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Work Stress and Early Atherosclerosis: Do Genetic Background and Pre-Employment Risk Factors Explain Conflicting Findings?

University of Helsinki
Department of Psychology
Research Reports n:o 40

Helsingin yliopiston
Psykologian laitoksen
tutkimuksia n:o 40

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ISSN 0781-8254
ISBN 952-10-3567-6 (nid.)
ISBN 952-10-3568-4 (pdf)
http://ethesis.helsinki.fi

Yliopistopaino, Helsinki 2006

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Mirka Hintsanen

Academic dissertation to be publicly discussed, by due permission of the Faculty of Behavioral Sciences at the University of Helsinki in auditorium XII, Main Building, Unioninkatu 34, Helsinki, on the 20th of December 2006 at 12 o'clock.

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ABSTRACT

According to the models conceptualizing work stress, increased risk of health problems arise when high job demands co-occur with low job control (the demand-control model) or the efforts invested by the employee are disproportionately high compared to the rewards received (effort-reward imbalance model). This study examined the association between work stress and early atherosclerosis with particular attention to the role of pre-employment risk factors and genetic background in this association. The subjects were young healthy adults aged 24-39 who were participating in the 21-year follow-up of the ongoing prospective "Cardiovascular Risk in Young Finns" study in 2001-2002. Work stress was evaluated with questionnaires on demand-control model and on effort-reward model. Atherosclerosis was assessed with ultrasound of carotid artery intima-media thickness (IMT). In addition, risk for enhanced atherosclerotic process was assessed by measuring with heart rate variability and heart rate. Pre-employment risk factors, measured at age 12 to 18, included such as body mass index, blood lipids, family history of coronary heart disease, and parental socioeconomic position. Variants of the neuregulin-1 were determined using genomic DNA.

The results showed that higher work stress was associated with higher IMT in men. This association was not attenuated by traditional risk factors of atherosclerosis and coronary heart disease or by pre-employment risk factors measured in adolescence. Neuregulin-1 gene moderated the association between work stress and IMT in men. A significant association between work stress and IMT was found only for the T/T genotype of the neuregulin-1 gene but not for other genotypes. Among women an association was found between higher work stress and lower heart rate variability, suggesting higher risk for developing atherosclerosis. These associations could not be explained by demographic characteristics or coronary risk factors.

The present findings provide evidence for an association between work stress and atherosclerosis in relatively young population. This association seems to be modified by genetic influences but it does not appear to be confounded by pre-employment adolescent risk factors.

Työstressi ja ateroskleroosi: selittävätkö geneettinen tausta ja varhaiset riskitekijät ristiriitaisia löydöksiä?

TIIVISTELMÄ

Tutkimuksessa tarkasteltiin työstressin ja nuorten aikuisten ateroskleroosin välistä yhteyttä ja sitä, selittääkö geneettinen tausta tätä yhteyttä. Lisäksi tutkittiin varhaisten, työikää edeltävien ateroskleroosin riskitekijöiden vaikutusta työstressin ja ateroskleroosin väliseen yhteyteen. Koehenkilöt olivat Lasten sepelvaltimotautiriski projektin 21-vuotis seurannasta, joka toteutettiin vuosina 2001 - 2002. Neureguliini-1 geenille määritettiin genotyypit. Ateroskleroosia arvioitiin mittaamalla kaulavaltimon seinämän paksuutta ultraäänellä. Lisäksi suurentunutta riskiä ateroskleroosin kehittymiselle arvioitiin mittaamalla sydämen sykettä ja syketaajuusvaihtelua. Työstressiä mitattiin Karasekin ja Siegristin työstressimallien avulla. Karasekin mallin mukaan työstressi ja siihen liittyvät terveyshaitat aiheutuvat työn kuormittavuuden ja työntekijän vähäisten työhönsä vaikuttamisen mahdollisuuksien yhdistelmästä. Siegristin mallin mukaan työstressiä ja siihen liittyviä terveyshaittoja aiheutuu, kun työn kuormittavuus on suhteettoman suurta työstä saataviin palkkioihin nähden.

Tulokset osoittivat, että miehillä korkeampi työstressi (Karasek) oli yhteydessä kaulavaltimon seinämän paksuuntumiseen, joka on merkkinä ateroskleroosista. Perinteiset ateroskleroosin ja sepelvaltimotaudin riskitekijät eivät heikentäneet tätä yhteyttä, kuten eivät myöskään varhaiset työikää edeltävät sepelvaltimotaudin riskitekijät. Naisilla korkeampi työstressi (Siegrist) oli yhteydessä pienempään sydämen syketaajuusvaihteluun, joka viittaa suurempaan ateroskleroosin kehittymisriskiin. Myöskään näitä yhteyksiä ei voitu selittää demograafisilla tekijöillä eikä sepelvaltimotaudin riskitekijöillä. Neureguliini-1 geeni muokkasi työstressin ja ateroskleroosin välistä yhteyttä miehillä. Merkitsevä yhteys työstressin ja ateroskleroosin välillä löytyi ainoastaan neureguliini-1 geenin T/T genotyypillä, mutta ei muilla genotyypeillä. Tulokset tukevat sitä, että työstressin ja ateroskleroosin välillä on löydettävissä yhteys jo nuorilla aikuisilla. Lisäksi tulokset viittaavat siihen, että geneettiset tekijät voivat muokata tätä yhteyttä, kun taas työikää edeltävät varhaiset riskitekijät eivät tämän tutkimuksen perusteella näytä vaikuttavan työstressin ja ateroskleroosin väliseen yhteyteen.

ACKNOWLEDGEMENTS

There are several people I would like to thank, and without whom writing this thesis would simply not have been possible.

My deepest gratitude I owe to my supervisor Professor Liisa Keltikangas-Järvinen for offering me this great opportunity to work under her knowledgeable supervision in her research group. Despite all her duties and busy schedule, her door has always been open. She has been a tremendous source of inspiration and knowledge and her enthusiasm for research has a catching nature that has greatly motivated me along these years.

Next, I would like to express my gratitude to my other supervisors Docent Marko Elovainio and Professor Mika Kivimäki. Marko Elovainio has always been willing to help and share his scientific knowledge. He has given me a lot of his time, which I am very grateful of. Mika Kivimäki has brilliant ideas and his advice has gotten us through many tricky review comments. Both have tirelessly reviewed and commented my texts and given valuable advice on numerous occasions.

I wish to thank the reviewers of my thesis, Professor Ulla Kinnunen and Docent Marianna Virtanen for their important comments that helped me to improve my thesis.

I am indebted to Sampsa Puttonen who has been almost like a fourth supervisor to me. He has patiently helped me with various problems, and his humour and cheerfulness have meant a lot to me, especially in the face of set-backs and difficulties. I also wish to thank Laura Pulkki-Råback for her help and advice and Pertti Keskivaara for his invaluable support in statistical matters. I wish to extend my gratitude to all the co-authors of the original publications of this thesis.

Warm thanks to my colleagues, especially Taina Hintsa, Mila Gustavsson, and Saija Alatupa, for their emotional support and for sharing the joys and sorrows of thesis writing. They have helped to keep the work stress levels down. I also want to thank Ritva Siukkola for her encouragement. She has made me realize the importance of celebrating when something has been achieved.

This work was carried out in the Department of Psychology at the University of Helsinki. I wish to thank the Psykonet Graduate School of Psychology, Otto A. Malm's Donation Fund, and Oskar Öflund's Foundation for making this work financially possible.

I am grateful for my mother Erja and my father Veijo for their support. I don't think I would have gotten nearly so far without them. They have always encouraged me and listened to my worries. They have always stressed the importance of education but at the same time allowed me to freely choose my own way. Finally, I wish to thank my husband Toni for his friendship and support. I am very grateful and happy that he is so proud of what I do. Without him, all other things would lack meaning.

Helsinki, November 2006
Mirka Hintsanen

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II Hintsanen, M., Elovainio, M., Puttonen, S., Kivimäki, M., Koskinen, T., Raitakari, O. T., & Keltikangas-Järvinen, L. Effort-Reward Imbalance, Heart Rate, and Heart Rate Variability: The Cardiovascular Risk in Young Finns Study. *International Journal of Behavioral Medicine*. (In Press).

III Kivimäki, M., Hintsanen, M., Keltikangas-Järvinen, L., Elovainio, M., Pulkki-Råback, L., Vahtera, J., Viikari, J. S. A., & Raitakari, O. T. Early Risk Factors, Job Strain and Atherosclerosis among Men in Their 30s: The Cardiovascular Risk in Young Finns Study. *American Journal of Public Health.* (In Press).

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1. INTRODUCTION

1.1 Psychological stress: conceptualization

Psychological stressors refer to events or circumstances in the environment that result in responses in the organism that may cause a psychological or physiological dysfunction or illness (Monroe, 2000). It is assumed that especially a chronic exposure to stressors is detrimental to health. According to Selye's general adaptation syndrome, prolonged stress eventually leads to stage of exhaustion in which the organism's ability to maintain its health is reduced (Selye, 1974). McEwen (1998) introduced the concepts of allostasis and allostatic load. Allostasis is an adaptive process involving physiological responses directed to maintaining homeostasis (balance). In the long run, however, adaptation to the stressors has a cost. When adaptive processes have to be active for too long, it causes "wear and tear" of the body which is called allostatic load (McEwen, 1998). Allostatic load may lead to psychological or bodily dysfunction or disease (McEwen, 1998).

