions and vigor referring to the strength with which these actions are performed.

*Temperament and early atherosclerosis.* Temperament traits in terms of Cloninger's temperament theory explain between-individual variation in atherosclerosis (Hintsanen et al 2009a). Higher NS and RD, and lower HA were associated with preclinical atherosclerosis. The effect sizes of the associations found were comparable to those of traditional risk factors of CHD, which is an important finding. Novelty seekers are likely to seek for novel situations and environments, and via that encounter stressful situations continuously, i.e. be exposed to stress frequently. High RD persons seek for approval and have desire to please others, potentially even at the expense of their own wellbeing. Harm avoidant persons are characterised by stress-proneness and therefore a positive relation between high HA and higher IMT would have been expected. Stress reactions of highly

harm avoidant persons increase in experimental settings, but in real life, however, they may have successfully learned to avoid stressful situations and thus be less exposed to stress.

In women, childhood hyperactivity has been shown to predict IMT in adulthood (Keltikangas-Järvinen et. al., 2006). It was concluded that childhood temperament may directly contribute to the development on IMT in women. This association might partly be explained by different environmental expectations for boys and girls. The same temperament plays a different roles in boys and girls (Kerr et. al., 1997). The association between childhood hyperactivity and adulthood IMT among women might be due to that high hyperactivity in girls may enhance the misfit with the environment which, in turn, may be related to chronic stress (Keltikangas-Järvinen et. al., 2006).

We have found an association between active temperament and early atherosclerosis among men. The results of a study on emotionality-activity-sociability temperament and preclinical atherosclerosis showed that a highly active temperament may contribute to early atherosclerosis in men, and that body mass may mediate this association (Pulkki-Råback et. al., 2011).

*Chronic stress and cardiac responsiveness.* Endothelial dysfunction is a marker of atherosclerotic risk (Bonetti et. al., 2003), and arterial elasticity indicated by carotid arterial compliance (CAC) may be an additional indicator of early atherosclerosis (Anderson 2006). We studied the role of chronic stress, endothelial dysfunction and arterial elasticity in regard to IMT. Chronic stress was indexed by vital exhaustion which is a state of unusual fatigue, a loss of mental and physical energy and increased irritability (Appels et. al., 1987), and has been referred as an indicator of long-term mental stress (Ingles et. al., 1999). Endothelial dysfunction was indexed by brachial flow-mediated dilation (FMD), and carotid elasticity by CAC. A significant VE and FMD, and VE and CAC interactions on IMT were found in participants with the very lowest FMD and CAC. It was concluded that chronic stress may especially harmful if the endothelium is not working properly (Chumaeva et al 2009a). Chronic stress was negatively related to FMD, which may imply that chronic stress may contribute to endothelial dysfunction. A study on the possible sex differences in the combined effect of chronic stress with impaired vascular endothelium functioning and the development of early atherosclerosis showed a significant VE x CAC interaction on IMT among men. High VE level was related to higher IMT among those men with low CAC (Chumaeva et. al., 2010b). These results imply that vital exhaustion is a risk only if it has resulted in ineffective cardiac stress reactivity. Chronic stress may induce imbalance of the autonomic function which may be the mechanism linking vital exhaustion and cardiac responsiveness to an increased risk of atherosclerosis.

Chronic stress in terms of major stressful life events and vital exhaustion has been related to arrhythmic events (Hintsa et. al., 2010c). A history of stressful life events and prolonged mental stress have been associated with arrhythmic events among subjects who are genetically predisposed to cardiac vulnerability (a sample of molecularly defined patients with long QT syndrome). In this group of patients the interaction of a gene defect and the environmental loading may contribute to the manifestation of arrhythmic events.

*Psychological factors and IRS.* Stress may be a trigger for the neuroendocrine and metabolic abnormalities characteristic to the metabolic syndrome. It has been shown that chronic stress may exert effects on waist-hip -ratio (WHR) and on subsequent metabolic alterations.

Chronic stress is suggested to exert a pathophysiological effect on WHR, on alterations in insulin and lipid metabolism, in fibrinolysis and in blood pressure. Perceived stress modifies an association between neuroendocrine mechanisms and metabolic syndrome. The associations may be explained by HPA-axis dysfunction, that is, a failure to adrenal hypoactivity to prevent overshooting of reactions to stress (Räikkönen et. al., 1997).

