Occupational Physical Activity

a n d

Circulatory Diseases

F i n a l R e p o r t

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LIST OF ABBREVIATIONS

CI	Confidence interval
CAS	Carotid artery stenosis
CVD	Cardiovascular disease
IHD	Ischemic heart disease
IMT	Intima media thickness
KIHD	Kuopio Ischemic Heart Disease Risk Factor Study
LTPA	Leisure time physical activity
OPA	Occupational physical activity
RC	Relative change
RCR	Ratio of relative change

ABSTRACT

Background. Low levels of habitual physical activity have been identified as a major risk factor for cardiovascular diseases. However, the evidence for this observation is primarily based on leisure time physical activity. Only few studies examined specifically the effect of occupational physical activity (OPA) and their findings have been inconsistent. In fact, several recent prospective studies linked higher levels of OPA with accelerated progression of atherosclerosis, cardiovascular morbidity, and increases in mortality. Work time determines the intensity of OPA and of other occupational exposures. Long work hours have been associated with myocardial infarction and mortality from coronary heart disease in some studies but not in others. Scarcity of prospective studies, confounding, health-based selection, and lack of repeat exposure measures in longitudinal studies may have been in part responsible for these inconsistent findings.

Objectives. The primary aim of this study was to investigate the effect of work time and different types and levels of OPA on chronic circulatory diseases while addressing key methodological issues by a prospective design, use of repeat measurements of exposures, adjustment for a comprehensive set of confounders, and dealing with the thorny issue of selection bias (the so-called healthy worker effect) by using subclinical outcome measures, i.e. change in carotid artery intima media thickness (IMT) and systolic blood pressure, instead of symptomatic cardiovascular disease or mortality outcomes.

A secondary aim of this study was to investigate whether these occupational risk factors are more strongly associated with change in IMT among men with pre-existing ischemic heart disease (IHD) or carotid artery stenosis (CAS) compared to men without these conditions as would be expected according to the hemodynamic theory of atherosclerosis.

Methods. This population-based prospective study of ultrasonographically assessed carotid intima media thickness (IMT) uses repeat measures of work time and OPA during baseline, 4-year, and 11-year examinations of 621 Finnish men who were 42-60 years old when they enrolled in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD). The KIHD study measured the most comprehensive set of biological, behavioral, social, and psychological cardiovascular risk factors of any study, allowing for the control of virtually all known possible confounders. The association between different measures of work time, energy expenditure, and work postures with 11-year change in maximum IMT was evaluated in regression models adjusting for 21 potential confounders including among other factors cholesterol, body mass index, leisure time physical activity, smoking, socio-economic status, and job stress. Analyses were also performed by baseline cardiovascular health status.

Key Findings. About one third of middle-aged men worked more than the standard 40-hour workweek. Work time was positively associated with accelerated progression of carotid atherosclerosis. Men with preexisting ischemic heart disease or carotid artery stenosis appear to be especially vulnerable to the effects of long work hours. Regardless of the specific occupational conditions that may constitute the pathways for the observed relationships between long work time and progression of atherosclerosis, findings suggest

that reducing weekly and yearly work time could have significant cardiovascular and public health benefits, especially in the aging working population.

The findings of this study do not support the notion that heavy physical labor has ceased to be a potential health hazard in the so-called modern service economy. To the contrary, the study shows that 30% of aging men, including over 50% of those with ischemic heart disease, were still exposed to excessive physical job demands based on current recommended maximum levels for relative aerobic strain. This study demonstrates for the first time that the observed high levels of energy expenditure and relative aerobic strain at work are associated with accelerated progression of carotid atherosclerosis, even after controlling for virtually all known cardiovascular risk factors, including blood pressure, smoking, cholesterol, body mass index, leisure time physical activity, aerobic fitness, socioeconomic status, and psychosocial job factors among others. Older workers, workers with pre-existing ischemic heart disease, and workers with carotid stenosis appear especially vulnerable to the atherogenic effects of increasing levels of energy expenditure.

Prolonged upright work postures are associated with an accelerated progression of atherosclerosis. Prolonged time walking on uneven ground or climbing stairs were the most relevant components of an upright work posture that by themselves were significantly associated with progression of atherosclerosis. The association of a standing work posture with progression of atherosclerosis varied by exposure assessment method used.

A prolonged upright work posture was also significantly associated with long-term increases in systolic blood pressure, a major risk factor for cardiovascular diseases.

Findings are consistent with the hemodynamic theory of atherosclerosis and known occupational risk factors for cardiovascular disease.

Implications. Job design, work organization, occupational health practice, and regulatory statutes dealing with working time and rest schedules need to assure that workers are protected from weekend work, long work hours, prolonged upright work postures, and excessive physical job demands. Protective measures are especially needed for older workers with age- or disease-related reductions in cardiorespiratory fitness, narrowing of carotid arteries, or manifest ischemic heart disease.

Additional research is needed to determine the overall cardiovascular disease burden and societal costs associated with excessive work hours, upright working positions, high levels of energy expenditure, and other occupational cardiovascular risk factors in order to quantify the potential benefits of worksite-based strategies for the prevention of circulatory diseases that are still the number one cause of death in industrialized countries.

TRANSLATION OF FINDINGS

This study shows that even in a so-called service economy the majority of middle-aged men work in non-sitting postures and that physical job demands exceed recommended levels in terms of relative aerobic strain for 30% of all men and for 50% of men with cardiovascular disease. In addition, a quarter of all men work in excess of the standard 5 day work week and more than 40 hours per week.

This study shows that increases in weekly workdays, weekly work hours, average yearly work hours, upright work postures, and high levels of energy expenditure at work were all significantly associated with an accelerated progression of atherosclerosis in the carotid arteries. Upright work postures were also associated with increases in systolic blood pressure. Both arteriosclerosis and elevated blood pressure are known strong risk factors for circulatory diseases such as ischemic hearth disease, myocardial infarction, or stroke.

The study is consistent with recent findings in the literature that – in contrast to leisure time physical activity – high levels of occupational physical activity may be a risk factor for cardiovascular diseases and mortality. This study observed an exponential dose-response-relationship between several measures of occupational physical activity and progression of atherosclerosis and could not detect any threshold effects. Similar results were seen for working time. The study also showed that employees with existing ischemic heart disease or beginning stenosis of their carotid arteries were especially vulnerable to the effects of overtime work and high levels of occupational physical activity.

Regulatory statutes dealing with working time and rest schedules need to assure that workers are protected from weekend work, long work hours, prolonged upright work postures, and excessive caloric job demands. Such prevention measures are especially needed for older workers with age- or disease-related reduced cardiorespiratory fitness, stenosis of carotid arteries, or manifest ischemic heart disease.

Design of workstations, work schedules, and job tasks should allow workers to limit exposure to prolonged upright working positions and to take rest breaks when needed. Evidence-based guidelines are needed to assist employers, workers, and occupational health and safety professionals in the evaluation and abatement of health risks associated with occupational physical activities, including the special circumstances of overtime work, shift work, and working consecutive days without traditional weekend rest periods. Job evaluations using ambulatory heart rate monitoring to estimate relative aerobic strain should be considered routinely for worker placement into jobs that require physical efforts other than mostly sitting at a desk, and for workers with prevalent cardiovascular disease. Such monitoring efforts should also be integrated in ergonomic job redesign and the planning of work modifications to promote cardiovascular health in employees who return to work after prolonged illness, periods of unemployment, or from other situations that may have led to their physical deconditioning.

Intervention studies are needed to determine feasibility and effectiveness of the intervention strategies suggested above.

Finally, additional research is needed to determine the overall cardiovascular disease burden and societal costs associated with excessive work hours, upright working positions, and high levels of energy expenditure in order to quantify the potential benefits of such worksite-based strategies for the prevention of circulatory diseases that are still the number one cause of death among men.

POTENTIAL PUBLIC HEALTH IMPACT

The study is consistent with recent findings in the literature that – in contrast to leisure time physical activity – high levels of occupational physical activity may be a risk factor for cardiovascular diseases and mortality. Study findings suggest that reducing work time and relative aerobic strain at work could have significant cardiovascular and public health benefits, especially in the aging working population.

Medical and occupational health and safety professionals need to integrate study findings into medical practice, job placement, return-to-work procedures, and ergonomic design of job tasks and workstations. Relative aerobic strain at work should be monitored among employees who perform physically demanding job tasks to reduce cardiovascular risks that have been associated with increasing levels of occupational physical activity.

Regulatory statutes, medical practice, and occupational health and safety interventions need to address the increased vulnerability of aging workers and of workers with cardiovascular diseases exposed to physical work demands, long work hours, and inadequate rest periods.

SCIENTIFIC REPORT

A. **BACKGROUND**

Circulatory diseases (CDs) - heart attack, stroke, and high blood pressure, among others – are responsible for more deaths than any other disease or injury in the U.S. Cardiovascular disease alone is the cause of 41 percent of all deaths, and an estimated 250, 000 to 350,000 people annually die of heart disease.[1] Stroke is the third leading cause of death in the U.S.,[2] and nearly a quarter of the population, about 60 million Americans, are considered hypertensive.[3] Rice et al. estimated that these CDs generate more costs than any other disease or injury. [4] The National Heart, Lung, and Blood Institute (NHLBI) estimated the costs to be $189 billion in 1992 and 274 billion in 1998.[5] This represents an increase in costs of more than 5% per year. Few estimates of the number of deaths and costs of occupational CDs are available, however.[6-9] The most recent study estimates 35,459 work-related deaths due to CDs, 289,320 work-related incidence cases of CDs, and a total cost of $15.4 billion in 1992.[10] These figures assume an occupational origin of 15 percent of all CDs, while previous assumptions based on the epidemiologic literature ranged from 1 to 40 percent.[6-9, 11]

Only one study of CDs attempted to provide estimates for specific job-related causes (as opposed to all job-related causes) and assigned 1% of CDs to noise, 7% to shift-work, 2 % to passive smoking, 3-13 % to job strain, and 42 % to sedentary work. [11, 12] Regardless of the methodological limitations of such estimates, sedentary work definitely ranks first on the list. This is in agreement with risk factor assessments in the general population, where the attributable risk of a "sedentary lifestyle" has also been ranked first, ahead of other traditional risk factors including smoking, hypertension, blood lipids, and obesity, in that order.[13] Clearly, sedentary work needs to be considered a major determinant of CDs with a substantial potential for primary prevention at the workplace.

In contrast to leisure time physical activity, little is known about the risks and benefits associated with specific physical work activities as they relate to circulatory health. Most epidemiological studies to date focused on leisure time physical activity and either failed

to differentiate between physical activity at work and during leisure time, or excluded occupational activities from their analyses altogether.[14-17] Moreover, while the beneficial effects of leisure time physical activity on the circulatory system are relatively well established, the literature about the health effects of occupational physical activity remains inconsistent.[18] Pioneering research in the 1950s and 60s comparing different occupational groups identified sedentary work as an important risk factor. [19-21] [22] However, these earlier studies were vulnerable to alternative explanations because of selection bias and uncontrolled confounding.