Lazarus' theory on stress and coping emphasizes that stress is not caused solely by environmental factors but by transaction between environment and the individual (Folkman & Lazarus, 1985; Folkman, Lazarus, Gruen, & DeLongis, 1986; Lazarus & DeLongis, 1983). Person's appraisal has a significant role in determining the stressfulness of the situation. In primary appraisal it is evaluated whether there is something important at stake and whether there is threat involved. In secondary appraisal the available coping resources are assessed. Primary and secondary appraisal are interdependent so that the outcome of one influences the outcome of the other. E.g. sufficient coping resources could diminish the perceived threat involved in the situation (Folkman & Lazarus, 1985).

1.2 Physiological effects of psychological stress

Psychological stress affects the body in several ways. Sympathetic branch of the autonomic nervous system (ANS) responds to psychological stress for example by increasing heart rate and constricting blood vessels. It also responds by increasing secretion of stress hormone epinephrine that reinforces these effects (Lovallo, 1997). Hypothalamic-pituitary-adrenal (HPA) system increases the secretion of stress hormone cortisol that can suppress immune system function, enhance catecholamine (e.g. epinephrine) synthesis, enhance glucose production and release of stored fat (Lovallo, 1997). Psychological stress might also affect the body by affecting health related behaviors. For example, psychological stress has been associated with health damaging behaviors like smoking, alcohol consumption and lack of physical activity (Weidner, Boughal, Connor, Pieper, & Mendell, 1997) which in turn increase the risk for coronary heart disease (CHD) (Wood & Joint European Societies Task Force, 2001).

There is evidence that psychological stress may predispose to negative health behaviors and predict atherosclerosis and CHD independently of other risk factors. For example a three-year follow-up study of over 10000 older women found that perceived stress predicted CHD independent of behavioral and physiological risk factors (Strodl, Kenardy, & Aroney, 2003). Another recent study utilizing repeated diary reports on daily experience found that individuals reporting less decisional control and more demands in their daily lives had more severe atherosclerosis (Kamarck et al., 2005).

1.3 Work stress: conceptualization

Several models have been developed to conceptualize work stress. The current study concentrates on two most influential models that have been studied particularly in relation to cardiovascular diseases and coronary heart disease (CHD). These models are Karasek's demand-control model

(Karasek, 1979) and Siegrist's effort-reward imbalance model (Siegrist, 1996). Both models concentrate on the work situation i.e. on environmental factors that, according to these models, cause stress. Both models also include environmental factors that can moderate the stressors. In addition to taking factors describing the work situation into account, the effort-reward imbalance model also includes a measure of a personality characteristic that is thought to predispose the person for the stressors and their negative effects.

1.3.1. The demand-control(-support) model

One of the most influential theories on work stress is Karasek's (1979) demand-control model. It has received substantial attention and yielded multitude of research especially in relation to cardiovascular diseases (CVD). The model specifies two work-related elements influencing job strain: job demands and control of the work situation (Karasek & Theorell, 1990; Karasek, 1979). The former refers to psychological stressors, such as time pressure and excessive workload. Job control (decision latitude) involves organization of work in terms of employees' opportunities to use their skills (skill discretion) and their authority to make decisions concerning their own activities (decision authority). According to the model, job strain and related health problems arise when high demands co-occur with low control. With the term stress, Karasek refers to the internal state of the individual. As this is not measured directly (but through demand and control) the model does not us the term work stress but the term job strain (Karasek, 1979).

Job strain has been formulated in several ways and a wide variety of methods for testing interactions between demand and control have been employed in different studies (Landsbergis, Schnall, Warren, Pickering, & Schwartz, 1994). The demand-control model was later extended by adding a third dimension, namely, social support (Johnson & Hall, 1988; Karasek & Theorell, 1990). According to this extended model (demand-control-support model) job demands, job control, and social support interact so that strain is highest when demands are high and control and social support are low. This is also called iso-strain.

1.3.2 The effort-reward imbalance model

Siegrist's (1996) effort-reward imbalance model has been developed relatively recently. The effort-reward imbalance model suggests that stress and negative health effects occur in work situations when the efforts invested by the employee are disproportionately high compared to the rewards received (Siegrist & Peter, 1994). Extrinsic effort refers to the demands of the job, such as workload, piecework, and work pressure. Rewards include monetary gratification (e.g. salary, financial benefits), esteem (e.g. positive feedback from co-workers and superiors), and status control (e.g. career opportunities, job security) (Siegrist & Peter, 1994). In addition to extrinsic effort, the effort-reward imbalance model also includes intrinsic effort, characterized by high need for approval and high commitment in relation to work-related demands (Siegrist, 1996; Siegrist et al., 2004). This motivational pattern is called overcommitment (Siegrist et al., 2004).

The theory assumes that the imbalance between effort and rewards is especially high when conditions of low rewards and high extrinsic effort are combined with a personal motivational pattern of high overcommitment i.e. high intrinsic effort (Siegrist et al., 2004). High effort low reward conditions are maintained when 1) there is no alternative (e.g. the situation in the labour market does not allow for a change of jobs), 2) adverse conditions are accepted for strategic reasons (e.g. in hope of promotion), or 3) one's motivational style is characterized by high overcommitment (Siegrist, 1996).

Recent developments in working life are characterized by increases in fixed-term employment (Booth, Dolado, & Frank, 2002) and in job insecurity (Nickell, Jones, & Quintini, 2002; Nätti, Kinnunen, Happonen, Mauno, & Sallinen, 2001). Organizational downsizing has been

found to increase the risk of cardiovascular mortality in employees who were not fired (Vahtera et al., 2004). Compared to continuous employment, fixed-term employment has been associated with psychological morbidity (Virtanen et al., 2005), and it is often accompanied by fewer benefits. There is reason to believe that an imbalance between efforts and rewards and resulting negative health effects may have increased along with the increasing number of fixed-term employees and increasing job insecurity. Accordingly, the effort-reward imbalance model seems to be well suited to measure work stress in present-day society and working life.

The effort-reward imbalance model shares some conceptual similarities with Karasek's (1979) demand-control model, as extrinsic efforts in Siegrist's model correspond quite closely to job demands in Karasek's model. Both models also include a factor that can moderate the effects of the environmental stressors of job demands and extrinsic efforts: Karasek's model includes job control whereas Siegrist's model includes reward. In this respect, the two models address different aspects of the work organization. Job control is related to authority and democracy in the work place, whereas reward reflects fairness and distributive justice (Siegrist et al., 2004). Another difference is that Siegrist's model is more related to general circumstances in the labour market, such as payment, career, and job security, whereas Karasek's model is more related to working conditions inside the organization (Siegrist et al., 2004). The most apparent distinction between the models is that in addition to job characteristics the effort-reward imbalance model also includes a factor reflecting personality (i.e. overcommitment). Studies conducted simultaneously for both models have shown improved estimation and prediction of CHD risk (Bosma, Peter, Siegrist, & Marmot, 1998; Peter et al., 2002).

1.4 Work stress as a risk factor for atherosclerosis and coronary heart disease (CHD)

CHD is a disease of the coronary arteries, which supply oxygenous blood to the heart (Scheidt, 1996). CHD is the end result of atherosclerosis (progressive narrowing and hardening of the arteries induced, for example, by deposition of fatty material) and it is manifested in angina pectoris, acute myocardial infarction, and sudden cardiac death (Scheidt, 1996). It takes several decades for CHD to develop. There are several established risk factors for CHD, such as smoking, overweight, physical inactivity, high cholesterol and high blood pressure (Pearson et al., 2002). These same risk factors are also risk factors for atherosclerosis.

An association between work stress, measured by the demand-control model, and severe forms of coronary heart disease (CHD), such as myocardial infarction, stroke and cardiovascular mortality has been repeatedly reported (Belkic, Landsbergis, Schnall, & Baker, 2004; Bosma et al., 1997; Hemingway & Marmot, 1999; Kivimäki et al., 2002; Schnall, Landsbergis, & Baker, 1994). However, remarkable null findings also exist. A recent study by Eaker, Sullivan, Kelly-Hayes, D'Agostino, and Benjamin (2004) found no association between job strain and CHD incidence in 3039 participants during a ten year follow-up period. Similarily Lee, Colditz, Berkman, and Kawachi (2002) found no association between job strain and incidence CHD in 35038 women during a follow-up period of four years. Less research has been conducted on association between CVD and demand-control-support model and there is not as strong evidence for this association (de Lange, Taris, Houtman, Kompier, & Bongers, 2003).

Similarly, as with demand-control model, several studies have supported the existence of an association between effort-reward imbalance and CHD (Chandola, Siegrist, & Marmot, 2005; Kivimäki et al., 2002; Kuper, Singh-Manoux, Siegrist, & Marmot, 2002; Peter & Siegrist, 1999; Siegrist, 1996; Siegrist & Peter, 1994; van Vegchel, de Jonge, Bosma, & Schaufeli, 2005) The majority of the studies on health effects of effort-reward imbalance have not examined the moderating effect of overcommitment (van Vegchel et al., 2005).

The underlying mechanisms of the association between effort-reward imbalance and CHD are unclear. It has been suggested that an imbalance between efforts and rewards may cause

autonomic arousal, which, if prolonged or frequent, could contribute to cardiovascular pathology (Peter & Siegrist, 2000; Siegrist & Peter, 1994). However, only limited empirical evidence on this mechanism is available (van Vegchel et al., 2005). More research on mechanisms of demand-control model in relation to CHD has been conducted, e.g. studies on the role of blood pressure (Schwartz, Pickering, & Landsbergis, 1996).