Psychological factors may explain a proportion of HPA-axis responses that are related to Insulin resistance syndrome (IRS). Type A behavior was related to a high level of mean basal ACTH and a low level of cortisol response to ACTH stimulation after dexamethasone suppression. Hostility was linked to a high level of mean basal cortisol and a high cortisol in cortisol/ACTH -ratio. Vital exhaustion that indexes chronic stress was related to a low level of mean basal ACTH and a decreased ACTH in relation to cortisol (Keltikangas-Järvinen et. al., 1997; Keltikangas-Järvinen et. al., 1996b). Stress modulated adrenal responsiveness may partly explain the IRS risk, and the risk of atherosclerosis, too. Chronic stress and stressful life-style have been related to the IRS (Räikkönen et. al., 1996b). Chronic stress in terms of vital exhaustion, and a stressful life-style (Type A behavior, hostility and anger) were associated with hyperinsulinemia, hyperglycemia, dyslipidemia, hypertension, and increased abdominal obesity. The secondary outcomes of allostatic load include metabolic, cardiovascular and immune parameters' alterations and potential to reach sub-clinical levels of these (McEwen 1998; 2008; McEwen & Stellar 1993). Therefore it is important to further investigate the role of stress-related personality and behavioral factors in regard to metabolic alterations.

*Psychological factors and HPA-axis responses.* The studies presented in this paragraph have been conducted among middle-aged male managers who responded questionnaires, participated in laboratory analyses, and were clinically examined in Helsinki University Central hospital (n=64-90). Results of a study on the relationships between the pituitary adrenal hormones, insulin and glucose in regard to chronic stress showed that basal ACTH level during oral glucose tolerance test was positively related to the cortisol response to ACTH at 60 minutes, the fasting insulin level, and the insulin to glucose ratio among chronically stressed men (Keltikangas-Järvinen et. al., 1998).

A neuroendocrine pattern characterized by an elevation in cortisol response to ACTH stimulation and dominance of cortisol in the ratio of mean basal cortisol level to mean basal ACTH level denoting a defeat type of reaction to stress differentiated borderline hypertensive men from normotensive men (Räikkönen et. al., 1996a). The results may imply that the variance shared by chronic stress, emotional distress and pituitary-adrenocortical hormones could be the mechanism by which stress influences and increased risk for hypertension.

Author, year	Study focus	Main findings
Hintsanen et. al., 2005	IMT: job strain and social support	In men, job strain was related to higher IMT.
Rosenström et al., 2010	IMT and job strain (2001 and 2007)	An association between job strain and IMT in 2001 among men. In men with large decreases in job strain-slower progression of IMT.
Hintsanen et. al., 2009a	IMT and Cloninger temperament	Higher NS and RD, and lower HA was associated with IMT.
Keltikangas-Jarvinen et. al., 2006	IMT and childhood temperament	In women, childhood hyperactivity predicted adulthood IMT.



Author, year	Study focus	Main findings
Pulkki-Råback et. al., 2011	IMT and EAS temperament	A highly active temperament may contribute to early atherosclerosis in men, and that body mass may mediated this association.
Chumaeva et. al., 2009a	IMT and chronic stress (VE) and endothelial dysfunction (FMD)	Significant VE and FMD, and VE and CAC interactions on IMT were found in participants with the very lowest FMD and CAC.
Chumaeva et. al., 2010b	IMT and chronic stress (VE), flow-mediated dilation (FMD), Carotid elasticity (CAC)	In men, a significant VE x CAC interaction on IMT. High VE level was related to higher IMT among those men with low CAC.
Hintsä et. al., 2010c	Arrhythmic events and chronic stress	A history of stressful life events and prolonged mental stress are associated with arrhythmic events in LQTS patients. The association between stressful life events and arrhythmic events was independent of age, sex, specifically focused drugs and LQTS subtype.
Räikkönen et. al., 1997	IRS and chronic stress (VE)	Chronic stress exerted effects on WHR and on subsequent metabolic alterations which denote a chance of adrenal steroid biosynthesis.
Keltikangas-Järvinen et. al., 1996b	IRS and psychological factors	A link between VE-anger out and net-increment of cortisol and the IRS.
Räikkönen et. al., 1996b	IRS and stress inducing life style (Type A behaviour, hostility and anger)	Chronic stress in terms of vital exhaustion, and a stressful life-style (Type A behavior, hostility and anger) were associated with hyperinsulinemia, hyperglycemia, dyslipidemia, hypertension, and increased abdominal obesity.
Keltikangas-Järvinen et. al., 1998	HPA-axis and chronic stress	Basal ACTH level during OGTT was positively related to the cortisol response to ACTH at 60 minutes, the fasting insulin level, and the insulin to glucose ratio among exhausted men.
Keltikangas-Järvinen et. al., 1997	HPA-axis responses and Type A behaviour (TABP), hostility, chronic stress (VE)	TABP was related to a high level of mean basal ACTH and a low level of cortisol response to ACTH stimulation after dexamethasone suppression; Hostility was related to a high level of mean basal cortisol and a high cortisol in cortisol/ ACTH ratio, and VE was related to a low level of mean basal ACTH and a decreased ACTH in relation to cortisol.
*Räikkönen et.al., 1996a	HPA-axis and Chronic stress (VE), anger	A neuroendocrine pattern characterized by an elevation in cortisol response to ACTH stimulation and dominance of cortisol in the ratio of mean basal cortisol level to mean basal ACTH level denoting a defeat type of reaction to stress differentiated borderline hypertensive men from normotensive men.