For example, in their pioneering works, Morris et al. attributed the lower risk of coronary heart disease among London bus conductors versus drivers to the sedentary work of the drivers.[21] Since then research has shown that the excess risk in cardiovascular disease among urban bus drivers is not experienced by rural bus drivers, and, in urban bus drivers, is independent of both leisure time and occupational physical activity. [23, 24] Instead the excess risk is now thought to be attributable to the high levels of job stress experienced by urban bus drivers,[25-28] a factor that may have confounded the reported association with sedentary work.[18, 29] Clearly, the lack of control for psychosocial job factors in most studies on occupational physical activity is a major limitation of the extant literature. The proposed study can address this limitation because, in addition to detailed information on leisure time and occupational physical activity, the Kuopio Ischemic Heart Disease Risk Factor Study collected data on job stress and other psychosocial factors. In fact, previous research demonstrated significant associations between job stressors and progression of atherosclerosis,[30] myocardial infarction, and cardiovascular and all cause mortality in this population.[31]

Among the higher quality epidemiological studies published during the last two decades (using more representative samples of the general population and adjusting at least for some confounders) some found reduced levels of risk,[32-36] some found no associations,[33, 36-42] and some found an increased risk [29, 43, 44] of cardio- and cerebrovascular disease with higher levels of occupational physical activity. Some studies show differential effects for occupational and leisure time physical activity, with leisure time physical activity being protective and occupational activity constituting a risk.[44] In the Framingham Study patterns differed by diagnostic groups: a protective

effect of habitual (leisure and occupational combined) physical activity was seen for cardiovascular mortality but the opposite effect was found for non-cardiovascular and all-cause mortality. Physical work demands showed a similar trend. [37] Therefore, to this date it remains unclear if and what type and level of occupational physical activity is beneficial.

Of special concern are three recent prospective studies investigating occupational physical activity at work independently reporting that more occupational physical activity is associated with increases, not decreases, in the risk of myocardial infarction and all-cause mortality.[29, 43] The WHO-sponsored 6-year prospective population-based MONICA study in Augsburg, Germany, found that occupationally physically active men experienced a 26 percent increased risk of myocardial infarction and a 91 percent increase in all-cause mortality after controlling for several confounders.[43] All-cause mortality was also elevated during 21 years of follow-up for Israeli government employees performing mainly physical labor. [44] Most recently, results from the CORDIS study of industrial employees in Israel show a hazard ratio of 1.82 (95%CI 1.18 - 2.81) for all cause mortality in workers with high physical workloads compared with workers having a low workload. Similar trends were noted for cardiovascular disease and cancer mortality. [29] Discussing these unexpected findings the authors propose that lack of control of confounding psychosocial job factors[43] or the failure to account for static working posture[29] may be the reason for these controversial results. However, no prospective study of occupational physical activity, or leisure time physical activity, for that matter, exists that controlled for these putative confounding variables, i.e., job stress and static work posture. Similarly, other reviewers noted that inconsistencies in the literature are at least partly attributable to the varying definitions of physical activity, the failure to take working posture into account, lack of variation in physical activity in homogenous samples, reporting and selection bias, and lack of control for confounding.[18]

There are also known cardiovascular risks associated with high levels of physical activity which could contribute to inconsistent findings. Persons with compromised coronary circulation may develop angina or acute myocardial infarction during vigorous activity.[45, 46] Arrythmias may be precipitated by a combination of exertion and

underlying heart disease, and some can lead to sudden death.[47-50] Work physiologists recognize the beneficial training effects of dynamic leisure time physical activity but report that heavy dynamic and, especially, static work on the job can have more of an overloading than a training effect on the cardiovascular system.[51-54] In contrast to popular perception that heavy work has become rare in industrialized countries, data from the 1990 National Health Interview Survey indicate that a large proportion (44%) of the working age population engages in hard physical activity during the work day; with 20 % reporting 1-4 hours of hard physical work per day, and 23 % more than 5 hours. Fifty percent of those reporting at least one hour of hard physical labor did not report any leisure time physical activity. A survey of Quebec, Canada, showed that 59% of workers (and 81% of those under age 25) work primarily in a standing position.[55] Clearly, a systematic investigation of the health effects of occupational physical activity needs to address both low and high levels of occupational physical activity as potential risk factors, and take the type of activity (static/dynamic), work posture, and leisure time physical activity into account.

Some specific limitations of extant studies of occupational circulatory diseases need to be addressed. Several studies have linked exposure to specific physical and psychosocial job factors with cardiovascular disease and mortality [56-60] but, similar to studies on physical activity at work, findings have also been both positive and negative.[57, 61-63] One major difficulty in examining the role of workplace factors in cardiovascular disease in general is the health-based selection of individuals in and out of specific work environments. Studies of chronic disease such as angina pectoris, myocardial infarction, and stroke and associated mortality are especially vulnerable to these selection effects. Persons with impaired health and higher seniority migrate into less demanding jobs which could lead to a spurious association between low demands at work and morbidity or mortality outcomes. Studying earlier, asymptomatic stages of the atherosclerotic disease process, can help avoid these selection issues. The development of ultrasound measurements able to detect beginning atherosclerotic changes in the carotid arteries allows researchers since the 1980s to look at the relationship between work characteristics and the progression of atherosclerosis in earlier, asymptomatic stages before disease-based selection effects occur.[64, 65] Ultrasound measurement of intima

media thickness (IMT) in the carotid arteries has been shown to be reliable, to relate to the extent of disease in the coronary arteries, and to have predictive validity with regard to risk of coronary events.[65-67] The current research takes advantage of this strategy to circumvent the thorny issue of selection bias in occupational epidemiology. Specifically, for each dimension of occupational physical activity, planned studies of morbidity and mortality outcomes are complemented by the study of progression of atherosclerosis in the carotid arteries. Repeat ultrasound measures of intima media thickness in both carotid and femoral arteries are the basis for measuring the atherogenic effects of occupational physical activity before any clinical manifest vascular disease with activity-related symptoms (e.g., angina pectoris or claudicatio intermittens) may have caused the participants to select in or out of specific jobs or to change the level of either occupational or leisure time physical activity. Any associations between physical activity and progression of atherosclerosis in asymptomatic individuals are less prone to selection bias and therefore especially valuable for a causal interpretation.

Based on previous research, hypotheses about the direction of the association need to be two-sided and allow for u-shaped relations and thresholds. The hypothesis of beneficial effects of occupational physical activity relies on respective evidence about the beneficial effects of leisure time or overall habitual physical activity. [14, 17] U-shaped dose-response curves need to be considered because they were reported in the previous literature.[68, 69] The hypothesis of detrimental effects of occupational physical activity derives from studies linking higher levels of activity with cardiac arrythmia and sudden death[47-49] and three relatively recent epidemiological studies mentioned above. [29, 43, 44] Since both hypotheses are biologically plausible, the goal of this research is to determine the overall net effect of the different mechanisms involved.

In addition to overall measures of energy expenditure at work, this research project addresses other dimensions of occupational physical activity, specifically the effects of a predominantly upright (standing or walking) work posture compared to sitting postures. The need for such an investigation has become apparent after two recent studies identified standing at work as a major risk factor for both progression of

atherosclerosis[70] and all-cause mortality.[29] For the first time, these two studies investigated standing at work separately from sitting at work. Previous studies typically combined work in a sitting posture with light work in a standing posture into a single category labeled – misleadingly - "sedentary work." Investigators from the Kuopio Ischemic Heart Disease Risk Factor Study reported that the amount of standing at work predicted 4-year progression of atherosclerosis in a population-based sample of 584 Finnish working men.[70] Most strikingly, men with pre-existing atherosclerosis of the carotid arteries (measured by ultrasound at baseline) or with ischemic heart disease (measured by questionnaire, ECG, and medication use at baseline) who reported prolonged standing at work had a 3-fold and 9-fold, respectively, increased progression of atherosclerosis compared to men not standing at work. These results were statistically significant and took into account 26 possible confounders including age, biological and behavioral risk factors, leisure time physical activity, heaviness of work, psychosocial job factors, and income, among others. Interestingly, investigators from the CORDIS study found a significantly elevated risk of mortality with standing at work (RR 2.62, 95% CI 1. 06-6.44) but not for sitting (RR 1.44, 95% CI 0.69-3.08) after adjustment for age, smoking, and systolic blood pressure,[29] suggesting that the main portion of the risk previously associated with "sedentary" work may in fact be due to a standing work posture.

The important implication of these findings, if replicated in this research project, is that a change from a predominantly standing work position to a sitting posture or to work in alternating postures may be able to reduce cardiovascular and all-cause mortality independent of changes in the actual work task or associated levels of energy expenditure. For example, cashier work in a supermarket can be performed in either a standing or sitting position. While the former is customary in North America, the latter is customary in most European countries, indicating a substantial potential for primary prevention. To fully appreciate this possibility for prevention one needs to consider that the ratio of static/dynamic muscle work is higher during standing than sitting, and that static work leads to different physiological responses than dynamic work does.[71] For example, physiological research has shown that static muscle contractions even in small

muscle groups lead to prolonged elevations of blood pressure, while dynamic work, performed at an identical level of energy expenditure, reduces blood pressure.[71-73] Such changes in blood pressure could be one of the main pathways for the observed effects of a standing work posture. However, other pathophysiological pathways may also play a role. Building on an established hemodynamic theory of atherosclerosis, we suggest a broader explanatory framework for these findings which not only explains why standing may cause the progression of atherosclerosis but also why progression is faster among individuals with pre-existing ischemic heart disease or sonographically determined arterial stenosis, and why researchers in the Framingham study[74] found a high correlation between varicose veins and coronary heart disease.[70] This framework is built on a biological model of disease causation which rests on established hemodynamic and humoral changes triggered by long-term standing, i.e., venous pooling during standing leading to reduced plasma volume, increased heart rate, increased pulse pressure, and changes in intravascular turbulence and wall shear stress causing injury and inflammatory processes in the arterial wall manifesting as atherosclerosis (see Attachment B1).[70] Increased turbulence and resulting changes in shear stress of the arterial walls are thought to be the main hemorheologic phenomena that induce endothelial damage in human a*rteri*es.[75-77] Such endothelial damage sets the stage for absorption of lipids and other pathogenic substances and cells into the arterial wall leading to an inflammatory process currently believed to be the basis of intima media thickening, the formation of atherosclerotic plaques, and stenosis of the arteries.[78] Since wall shear stress is an exponential function of vessel radius, such changes in lumen diameter and endothelial surface structure will lead to increasing hemodynamic changes during progression of lumen-reducing atherosclerosis, explaining the higher rate of progression of atherosclerosis in individuals with pre-existing beginning stenosis.[70]

This model is consistent with empirical evidence for the co-emergence of varicose leg veins and high incidence of atherosclerotic diseases in the Framingham study, a finding which could not be explained by traditional risk factors.[74, 79] According to the hemodynamic model, varicose veins contribute to atherosclerosis by an increased venous pooling during standing leading to a further reduction in plasma volume, triggering the

Renin-Angiotensin-system, increasing heart rate and systolic blood pressure, and resulting in arterial flow changes which in turn lead to atherogenic turbulence and shear stress changes on the arterial wall as described above.