There are several potential mechanisms through which stress can affect cardiac health. Stress may increase biological risk factors of CHD (Coleman, Friedman, & Burright, 1998; Kouvonen, Kivimäki, Cox, Cox, & Vahtera, 2005) such as high cholesterol, high blood pressure and high body weight. It may also have an effect on behaviours increasing risk of CHD (Wood & Joint European Societies Task Force, 2001), such as smoking (Kassel, Stroud, & Paronis, 2003), alcohol consumption (Brady & Sonne, 1999), and sedentary life style (Wemme & Rosvall, 2005). Furthermore, stress may act as a trigger for a cardiac event such as myocardial infarction among vulnerable persons (Culic, 2006).

CHD is a multi-factorial disease that produces clinically significant changes relatively late in life. The fact that only a small number of studies on work stress and the early stages of CHD have been conducted so far and most studies have been conducted on participants over age 40 may stem from the lack of techniques for assessing sub-clinical stages of CHD, such as atherosclerotic process. In addition, as research has tended to concentrate on CHD in men, much less is known about the effects of work stress on young women. It has been noted that the demand-control hypothesis has not received as much support in women as it has in men (Theorell & Karasek, 1996).

Recently, noninvasive techniques, such as ultrasound measurement of intima-media thickness (IMT), have been developed to directly assess early stages of the atherosclerotic process. Carotid artery IMT is a marker of subclinical atherosclerosis, and increased IMT has been shown to predict future CHD (O'Leary & Polak, 2002; Simon, Gariepy, Chironi, Megnien, & Levenson, 2002).

The few previous studies that have examined the association between job strain or its components and IMT have produced mixed findings. In the study by Rosvall et al. (2002), women who experienced high demands and low job control had higher IMT compared to women with a combination of low job demands and high job control (mean difference 0.15 mm). In addition, women who had high job demands and high job control had thicker IMT compared to women with a combination of low demands and high control (mean difference 0.10 mm). No association between components of job strain and IMT was found in men. However, Nordstrom and colleagues (Nordstrom, Dwyer, Merz, Shircore, & Dwyer, 2001) found work-place demands and intrusion of work concerns into home life to be associated with higher IMT in men but not in women. A study by Muntaner et al. (1998) reported no association between job strain and IMT, but higher skill discretion and decision authority were associated with lower IMT. The only longitudinal study using IMT as an outcome measure, the Kuopio Ischaemic Heart Disease Risk Factor Study of Finnish men, reported that high job demands combined with low financial rewards (Lynch, Krause, Kaplan, Salonen, & Salonen, 1997) or high stress induced reactivity (Everson et al., 1997) predicted higher IMT.

As the subjects in all these studies, examining the association between job strain or its components and IMT, were at least 40 years old, the results cannot be generalized to younger populations. Furthermore, most of the previous studies did not control for the effect of occupational status although the indicators of socio-economic position are important factors that may confound the association between job strain and CHD (Macleod et al., 2002). So far, the combined effects of job demands and job control on IMT have only been examined in two (cross-sectional) studies and no previous study has explored the interaction between job strain and social support.

In addition to IMT, measuring cardiac activity with heart rate (HR) and heart rate variability (HRV) may offer another way to study atherosclerosis and sub-clinical stages of CHD. HRV may be considered an objective measure of autonomic arousal (Task Force, 1996), and reduced HRV has

been shown to predict incident CHD in the general population (Dekker et al., 2000; Tsuji et al., 1996). In clinical studies, lower HRV has been associated with the progression of atherosclerosis beyond the effect of traditional risk factors (Huikuri et al., 1999; Jokinen et al., 2003). High HR has also been found to be an independent cardiovascular risk factor (Palatini & Julius, 2004) and, in patient populations, an independent predictor of cardiovascular mortality (Habib, 1997).

To our knowledge, only two previous studies have examined the association between effort-reward imbalance and HRV (Hanson, Godaert, Maas, & Meijman, 2001; Vrijkotte, van Doornen, & de Geus, 2000), and these studies have produced mixed findings. Vrijkotte et al. (2000) reported that subjects with higher effort-reward imbalance had lower HRV (indicated by RMSSD) although this association did not reach significance. In contrast, Hanson et al. (2001) reported that higher effort-reward imbalance was associated with higher HRV (indicated by HF), but only later in the working day. The authors interpreted this result reflecting lower mental effort expended on work duties later in the day by employees experiencing higher effort-reward imbalance. In both studies, sample sizes were fairly small ($N \leq 109$), and the subjects were mostly white-collar workers and represented a narrow range of occupations. Furthermore, only men were included in the study by Vrijkotte and colleagues (2000) and apart from smoking, no behavioral or biological risk factors of CHD were taken into account in the study by Hanson et al. (2001).

1.5 Pre-employment risk factors as possible confounders in the association between work stress and CHD

Several studies have shown that cholesterol concentration, body mass index, blood pressure and socioeconomic position in childhood or adolescence predict atherosclerosis and CHD later in life (Li et al., 2003; Lynch & Smith, 2005; Raitakari et al., 2003). There is also evidence suggesting that early life risk factors have an impact on stress perceptions in adulthood (Harper et al., 2002; Meaney, 2001). For example, childhood socioeconomic position has been found to be associated with adulthood cynical hostility and hopelessness (Harper et al., 2002) and with adulthood job strain (Hintsa et al., 2006). Furthermore, parental care in childhood seems to be associated with later stress reactivity of the child (Meaney, 2001). These early influences on both adult CHD risk and stress perception could confound evidence regarding the status of job strain as a risk factor for CHD in adult populations. Indeed, it is unclear whether part of the association between job strain and CHD may be attributable to influences from childhood or adolescence.

1.6 Neuregulin-1 genotype as a modifier of the association between work stress and CHD

Despite numerous reports of an association between job strain and CHD (Belkic et al., 2004; Bosma et al., 1997; Hemingway & Marmot, 1999; Kivimäki et al., 2002; Schnall et al., 1994) null findings have also been published (Eaker et al., 2004; Lee et al., 2002) as already mentioned above. Individual differences in innate stress vulnerability might account for part of these mixed findings. Neuregulin-1 is a potential candidate gene that may affect processes, such as development of autonomic nervous system, that are related to stress vulnerability. Genetic disposition may therefore modify the association between job strain and CHD.

The neuregulin-1 (NRG-1) gene is one of the four genes in the neuregulin gene family. It produces a signaling protein, neuregulin-1, that transmits cell-cell interaction in the heart, in various parts of the nervous system, and elsewhere in the body (Falls, 2003). Animal studies have shown that the neuregulin-1 protein (Garratt, Özcelik, & Birchmeier, 2003) and the NRG-1 gene (Zhao & Lemke, 1998) have a role in heart development, and Zhao et al. (1998) have found that the neuregulin-1 protein facilitates growth and survival of cultured cardiomyocytes in adult rats. Furthermore, it has been observed that neuregulin-1 has a negative inotropic effect on the cardiac muscle and that this effect persists during beta-adrenergic activation (Lemmens, Fransen, Sys,

Brutsaert, & De Keulenaer, 2004), a well-known correlate of stress (Dimsdale, Mills, Patterson, Ziegler, & Dillon, 1994). Therefore, Lemmens et al. (2004) have suggested that negative inotropic effect of neuregulin-1 is beneficial, as it can be assumed to diminish myocardial oxygen consumption in stressful situations. The neuregulin-1 protein also activates nitric oxide synthase (Lemmens et al., 2004), which has a role in the atherosclerotic process (Kawashima & Yokoyama, 2004). In humans, neuregulin genes have been found to be overexpressed in atherosclerotic lesions, and it has been suggested that NRG may be involved in CHD development (Panutsopulos et al., 2005).

Research indicates that NRG-1 may also be implicated in the development and functioning of the autonomic nervous system. Studies conducted on mice have shown that the NRG-1 gene is necessary for the development of the sympathetic nervous system (Britsch et al., 1998) and that it may be important for maintaining parasympathetic activation, which balances excess beta-adrenergic activation (Okoshi et al., 2004). Considering that the autonomic nervous system is a central physiological mediator for stress (McEwen, 1998), these results imply that the NRG-1 gene may have an effect on stress reaction. In relation to work stress, no previous research on genotype influences has been published.