Table 1. Summary of results of the epidemiological studies.



## 9.2 Experimental studies

In the series of our studies on experimental stress we have found that psychological factors are related to experimentally induced stress. The typical psychological stressors in the laboratory are an acoustic startle probe, a mental arithmetic task, and a public speaking task. The experimental stressors in the laboratory in our studies were a mental arithmetic (the three best participants would be awarded a prize of \$40, appetitive task), and a startle and a reaction time tasks (aversive tasks). Exaggerated heart rate reactivity to stress may imply disease proneness. It has been suggested that heightened heart rate responses to stress may be a risk for development of atherosclerosis and coronary heart disease (Matthews, 1986, Krantz & Manuck, 1984). Temperament may also be important in regard to stress-related cardiac reactivity and may even predispose the individual to elevated risk profile of the metabolic parameters. Temperament refers to individual differences in arousability of behavioural and physiological systems. There are prominent individual differences in the mode of autonomic response to stress (Cacioppo 1994).

The self-reported emotions have been measured according to the Larsen and Diener (1992) circumplex model of affects (Larsen & Diener 1992). Emotions can be defined as action tendencies or action dispositions (Lewis & Haviland 1993). Two general dimensions of affects are valence (pleasant/unpleasant) and activation or arousal (Larsen & Diener 1992). The two-dimensional circumplex model of affect consists of eight sections which are: high/low activation, unpleasant/pleasant, activated/ unactivated unpleasant, and activated/unactivated pleasant. We have also used the Watson's and Tellegen's model of positive affectivity (PA) and negative affectivity (NA) to measure the general affective orientation during laboratory tasks (Watson et. al., 1988) in our studies.

Temperament may predispose the person to stress and negatively biased environmental and personal interpretations. In an experimental study it has been reported that temperament in terms of Gray's concept explains emotional reactions during laboratory stress (Heponiemi et. al., 2003). This model was used to structure the self-reported affects in our study. The experimental stressors in the laboratory were a mental arithmetic, a startle and a reaction time tasks. The main finding was that BIS sensitivity was related to activated unpleasant affects (e.g. anxious, fearful, tense) during reaction time and startle tasks whereas BAS sensitivity was associated with activated pleasant affects (e.g. vigorous, lively) during mental arithmetic task. BIS sensitivity is, thus, likely to predispose a person to emotional distress in stressful situation regardless of the nature of the stressor, and also probably to a higher stress proneness. Thus, BIS sensitivity may increase one's stress vulnerability by predisposing the person to poor and inactive coping. BIS has been previously related to negative affectivity (Heponiemi et al 2003). BIS sensitivity may also influence person's focus of attention and predispose to bias towards negative cues of the environment because it has been suggested that high BIS-persons would be negatively biased in environmental interpretations.

We have found that temperament trait persistency (in terms of Cloninger's concept) interacted with chronic stress predisposing to a high physiological stress reactivity (Keltikangas-Järvinen & Heponiemi 2004). Chronic stress was indexed by vital exhaustion. Vital exhaustion was associated with parasympathetic withdrawal, i.e. low RSA magnitude, during stressful tasks in laboratory. Temperament trait persistence was likely to strengthen cardiac stress reactivity of exhausted women. Findings suggest that background stress may

decrease one's capacity to cope with acute stress and be related to continuous physiological stress.

According to Gray's theory, BAS sensitivity refers to strong reaction to incentives and thus BAS is assumed to primarily be activated by appetitive stimuli such as reward and termination of punishment (Gray 1991). We found that BAS sensitivity was related to heart rate reactivity and parasympathetic withdrawal during the tasks (Heponiemi et. al., 2004). The relationship between BAS temperament and cardiac reactivity might be mediated by the parasympathetic nervous system. HR expresses the balance between the parasympathetic and sympathetic nervous system. Normal parasympathetic control of heart is suggested to promote good health, may protect the heart and dampen the sympathetic reactions to stress (Porges 1992) whereas low parasympathetic control of HR has been associated with cardiovascular diseases (Tsuiji et. al., 1996).