Although the epidemiological literature on the occupational etiology of varicose veins has been considered inconclusive by some reviewers[80, 81], higher quality population-based studies adjusting for confounding factors provide convincing evidence that varicose veins themselves are in part caused by long-term occupational standing.[79, 82-84] A recent investigation of all gainfully employed Danes, with 3-year follow-up showed that prolonged standing at work was associated with a relative risk for first hospitalization due to varicose veins of the lower extremities of 1.85 (95% CI 1.33-2.36) for men and 2.63 (95% CI 2.25-3.02) for women after adjustment for age, social group, and smoking.[83]. While diseases of the arterial branch have been the subject of intensive research efforts during several decades, much less effort has been devoted to the study of circulatory diseases of the venous system, although varicose veins are one of the 10 leading reasons for hospitalization in industrialized countries,[83, 84] and may lead to disabling and sometimes fatal conditions such as thrombophlebitis, thrombosis of deep veins, and pulmonary embolism and infarction. The proposed research will therefore, for the first time in the life of this cohort, gather and analyze data of these important circulatory diseases of the venous system.

The aforementioned studies and pathophysiological mechanism give rise to the hypothesis that prolonged standing at work and the resultant hemodynamic changes may play a causal role in circulatory diseases of both the arterial and venous branch of the circulatory system. However, it is necessary to (1) replicate these findings, and (2) test the standing hypothesis in studies designed with different methodologies before any final etiologic conclusions can be drawn. Especially, the reported link between prolonged standing and progression of atherosclerosis needs to be validated by a prospective study of the association between standing exposure and clinically manifest disease. The proposed investigation will achieve the first task by replicating the findings regarding progression of atherosclerosis at 4-year follow-up in a new study of the same population

with 11 years of follow-up. In this new proposed study, repeat measures of exposure (at 4-year follow-up), and simultaneous consideration of the amount of sitting, walking and other activities will yield more precise risk estimates. The second task will be achieved by conducting a series of new analyses directly linking standing at work with (a) 11-year incidence of manifest CDs, (b) arteriovascular and all-cause mortality, and (c) thrombophlebitis and pulmonary embolism/infarction.

In summary, while lack of physical activity in general, and leisure time physical activity in particular, has been widely recognized as one of the major risk factors for chronic diseases of the circulatory system and all-cause mortality, and while substantial progress has been made in advocating the potential benefits of increasing leisure time physical activity, workplace health promotion programs, and individual- and community–based programs to change such individual behaviors have been of limited success, especially among high risk blue collar and service sector working populations. While epidemiological studies suggest a substantial potential for preventing cardiovascular disease through changes in occupational physical activity, workstation design, and alternating working postures, the extant literature on occupational physical activity and circulatory health is characterized by a lack of information regarding the specific characteristics of beneficial and detrimental activities, inconsistent findings, and considerable methodological problems. This lack of reliable information constitutes a significant barrier for developing effective primary prevention strategies at the workplace. The proposed research overcomes several limitations of previous studies by (a) using a prospective design with 11-year follow-up yielding sufficient sample sizes for the study of several cardio- and cerebrovascular morbidity and mortality outcomes, (b) employing repeat measures of physical activity during follow-up to reduce exposure misclassification, (c) addressing the issue of disease-based selection bias with an investigation of pre-clinical (asymptomatic) progression of atherosclerosis (measured directly by ultrasound of both carotid arteries), (d) taking into account an unprecedented comprehensive list of possible confounders including, among others, psychosocial job factors, working posture, and leisure time physical activity, and (e) complementing one-dimensional measures of physical activity based on energy expenditure by the

physiologically important ratio of static to dynamic work and work posture in accordance with a hemodynamic theory of atherosclerosis. The study will provide information needed for counseling both the healthy worker and the employee who has been diagnosed with cardiovascular disease. It is anticipated that this research will provide important information necessary to realize the substantial potential for primary and tertiary prevention of circulatory disease at the workplace.

B. SPECIFIC AIMS

The long-term goal of this project is to yield useful information for the prevention of chronic diseases of the circulatory system, associated disability, and premature death in the aging working population. The primary aim of this study is to determine the effects of different types and levels of occupational activity on cardiovascular health while adjusting for leisure time physical activity, and demographic, biological, behavioral, and psychosocial risk factors including socioeconomic status and job stress. The secondary aim of the study is to investigate interactions of occupational physical activity with pre-existing atherosclerosis of the carotid arteries and ischemic heart disease at baseline.

Specifically, the following hypotheses will be tested (aims 1-5 are aims of the originally proposed study, aim 6 was added later in the course of this project):

(1) Intensity, frequency, and duration of occupational physical activity measured in metabolic units times hours per day (daily energy expenditure) is associated positively or inversely with (a) progression of carotid atherosclerosis (intima media thickness), (b) change in systolic blood pressure (c) incidence of acute myocardial infarction, (d) incidence of cerebrovascular disease including stroke, (d) incidence of cardiovascular mortality, (e) incidence of all-cause mortality, (f) and hospitalization due to thrombophlebitis in the lower extremities or pulmonary embolism/infarction, during 11-years of follow-up.

(2) Type of occupational physical activity is associated with incident circulatory diseases and mortality, during 11 years of follow-up. Specifically, (a) a high ratio of static / dynamic work activities, or (b) a predominantly standing working posture are positively associated with the six outcomes listed above under hypotheses 1 a-f.

(3) Occupational physical activity, both in terms of energy expenditure and in terms of type of activity, interacts with baseline cardiovascular health. Specifically, occupational physical activity will be associated with larger relative increases in risk for

progression of atherosclerosis and incidence of circulatory diseases among subjects with (a) pre-existing atherosclerotic carotid stenosis or with (b) ischemic heart disease than among subjects without these conditions.

(4) The effects of occupational physical activity in terms of energy expenditure, ratio of static/dynamic work, and working posture are moderated by the frequency, intensity, and duration of leisure time physical activity.

(5) Associations stated under hypotheses 1-4 are independent of possible confounders including demographic, biological, psychological, and behavioral risk factors, leisure time physical activity, psychosocial job factors, and education and income.

(6) (Additional new hypothesis): Work time (days per week, weekly and yearly work hours, employment intensity) is associated with progression of atherosclerosis after adjustment for possible confounders and interacts with pre-existing cardiovascular disease.

Modification of study aims. The original study plan called for the analyses of two continuous outcome measures, 11-year change in systolic blood pressure (SBP) and carotid intima media thickness (IMT), and of several dichotomous outcome measures (cardiovascular diseases such as myocardial infarction and mortality). The specific aims of this study have in principle not been modified. However modifications were made to the list of predictors and outcomes studied. Specifically, we expanded the scope of the project with respect to the predictor variables of interest. While the original aim 1 called for the examination of the effect of energy expenditure per typical workday at baseline we added four additional measures of energy expenditure and examined their effects on 11-year progression of atherosclerosis. Two of these added measures are relative energy expenditure measures assessed at baseline (relative aerobic strain, percent oxygen uptake reserve), and two are measures of energy expenditure that take exposure changes during follow-up into account (total cumulative amount of energy expenditure during follow-up, and energy expenditure per potential workday during follow-up). In addition, we added a

new specific aim to investigate the effects of several work time measures (daily and weekly work hours, days worked per week, average yearly work hours, employment intensity) on the progression of atherosclerosis while controlling for confounding factors. These expansions on the predictor side were balanced by a reduced number of outcome measures: we focused on the analyses of continuous outcomes (systolic blood pressure, 11-year progression of carotid atherosclerosis) and have not yet analyzed dichotomous cardiovascular disease and mortality outcomes. This shift of focus was necessary because of disruptions in study personnel due to long-term disability of research staff as described in the previous progress report, and because of an unexpected temporary inability of the University of Kuopio to obtain and release mortality and hospitalization data as planned during a couple of years when the University of Kuopio was dealing with an overhaul of their regulations regarding data access. Now all relevant hospitalization and mortality follow-up data have been obtained and the investigators plan to complete outstanding analyses with dichotomous disease outcomes in the near future. However, it should be noted that the outcome measures analyzed so fare are of particular relevance for the assessment of the benefits and risks associated with occupational physical activity because they represent pre-clinical conditions that can be detected before health-based selection out of the job occurs and therefore help to reduce bias due to the so-called healthy worker effect, an issue that has plagued previous research in this area as described in the background section of this report above.

C. **METHODS**

1. Study Sample

Subjects were Finnish men, 42-60 year old at baseline, who participated in the Kuopio Ischemic Heart Disease Risk Factor Study, an 11-year prospective population-based investigation of established and potential risk factors for heart disease and extra-coronary atherosclerosis.

Details of the study design are published elsewhere [85, 86]. In all, 2,682 men who resided in the town of Kuopio or its surrounding rural communities in eastern Finland participated in the study. Baseline data were collected in two cohorts, a random sample of 1,166 men age 54 years initiated in March 1984, and an age-stratified random sample of 1,516 men age 42, 48, 54, and 60 years initiated in August 1986 (participation rate 78%).

Ultrasound measurements of IMT of the common carotid arteries were conducted beginning in March 1987 on 1,229 men in the second cohort. These 1,229 men were invited to participate in a follow-up assessment approximately four years post-baseline. By that time, 47 had died or were suffering severe illness, 37 had moved or could not be contacted, and 107 refused, leaving 1,038 participants (participation rate 84.5%). Of these, 1007 men were alive prior to the start of a follow-up 11-year post baseline. Follow-up exams were scheduled between March 1998 and February 2001. During this time, 58 more men died before being examined, 38 had a severe illness, 27 had moved or could not be contacted, 25 refused and 5 did not participate for other reasons leaving 854 participants in the 11-year follow-up (participation rate 84.8%).

Of the 854 participating in the 11-year follow-up, 223 were excluded because they had not worked at all between baseline and 11-year follow-up, 2 because they did not participate in the 11-year ultrasound examination, 2 because of non-reliable information

on working time (they had reported working 24 hours during their last work day and no alternative information on typical work hours was available for them), and between 6 and 36 men because of missing values on one or more of the exposure variables, leaving between 591 and 621 men for analyses. Missing values for one or more covariates had been replaced by sample mean values in 11, i.e. less than 1.8% of observations. Follow-up time between ultrasound examinations ranged from 9.23 to 13.82 years (mean 11.13 years.)

The following section describes completed studies of the association between different dimensions of occupational physical activity and 11-year change in systolic blood pressure and 11-year progression of carotid atherosclerosis in those men who had worked at least 1 day after baseline, underwent ultrasound examinations of their carotid arteries at both baseline and at 11-year follow-up, and had complete information on all covariates. Sample sizes differed slightly (range from 591 – 621) because of missing information regarding the particular exposure measure studied.

2. Assessment of Cardiovascular Health Outcomes

2.1. Blood Pressure

Blood pressure was measured with a random-zero sphygmanometer after a supine rest of five minutes. Three measurements were then taken while the subject was still supine, one while standing, and two while sitting, in that order. The average of these six measurements was used for our analyses. The difference between systolic blood pressure at baseline and 11-year follow-up defines the outcome variable **"11-year change in systolic blood pressure (SBP)."**

2.2. Intima media thickness of carotid artery walls

Intima media thickness (IMT) measurements served as an indicator of carotid atherosclerosis and were taken at approximately 100 sites along a 1.0 to *1.5* cm section of both the left and right common carotid artery below the carotid bulb using high-resolution B mode ultrasonography. Measurements were made with the subjects supine and the image focused on the posterior (far) wall. Additional technical details are published elsewhere [65]. IMT was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line. Maximum IMT for the subject was defined as the average of the maximum IMT values from the right and left common carotid arteries. The maximum narrowing of the lumen is most relevant for arterial flow changes according to the hemodynamic theory. Our outcome measure was defined as the natural log of maximum IMT at 11 years minus the natural log of maximum IMT at baseline. Reliability of baseline and longitudinal ultrasonic measurements of carotid IMT is high [87-89]. Ultrasound measurements of both carotid arteries at baseline and 11-year follow-up examinations were used to determine **11-year change in carotid intima media thickness (IMT)** as the outcome measure of 11-year progression of atherosclerosis.