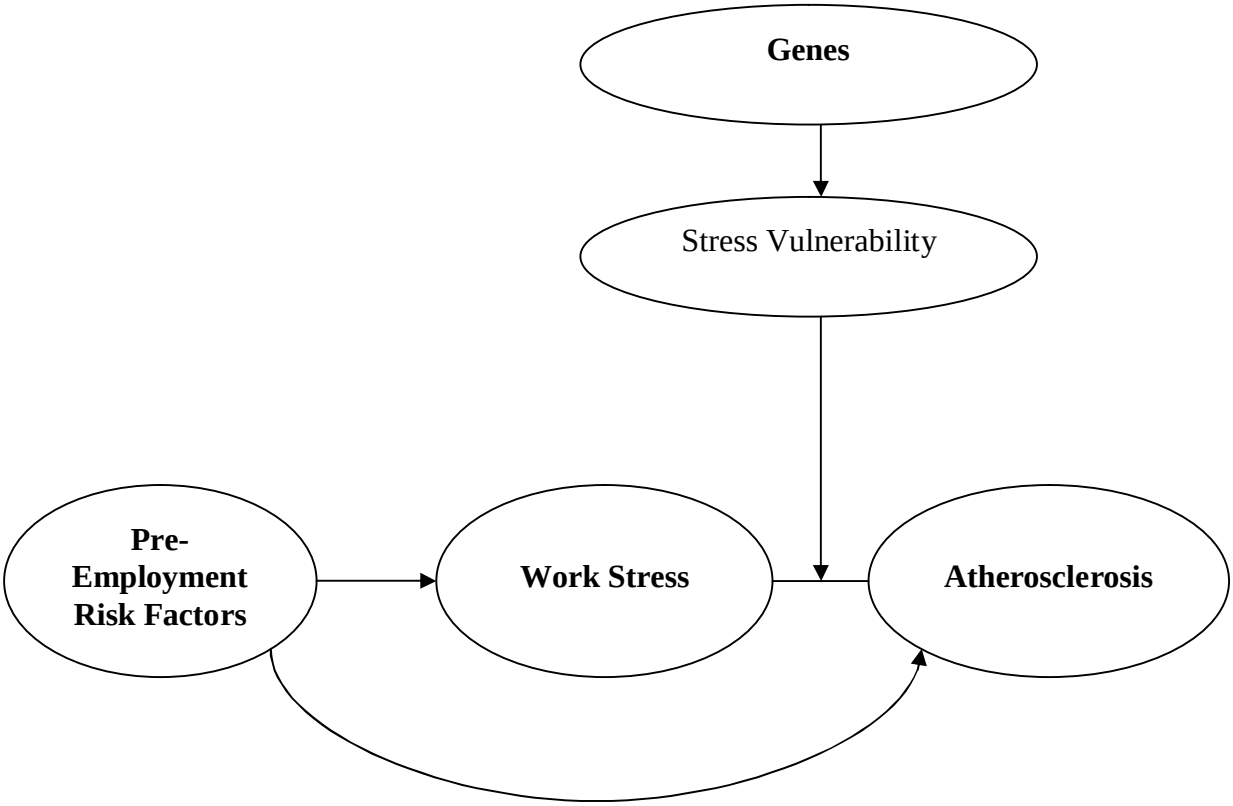
1.7 Aims of the present study

The main aim of the present study was to examine the association between work stress and atherosclerosis in young adult men and women under the age of forty, and whether genetic background could modify this association. In addition, possible influences of pre-employment risk factors on the work stress – atherosclerosis relation were examined.

By concentrating on these issues, the current study aims to bring new knowledge related to less studied or completely unexamined areas of work stress – CHD research. No previously published studies on genotype effects exist. Also, there is very limited knowledge about the role of pre-employment risk factors of CHD (Brunner et al., 2004; Hemmingsson & Lundberg, 2006). Furthermore, there is less studies that have, in addition to men, included women and there is a lack of studies conducted on young adults under the age of forty.

Work stress was assessed with the demand-control model and the effort-reward imbalance model. Atherosclerosis was measured on the basis of carotid artery IMT. Risk for enhanced atherosclerotic process was measured with HR, and HRV. Four separate studies were conducted. Figure 1 represents the focus of the current study.

Figure 1. Focus of the current study.



Study I

The aim of study I was to examine whether job strain and social support and their interaction are associated with early non-symptomatic atherosclerosis measured on the basis of carotid artery IMT in young adults (under the age of 40) with no apparent CHD. A wide variety of CHD risk factors were controlled for, including occupational status that has not often been taken into account in previous studies on job strain and IMT. Associations between IMT and the components of job strain, i.e. job demands and job control, were also tested to define the relative significance of these two components. We hypothesized that higher job strain and lower social support, and a three-way interaction between higher job demand, lower job control and lower social support are related to higher IMT.

Study II

The aim of this study was to examine associations between effort-reward imbalance, HR, and HRV. Association between HR and HRV with components of effort-reward imbalance, i.e. effort and reward, were also tested to define the relative significance of these two components. Unlike the previous studies, the current study included both men and women and had participants from a wide variety of occupations and from different occupational levels. Furthermore, several risk factors of CHD that were not previously always considered were controlled for, and the potential effects of medication and other factors (coffee) on HRV were also taken into account. Overcommitment was not examined as suitable measures were not available in the data of this study. It was hypothesized

that higher effort-reward imbalance is associated with higher HR and with a higher level of a HRV measure reflecting sympathetic tone and with a lower level of HRV indices reflecting vagal tone.

Study III

The aim of Study III was to examine whether biological, familial, and socioeconomic risk factors of atherosclerosis and CHD in adolescence (pre-employment risk factors) confound the association between job strain and atherosclerosis in men.

Study IV

The aim of study IV was to examine the role of the neuregulin-1 gene as a modifier of the association between job strain and IMT. The main effects of the neuregulin-1 genotype with job strain and with IMT were also examined. It was hypothesized that an interaction between the neuregulin-1 genotype and job strain would have an effect on IMT. As there is a lack of previous studies, and the functional role of neuregulin-1 gene was not known, the direction of the effect was not included in this hypothesis.

2. METHODS

2.1 Subjects

The subjects were 2104 young adults (889 men and 1215 women) aged 24-39 years participating in the 21-year follow-up of the ongoing prospective "Cardiovascular Risk in Young Finns" study (CRYF) in 2001-2002. The subjects for the baseline sample in 1980 (n = 3596) were selected randomly from six different age cohorts (3-, 6-, 9-, 12-, 15-, and 18- year-olds) in the population register of the Social Insurance Institution, a database covering the whole population of Finland. The design of the CRYF study and the selection of the sample have been described in detail by Åkerblom et al. (1991). Only participants who were known to be currently employed in a full-time job and who did not have diagnosis of diabetes mellitus (n = 11) or ischemic heart disease (n = 1) were included in the studies. Information on diabetes and ischemic heart disease were received from the participants by asking if they had been diagnosed by a doctor of having these diseases. Neuregulin-1 genotype was determined for 1538 randomly selected participants. The final number of participants varies across Studies I – IV, as the participants included in the studies were required to have complete data for all study variables. There were 1020, 863, 358, and 706 participants in Study I, Study II, Study III, and Study IV, respectively. Study III included only men and only the three oldest age cohorts. Study III used data on biological and socioeconomic risk factors from 1980, and family history of coronary heart disease was assessed using baseline and follow-up data. Number of participants and gender, age, and work stress distributions in Studies I-IV are presented in Table 1. Research design, variables, and main statistical method used in studies I-IV are presented in Table 2. All participants gave written informed consent, and the study was approved by local ethics committees.

Table 1. Number of Participants and Gender, Age, and Work Stress Distributions in Studies I-IV

	Study 1		Study2				Study 3		Study 4	
	Number	%	Number	%	Mean	sd	Number	%	Number	%
Participants (final sample)	1020		863				358		706	
Gender										
Men	478	46.9	406	47.0			358	100	357	50.6
Women	542	53.1	457	53.0					349	49.4
Age										
24	104	10.2	94	10.9					68	9.6
27	163	16.0	127	14.7					114	16.1
30	177	17.4	156	18.1					116	16.4
33	184	18.0	157	18.2			170	33.9	120	17.0
36	196	19.2	172	19.9			174	34.7	139	19.7
39	196	19.2	157	18.2			158	31.5	149	21.1
Job strain										
Low	298	29.2					111	31.0	216	30.6
Intermediate	398	39.0					135	37.7	268	38.0
High	324	31.8					112	31.3	222	31.4
Effort-reward imbalance*					_0.128	0.144				

* Mean and standard deviation is reported for effort-reward imbalance which was measured with a logarithmically transformed continuous variable.

Table 2. Research Design, Variables, and Main Statistical Method Used in Studies I-IV

	Study 1	Study2	Study 3	Study 4
Research design	Cross-sectional	Cross-sectional	Longitudinal	Cross-sectional
Independent variables	Job strain Job demand Job control Social support	Effort-reward imbalance Effort Reward	Job strain	Job strain Neuregulin-1
Dependent variables	IMT	HR HF LF/HF RMSSD pNN50	IMT	IMT
Control variables	Age Education Occupation Smoking Alcohol Physical activity Social support BMI HDL LDL	Age Education Occupation Smoking Alcohol Physical activity Social support BMI SBP DBP	Age Occupation[1] Smoking[2] BMI[2] HDL[2] LDL[2] Triglycerides[2] SBP[2] Family history of CHD	Age Education Occupation Smoking Alcohol Physical activity Social support BMI HDL LDL SBP DBP
Main statistical method	Regression analysis	Regression analysis	Regression analysis	Regression analysis

[1] Parental occupational position

[2] Measured at age 12-18

2.2 Measures

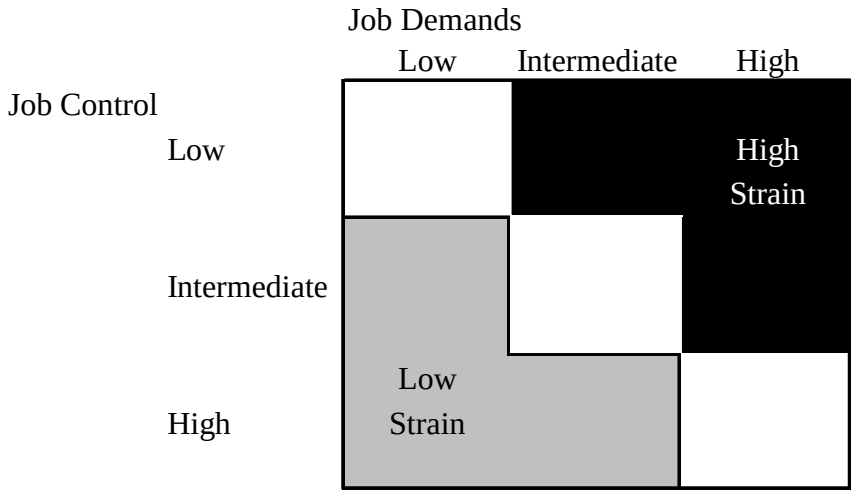
2.2.1 Job strain (Studies I, III, IV)

Job demands were measured with a 3-item scale ($\alpha > 0.61$) from the Occupational Stress Questionnaire (OSQ, $\alpha = 0.87$) (Elo, Leppänen, Lindström, & Ropponen, 1990) developed at the Finnish Institute of Occupational Health. The items used in the current study were: “Do you have to hurry to get your work done?”, “Does your work have phases that are too difficult?”, and “Is your work mentally strenuous?” These items correspond quite closely to demands in Karasek´s (1979) Job Content Questionnaire. Responses were obtained on a 5-point scale ranging from 1 (never) to 5 (all the time).