Temperament in terms of Cloninger's concept, that is HA, has been related to chronic stress, and when associated with vital exhaustion, likely to predispose negative affects when accompanied by exhaustion (Heponiemi et. al., 2005). The level of vital exhaustion among healthy persons was related to unpleasant affects such as sadness, fear, anxiety and anger. In other words, the participants with high level of vital exhaustion felt more tense, fearful, anxious, sad, depressed, angry and irritated during stress, and less lively than participants with low levels of vital exhaustion. Furthermore, inherited temperament may increase proneness to exhaustion and predispose to negative affects when feeling exhausted. The results imply that temperamental tendency to perseverance combined with stressful environmental loading may predispose to exhaustion. Temperament may predispose an exhausted person to negative affects and lead to individual differences in stress vulnerability.

Cloninger's psychobiological model of temperament and character postulates that each of the temperament dimensions is associated with a specific emotional experience. We tested this assumption and found that NS was associated with dullness during monotonous and aversive situations and with a higher level of pleasantness during the initial baseline period and the appetitive situation. HA was associated with higher levels of fear and unpleasant emotions and lower levels of positive emotions, depending on the situational cues. The study provides support for the validity of Cloninger's temperament dimensions as predictors of emotional responses during different challenges. Especially, novelty seeking and harm avoidance appear to have a significant influence on emotional experience (Puttonen et. al., 2005).

Temperament in terms of Cloninger's concept is related to a perception of stress during experimentally induced stress (Ravaja et. al., 2006). HA was consistently associated with high anticipated threat prior to stressors and high perceived stress after the stressors. In addition, the interaction of HA and NS predicted threat appraisals prior the task. Low HA and high NS was associated with higher threat before the social task (public speech). Individual differences in perceived threat may be important because it is assumed that the primary appraisal of threat affects psychological and physiological responses to stressors (Lazarus & Folkman 1984).

Novelty seeking temperament has been associated with higher IMT (Hintsanen et. al., 2009b). Cardiac stress reactivity and recovery was studied among extremely high and extremely low scorers of novelty seeking. We examined whether novelty seeking is

associated with cardiac reactions to a laboratory challenge. The results suggest that, that high novelty seekers may be more stress resilient because they might have faster cardiac recovery after stress (Hintsanen et. al., 2009b).

A study of hemodynamic and other autonomically mediated responses to mental stress in laboratory and the parameters of IRS among adolescent boys showed that a high level and an increasing trend of heart rate (HR) and finger blood volume (FBV) were related during challenging tasks (Keltikangas-Järvinen et. al., 1996a). Automatically mediated physiological responses (HR, HRV, FBV and skin conductance level, SCL) to experimentally induced stress are related to serum insulin level and other parameters of IRS in adolescent boys. The finding suggests that trends of psychophysiological responses to task-induced stress implicate important individual differences in stress modulation. In addition, results imply a relationship between stress-induced sympathetically mediated physiological responses and the metabolic and anthropometric parameters constituting IRS in healthy adolescent boys.

Individuals differ widely in the extent to which they are prone to experience normal daily challenges as positive or negative. Watson's and Tellegen's model of positive affectivity (PA) and negative affectivity (NA) was used to measure the general affective orientation during laboratory tasks (Watson et al 1988). PA included emotions such as active, enthusiastic and energetic, and NA refers to being distressed, fearful and nervous. A study examining the relationship between PA and NA to autonomic cardiac reactivity during laboratory tasks reports that participants with high levels of PA during varying laboratory tasks exhibited high parasympathetic reactivity and heart rate reactivity (Heponiemi et. al., 2006). However, against expectations, high levels of NA were not related to sympathetic arousal. It was concluded that cardiac reactivity may be associated with positive involvement and enthusiasm, and thus, should not be automatically considered as pathological.