2.3. ***Assessment of cardiovascular health status at baseline***

Baseline carotid ultrasound measures were used to identify men with **pre-existing carotid artery stenosis** defined as a minimum 20% arterial lumen reduction through artherosclerotic plaque. **Ischemic heart disease** at baseline was defined by either a history of myocardial infarction or angina pectoris, or current use of ant-angina medication, or positive findings of angina on the London School of Hygiene cardiovascular questionnaire.

2.4. ***Hospitalisation due to cardiovascular diseases***

Records of all study participants were linked to the Finnish national hospitalization registry during each of the 11 years of follow-up. Finnish collaborators linked the data and removed all identifying information before sending them back to the US researchers. Hospital discharge diagnoses were coded according to the $_{S}$tn, 9th, or 10^{th} version of the International Classification of Diseases (ICD). The following diagnoses were recorded for all study participants during follow-up (respective ICD-10 codes in parenthesis): All cardiovascular disesases (100-25), acute myocardial infarction (I21-22), pulmonary embolism and infarction (I26), cerebrovascular disease (I60-69), stroke (I60-64), non-traumatic intracranial hemorrhage (I60-62), cerebral infarction (I63), transient cerebral ischemia (G45), intermittent claudicatio of lower extremities (173.9), Phlebitis and Thrombophlebitis of the lower extremities (I71-72), and varicose veins of lower extremities (I83).

2.5. ***Cardiovascular and all-cause mortality***

Finnish collaborators linked the study data with centralized Finish registries providing date and main cause of death for any participant dying within Finland. All-cause mortality data were provided together with groups of specific causes of death such as violent and non-violent deaths, and deaths caused by cardiovascular disease, myocardial infarction, cerebrovascular disease, stroke, or cancer.

3. Assessment of Work Time and Occupational Physical Activity

Baseline, 4-year and 11-year follow-up information from physical examinations, questionnaire surveys, structured occupational interviews, and record linkage with social security administration data were used to create key (exposure) measures of work time and occupational physical activity that account for periods of unemployment, prolonged sickness absence, and early or disability retirement during follow-up. Missing values of covariates were replaced by occupation or (if not available) by population mean values, in less than *1.7%* of observations.

3.1. ***Data Collection – Survey Instruments and Registry Information***

An occupational physical activity **interview** was administered by trained interviewers at the baseline, four-year, and 11-year follow-up to men who had worked at least some time in the past 12 months. The interview addressed a typical workday. Subjects were asked, with an accuracy of 15 minutes, how long they had performed the following activities at work: sitting, standing, walking on level ground, walking on uneven ground, climbing stairs, or any other activities. The 12 months test-retest correlations for the occupational activity interview was found to be 0.69 indicating good reliability of the instrument [90]. Lifetime job stability among people living in the
Kuopio region is relatively high [91] reducing the probability of misclassification of work activities between follow-up examinations.

A self-administered **questionnaire** was also completed at baseline, four-year, and 11-year follow-up, and provided information on work status (working full time, working part time, unemployed, retired, not working for other reason). Those not currently working were asked about the year when an unemployment or retirement period began and the number of days worked per week in the last job, and number of hours worked per day. For those working, workdays per week, the number of hours and minutes worked per

day, and the number of days they missed work due to illness during the past 12 months were assessed.

The self-administered questionnaire and occupational physical activity interview data were linked to the **pension registers** of the social insurance institution and the central pension security Institute of Finland covering all old-age, disability, and early retirement pensions of the subjects from baseline through the end of May 2000. These administrative retirement data were used to obtain more exact retirement dates (month/year rather than just year) for the men who reported they had retired between follow-up surveys. **Occupation** was assessed by questionnaire and 3-digit coded according to the Finnish Classification of Occupations of Tilastokeskus (Centre of Statistics of Finland).

*3.2. Assessment **of** work time*

We used five different measures of work time in our analyses, three based on information available at **baseline** and two that integrated **repeat** information from baseline, 4- and 11-year surveys and administrative follow-up data on retirement:

(1) Days worked per week at baseline was available from questionnaires.

(2) Hours worked per day at baseline were calculated from interview data excluding lunch, coffee, and other breaks. In ten cases interview data were not available and hours worked per day were assessed by questionnaire excluding lunch breaks only (other breaks were not assessed by questionnaire).

(3) Hours worked per week at baseline were calculated as the product of measures (1) and (2). This is the key traditional work time measure used in most research, labor statistics, and regulatory and labor-management bargaining contexts.

(4) Employment intensity during follow-up is the ratio of calendar years working during follow-up (excluding periods of unemployment or retirement) divided by calendar years of follow-up. It uses self-report to account for periods of unemployment and

registry information to account for any form of retirement. In contrast to the next measure, employment intensity does not account for varying hours worked per week.

(5) Average hours worked per year of employment during follow-up is the average time worked per calendar year when employed during follow-up accounting for hours per week (excluding breaks), vacation time, and employment duration. Within each follow-up segment hours per week were computed as the average of the beginning and final values of the segment. This measure utilizes repeat baseline, 4-year, and 11-year information to better characterize the average work intensity accounting for changes in exposure during follow-up.

3.3. *Assessment of variables needed to determine energy expenditure at work*

We estimate energy expenditure (EE) at work by using interview data on time spent in various **activities at work** during a typical workday and combine this with reference data giving the **energy requirements (kcal/kg/hour)** of these activities. This method was used at baseline and the 4- and 11-year follow-up surveys. Additionally, **cardiorespiratory fitness** and the **body weight** of the subjects were measured at baseline. Other basic data were the **number of days worked per week** at each examination time, and dates of ultrasound examinations. Finally, information about **sick leave** (only for the 12 months before follow-up surveys), **unemployment,** and **retirement** (both for the entire follow-up period) were obtained to estimate the actual time spent working during each follow-up segment. These basic measurements provided the data for constructing 5 measures of EE at work that were used as predictors in this report. We first describe the basic measurement of EE per typical workday at each examination, and the determination of cardiorespiratory fitness. Then we describe the 5 measures of work-related EE in more detail.

3.3.1. Assessment of energy expenditure per typical workday at baseline, 4, and 11 years

EE reflects the duration and intensity of each occupational physical activity. The duration (hours / typical day) of different physical activities at work was assessed by an

occupational interview. The energy requirement of these activities was estimated as multiples of the baseline metabolic rate (MET) in kilocalories/kg/hour of an average male with values of 1.6 for work while sitting, 2.4 for standing, 3.3 for walking on level ground, 4.9 for walking on uneven ground, 7.3 for climbing stairs and a mean value of 3.9 for other non-specified activities based on previously published data [92, 93]. EE in kcal for each reported activity is calculated by multiplying the duration (hours per day) by the respective intensity (MET) and body weight (kg) of the individual. The sum of these estimates gives the EE measured in kcal per typical workday. These measures were obtained at baseline, and the 4-year and 11-year follow-up interviews.

3.3.2. Assessment of cardiorespiratory fitness at baseline

Cardiorespiratory fitness (a.k.a. aerobic capacity or VO_2max) was assessed by a maximal but symptom-limited exercise test on an electrically braked ergometer as explained in detail elsewhere [86, 94, 95]. Oxygen consumption was measured using respiratory gas exchange analysis. Maximal oxygen uptake (VO_2max) was defined as the highest value or the plateau in oxygen uptake and was standardized by body weight and measured as ml 0_2 per kg per minute.

3.4. *Alternative measures of energy expenditure*

Using the basic data described above, the following 5 measures of work-related EE were constructed:

(1) Energy expenditure per typical workday at baseline

This measure is simply the baseline assessment of EE per typical workday using the method that is described above. It does not take account of any changes in the duration or mix of activities during follow-up nor does it account for such things as periods of unemployment or termination of work due to retirement. In contrast, the following measure does take such changes into account.

(2) Total amount (a.k.a. volume) of energy expenditure at work during 11 years of follow-up

Total work-related EE was first calculated separately for the two follow-up segments, 0-4 years and 4-11 years, and these were added to get the result for the full follow-up period from 0-11 years. The first step in these calculations was to determine the number of calendar days (including weekends) during each of the two follow-up segments defined by dates of the "bracketing" ultrasound measurements. The total work-related calendar time in each segment was reduced by vacation, unemployment, sick leave, and retirement. Then, in each segment, the resulting actual duration of work time (in calendar days) was multiplied by the average of the EEs (kcal/calendar day) at the beginning and end of the segment. At each examination time, kcal/calendar day was obtained by multiplying the EE per typical workday by number of workdays per week divided by 7. This latter factor distributed the energy expended in the workweek over the 7-day calendar week.

(3) Energy expenditure per potential 8-hour standard workday during follow-up

This measure is the ratio of the total energy expended during the actual work time from baseline to 11 years divided by calendar time during which the subject could potentially have worked during the follow-up period assuming regular standard 8-hour workdays, 5-day workweeks, and 46 workweeks per year (representing the Finnish standard 1840 work hours per year). In other words, total EE during follow-up is expressed as an intensity measure calibrated to available standard workdays during the same period. If each subject had worked the standard work time between baseline and their final follow-up examination, this measure would be perfectly correlated with the total work-related EE during 11 years of follow-up. It differs from that measure by accounting for some person-to-person variation in the typical length of their workdays, workweeks, and duration of employment during follow-up. In contrast to relative measures of EE taking cardio-respiratory fitness into account (described next), this measure takes into account the potentially available number of regular standard workdays between ultrasound examinations for each individual.

(4) Relative aerobic strain (RAS) at baseline (a.k.a. %VO2max)

RAS is a relative EE measure that expresses the caloric demands of work as a percentage of the individual worker's aerobic cardiorespiratory fitness or maximal work capacity [96]. RAS has traditionally been used to define recommended maximum levels of aerobic work demands. Assessment of RAS was based only on measurement obtained at baseline since this is the only examination time for which VO_2max data were generally available.

(5) Percent oxygen uptake reserve (a.k.a. %VO2Res

Percent reserve oxygen uptake is an alternative relative EE measure that expresses the caloric demands of work in relation to the individual workers' aerobic cardiorespiratory fitness or maximal work capacity as the percentage of reserve oxygen uptake (%VO2Res) [97]. While %VO_2max is based on the total EE at work including the energetic cost of metabolic rate for both rest and work activity, %VO_2Res is based on the EE associated with the work activity only and measured as %VO_2**Res** = (VO_2work – 3.5) / (VO_2max –3. 5) x 100% because the resting EE is 1 MET = 3.5 ml 0_2/kg per minute [97, 98]. In our study, VO_2work was determined by calculating the weighted average of MET during work activities based on the occupational interview multiplied by 3.5 ml/kg per minute. Recently, %VO_2Res has been suggested as the preferred measure of relative EE for use in job analyses and epidemiological field studies because it allows for more adequate comparisons than %VO_2max when EE varies greatly in the study population. A further advantage of this measure is the fact that, in contrast to %VO_2max, %VO2Res corresponds directly to percent heart rate reserve that can be measured more easily in the field than percent oxygen uptake reserve itself [97].