Job control was measured with the Job Content Questionnaire (Karasek, 1985), which includes nine items for job control ($\alpha = 0.87$). Responses were given on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree).

Several formulations of job strain have been used in previous studies (Landsbergis et al., 1994). In Studies I, III, and IV the distributions of job demands and job control were divided into tertiles (Green & Johnson, 1990; Kivimäki et al., 2002; Landsbergis et al., 1994). As in a previous study by Green and Johnson (1990) the highest two tertiles in demands combined with lowest two tertiles in job control formed the high strain category, and lowest two tertiles in demands combined with highest two tertiles in control formed the low strain category. All other combinations were placed into the intermediate strain category. Job strain was coded as an ordinal variable ranging from 1 to 3, with higher values indicating higher strain. Figure 2 presents the composition of the tertile-based job strain variable. In Study 1 four other job strain formulations (Landsbergis et al., 1994) were constructed in order to replicate the main results. Quadrant term was based on dichotomized demands and job control scores at the medians. Employees with high strain were those with job demand score above the median and job control score below the median. All other employees belonged to the no-strain group. The second alternative, linear term, was a continuous job strain variable obtained from the following equation: (0.5 x job control score) – (0.5 x job demand score). The third alternative, quotient term, was formed by dividing job demands by job control. The fourth alternative was a multiplicative interaction term (demand x control) calculated for each gender using centralized values for demand and control. In all scales, sums were calculated for only those participants who had responded to a minimum of 50% of the items of the scale. The participants who had higher number of missing values were excluded from the analyses.

Figure 2. Composition of the Tertile-Based Job Strain.



2.2.2 Social support (Studies I, II, IV)

Social support was assessed with the Perceived Social Support Scale-Revised consisting of 12 items ($\alpha = 0.94$) measuring social support received from family and friends (Blumenthal et al., 1987). Responses were given on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree). Again, sums were calculated for only those participants who had responded to a minimum of 50% of the items of the scale.

2.2.3 Effort-reward imbalance (Study II)

Effort was measured using the same items as job demands, and the effort scale ($\alpha = 0.60$) was set as the job demand scale. The items used correspond quite closely to those in the original effort scale (Siegrist, 1996; Siegrist et al., 2004). Responses were obtained on a 5-point scale ranging from 1 (never) to 5 (all the time).

Reward was also measured with a 3-item scale ($\alpha = 0.59$) from the Occupational Stress Questionnaire. The items used in the current study were: "Do you get help and support from your superior if needed?" (1: very little, 5: very much), "How do your co-workers get along with each other on the workplace?" (Their relationship is: 1: bad - tense, resentful, etc., 5: very good), and "How satisfied are you with your current employment?" (1: very unsatisfied, 5: very satisfied). These items are somewhat similar to the reward items in the effort-reward imbalance questionnaire (Siegrist et al., 2004) but they only represent esteem component of reward and not monetary and status control components.

In the effort and reward scales, mean scores were calculated for only those participants who had responded at least to half of the items of the scale. Effort-reward imbalance was formulated as a continuous variable, dividing effort by reward (Siegrist et al., 2004). A logarithmic transformation was performed to correct for skewness. This formulation is recommended by Siegrist et al. (2004) as it seems to lead to higher statistical power (Kuper et al., 2002; Niedhammer, Tek, & Starke, 2004).

2.2.4 CHD risk factors (Studies I, II, IV) and coffee consumption (Study II)

The following CHD risk factors (Lett et al., 2005; Wood & Joint European Societies Task Force, 2001) were measured: educational level, occupational group, smoking status, alcohol consumption, physical activity, body mass index (BMI), systolic blood pressure (SBP; not in Study I) diastolic blood pressure (DBP; not in Study I), high-density lipoprotein cholesterol (HDL-C; not in Study II), low-density lipoprotein cholesterol (LDL-C; not in Study II) and social support (the lack of; described above). Coffee consumption (Study II) was measured as it may affect HRV (Tsuji et al., 1996).

Socio-economic status (SES) was indicated by educational level and occupational group. Educational level was classified as 1) low (comprehensive school), 2) intermediate (secondary education), or 3) high (academic; graduated from a polytechnic or studying at or graduated from a university) (Kivimäki et al., 2005). Classification into occupational groups was based on the criteria of the Central Statistical Office of Finland. Three groups were formed: 1) manual, 2) lower non-manual, and 3) upper non-manual (Kivimäki et al., 2005). Entrepreneurs, who formed a very heterogeneous group of their own in the original measure, were placed to the aforementioned occupational groups according to educational level (low, intermediate, and high education corresponding to manual, lower non-manual and upper non-manual occupational groups respectively) (Kivimäki et al., 2005).

Health-related behaviors included smoking status (daily smokers vs. others), alcohol consumption (how often beer, wine, or spirits was used at least six portions or more on one occasion (one portion equals to12 grams of pure alcohol): 1 = once a year or never, 2 = 2-6 times a year, 3 = once a month, 4 = 2-3 times a month, 5 = once a week, 6 = at least twice a week), coffee consumption (cups / day), and physical activity (an index formed of five variables describing intensity of physical activity, frequency of intensive physical activity, hours/week of intensive physical activity, average duration of physical activity, and participation in structured sports, e.g. in a sports club). The physical activity index has been described in detail by Telama, Yang, Laakso, and Viikari (1997). "One hour a week of intensive physical activity" was coded as one, and sports

club membership was coded as follows: no = 1, yes = 2, yes – once a week = 2, yes – many hours/times a week = 3. High scores on the physical activity index indicated high physical activity.

Biological risk factors measured were BMI (kg/m²), SBP, DBP, HDL-C, and LDL-C. Blood pressure was measured with a random zero sphygmomanometer. All measurements of lipid levels were performed in duplicate in the same laboratory. Standard enzymatic methods were used for measuring levels of HDL cholesterol. LDL cholesterol concentration was calculated using the Friedewald formula (Friedewald, Levy, & Fredrickson, 1972). The use of these methods has been described previously (Porkka et al., 1997; Viikari et al., 1991).

2.2.5 Pre-employment risk factors (Study III)

The biological and socioeconomic risk factors at age 12–18 years in 1980 included body mass index, serum lipids (LDL cholesterol, HDL cholesterol, triglycerides), systolic blood pressure, smoking, and parental occupational status (Raitakari et al., 2003). Parental occupational status was categorized on three levels: manual, lower grade non-manual, and higher grade non-manual. Data on the parent with higher occupational status were used (Kivimäki et al., 2006). Family history of coronary heart disease was considered positive if the participant's father or mother had been diagnosed with coronary heart disease, suffered from myocardial infarction, or if either of them had had percutaneous coronary intervention or coronary by-pass surgery at or before the age of 55 years. Information on family history of coronary heart disease was received from the participants in 2001 by asking if their mother or father had been diagnosed by a doctor of having the aforementioned diseases.

2.2.6 Carotid intima-media thickness (Studies I, III, IV)

To assess carotid intima-media thickness, ultrasound studies were performed between September 2001 and January 2002 using Sequoia 512 ultrasound mainframes (Acuson, CA, USA) with 13.0 MHz linear array transducers. The left carotid artery was scanned by ultrasound technicians following a standardized protocol (Raitakari et al., 2003). In brief, a magnified image was recorded of the angle showing the greatest distance between the lumen-intima interface and the media-adventitia interface. A moving scan (duration 5 seconds) that included the beginning of the carotid bifurcation and the common carotid artery was recorded and stored in digital format on optical discs for subsequent off-line analysis. The digitally stored scans were manually analyzed by a single reader who was blinded to subjects' details. The analyses were performed using ultrasonic calipers. From the 5-second clip image, the best quality end-diastolic frame was selected (incident with the R-wave on a continuously recorded electrogardiogram). From this image, at least four measurements of the common carotid far wall were taken approximately 10 mm proximal to the bifurcation in order to derive mean carotid IMT. We have reported a 6.4% between-visit coefficient and a 5.2% between-observer coefficient of variation in the IMT measurements (Raitakari et al., 2003).

2.2.7 Cardiac activity (Study II)

Electrocardiogram (ECG) data were obtained during a three minute period of controlled breathing at a frequency of 0.25 Hz with three Ag/AgCl electrodes placed in a configuration which closely corresponded to the connection V3. During ECG measurement, participants were in supine position. The ECG signal was digitized at 200 Hz. Next, R peaks were identified from a stationary data period and the RR time series and HR time series were formed. HRV was analyzed in both the time domain and the frequency domain. To calculate the frequency domain measures, the time series were detrended and resampled at 5 Hz. The power density spectra of HRV was then computed over

low-frequency and high-frequency bands using a fast Fourier transform algorithm and the Hanning window function. The required measurement interval for HF is approximately 1 minute and for LF approximately 2 minutes (Task Force, 1996).