Acute mental stress may contribute to the cardiovascular disease progression via autonomic nervous system controlled negative effects on the endothelium. We examined the interactive effect of acute mental stress-induced cardiac reactivity/recovery and endothelial function on the prevalence of carotid atherosclerosis. The results showed a significant interaction of FMD and cardiac RSA recovery for IMT, and a significant interaction of FMD and pre-ejection period (PEP). P recovery for IMT. Among participants with low FMD, slower PEP recovery was related to higher IMT. Among individuals with high FMD, slow RSA recovery predicted higher IMT. It seems that the development of endothelial dysfunction may be one possible mechanism linking slow cardiac recovery and atherosclerosis via autonomic nervous system mediated effect. Cardiac recovery plays a role in progression of atherosclerosis in persons with high and low FMD. The role of sympathetically mediated cardiac activity seems to be more important in those with impaired FMD, and parasympathetically mediated in those with relatively high FMD (Chumaeva et al 2010a; Chumaeva et. al., 2009b).

High parasympathetic reactivity during stress is considered as appropriate stress response whereas an inability to suppress parasympathetic tone is related to experienced stress and stress vulnerability (Porges 1992). When considering the potential mechanisms (summary over all our findings including the temperament-related experiments) between stress and CHD risk slow cardiac recovery is of high importance. It seems that the important role of stress in CHD risk is played rather by parasympathetic underactivity than sympathetic overactivity.

Author, year	Study focus	Main findings
Heponiemi et. al., 2003	Self-rated affects and BIS-BAS temperament (n= 95)	BAS was related to pleasant affects with an especially great increase of activated pleasant affect (vigorous, peppy, lively) during an appetitive task. BIS was related to unpleasant affects with a great increase of activated unpleasant affects (anxious, fearful, tense) during an aversive task.
Keltikangas-Järvinen et. al., 1996	Cardiac reactivity, chronic stress (VE) and temperament (n=76)	Chronic stress was related to parasympathetic withdrawal. Chronically stressed women expressed the highest level of physiological reactivity. Among the chronically stressed the initial parasympathetic tone had no effect whereas in the non-chronically stressed parasympathetic reactivity was greatest when initial parasympathetic tone was high.
Heponiemi et. al., 2004	Cardiac autonomic stress profiles and BIS-BAS temperament (n=65)	BAS was related to HR reactivity and parasympathetic withdrawal during the tasks.
Heponiemi et. al., 2005	Affects, chronic stress and temperament (n=76)	Chronic stress was related to unpleasant state affects other than state fatigue. Temperament modified the relationship between chronic stress and affects. Chronic stress was related to harm avoidance.
Puttonen et. el., 2005	Affective responses during challenge and temperament	NS was associated with dullness during monotonous and aversive situations and with a higher level of pleasantness during the initial baseline period and the appetitive situation. HA was associated with higher levels of fear and unpleasant emotions and lower levels of positive emotions.
Ravaja et. al., 2006	Threat, stress and performance appraisalsand temperament (n= 97)	Temperament traits are related to threat, stress and performance appraisals. HA was related to high anticipated threat prior to the stressors.
Hintsanen et. al., 2009b	Cardiac stress reactivity and recovery and temperament (n= 29)	High novelty seekers may be more stress resilient because they had faster cardiac recovery than others.
Keltikangas-Järvinen et. al., 1996a	IRS parameters (insulin, HDL, TG, SBP, SSF, STR) and mental stress (n=48)	Automatically mediated physiological responses (HR, HRV, FBV and SCL) to experimentally induced stress are related to serum insulin level and other parameters of IRS in adolescent boys.
Heponiemi et. al., 2006	Cardiac reactivity, facial muscle movements and positive and negative affects (n=77)	Experiencing positive affects was related to more pronounced parasympathetic, heart rate, and orbicularis oculi reactivity.
Chumaeva et. al., 2009b	IMT and chronic stress (VE), cardiac stress reactivity and recovery (n=69)	Among the highly exhausted men aged 28-37, lower HR reactivity was related to greater IMT.
Chumaeva et. al., 2010a	IMT and chronic stress (VE), cardiac stress reactivity and recovery, flow-mediated dilation (FMD) (n= 81)	A FMD and cardiac RSA interaction, and FMD and PEP recovery for IMT. Among participants with low FMD, slower PEP recovery was related to higher IMT. Among individuals with high FMD, slow RSA recovery predicted thicker IMT.

Table 2. Summary of the results of experimental studies.



### 9.3 Work stress

Several epidemiological studies have shown the association between work stress and CHD risk but there are also non-significant findings (Belkic et al 2004; Lange et al 2003; van Vegchel et al 2005). To explain conflicting findings, it is important to study whether the excess CHD risk among employees with high job strain is confounded by the pre-employment, personality and genetic effects. Therefore, we have focused on a novel perspective of examining effects of biological, psychological and socioeconomic factors in early life and adolescence, i.e. the period before entering work life, on perceptions of work stress and early atherosclerosis.