3.5. *Assessment of the proportion of workers exceeding the recommended maximum level of relative aerobic strain at work*

A maximum RAS of 33%VO_2max has traditionally been recommended as a safe level of aerobic work demands for a typical 8-hour workday based on the physiological criteria of a steady state of blood lactate or heart rate [99, 100]. However, no widely accepted

recommendations are available for non-8-hour work shifts to which an increasing proportion of workers are being exposed. Rogers adapted the 8-hour standard to 4-, 10-, and 12-hour work shifts [99]. A recent laboratory study by Wu [101] among 7 young males suggests that recommendations need to be adjusted upward to 34% for 8 hours, further upward to about 43.5% for a 4-hour day, and downward for longer shifts to about 28.5% for a 12-hour day based on a steady-state heart rate plus maximal 10 beats at the end of the work period as criterion for sustainable maximal work efforts. However, empirical laboratory data were not gathered beyond 10-hour periods and extrapolation to longer shifts may be problematic. One of the features of Wu's exponential function used to fit the data is that maximum allowable RAS is not substantially reduced for work shifts that exceed 8 hours. For example, the result of RAS=34% for an 8 hour work day changes to 32.4, 31, 29.7, 28.5, 27.4, 26.4, 25.4, and 24.5% for work days equal to 9, 10, 11, 12, 13, 14, 15, and 16, respectively. These limited reductions for longer work shifts seem somewhat implausible, but unfortunately the literature does not provide an empirical based alternative to this extrapolation outside of the range of the empirical data used by Wu to construct the formula. In acknowledgement of these uncertainties we present the proportion of workers exceeding recommended levels of EE by two assessment methods; the first assuming that all men work standard 8-hour days, and the second with adjustment for length of workdays based on Wu's results.

3.6. Assessment of work postures

Work postures were assessed by both questionnaire and occupational interview. The questionnaire survey instrument asked respondents how much they work in four kinds of work positions: sitting, standing, walking, and (combined into one category) crouching, lying, and crawling. For each item four answer options were provided on an ordinal scale from "not at all" to "very much." Workers, especially those with pre-existing cardiovascular disease, who reported "standing very much" at work suffered a significantly greater 4-year progression of carotid atherosclerosis than those not standing at all at work as reported previously.[102] The pathophysiological model of how an upright work posture may influence progression of atherosclerosis has been formulated

for this earlier study, however, previous analyses were limited to standing and did not differentiate between different types of upright work postures or the type of surface people work and walk on. The occupational interview assessed these factors in more detail and is being used as the primary source for the assessment of work postures in this current investigation.

Specifically, the occupational interview assessed work postures as activities in minutes during a typical workday at baseline, 4-year, and 11-year on a continuous scale with an accuracy of 15 minutes. Activities included **sitting, standing, walking on level ground, walking on uneven ground, climbing stairs,** and other activities not further classified. Exposures to standing, walking (on even or uneven ground), and climbing stairs were combined in a measure of **"upright"** work posture. **Baseline values, weighted averages of baseline,** 4- **and 11-year values, and cumulative measures of duration in each work posture** are being analyzed separately in this study. In addition, measures of work posture in relation to the time spent at work in other activities are being investigated including the **percent of daily work time spent in each posture.**

Information on the daily duration of work in an upright posture was combined with information on the relative amount of time spent at work during follow-up creating an intensity measure of work in an upright position, called **"proportion of time upright at work during follow-up."** Specifically, this measure was created as the total number of minutes in an upright work posture during follow-up multiplied by the ratio of the time actually spent at work during follow-up divided by the total potential work time during follow-up. The potential work time during follow-up was conceptualized as the total standard Finnish work time during the entire follow-up period. Accordingly, the potential standard work-time was calculated as the total number of calendar days between baseline and 11-year ultrasound examinations multiplied by 5/7 x 8/24 x 46/52.2 to convert calendar time into the standard Finish work time, i.e. eight hours per day, five days per week, and – accounting for the legal minimum of vacation and holidays – 46 weeks per year.

4. Assessment of ***Covariates***

In multivariate analyses we adjust for up to 21 potential confounders. They can be grouped into five categories: **(1) demographic and technical factors:** age, participation in an unrelated lipid lowering trial, baseline maximum IMT values, 11-year sonographer (all baseline ultrasounds were conducted by the same person); (2) **biological factors:** blood glucose, fibrinogen, serum LDL cholesterol, serum HDL cholesterol, use of cholesterol lowering medication, systolic blood pressure, use of blood pressure lowering medication, body mass index; **(3) behavioral factors:** alcohol use, smoking, conditioning LTPA, and cardiorespiratory fitness; **(4) socioeconomic status (SES)** measured by personal income; and **(5) psychosocial work-related factors:** social support from coworkers or supervisors, stress from work deadlines, and mental strain at work. SES, psychosocial work factors, and all behavioral factors except cardiorespiratory fitness were assessed by self-administered questionnaires at baseline, 4-year, and 11-year follow-up.

A complete list of covariates and their distribution by cardiovascular disease status is provided in **Tables 1 and** 2. Details of the measurement of these variables have been described previously [31, 103]. In the following we give a short summary of the measurement of some key covariates:

Blood pressure was measured with a random-zero sphygmanometer after a supine rest of five minutes. Three measurements were then taken while the subject was still supine, one while standing, and two while sitting, in that order. The average of these six measurements was used in our analyses. BMI was defined as weight in kilograms divided by height in meter squared at baseline. Use of cholesterol and blood pressure lowering medications was assessed by questionnaire.

Alcohol consumption in grams per week during the past 12 months was assessed with a structured quantity-frequency method using the Nordic Alcohol Consumption Inventory [104]. Cigarette use was a four level categorical variable: never smoked, former smoker, irregular smoker, regular smoker. In preliminary analyses, tertiles of regular smoking were used. The tertiles were then collapsed into one category ("current smoker") because

effect sizes were very similar for these tertiles and the confidence intervals overlapped widely. Conditioning leisure time physical activity LTPA), in hours per year, was measured using a modified version of the Minnesota Leisure Time Physical Activity questionnaire [105] that included the 16 most common leisure time physical activities of middle-aged Finnish men [92]. Respondents were asked to estimate the duration, frequency, and intensity of each of 16 activities performed for each of the 12 previous months. Hours of conditioning physical activities with a mean intensity of 6.0 MET have been associated with decreased risk of myocardial infarction in this cohort [94]. Cardiorespiratory fitness VO_2max , on the basis of respiratory gas exchange, was measured as ml/kg/min by a maximal symptom-limited bicycle ergometer test at baseline [94].

Socioeconomic status (SES) was measured by personal income in Finn Marks, social support at work from coworkers and supervisors was measured by several standard items, stress from work deadlines was measured by 1 item, and a 10-item mental strain index measured job stress as described previously [31].

*S. **Statistical Analyses***

Both repeat-measure and change-score analyses have been performed for the two continuous outcome measures (11-year change in SBP or IMT, respectively). **Log-transformation** of the IMT change outcome measure was performed to assure normality of data for the respective multivariate regression analyses. **Multivariate regression analyses** were performed separately for each predictor variable of interest and separately for each outcome measures. All analyses included several models with incremental adjustment for up to 21 potential confounders including age, baseline IMT and sonographer (in studies of IMT), baseline SBP. The following paragraphs provide more details about the statistical analyses performed.

The baseline characteristics of men with and without cardiovascular disease (IHD or CAS) were compared using t-tests for continuous and chi square tests for categorical variables.

To study the progression of maximal intima media thickness (max IMT) over 11 years of follow-up, we used multiple linear regression analysis implemented in Stata 9.2. The outcome for these analyses was $[\ln(y_F) - \ln(y,)] / At$ where y, is the initial max IMT at baseline and $_{YF}$ is the final max IMT at the follow-up examination At years after the baseline exam. The max IMT values at baseline and follow-up were ln-transformed because this normalized the original skewed max IMT measurements. Also, the residual distribution of the changes in ln(max IMT) was more nearly normal than changes based on max IMT without transformation. The division by At handles variation from the nominal follow-up time of 11 years by expressing change on a per year basis. In these analyses, we included a predictor based on a measure of work-time intensity along with some or all of the 21 covariates listed in Appendix A. Continuous covariates were centered at the mean.

The use of changes in in-transformed max IMT leads naturally to interpretation of results in terms of relative change and percent change. Relative change is $RC = y_F / y$, and notice that $[\ln(y_F) - \ln(y,)] / At = \ln(y_F / y_1) / At$ =1n(RC) / At.

Consequently, for any specified values of predictors, the fitted model provides a way to estimate average ln(RC) / At, symbolized as $E[ln(RC) / At]$. A corresponding estimate of E[RC] over K years instead of per year is obtained from $E[RC]_K = 0 \exp(E[\ln(RC)\ ] K /At)$ where 0 is the back transformation correction factor {Duan},which, with our data, was so close to 1 that it had no effect. Correspondingly, the average percent change for K years, $E[PC]_K=100(E[RC]_K - 1)$.

Several tables present the estimated expected average percent change for 11 years using the coefficients from the fitted model. We calculated estimated relative change for the minimum, median, and maximum value for each work time measure. Other variables were set to zero which corresponds to using the mean value for centered continuous variables and the reference level coded 0 for any predictors used to represent categorical variables. We also studied whether or not the association between the work-time variable and the outcome was different for the subgroups with and without IHD at baseline. Similar subgroup-specific results were examined for subgroups with and without CAS (vascular lumen reduced by at least 20 percent) at baseline.

The relative change ratio (RCR), defined as the ratio of the relative change at a comparison level of a predictor of interest divided by the relative change at a reference level for the predictor, provides a summary measure of association between an exposure measure, x, , and the outcome. The RCR depends on the years of follow-up (K). With a multiple regression model, $E[ln(RC) / At] = B_0 + B_1x_1 + \ldots + B_Px_p$, in which there are no interaction terms involving the predictor, x_1, the RCR for K years of follow-up is $RCR = \exp(B,A,K)$where $A, = x; - xR$ is the difference between the comparison level and the reference level for the predictor, $x1.$

To check the adequacy of a simple linear representation of the exposure variables, we assessed whether significantly improved fit resulted from using both linear and quadratic terms in the fully adjusted model. Models without the quadratic term were not rejected in favor of those with the quadratic terms. However, because our outcome measure was log-transformed all relationships found in these linear models represent a curvilinear exponential dose-response relationship.