The frequency domain measures used in the subsequent analyses were HF (0.15-0.5 Hz) and the ratio between LF (0.04-0.15 Hz) and HF (LF/HF). HF is a measure of cardiac parasympathetic activation, whereas LF/HF is thought to reflect sympathovagal balance or sympathetic control of the heart (Task Force, 1996). The time domain measures reflecting parasympathetic activation (Task Force, 1996) were RMSSD and pNN50. RMSSD, pNN50 and HF are highly correlated with each other (Task Force, 1996). HR was measured in beats per minute. HR is largely an expression of the joint effect of the sympathetic and the parasympathetic branches of the autonomic nervous system (Jennings, 2000).

2.2.8 Neuregulin-1 genotyping (Study IV)

Genomic DNA was extracted from peripheral blood leukocytes using a commercially available kit (Qiagen Inc, Hilden, Germany), and DNA samples were then genotyped by employing the 5'exonuclease assay (Livak, 1999). For the PCR, primers and allele-specific fluorogenic probes with conjugated minor groove binder groups were synthesized in conjugation with Applied Biosystems (Foster City, CA, USA) using the sequence (SNP8NRG221533) found on the deCODE Genetics Web site (Stefansson et al., 2003) and GenBank (accession number AF491780). The PCR reaction mixture consisted of genomic DNA, 1 × Universal PCR Master Mix, 900 nM of each primer and 200 nM of each probe. Amplification was performed using the TaqMan Universal Thermal Cycling Protocol. After PCR, end-point fluorescence intensity was measured by the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA), and allelic discrimination was performed. All genotyping was performed blinded to patient outcome. Known samples were included in each run as a quality control. SNP8NRG221533 is located in the first promoter of NRG-1 gene and in the first exon of isoform GGF2 (Stefansson et al., 2003).

2.3 Statistical analyses

Study I. Multiple linear regression analysis was used for examining the association between job strain and IMT, between components on job strain (job demands, job control) and IMT, and between social support and IMT. A 3-way interaction between job demands, job control, and social support was also tested in a linear regression analysis. The interaction was tested using centralized values, and the main effects of age, job demand, job control, and social support and 2-way interactions were included in the model.

Study II. Multiple linear regression analysis was used for examining the association between effort-reward imbalance and cardiac measures (HR, RMSSD, pNN50, HF, LF/HF) and associations of effort and reward with cardiac measures.

Study III. Multiple linear regression analysis was used for examining the association between job strain and IMT. In addition to age, the association between job strain and IMT was additionally adjusted for adolescent risk factors so that their contribution could be evaluated.

Study IV. NRG-1 genotype was treated as a dichotomous variable (1 = T/T, 2 = T/C or C/C) in the analyses. One-way age-adjusted ANCOVA was used to examine the main effects of NRG-1 on IMT and on job strain. The interaction between job strain and NRG-1 genotype on IMT was tested using centralized values in a linear regression analysis in a model including the main effects of age,

job strain, and NRG-1 genotype. The associations between job strain and IMT in the NRG-1 groups were evaluated using multiple linear regressions.

3. RESULTS

The main results of the four studies are summarised below. Details of the studies are available in the original publications.

3.1 The relationship between job strain and early atherosclerosis

As presented in Table 3 job strain (tertile-based score) was significantly associated with IMT after adjustment for age in men ($\beta = .102$, $p = .019$). This association was not attenuated by additional adjustments. As shown in Table 4 these results could be replicated with two other job strain formulations. Job demand was also significantly associated with IMT in men after adjustment for age ($\beta = .096$, p. = .028), whereas job control was not ($\beta = -.037$, $p = .396$). No significant associations for job strain, job demand or job control with IMT were found in women.

Social support was not associated with IMT either in men or in women in an age-adjusted model. Three-way interaction effects of social support, job demand, and job control on IMT were analyzed for each gender using centralized values. No three-way interaction effects on IMT were found beyond the two-way interactions and main effects of age, job demand, job control, and social support.

Table 3. Linear Regression Analyses of Job Strain and CHD Risk Factors Predicting Carotid IMT in Men

	Model 1 Adjusted for age			**Model 2** Adjusted for socio-economic status			**Model 3** Adjusted for health related behaviors			**Model 4** Adjusted for social support			**Model 5** Adjusted for biological variables			**Model 6** All adjusted		
	Adjusted R^2		.105	Adjusted R^2		.103	Adjusted R^2		.103	Adjusted R^2		.111	Adjusted R^2		.128	Adjusted R^2		.127
Predictor variable	Beta	p	R^2 change	Beta	p	R^2 change	Beta	p	R^2 change	Beta	p	R^2 change	Beta	p	R^2 change	Beta	p	R^2 change
Age	.315	<.001		.309	<.001		.323	<.001		.320	<.001		.271	<.001		.275	<.001	
Education				-.043	.447											-.038	.495	
Occupation				.034	.552											.026	.645	
Smoking status							-.007	.886								.000	.994	
Alcohol consumption							.011	.811								-.012	.799	
Physical activity							.053	.240								.045	.329	
Social support										.088	.052					.080	.075	
BMI													.160	.001		.156	.001	
HDL-C													.039	.388		.035	.455	
LDL-C													.054	.232		.061	.183	
Job strain	.102	.019	.010	.103	.021	.010	.105	.016	.011	.126	.005	.015	.102	.018	.010	.127	.005	.014

Table 4. Multiple Regression Analyses of Different Formulations of Job Strain Predicting Carotid IMT in Men

	Age adjusted			Fully adjusted[a]		
Job strain formulation	Beta	p	R^2 change	Beta	p	R^2 change
Quadrant term	.032	.458	.001	.040	.367	.002
Linear term	.099	.023	.010	.111	.015	.011
Quotient term	.088	.043	.008	.094	.039	.008
Tertile split	.102	.019	.010	.127	.005	.014
Multiplicative term[b]	.070	.109	.005	.060	.177	.003

[a] Adjusted for age, education, occupation, smoking status, alcohol consumption, physical activity, social support, BMI, HDL-C, and LDL-C.

[b] Additionally adjusted for job demands and job control in both models.

3.2 The relationship between effort-reward imbalance and cardiac activity

Table 5 presents associations between effort-reward imbalance and cardiac measures in women. High effort-reward imbalance was associated with lower RMSSD (β = -.102, p = .027) and lower pNN50 (β = -.109, p = .018) in the age-adjusted model. These associations remained significant after additional adjustments. Positive associations of effort-reward imbalance with HR (β = .078, p = .098) and LF/HF (β = .082, p = .076) and a negative association with HF (β = -.075, p = .102) approached significance in the age-controlled model. Adding other covariates to the model reduced the significance level of these associations to some extent.

Low reward was significantly associated with higher HR in all models in women (β < -.116, p < .010). Low reward was also associated with lower RMSSD (β = .096, p = .036) and lower pNN50 (β = .092, p = .045) in age-adjusted models. Effort was not significantly associated with any measure of cardiac activity. In men, there were no significant associations of effort-reward imbalance or its components with any outcome measure.

Table 5. Linear Regression Analyses of Effort-Reward Imbalance Predicting Heart Rate and Heart Rate Variability in Women (n = 457)

	Heart Rate			**RMSSD**			**pNN50**			**HF**			**LF/HF**		
	Beta	p	R^2 Change[1]	Beta	p	R^2 Change[1]	Beta	p	R^2 Change[1]	Beta	p	R^2 Change[1]	Beta	p	R^2 Change[1]
Model 1	.078	.098	.006	-.102	**.027**	.010	-.109	**.018**	.012	-.075	.102	.006	.082	.076	.007
Model 2	.078	.098	.006	-.097	**.036**	.009	-.105	**.023**	.011	-.070	.125	.005	.073	.113	.005
Model 3	.092	.044	.008	-.107	**.018**	.011	-.114	**.012**	.013	-.078	.086	.006	.076	.099	.006
Model 4	.095	.038	.009	-.107	**.019**	.011	-.116	**.011**	.013	-.075	.097	.006	.072	.116	.005
Model 5	.068	.129	.004	-.090	**.047**	.008	-.100	**.027**	.009	-.063	.164	.004	.065	.164	.004

Model 1 - Adjusted for age

Model 2 - Adjusted for age, educational level, and occupational status

Model 3 - Adjusted for age, educational level, occupational status, BMI, SBP, and DBP

Model 4 - Adjusted for age, educational level, occupational status, BMI, SBP, DBP, and social support

Model 5 - Adjusted for age, educational level, occupational status, BMI, SBP, DBP, social support, smoking status, alcohol consumption, coffee consumption, and physical activity

[1] R^2 Change calculated for effort-reward imbalance.

3.3 Pre-employment CHD risk factors and association between job strain and early atherosclerosis

Only men were included in this study. Most of the adolescent risk factors (BMI, LDL cholesterol, triglycerides, SBP, family history of CHD) predicted adult IMT. Table 6 presents a dose-response relationship between higher job strain and greater IMT after adjustment for age. Further adjustments for risk factors in adolescence separately or together had little effect on this association.