*Pre-employment factors and work stress.* We have examined whether pre-employment factors influence perceptions of work stress in adulthood. The socioeconomic conditions in childhood and adolescence may also contribute to perceptions of work stress in adulthood. Lower parental socioeconomic position (SEP), that is low paternal and maternal education and low family income, has been shown to predict increased job strain of the offspring in adulthood (Hintsa et. al., 2006). Part of the effect of low parental SEP on job strain and job control was mediated by participants' education. In addition, high parental SEP in the childhood family predicted higher rewards at work in adulthood among women (Hintsa et. al., 2007). We also found a strong positive relationship between parental SEP and the participants' educational attainment. A potential explanation for the predictive relationship between parental SEP and participants' education is that highly educated parents may offer good educational resources and through that enhance the educational attainment of their offspring. These findings indicate that pre-employment factors should be taken into account as potential confounders in future research on job strain-CHD risk associations.

Stressful childhood environments are suggested to contribute to later stress vulnerability. It has been shown that deficient nurturing attitudes in childhood predict offspring's work stress and low job control in adulthood (Hintsanen et. al., 2010). Deficient nurturing attitudes were indicated by intolerance of the mother towards the normal activity of the child, and low emotional warmth by the mother towards to the child. Deficient nurturance may also have indirect stress-inducing effects: the development of social skills has previously been related to child-rearing styles (Steelman et. al., 2002). Social skills are very important in the contemporary work as team work and personal networks have become increasingly important. Furthermore, inadequate social skills are likely to be sources of stress.

*Temperament and personality in perceptions of work stress.* Temperament traits may predispose the individual to experience work stress. Temperament in terms of Cloninger's concept is related to work stress, also to the components that are expected to reflect environmental loading by characteristics at work (Hintsa et. al., 2010a). Low NS and high HA predicted higher job strain. High NS, low HA and high P predicted higher long-term job control. Partly inherited, quite stable temperamental tendencies seem to contribute to job strain and its components. High NS seems to protect from job strain whereas high HA may predispose the individual to long-term work stress. HA may increase the number of stressful encounters at work because the individual predisposition to experience stress more easily. HA has previously been related to inefficient coping strategies such as rumination, resignation and escaping from stressful situations. Therefore, HA may lead to the selection of less efficient coping strategies and subsequently influence the time it takes to recover from stress.



Furthermore, it has been documented that temperament traits negative emotionality and sociability predict work stress. Negative emotionality refers to tendency to easily react with anger or fear and sociability a tendency to enjoy being in the company of others and to search for others company (Buss & Plomin 1984). The results have shown that higher negative emotionality and lower sociability systematically predict higher perceived job strain and effort-reward imbalance (ERI) (Hintsanen et. al., 2011).

*Type A behaviour – work stress.* Personality may also predispose a person to experience work stress. Type A behaviour is a stress–related personality type originally found by Friedman and Rosenman, and it has been related to risk of CHD. Type behaviour is characterized by aggressiveness, feelings of time urgency, competitiveness, easily aroused anger/hostility, and hard-driving elements. Ambition and competitiveness are very relevant traits in regard to work context. Type A persons have high need for control, and demanding and challenging situations are likely to elicit Type A behaviour. Of the components of Type A behaviour, high leadership was found to predict low long-term work stress while high hard-driving (taking things seriously, high responsibility and competitiveness,) predicted higher long-term work stress (Hintsanen et. al., 2010b). Furthermore, high aggression and eagerness-energy may predispose the employee to unfavourable effort-reward condition. Thus, it seems that different Type A behaviour components may have divergent influence on long-term work stress. These results suggest that more attention should be paid to individual factors and stress vulnerability in work stress research. Our findings strongly suggest that stress sensitivity may have childhood roots.

*Do pre-employment factors explain work stress-CHD risk association?* We have also aimed at examining the possible explanation for conflicting findings in work stress – CHD risk research. Therefore a series of studies examining the role of confounding factors in the work stress – CHD risk associations have been conducted. A prospective study on the contribution of biological, familial and socioeconomic risk factors in adolescence to the association between adulthood job strain and IMT reported that these pre-employment factors did not confound the relationship between job strain and early atherosclerosis in men (Kivimäki et. al., 2007). The findings of this study support the role of job strain as a risk factor for increased CHD risk.