D. RESULTS

1. Characteristics of the study population

At baseline, the average age in the study cohort was 49.5 years (SD 5.9), with 203 men at age 42, 190 at age 48, 169 at age 54 and 58 at age 60. Conditioning LTPA averaged 119 hours (SD 98) per year, BMI 25.6 kg/m2 (SD 3.2), alcohol consumption 78 g per week (SD 99), and 25.5 percent were regular smokers. Distribution of selected occupational exposures and all covariates are presented by cardiovascular health status at baseline in tables 1 and 2. Note that sample sizes differ slightly because of the pattern of missing values for the two different sets of occupational exposure variables (work time and energy expenditure) included in the tables (and in the respective analyses presented later). The distribution of all independent variables **by baseline status of carotid artery stenosis** (CAS) are listed in **Table 1.** Compared to men without stenosis, men with stenosis were older, earned less, had higher levels of LDL-cholesterol and fibrinogen, lower levels of cardiorespiratory fitness, and were more likely to take medication to lower blood lipids or blood pressure. On average, they worked about 1.5 hours more per week at baseline and had longer periods of unemployment or retirement during follow-up. Similar differences were found between men with and without ischemic heart disease (IHD) at baseline. The distributions of all independent variables **by IHD at baseline** are listed in **Table** 2. Men with IHD were older, earned less, reported more mental strain at work, and had higher levels of fibrinogen, and lower values of blood pressure and cardiorespiratory fitness. As expected, men with IHD spent less energy per potential standard workday than those without IHD. However, they were exposed to higher levels of EE at work compared to men without IHD with respect to all other EE measures.

2. Progression of atherosclerosis

Maximum IMT at baseline averaged 0.91mm (SD 0.21 mm, range 0.54 — 2.62 mm). The average change in maximum IMT was 0.027 mm per year (SD 0.017, range -0.033 —0. 095 mm) corresponding to a 0.33 mm (SD 0.24, range -0.82 — 1.75 mm) change during the entire 11-year follow-up. In this report we focus on percent change in maximum IMT which was on average 2.72% per year (95% CI 2.59 — 2.85) and 30.3% (95% CI 28.8 —31. 7%) during the entire follow-up period (average 11.13 years, SD 0.55, range 9.23 —13.82).

3. Distribution of work time

Table 3 shows the distribution of work time in the study sample by follow-up time. At baseline, weekly workdays ranged from 3 to 7, and hours from 16 to 91 per week. On average, men were employed 68% of the follow-up time and worked 1340 hours per year (range 23 — 3922) which is 71% (range 1 — 213%) of the standard Finish work year of 1840 hours (40 hours per week, 46 weeks per year).

4. Percentage of men exceeding Finnish work time standards

Table 4 shows the percentage of men exceeding Finish work time standards by follow-up time. The standard 5-day workweek was exceeded by 18.2 % of men at baseline (9.7 percent worked 6 days, and 8.5 percent worked 7 days per week, data not shown). Eleven years later, every fifth man (20.8%) worked more than 5 days (12.5% worked 6 days, and 8.3% worked 7 days per week, data not shown). The standard 8-hour workday and 40-hour workweek were exceeded by about one third of all men. The standard 1840 yearly work hours were exceeded on average by 26.6% of all men between baseline and 4-year follow-up, and by 15.9% during the later part of the study. These percentages are lower than the 33% for weekly work hours at baseline in part because actual yearly working time was reduced due to unemployment or retirement periods for 66% of all men.

5. Measures of *association between work time and progression* of *atherosclerosis*

Table 5 shows that the relative change ratio (RCR) in maximum IMT during the 11-year follow-up period is significantly and positively associated with the number of days worked per week at baseline and annual work hours actually worked during 11 years of follow-up. No significant associations were found with daily work hours or employment intensity. The effects vary little with incremental adjustment for covariates. The ratios of RC (i.e. RCR) range from 1.02 (employment intensity) to 1.14 (days per week) in the fully adjusted models.

Table 6 displays the percent changes in IMT among all men during the 11-year follow-up at minimum, median, and maximum levels for each alternative measure of work time, together with the respective RCRs. Men who worked on average 3 days per week (minimum), experienced a 23 percent change in IMT, those working 5 days per week (median) experienced a 31 percent increase, and those working 7 days per week (maximum) experienced a 40 percent increase in IMT. The highest percent change in IMT over 11-years was observed for maximum hours worked per year (41.1%, 95% CI 32.4% – 50.4%, p=0.038).

6. Measures of *association between work time and progression* of *atherosclerosis by baseline cardiovascular health status*

At baseline, 79 (13%) men had pre-existing IHD and 129 (21%) showed CAS during the ultrasound examination, with 32 of them (41% of men with IHD and 25% of men with CAS) having both conditions.

Table 7 shows percent changes of IMT separately for men with and without pre-existing IHD, and their respective RCRs. Among men with median or higher work time, men with IHD experienced consistently higher rates of IMT change than men without IHD at baseline across all exposure measures. Significant interactions ($p<=0.10$) were found between IHD and days per week ($p=0.058$), hours per day ($p=0.016$), and hours per

week (p=0.008). For those working the maximum of 91 hours per week at baseline, the 11-year percent change in IMT was 33.7% among men without IHD and 73.1% for men with IHD, the estimated RCR was 1.38 (95% CI 1.09 –1.75, p=0.008). It can be seen that the overall association between change in IMT and work time was mostly due to changes among the subgroup of men with IHD where associations were statistically significant for most measures despite the small sample size (n=79). In men without baseline IHD marginally significant effects were observed for days worked per week and average annual work hours.

Table 8 shows percent changes of IMT and RCRs separately for men with and without preexisting CAS. Among men with median or higher work time, men with CAS experienced consistently substantial higher rates of IMT change than men without CAS across all exposure measures. Significant interactions (p<=0.10) were found between CAS and hours per day at baseline (p=0.036), employment intensity (p=0.082), average annual work hours (p=0.030), and weekly work hours (p=0.100) In men with CAS, significant associations were observed for hours per day, per week, and per year, associations with days per week and employment intensity were marginally significant. In men without CAS only the association with days per week was significant.

7. ***Established cardiovascular risk factors, other covariates, and change in IMT after control for average yearly work hours***

The predictive role of established cardiovascular risk factors and other covariates in the progression of atherosclerosis was determined in the same fully adjusted regression model used in tables 5-8. All 21 covariates were examined simultaneously in the same model that including average hours worked per year employed. Statistically significant associations with change of IMT were observed for age, baseline IMT, participation in placebo group of unrelated trial of lipid-lowering medication, LDL-cholesterol, systolic blood pressure, proportion of follow-up time under lipid-lowering medication, and current regular smoking. The remaining 14 covariates including known predictors of

□VD such as income, BMI, conditioning LTPA, job stress, and plasma fibrinogen were not statistically significant. Regression coefficients and p-values are shown in **Table 9.**

8. Distribution of energy expenditure at work

Table 10 shows the distribution of energy expenditure (EE) measures by age-cohort and survey time. At baseline, EE per typical workday ranged from 616 to 5418 kcal/day with an average of 2046 kcal/day. The average changed little after 4 years (2032 kcal/day) and dropped slightly to 1916 kcal/day after 11 years. Relative EE measures show an increase with age indicating that physical demands at work are relatively higher for older compared to younger workers.

9. Percentage of men exceeding recommended levels of relative aerobic strain at work

Table 11 shows the proportion of men by age group that exceed recommended maximum levels of RAS, i.e. 33% for work involving mostly lower extremities according to Method 1 [99, 100, 1061, and 34% according to Method 2. At baseline, 29.6 (Method 1) to 31.2 % (Method 2) of all men exceeded these levels and there is a monotone increase in the proportion of men exposed to excessive levels of RAS from about 20% of men in the youngest age group up to 53 % of men in the oldest age group. The proportion of men experiencing excessive aerobic strain is higher (50-52%) in those with IHD than in those without IHD (26-28%).

By occupational group, the recommended (Method 1) level was exceeded by 70% of the 71 men working in agriculture, forestry or commercial fishing, 44% of 191 men working in manufacturing or construction, 26% of 27 service workers, 25% of 60 men in sales, 24% of 58 men employed in transport or communication, 5% of 55 men employed in administrative, managerial, or clerical jobs, and 5 % of 139 in technical, science, or artistic work (data not shown).

10. Measures of association between energy expenditure and IMT progression

Table 12 shows that the relative change ratio (RCR) in maximum IMT during the 11-year follow-up period is significantly associated with all EE measures. The effect measures vary little with incremental adjustment for covariates. Absolute measures of EE in kcal are associated with RCRs ranging from 1.13 to 1.18 in the fully adjusted model (last column of Table 12). The adjusted relative EE measures showed the highest RCRs (RCR=1.23 and 1.24, respectively).

To check for thresholds and non-monotone dose-response relationships we explored models with categorical exposure measures and also by entering quadratic terms of exposure variables in the model. These models did not provide any evidence for thresholds and confirmed a positive monotone exponential association between all EE measures and change in IMT.

11. Energy expenditure and percent change of IMT

Table 13 displays the percent changes of IMT for all men during the 11-year follow-up at minimum, median, and maximum levels for each alternative measure of EE together with the respective relative change ratios. The highest percent change was observed for men at maximum %VO_2Res (60%, 95% confidence interval 38% – 85%).

12. Energy expenditure and percent change of IMT by baseline cardiovascular health status

Table 14 shows percent changes of IMT separately for men with and without pre-existing IHD, and their respective relative change ratios. Across all exposure measures, men with IHD experienced consistently higher rates of IMT change than men without IHD at baseline. Significant interactions ($p<O.10$) were found between IHD and kcal per typical day at baseline, RAS, and %VO_2Res. At the maximum RAS of 119%, 11-year change in IMT among men with IHD (90%) was nearly twice as much than among those

without IHD (46%). **Figure 1** shows the same comparison for minimum (6), mean (22; not median), and maximum (142) values of %V02Res.

Table 15 shows percent changes of IMT and relative change ratios separately for men with and without preexisting carotid artery stenosis. Across all exposure measures, men with carotid stenosis experienced consistently higher rates of IMT change than men without preexisting stenosis. Significant interactions ($p<0.20$) were found between carotid stenosis and total amount of EE and kcal per potential 8-hour standard workday.

There was some overlap between the two cardiovascular health status subgroups: 40.3% of men with IHD also had stenosis of carotid arteries, and 24.4% of men with carotid stenosis also had IHD.

13. Distribution of work postures

Table 16 shows the distribution of time spent in different work postures by age cohort and survey-time. There was a wide variation in time spent in different work postures within all age groups and survey dates ranging from 0 to 780 minutes per day. At baseline, men spent about 41% of their time sitting at work (including break time). At 4 and 11 years the percentage was 46%. On average, men spent most of their work day in upright work postures (59% at baseline), including standing (18%), walking on level surfaces (27%), walking on uneven surfaces (9%), and climbing stairs (5%).

14. Measures of association between work postures and IMT progression

Associations between work postures and progression of atherosclerosis vary depending on the type of exposure measure used. Table 17 shows the results for baseline measures of work postures and the following tables 18- 21 for weighted averages and posture intensity measures taking repeat measures at 4-year and 11-year follow-up into account. Complete information on work postures at baseline was available for 612 men (= n in Table 17). When baseline values were not available but men worked between

baseline and 4 years, information from 4-year and 11-year was used to create weighted averages resulting in a total sample of n=621 (in Tables 18-21).

Table 17 shows that the relative change ratio (RCR) in IMT during the 11-year follow-up period is not associated with baseline measures of a sitting or standing work posture. Walking on level ground at baseline is associated with a slight reduction in the rate of 11-year IMT progression, albeit not statistically significant (RCR=0.94, p=0.136 in the fully adjusted model 4). Walking on uneven ground and climbing stairs both showed a statistically significant increase in the rate of IMT progression (RCR=1.07 and 1.14, respectively). The effect measures vary little with incremental adjustment for covariates. An upright posture at baseline (standing, walking, climbing stairs combined) showed no significant association with IMT progression.