Table 6. Means (mm) of Carotid Artery IMT by Levels of Job Strain Among Men Aged 33–39 Years

Adjustment for risk factor at age 12 – 18 years (in addition to age)	Job Strain			p for trend[1]
	Low (n=111)	Intermediate (n=135)	High (n=112)	
None	0.606	0.616	0.637	0.03
BMI	0.607	0.617	0.635	0.04
HDL-C	0.605	0.616	0.637	0.03
LDL-C	0.606	0.617	0.636	0.03
Triglycerides	0.607	0.617	0.635	0.04
SBP	0.606	0.617	0.635	0.04
Smoking	0.605	0.616	0.637	0.03
Family history of CHD	0.605	0.617	0.637	0.02
Parental occupational position	0.608	0.618	0.639	0.03
All	0.619	0.619	0.639	0.03

[1] Based on linear regression analysis (low strain=1, intermediate strain=2, high strain=3).

3.4 Neuregulin-1 genotype as a modifier of the association between job strain and early atherosclerosis

The percentage of participants carrying genotypes T/T, T/C, and C/C were 33.6%, 48.5%, and 17.9% in men and 31.2%, 52.1%, and 16.6% in women, respectively. A significant association between NRG-1 and IMT was found in women ($F(1,346) = 6.029$, $p = .015$). Adjustments for social support and other CHD risk factors did not attenuate this association. Women with the T/T genotype had thicker IMT compared to the women in the other genotype group (0.60 ± 0.10 and 0.57 ± 0.09 mm [mean ± SD], respectively).

A significant interaction between job strain and NRG-1 genotype group on IMT was found in men ($\beta = -.180$, $p = .040$) but not in women. Age-adjusted regression models describing this interaction among men are presented in Table 7. A significant association between job strain and IMT was produced in the T/T genotype ($\beta = .245$, $p = .006$) but not in the other genotype group (T/C and C/C combined; $\beta = .034$, $p = .585$). The association found in the T/T genotype was not attenuated by additional adjustments.

Table 7. Linear Regression Analyses of Job Strain Predicting Carotid IMT in Neuregulin-1 Genotype T/T and in a Group Comprising Genotypes T/C and C/C in Men

	Neuregulin-T/T (n = 120)		**Neuregulin-T/C and C/C** (n = 237)	
	Beta	p	Beta	p
Model 1	.245	**.006**	.034	.585
Model 2	.255	**.005**	.035	.572
Model 3	.257	**.004**	.037	.544
Model 4	.291	**.001**	.060	.346
Model 5	.227	**.011**	.025	.678
Model 6	.281	**.003**	.058	.365

Model 1 - Adjusted for age
Model 2 - Adjusted for age, educational level, and occupational status
Model 3 - Adjusted for age, smoking, alcohol consumption, and physical activity
Model 4 - Adjusted for age and social support
Model 5 - Adjusted for age, BMI, HDL-C, LDL-C, SBP, and DBP
Model 6 - Adjusted for age, educational level, occupational status, smoking, alcohol consumption, physical activity, social support, BMI, HDL-C, LDL-C, SBP, and DBP

4. DISCUSSION

4.1 Work stress and atherosclerosis as indicated by IMT

Our study showed a significant association between job strain (indicated by a combination of low job control and high demands) and increased thickness of the carotid intima-media (IMT) in men. The association was not accounted for by other known risk factors for atherosclerosis, such as age, social support, socio-economic status, smoking, alcohol consumption, physical activity, body mass index, and serum cholesterol. Furthermore, pre-employment risk factors did not have a confounding effect on this association. High job demands explained a larger proportion of the effect of job strain on IMT than did low job control. NRG-1 genotype moderated the job strain – IMT association in men so that the association was found only in carriers of T/T genotype of the NRG-1 gene. In women no significant relationship between job strain or its components and IMT was found but effort-reward imbalance was associated with lower heart rate variability, a predictor of atherosclerosis.

In line with our results for men, previous studies have found associations between components of job strain and IMT (Everson et al., 1997; Lynch et al., 1997; Muntaner et al., 1998; Nordstrom et al., 2001). However, null findings between job strain and IMT have also been reported. Rosvall et al. (2002) and Muntaner et al. (1998) found no association between job strain and IMT in men who were substantially older than our study population. Their findings accord with research on CHD in which weaker associations between job strain and CHD were found in samples with participants above age 55 than in samples with participants under that age (Theorell & Karasek, 1996). Selection effects may contribute to such differences. As most studies examining associations between job strain and CHD have included subjects in full-time employment, their results may show somewhat weaker associations than results from samples that include participants that have lost their jobs. This is caused by “the healthy worker effect”, that is, healthy people tend to remain in the work force, while those with the most health problems tend to select themselves out. This effect is likely to be emphasized in older populations (as CHD is more common in older people), leading to differing research findings for different age groups. Other potential explanations for null findings include increased masking of conventional risk factors at older ages, and reduced accuracy of job strain assessment for employees older than 55.

We found that higher job demands were associated with higher IMT. Moreover, this association largely explained the effect of job strain on IMT. The results of a recent study by Kuper and Marmot (2003) suggest that the role of job demands may be stronger than earlier research has indicated (Bosma et al., 1998; Schnall et al., 1994). Our results of IMT are in line with this suggestion.

Social support was not associated with IMT. The enlarged hypothesis of the demand-control-support model was also not supported by the present results. Although this confirms the results of earlier research (de Jonge & Kompier, 1997), some methodological limitations may have contributed to our null findings. Despite our fairly large sample size, it is possible that our analyses lacked sufficient statistical power to measure the three-way interaction. The fact that we did not measure social support specifically as support at work but merely as a general measure of social support received from family and friends may have also played a role.

It is not surprising that we found no association between job strain and IMT in women. It has been noted that the job strain hypothesis has not received as much support in women as it has in men (Theorell & Karasek, 1996). The stress related to unpaid work done at home may confound the job strain associations in women, as women still take the main responsibility for most tasks at home (Hall, 1992; Lundberg & Frankenhaeuser, 1999; Niemi, 1994). In addition, CHD develops later in women than in men (Bello & Mosca, 2004). It may have been difficult to find associations between

job strain and cardiovascular health in young women because measurable differences had not yet developed.

To conclude, according to the results of the current study, higher job strain seems to be associated with higher IMT (indicating atherosclerosis) in men but not in women. As compared to job control, job demand appears to be mainly responsible for this association. Pre-employment risk factors could not explain the association between job strain and IMT in men. In the present study, social support was not associated with IMT and there was no three-way interaction between job demand, job control and social support.

4.2 Work stress and risk for developing atherosclerosis indicated by cardiac measures

We found that higher effort-reward imbalance was associated with lower levels of HRV indices, namely RMSSD and pNN50, among women but not among men. These associations were not attenuated by additional adjustments for educational level, occupational status, BMI, blood pressure, social support, smoking, alcohol and coffee consumption, and physical activity. Accordingly, associations of high effort-reward imbalance with high HR and LF/HF and with low HF approached significance in women.

Our results suggest that women with high effort-reward imbalance tend to have low vagal tone, indicating low parasympathetic activation. In addition, high LF/HF and HR combined with low vagal tone indicated higher sympathetic activation in women with high effort-reward imbalance. Low parasympathetic activation (Myrtek, Weber, Brügner, & Müller, 1996; Rozanski & Kubzansky, 2005) combined with high sympathetic activation (Matthews, Gump, & Owens, 2001; Rozanski & Kubzansky, 2005) characterizes the presence of chronic stress. As low HRV has been associated with atherosclerosis and found to predict CHD, our results also imply that, in women, autonomic activation may be one of the mechanisms through which high effort-reward imbalance may cause higher risk for developing atherosclerosis and CHD.

Further analyses of the components of effort-reward imbalance showed that, in women, low rewards were associated with high HR and reduced vagal activity (RMSSD and pNN50), whereas effort did not reach significant associations with any cardiac measure. Thus, rewards seem to explain a larger proportion of the associations of effort-reward imbalance to HR and HRV indices than effort. This result was expected. Reward, but not effort, has previously been found to increase cardiovascular mortality (Kivimäki et al., 2002). Furthermore, reward contains components, such as fair treatment, that have predicted cardiovascular mortality and CHD on their own (Elovainio, Leino-Arjas, Vahtera, & Kivimäki, 2006; Kivimäki et al., 2005).

In men, there were no significant associations for effort-reward imbalance, reward, or effort with any cardiac measure. It is important to note that in previous research the association between work stress and CHD has generally received more support in men than in women. This is also in accordance with our results on associations between job strain and IMT in Study I.

The gender specificity of our current findings on association of effort-reward imbalance and reward with cardiac measures may be explained by general stress-related differences in autonomic nervous system function between men and women. It has previously been shown that women tend to have more pronounced HR responses to stress (Allen, Stoney, Owens, & Matthews, 1993; Collins & Frankenhaeuser, 1978; Girdler, Turner, Sherwood, & Light, 1990; Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004) and possibly more pronounced parasympathetic withdrawal in reaction to stress compared to men (Collins & Frankenhaeuser, 1978; Girdler et al., 1990). Higher level of vagal tone in women (Antelmi et al., 2004; Stolarz et al., 2003) makes larger decreases possible in women than in men. Therefore, it is conceivable that associations between stress (effort-reward imbalance) and parasympathetic function are more readily recognizable in women than in men.

Sympathetic reaction, on the other hand, may be attenuated in pre-menopausal women because of the effects of estrogen (Du, Riemersma, & Dart, 1995; Komesaroff, Esler, & Sudhir, 1999). Consequently, associations between stress and sympathetic function would be likely to be more pronounced in men than in young women. The reason why we did not find an association between effort-reward imbalance and LF/HF in men may relate to the fact that LF/HF does not measure sympathetic control alone but reflects parasympathetic activity as well (Task Force, 1996). Role of pre-employment risk factors was not examined in relation to effort-reward imbalance and HRV. Its role could be explored in future studies.