In a study among Finnish men, it was found that personality trait leadership (willingness to always win, being selected as a leader in group activities, being socially active and having many hobbies), which is a component of Type A behaviour, attenuated the association between job strain and IMT (Hintsanen et. al., 2008). Low leadership in adolescence predicted higher job strain 15 years later, and this personality characteristic attenuated the association between job strain and IMT by 17% to nonsignificant. It was concluded that leadership component of Type A behaviour may represent a non-risk component of Type A behaviour, and that personality characteristics might also be important to include in work stress-CHD risk studies.

A study among British male civil servants showed that selected pre-employment factors such as family history of CHD, height, paternal education and social class, and number of siblings were related to increased risk for CHD. The significant hazard ratios (HR) for CHD found were 1.33 for family history of CHD, 1.18 for each quartile decrease in height, and 1.16 for each category increase in number of siblings. Psychosocial factors at work also

predicted CHD: the significant HR was 1.72 both for low job control and low organisational justice (Hintsa et. al., 2010d). However, the association between psychosocial factors at work and CHD incidence was largely independent of selected pre-employment factors.

Author, year	Study focus	Main findings
Hintsa et. al., 2006	Job strain and pre-employment factors	Lower parental SEP and higher parental life dissatisfaction independently of the number of siblings and educational level predicted job strain in adulthood 18 years later. The effects were partly mediated by participants' education.
Hintsa et. al., 2007	ERI and pre-employment factors	High rewards were predicted by high parental life satisfaction in men and by high parental SEP in women.
Hintsanen et. al., 2010	Job strain, ERI and maternal nurturing attitudes	Deficient emotional warmth in childhood predicted lower adulthood job control and higher job strain.
Kivimäki et. al., 2007	Job strain-IMT association and early risk factors	Pre-employment influences did not confound the association between job strain and IMT.
Hintsa et. al., 2008	Job strain-IMT association and pre-employment factors	Type A personality leadership component attenuated the association between job strain and IMT by 17% to non-significant. Pre-employment family factors had only modest effect on this association.
Hintsanen et. al., 2007	Job strain-IMT association and NRG-1	Job strain was associated with increased IMT among men with T/T genotype of NRG-1. A direct association between NRG-1 and IMT was found in women.
Hintsanen et. al., 2008	Job strain-IMT association and COMT	In men, job strain was associated with increased IMT in Val/Val carriers.
Hintsa et. al., 2010d	Psychosocial factors at work and CHD, and pre-employment factors	The association between psychosocial factors at work (low job control and organisational justice) and CHD was largely independent of the selected pre-employment factors. Increase in number of siblings, quartile decrease in height and family history of CHD predicted development of CHD.
Hintsanen et. al., 2010	Job strain, ERI and maternal nurturing attitudes	Deficient emotional warmth in childhood predicted lower job control and higher job strain in adulthood independently of age, sex, SES in childhood, maternal mental problems, and participants' hostility and depressive symptoms.
Hintsa et. al., 2010a	Long-term job strain, job control and job demands (6 years) and temperament	Low NS and high HA predicted higher long-term job strain. Higher NS, lower HA and higher P predicted higher long-term job control. Higher HA and higher P predicted higher long-term job demands.
Hintsanen et. al., 2011	Job strain, ERI and temperament	Higher negative emotionality and lower sociability systematically predicted higher perceived job strain and ERI. Activity predicted higher perceived ERI.
Hintsa et. al., 2010b	Job strain, ERI and personality (Type A behaviour)	High leadership (Type A dimension) predicted lower long-term job strain and higher long-term job control. High hard-driving predicted higher long-term job strain. High aggression, hard-driving and eagerness-energy predicted ERI.

Table 3. Summary of results of the work stress studies.

*Do genetic factors contribute to the association between work stress and IMT?* We have extended our research to clarify whether genetic predispositions explain an association between stress and its health outcomes. When trying to indentify groups at risk, examining whether an interaction between genotype and job strain may predispose to increased atherosclerotic processes is important. Another study reports that the association between job strain and greater IMT was found only among men with the T/T genotype of NRG-1 gene (Hintsanen et. al., 2007). Thus, the T/T genotype may be a marker of genetic susceptibility to the negative health effects of job strain on early atherosclerosis in men. Job strain has been related to higher IMT among men with Val/Val genotype of the catechol-O-methyltransferase (COMT) gene (Hintsanen et. al., 2008). This implies that Val/Val carriers may be at higher risk for negative health effects of job strain. It seems that the new study strategy of taking the genetic influences into account in identifying groups at risk for negative effects of work stress on cardiovascular risk may be worthwhile.