Table 18 shows results for the weighted averages of postures at baseline, 4-year, and 11-year and a similar pattern of results is seen as in table 17 for baseline postures. Again, walking on uneven ground and climbing stairs both showed a statistically significant increase in the rate of IMT progression. Effect sizes were slightly stronger using repeat measures of exposure compared to baseline values only (RCR=1.08 and 1.18, respectively).

Upright postures (standing, walking, climbing stairs combined) as weighted average of intensity (time upright/time at work of a typical workday) during follow-up showed no associations with IMT progression. The proportion of time upright at work during follow-up, a measure of intensity of upright work that also takes into account the proportion of potential standard work time during follow up that was actually spent at work, was significantly and positively associated with the rate of IMT progression (RCR=1.13, p=0.004).

To check for thresholds and non-monotone dose-response relationships we explored models with categorical exposure measures and also by entering quadratic terms of exposure variables in the model. These models did not provide any evidence for thresholds and confirmed monotone exponential dose-response relationships for walking

on uneven ground, climbing stairs, and the proportion of time upright at work during the 1-year follow-up.

Table 19 shows percent change of IMT during 11 years of follow-up at minimum, median, and maximum average durations and intensities of different working postures for all men regardless of baseline cardiovascular health status. For example, men climbing stairs on average 5 hours per day (the maximum observed) experienced a 54 percent increase in IMT compared to a 31 percent increase among men not having to climb chairs during their work (the majority of men).

15. Work postures and percent change of IMT by baseline cardiovascular health status

Table 20 shows percent changes of IMT separately for men with and without pre-existing IHD, and their respective relative change ratios. Across all median exposure values, men with IHD experienced consistently higher rates of IMT increases than men without IHD at baseline. Significant interactions ($p<0.20$) were found between IHD and walking on uneven ground, climbing stairs, and intensity of upright work posture, and the proportion of time upright at work during 11 years of follow-up. At the maximum value of the latter measure, 11-year change in IMT among men with IHD was 72 percent compared to 42 percent among those without IHD.

Table 21 shows percent changes of IMT and relative change ratios separately for men with and without preexisting carotid artery stenosis. Across all exposure measures, men with carotid stenosis experienced consistently higher rates of IMT increases than men without preexisting stenosis. Significant interactions ($p<0.20$) were found between carotid stenosis and walking on level ground, walking on uneven ground, intensity of upright work posture, and proportion of time spent upright at work.

There was some overlap between the two cardiovascular health status subgroups: 40.3% of men with IHD also had stenosis of carotid arteries, and 24.4% of men with carotid stenosis also had lHD.

16. *Upright work posture and 11 year change in systolic blood pressure*

The relationship between occupational physical activity and change in blood pressure during follow-up was explored with selected work posture variables. Specifically, we examined the association between an upright work posture (standing, walking, or climbing stairs) and 11-year change in systolic blood pressure (BP), where change in BP was measured as BP at 1 1-year follow-up minus BP at baseline.

Results of these investigations need to be considered preliminary because all analyses were performed using an earlier data set that may contain coding errors that have been corrected later in the project. Further, the operationalization of the primary exposure variable "average percentage of time upright at work per year", differed from the calculation of the weighted averages described above. Finally, for multivariate BP analyses missing values on covariates had not been replaced by mean values in these earlier analyses and missing values on the duration of an upright work posture at one survey date were not replaced by values from the adjacent survey date. This resulted in a smaller study sample (n=602) than used in analyses of IMT change described above (n=621). Because of the need to rerun all analyses with an updated data set we only summarize some main findings in this report and do not present tables with complete results.

The average percentage of time upright at work per year ranged from zero to 43%. The association of the average percentage of time upright at work per year and average yearly change in systolic blood pressure between baseline and 11 years was studied in a multiple linear regression model controlling for 18 covariates, including technical, demographic, biomedical, psychosocial work, and behavioral factors, namely, leisure time physical activity, smoking, and alcohol consumption. Systolic blood pressure increased an average of 0.35 mm Hg per year, or 3.85 mm Hg over the 11-year follow-up period, among men who spent zero time in an upright body posture at work and who

were in reference categories and had average values on continuous covariates. Otherwise similar men, who were in an upright work posture 43% of the year, had a corresponding increase in systolic blood pressure of 1.18 mm Hg per year, or 13 mm Hg over 11 years ($p = .009$). Age, income, and use of cholesterol-lowering medications were the only other factors found to have a significant positive association with change in systolic blood pressure. The increases in age ($p < 0.001$) and income ($p=0.03$) needed to get the same effect found for men in an upright work posture 43% of the year are 20 years and 44, 000 Finnish marks. Neither BMI nor time spent in conditioning leisure time physical activities had an effect on systolic blood pressure change. These results suggest that prolonged time in an upright posture at work constitutes a risk factor for increases in systolic blood pressure comparable to 20 years of aging, which in turn is one of the accepted major risk factors for the development of cardiovascular disease.

E. CONCLUSIONS

The primary aim of this study was to determine the effects of different types and levels of occupational activity on cardiovascular health among middle-aged men while adjusting for leisure time physical activity, and demographic, biological, behavioral, and psychosocial risk factors including socioeconomic status and job stress. The secondary aim of the study was to investigate interactions of occupational physical activity with pre-existing atherosclerosis of the carotid arteries and ischemic heart disease at baseline.

This report describes the effects of occupational physical activity on intima media thickness (IMT) of the carotid arteries over an eleven-year period. Increase in thickness of this inner lining of the arterial wall is a standard measure of progression of atherosclerosis, a disease process that may lead to obstruction of blood flow to vital organs and to cardiovascular and cerbrovascular diseases such as myocardial infarction or stroke. The report also describes the effect of occupational physical activity on 11-year change in systolic blood pressure. Elevated blood pressure is an important established risk factor for cardiovascular and cerebrovascular disesases.

Several dimensions of occupational physical activity have been investigated in this study: Work time (e.g. days worked per week, weekly and yearly work hours), energy expenditure at work (e.g. the number of kilocalories spent at work per day or per year), relative aerobic strain, and the time spent in different work postures (sitting, and several upright work postures including standing, walking on level ground, walking on uneven ground, and climbing stairs).

The following paragraphs summarize key findings and conclusions from this study, organized by type of occupational exposure and specific cardiovascular disease outcome studied:

Work time and** 11 **year progression** of **atherosclerosis:

1) A high prevalence of overtime work was observed in the aging Finish working population both at baseline and during follow-up based on several work time measures. The standard 8-hour workday and 40-hour workweek were exceeded by about one third of all men. The standard 1840 yearly work hours were exceeded on average by 26.6% of all men between baseline and 4-year follow-up, and by 15.9% between 4- and 11-year follow-up.
2) Both the number of days worked per week and the average yearly work hours predicted 11-year progression of carotid atherosclerosis even after adjustment for 21 biological, behavioral, and psychosocial risk factors including blood lipids, leisure time physical activity, job stress, and socioeconomic status among others. Men who worked on average 3 days per week experienced a 23 percent increase in intima media thickness of their carotid arteries, those working 5 days per week experienced a 31 percent increase, and those working 7 days per week experienced a 40 percent increase in IMT.
3) Men with ischemic heart disease (IHD) at baseline experienced consistently higher rates of IMT change than men without IHD across all work time measures. For those working the observed maximum of 91 hours per week at baseline, the 11-year percent change in IMT was 33.7% among men without IHD and 73.1% for men with IHD. In fact, the association between work time and change in IMT observed for all men was mostly due to changes among the subgroup of men with IHD. However, even for men without baseline IHD more days worked per week and more average annual work hours also predicted higher increases in IMT, although these associations did not reach statistical significance due to a smaller sample size.
4) The association between all work time measures and IMT was consistently stronger in men with carotid artery stenosis at baseline compared to those without pre-existing stenosis. The number of days worked per week were a statistically significant predictor of progression of atherosclerosis in both groups of men.
5) Findings are consistent with the hemodynamic theory of atherosclerosis that predicts stronger effects among men with preexisting cardiovascular disease.

6) All associations between work time and IMT followed a monotone exponential dose response relationship, i.e. no thresholds were observed and the effects of work time on IMT became relatively stronger with longer durations of work time.
7) Regardless of the specific occupational conditions that may constitute the pathways for the observed relationships, findings suggest that reducing excessive work time could have significant cardiovascular and public health benefits especially in the aging working population.
8) Aging workers, especially those with pre-existing cardiovascular disease, could benefit from reducing their work time and should be made aware of this possibility in general, cardiological, occupational and rehabilitation medicine practice.

Energy expenditure, relative aerobic strain, and progression of atherosclerosis

1) Middle-aged men spent on average about 2000 kilocalories at work during a typical workday through moving their body or maintaining their work posture alone, i.e. not counting energy spent by handling or moving objects at work. Although aerobic capacity falls substantially with increasing age, the estimated energy demands on the job did not decrease substantially during 11-years of follow-up among working men. In fact, relative energy expenditure measures show an increase with age, indicating that physical demands at work are relatively higher for older workers compared to younger workers in this group of middle-aged men.
2) The recommended maximum level of 33 percent relative aerobic strain (RAS) at work was exceeded by about 30 percent of all men. There is a monotone increase in the proportion of men exposed to excessive levels of RAS from about 20% of men in the youngest age group at baseline (42 years) up to 53 % of men in the oldest age group (54 years). The proportion of men experiencing excessive aerobic strain is nearly double as high (50%) in those with IHD than in those without IHD (26%).

3) Excess energy demands vary by occupation. Recommended maximum levels of RAS were exceeded by 70% of men in agriculture, forestry or commercial fishing, 44% in manufacturing or construction, 26% in services, 25% in sales, 24% in transport or communication, 5% in administrative, managerial, or clerical jobs, and 5% in technical, science, or artistic work.

4) Higher levels of energy expenditure at work are associated with a higher rate of progression of atherosclerosis in a monotone exponential dose-response relationship. Relative aerobic strain showed one of the strongest associations with IMT change. There was no evidence for any protective or threshold effects.

5) Men with ischemic heart disease and men with carotid artery stenosis at baseline experienced consistently higher rates of IMT increase than men without pre-existing cardiovascular conditions even after control for aerobic fitness and all other confounding factors.

6) This study demonstrates for the first time that high energy expenditure at work is associated with accelerated progression of carotid atherosclerosis even after controlling for virtually all known cardiovascular risk factors, including LTPA, aerobic fitness, socioeconomic status, and psychosocial job factors which have been rarely controlled simultaneously. Older workers, workers with pre-existing IHD, and workers with carotid stenosis appear especially vulnerable to the atherogenic effects of increasing levels of energy expenditure.

7) The findings also lend epidemiological support to the hemodynamic theory of atherosclerosis.

8) The results of this study do not support the notion that heavy physical labor has ceased to be a potential health hazard in the so-called modem service economy. To the contrary, the study shows that a substantial proportion of aging men and over 50% of those with IHD in this sample are still exposed to excessive caloric job demands based on current recommended maximum levels for RAS.