In sum, the results of the present study imply that higher effort-reward imbalance may be associated with lower HRV (indicating higher CHD risk) among women but not among men. As compared to effort, reward seems to be mainly responsible for this association. Furthermore, low rewards may be also associated with higher HR in women.

4.3 Genetic susceptibility

To our knowledge the current study is the first to examine genotype influences interacting with job strain. Although it is known that a given level of strain does not necessarily induce a corresponding CHD risk in all individuals, factors predicting groups at a greater risk have remained unclear. This study shows that an innate genetic predisposition may act as such a moderating factor. In Study IV we found that the relationship between job strain and IMT was evident only among men with the T/T genotype of the NRG-1 gene, but not among the other two genotypes. Thus, the T/T genotype of the NRG-1 gene may be a marker of genetic susceptibility to the adverse effects of job strain on atherosclerosis in men. In women, no corresponding job strain genotype interaction was found.

Differences in the development and functioning of the autonomic nervous system between T/T and other NRG-1 genotypes are potential explanatory factors for the NRG-1 genotype interaction. During job strain the T/T genotype could, for example, generate exceptionally high sympathetic activity, which has been associated with arterial wall thickening (Dinenno, Jones, Seals, & Tanaka, 2000).

The lack of interaction of job strain with the NRG-1 genotype in women is not surprising, because we were unable to find an association between job strain and IMT among women in our data and because the job strain hypothesis has not received as much support in women as it has in men (Theorell & Karasek, 1996), as discussed above. However, we found that women with the T/T genotype had thicker IMT compared to the women in the other genotype group (T/C and C/C combined). Thus, instead of moderating the association between job strain and IMT, NRG-1 genotype was directly associated with IMT in women. Our results are in line with evidence of the multiple roles of neuregulin-1 protein in cardiac development and functioning. Nevertheless, it is difficult to explain why this association was found in women but not in men.

To conclude, the current study indicates that NRG-1 genotype may interact with job strain in men so that higher job strain may be associated with higher IMT (indicating atherosclerosis) only in T/T genotype. Furthermore, T/T genotype, as compared to the other genotypes, might be associated with higher IMT in women.

4.4 Clinical significance

In absolute terms, the effect sizes of our results seem rather small. However, there are at least two reasons why large effect sizes cannot even be expected. First of all, in addition to work stress, variance in IMT and in cardiac activity is induced by several other factors (such as factors controlled for in our current studies) meaning that only a small proportion of IMT and cardiac activity can be affected by work stress or even stress in general. Secondly, our participants were young adults and had therefore had relatively short working histories. Consequently the deleterious

effects of work stress had only accumulated during a few years, which is only a fraction of the exposure some older subjects in other studies have had with decades of work history behind them.

4.5 Methodological considerations

A major strength of this study is that the development of atherosclerosis was measured non-invasively with IMT ultrasound, which made it possible to study the early, non-symptomatic phase of atherosclerosis among adults without manifest symptoms of cardiovascular diseases. This kind of information is especially valuable, because little is known about the role of job strain in the early stages of atherosclerosis. A further advantage arising from studying the non-symptomatic phase of atherosclerosis is that no symptoms of CHD were present that could bias the perception of job strain and act as confounders of the associations between job strain and IMT. Another strength of this study is the long follow-up time that made it possible to take the pre-employment risk factors into account.

As our study on work stress and atherosclerosis risk was cross-sectional, no conclusions about cause and effect relationships or temporal order between the constructs can be drawn. However, although we used self-reports to measure job strain and effort-reward imbalance, the possibility of reversed causality (atherosclerosis affecting work stress perceptions) was unlikely as the participants were free from ischemic heart disease and diabetes. Unlike in some previous studies, extensive exclusions because of CVD were avoided because of the age profile of our sample. The possibility of confounding cannot be fully eliminated in epidemiological studies, such as ours, but a major confounding is unlikely, as the findings remained largely unchanged after controlling for a variety of different risk factors from adulthood and adolescence.

Differences between included and excluded participants tended to be small in the current study. Previous attrition analyses, comparing baseline (1980) characteristics in participants and in dropouts of 2001 follow-up, showed that the participants lost in follow-up were more likely to be male and younger (Juonala et al., 2004). Previous age-adjusted analysis indicated that no significant differences between dropouts and participants of 2001 follow-up were found for LDL-C, HDL-C, triglycerides, systolic blood pressure, diastolic blood pressure, and BMI measured at baseline (Juonala et al., 2004). Therefore, in general, the attrition seems not to be systematic. However, in the current study, the youngest age groups might be somewhat underrepresented. As the analyses were conducted separately for men and women, the larger attrition of men is not likely to affect the current results.

In job strain and effort-reward imbalance research, a large variety of different scales have been employed to indicate the components of the Demand-Control model and effort-reward imbalance model. To measure job control a standard questionnaire was used (Karasek, 1985). To indicate demands, the Occupational Stress Questionnaire, a non-standard measure of workload, was employed, as this measure has been widely used in Finland (Elo, 1994; Elo, Leppänen, Lindström, & Ropponen, 1992). Effort and reward were also measured with items derived from the Occupational Stress Questionnaire. Further research is needed to assess whether our findings can be replicated using more standard measures of job demands and effort and rewards, such as the Job Content Questionnaire (Karasek, 1985) and the Effort-Reward Imbalance Questionnaire (Siegrist et al., 2004). Future studies on effort-reward imbalance model should also examine the moderating role of overcommitment, a component, not included in the present study.

Tertile-based formulation of job strain was used in the current study. In addition to this formulation there are many other ways to construct job strain variable (Landsbergis et al., 1994). The results of Study 1 could be produced with several job strain formulations indicating the robustness of the findings.

As our findings are the first results on the interaction between genotype influences and job strain, they should be taken cautiously. In addition, it has to be noted that the effects of the NRG-1

SNP examined in the current study may alternatively be explained by a possible linkage to other SNPs of the neuregulin-1 gene. Studies examining multiple SNPs or haplotypes are needed to clarify this issue. However, as mentioned, the current study is the first to report an interaction between a genotype and job strain associated with atherosclerosis. The present study, therefore, opens a new area of work stress research.

4.6 Conclusions and practical implications

The present results have provided evidence that work stress, measured by the demand-control model and the effort-reward imbalance model, may be related to deteriorating cardiac health already in early adulthood prior to the manifestation of actual symptoms of CHD. Evidence for this association was found in both men and women, although separate studies, using different conceptualizations of work stress and different end points, showed diverging results for men and women. More research is needed to explain these diverging results and to explore the possible mechanisms behind the differences between the sexes. In particular, whether the effects of stress on cardiac health are mediated through different pathways in men and women? As discussed above, the negative effects of stress may be mediated to a greater extent, for example by changes in sympathetic activity in men and by changes in parasympathetic activity in women. Regarding the association between job strain and IMT the differing findings between men and women may be explained by the age of the current cohort as CHD develops later in women than in men.

Our results on pre-employment risk factors suggest that risk factors of atherosclerosis and CHD in adolescence do not confound the association between job strain and atherosclerosis. Further studies are needed to confirm this finding.

The interaction for neuregulin-1 genotype with job strain on IMT in men suggests that associations between job strain and atherosclerosis may be complicated by genetic influences. The present study is apparently the first to report genotype influences interacting with job strain. Therefore, our current findings suggest a new area of research for psychosocial cardiovascular epidemiology. The results of a subsequent study of these data on another gene, catechol-O-methyltransferase, also support relevance of genotype effects (Hintsanen et al., 2006).

The current results imply that genetic influences could, in part, explain the conflicting findings in job strain literature. Genotype distributions may vary in different populations. For example, in NRG-1 gene, extreme population differences have been found to exist in allele frequencies (Gardner et al., 2006). Null findings may be produced for example when relatively few participants are carriers of genotype T/T of NRG-1 gene or another “at risk” genotype of some other gene. Furthermore, some genes may be associated with factors that could lead to selection effects. For example, genotype may influence personality which in turn may influence occupational choices. Therefore, through effects of personality a certain genotype could increase the likelihood of a carrier of this genotype to end up in a high strain job. Hypothetically, if this same genotype would also protect the person from the negative health effects of stress, null findings between job strain and CHD might be produced, as high stressfulness of the work environment and low susceptibility of the person for the effects of stress, would counteract each other. Moreover, genetic variation might influence the coping strategies used under strain as well as the propensity to risk behaviours.

It is important that genetic influences are explored further taking into account that unmeasured genetic influences may act as modifiers in the job strain – atherosclerosis association. Genetic influences may help in identifying the groups that are at risk and inform potential mechanisms underlying the associations between work stress, atherosclerosis, and CHD. It is important to improve the health and working conditions of all employees. However, special attention could be directed to those at the highest risk.

In terms of practical implications, our results support the view that negative health effects of work could be reduced by reducing job strain and by reducing effort-reward imbalance. According to the demand-control model, job strain can be reduced either by increasing job control or by decreasing job demands. However, our current findings indicate that increasing job control alone may not be sufficient to reduce the detrimental effects of work on cardiac health, as associations of job strain with early atherosclerosis were mostly explained by high job demand. In addition, high job demand on its own was associated with increased IMT whereas low job control was not.

Considering the associations we found for reward with cardiac measures and for effort-reward imbalance with cardiac measures, increasing the rewarding aspects of work could be especially efficient for reducing negative health effects of work, as it would simultaneously decrease effort-reward imbalance. Furthermore, our results were produced measuring rewards with other factors than financial compensation. This implies that increasing rewards can be, at least to some extent, realized without increasing costs.

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