In sum, all the findings described here imply that although work stress seems to increase the CHD risk, there are some pre-employment factors that should be taken into account in work stress-CHD risk studies. In addition, this evidence should motivate the development of systematic intervention strategies for large-scale studies testing whether reducing work stress, giving employees a stronger say in decisions about their work and enhancing a righteous manner of treating employees at work would reduce CHD.

#### 9.4 Statistical problems

In this section we discuss shortly three general problems in statistical modelling of population data that we think are particularly central for behavioural epidemiology. If objective of science is to go beyond what can be seen with naked eyes, implication is that our observations depend on the instruments we use. One such instrument is the statistical model. Careful scrutiny of instrument limitations is every bit as important as the results they provide.

Linear models between behavioural variables are most frequently used in epidemiological studies, while psychological theories rarely assume independency or linearity, and also many of the above cited studies demonstrated some interaction effects. Questionnaire-based measures are typically thought to contain measurement error. Measurement error makes the estimation of nonlinear and interactive effects between variables notoriously hard (Carroll et. al., 2006; Griliches & Ringstad 1970). A lot of methodological development is warranted regarding modelling of general nonlinearities in this context, and either more precise measurements or more precise models of measurement error may be the prerequisite. Also, exponentially increasing amounts of data are required for the data-driven exploration of increasingly high dimensional interactions (Wasserman 2006). In below, we turn to problems that are present even when linear approximation is reasonable.

Often questionnaire-based measurement instruments entertain floor/ceiling-effect (inadequate sampling of true variation) and/or measurement error. Using a variable suffering from either one as a covariate in ordinary (and generalized) linear regression model can results in bias and false findings if the covariate is correlated with another 'independent' (predictor) variable (Austin & Brunner 2003; Brunner & Austin 2009; Carroll et al 2006). These problems could be addressed, along with those arising from more familiar overfitting problem (Babiyak 2004), from the point of view of combined cross-validation and partial least squares regression (Abdi 2010; Rosipal & Kramer 2006).

In this young field of science, often little is known about precise type of measurement error, and model assumptions rarely are firmly established. Partial least squares regression handles well a range of error types (Reis & Saraiva 2004) and cross-validation is able to control for errors in assumptions (Arlot & Celisse 2010). For these (and other) reasons this combination holds promise beyond many more commonly encountered choices of explorative data analysis.

Finally, both linear and nonlinear models typically assume that model holds over entire study population, whereas often only a part of the study population displays an effect. Genetic vulnerability and gene-environment interactions are clear examples of interacting variables that may not always be available in the data (Caspi et. al., 2010; Keltikangas-Järvinen & Jokela 2010). A statistical null finding can thus result from an inappropriate combination of heterogeneous groups instead of the lack of association. Such grouping of data according to latent (unobserved) variable can be modelled with mixture (weighted sum) of statistical models (McLahlan & Peel 2000).

Although mixture models are frequently referred as readily available and their utility is apparent, they are not a similarly well-researched topic as many other familiar statistical models. Their estimation actually involves technical difficulties known as singularities of parameter space (Watanabe 2009). This is a way of saying that more than one set of model parameters can result in the exact same model and that miniscule changes in parameters may cause drastic changes in the resulting model. This is undesirable phenomenon because one often interprets the data in terms of model parameters (e.g. regression slope). Mathematical theories that are most frequently used to analyze statistical models cannot cope with these difficulties, and new developments seem important (Watanabe 2009).

Above we discussed of some pertinent difficulties that still hinder most statistical modelling attempts in the field, from linear to nonlinear and mixture models. We feel that scientists applying these methods are not always sufficiently informed about involved difficulties. Current section attempted to fill this gap to a small degree and point some important methodological research topics, not to discourage researchers from doing their best possible work.

## 10. Conclusions

The findings of the Young Finns Study imply that stress is related to an increase of CHD risk through several pathways. The results also imply that more attention should be paid to pre-employment factors and individual differences in work stress research.

Stress affects people differently, that is, there are differences in individuals in stress proneness and what is considered as a stressor. These individual differences in stress experience stem from inherited characteristics and life experiences from childhood on. The influence of stress on cardiovascular health may be mediated through several different mechanisms. Based on our research it seems that the important role of stress in CHD risk is played rather by parasympathetic underactivity than sympathetic overactivity. Stress has to be measured appropriately and accurately keeping several different aspects of stress in mind: source of stress, the duration of stress, and individual vulnerability to stress have to be kept in mind when studying the role of stress in pathogenesis of CHD.



However, the research also shows that studying stress-health associations and the etiological role of stress in CHD is complicated and needs accurate measuring, appropriate statistical methods and population-based longitudinal study designs.

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## **Cardiovascular Risk Factors**

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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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