9) Job evaluations using ambulatory heart rate monitoring to estimate RAS or percent oxygen uptake reserve should be considered for every job requiring physical efforts other than mostly sitting at a desk and for the evaluation of work modifications for workers with CVD.

10) Regulatory statutes dealing with work time and rest schedules need to assure that workers are protected from excessive aerobic strain even if individual monitoring is not available. Such prevention measures are especially needed for older workers with age- or disease-related reduced cardiorespiratory fitness, existing IHD or known atherosclerosis.

Work posture and I1 year progression of atherosclerosis

1) Work postures varied widely among middle-aged men. On average, men spent most of their workday (59% at baseline) in upright work postures, either standing (18%) , walking (36%), or climbing stairs (5%).
2) Associations between work postures and progression of atherosclerosis varied depending on type of work posture and assessment method. Based on exposure assessment by interview and using continuous exposure measures, no significant associations with IMT change were found for baseline measures of sitting or standing or for a combined measure of all upright positions (standing, walking on level ground, walking on uneven ground, and climbing stairs). However, when investigated separately, time spent walking on uneven ground and time spent climbing stairs showed significant positive associations with IMT increase. In addition, the proportion of potential work time during follow-up that was spent upright at work (a measure of intensity of upright work that also takes into account the potential standard work time during follow up that was actually spent at work) was significantly and positively associated with the rate of IMT progression. Finally, analyses based on exposure assessment by questionnaire using ordered categorical variables, showed that a standing at work was significantly associated with 11-year progression of atherosclerosis confirming results of an earlier study on 4-year progression of IMT in the same cohort that had used the same exposure categorlies.
3) Men with pre-existing IHD or carotid artery stenosis experienced consistently higher rates of progression of atherosclerosis than men without such conditions. These results are consistent with the hemodynamic theory of atherosclerosis.

Work posture and 11 year change in systolic blood pressure

1) An upright work posture is positively associated with systolic blood pressure even after control for confounding factors. During the 11-year follow-up period systolic blood pressure increased 13mm among men who spent 43% of their work time in an upright posture in comparison to an average increase of 3.85 mm Hg among men who spent zero time in an upright body posture at ($p = 0.009$).
2) Posture-related increases in blood pressure may be one of the pathophysiological pathways linking an upright work posture with progression of atherosclerosis.

Main conclusions and implications

About one third of middle-aged men work more than the standard 40-hour workweek. Work time is positively related to accelerated progression of carotid atherosclerosis. Men with preexisting ischemic heart disease or carotid artery stenosis appear to be especially vulnerable to the effects of long work times. Findings are consistent with the hemodynamic theory of atherosclerosis and known occupational risk factors for cardiovascular disease. Regardless of the specific occupational conditions that may constitute the pathways for the observed relationships between long work time and progression of atherosclerosis, findings suggest that reducing weekly and yearly work time could have significant cardiovascular and public health benefits, especially in the aging working population.

The results of this study do not support the notion that heavy physical labor has ceased to be a potential health hazard in the so-called modem service economy. To the contrary, the study shows that about one third of aging men, including over 50% of those with ischemic heart disease, are still exposed to excessive caloric job demands based on current recommended maximum levels for relative aerobic strain.

This study demonstrates for the first time that the observed high levels of energy expenditure and relative aerobic strain at work are associated with accelerated progression of carotid atherosclerosis, even after controlling for virtually all known

cardiovascular risk factors, including blood pressure, smoking, cholesterol, body mass index, leisure time physical activity, aerobic fitness, socioeconomic status, and psychosocial job factors among others. Older workers, workers with pre-existing ischemic heart disease, and workers with carotid stenosis appear especially vulnerable to the atherogenic effects of increasing levels of energy expenditure.

Prolonged upright work postures are associated with an accelerated progression of atherosclerosis. Prolonged time walking on uneven ground or climbing stairs were the relevant components of an upright work posture that were significantly associated with progression of atherosclerosis. The association of a standing work posture with progression of atherosclerosis varied by exposure assessment method used. When exposure was measured in categories directly derived from questionnaires those standing much at work experienced a significantly faster progression of atherosclerosis than those who did not work standing, inconsistent with findings of an earlier study showing that standing at work was associated with 4-year progression of atherosclerosis in this population. However, a continuous measure of the amount of standing at work derived from occupational interview data showed no association. Further analyses are needed to explain this inconsistent finding.

A prolonged upright work posture was significantly associated with long-term increases in systolic blood pressure, a major risk factor for cardiovascular disesases.

The hemodynamic theory of atherosclerosis predicts that longer work time, upright work postures, and higher levels of energy expenditure at work lead to increased blood pressure and increased heart rates at work that cause intraarterial blood flow changes (increased turbulence, reduced wall shear stress) that are partially responsible for injury, inflammation, and plaque formation in arterial vessels leading to atherosclerosis and associated disabling or fatal cardiovascular diseases. The hemodynamic theory of atherosclerosis also predicts that men with pre-existing heart disease or carotid artery stenosis should be more vulnerable to the atherogenic effects of occupational physical

activity. All findings of the study are consistent with the established hemodynamic theory of atherosclerosis.

Regulatory statutes dealing with work time and rest schedules need to assure that workers are protected from weekend work, excessive work hours, prolonged upright work postures, and excessive caloric job demands. Such prevention measures are especially needed for older workers with age- or disease-related reduced cardiorespiratory fitness, stenosis of carotid arteries, or manifest ischemic heart disease.

Design of workstations, work schedules, and job tasks should allow workers to limit exposure to prolonged upright working positions and to take rest breaks when needed. Evidence-based guidelines are needed to assist employers, workers, and occupational health and safety professionals in the evaluation and abatement for health risks associated with occupational physical activities, including the special circumstances of overtime work, shift work, and working consecutive days without traditional weekend rest periods. Job evaluations using ambulatory heart rate monitoring to estimate relative aerobic strain or percent oxygen uptake reserve should be considered routinely for worker placement into jobs that require physical efforts other than mostly sitting at a desk, and for workers with prevalent cardiovascular disease. Such monitoring efforts should also be integrated in ergonomic job redesign and the planning of work modifications to promote cardiovascular health in employees who return to work after prolonged illness, periods of unemployment, or from other situations that may have led to their physical deconditioning.

Finally, intervention studies are needed to determine feasibility and effectiveness of the prevention strategies suggested above. Additional research is also needed to determine the overall cardiovascular disease burden and societal costs associated with excessive work hours, upright working positions, and high levels of energy expenditure in order to quantify the potential benefits of such worksite-based strategies to prevent circulatory diseases.

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G. **TABLES**

Table 1: Characteristics of the study population and distribution of independent variables by carotid artery stenosis status at baseline (N=621)

Independent Variables	**Men without stenosis (n=492)**	**Men with stenosis (n=129)**	**Difference (t-test or chi-square test)**
	Mean (SD) or n (%)	**Mean (SD) or n (%)**	**P-value**
Age and technical factors			
Age at baseline (years)	48.4 (5.6)	53.7 (5.0)	0.001
Log of maximum IMT at baseline (log mm)	-0.036 (0.178)	0.138 (0.230)	0.001
Sonographer at 11-year'			
A	16 (3.3%)	5 (3.9%)	0.193
B	3 (0.6%)	3 (2.3%)	
C	473 (96.1%)	121 (93.8%)	
Participant in placebo group of lipid lowering drug trial	33 (6.7%)	10 (7.8%)	0.677
Participant in treatment group of lipid lowering drug trial	29 (5.9%)	11(8.5%)	0.278
Biological Factors			
Blood glucose average2 (mmolll)	4.9 (0.8)	5.0 (0.8)	0.445
Plasma fibrinogen average[2](g/1)	3.0 (0.5)	3.2 (0.4)	0.001
Bodymass-Index baseline	26.6 (3.2)	26.4 (3.2)	0.579
LDL-cholesterol at baseline (mmol/1)	3.8 (0.9)	4.0 (0.9)	0.004
HDL-cholesterol at baseline (mmolll)	1.3 (0.3)	1.3 (0.3)	0.535
Systolic blood pressure at baseline	130.5 (14.4)	132.4 (15.6)	0.185
Proportion of follow-up time under lipid-lowering medication	0.01 (0.06)	0.04 (0.13)	0.034
Proportion of follow-up time under blood pressure lowering medication	0.16 (0.31)	0.30 (0.40)	0.001

(Table 1 cont.)

Behavioral Factors			
Alcohol consumption average[2] (g/week)	79.6 (96.9)	72.9 (104.1)	0.488
Smoker			
no	199 (40.5%)	33 (25.6%)	0.007 4
former	136 (27.6%)	(34.1%)	
irregular	40(8.3%)	8(6.2%)	
current	117(23.8%)	44(34.1%)	
Conditioning LTPA (average[2] hours/year)	118.7 (100.3)	128.1 (106.5)	0.353
Cardiorespiratory fitness (ml 02/kg/min)	34.4 (7.1)	30.2 (6.9)	0.001
	12.2 (6.9)	9.7 (5.0)	0.001
Socioeconomic Status			
Personal income (average2 1000 FIM/yr)			
Psychosocial Job Factors			
Social support at work	5.9 (2.2)	6.0 (2.6)	0.775
Mental strain at work index	12.0 (5.1)	12.2 (6.0)	0.670
Stress from work deadlines	XXX	XXX	0.475
Yes			
No			
Work time			
Days per week (baseline)	5.2 (0.6)	5.3 (0.8)	0.161
Hours per day (baseline)	8.0 (1.5)	8.1 (1.6)	0.438
Hours per week (baseline)	41.9 (11.3)	43.5 (13.2)	0.201
Employment intensity (between baseline and 11-year)	0.73 (0.31)	0.50 (0.31)	0.001
Average hours per year employed (between baseline and 11-year)	1384 (697)	1006 (719)	0.001

1) All ultrasound examinations were performed by the same sonographer at baseline
2) Average of baseline, 4-year and 11-year values

Table 2: Characteristics of the study population and distribution of independent variables by ischemic heart disease (IHD) status at baseline (N=612)

Independent Variables	**Men without IHD (n=535)**	**Men with IHD (n=77)**	**Difference (t-test or chi-square test)**
	Mean (SD) or n (%)	**Mean (SD) or n (%1**	**P-value**
Age and technical factors			
Age at baseline (years)	49.1 (5.9)	52.3 (5.5)	0.001
Log of maximum IMT at baseline (log mm)	-.013 (0.19)	-.056 (0.25)	0.018
Sonographer at 11-years			
A	19 (3.6%)	2 (2.6%)	
B	6 (1.1%)	0	
C	510 (95.3%)	75 (97.4%)	0.585
Participant in placebo group of lipid lowering drug trial	37 (7.0%)	6 (7.8%)	0.778
Participant in treatment group of lipid lowering drug trial	34 (6.4%)	6 (7.8%)	0.633
Biological Factors			
Blood glucose average[2] (mmol/1)	4.9 (0.9)	4.9 (0.7)	0.755
Plasma fibrinogen average2(g/1)	3.0 (0.5)	3.1 (0.4)	0.044
Bodymass-Index baseline	26.5 (3.2)	26.8 (3.3)	0.419
LDL baseline (mmol/1)	3.8 (0.9)	3.9 (1.0)	0.223
HDL baseline (mmol/1)	1.3 (0.3)	1.3 (0.3)	0.684
Systolic blood pressure at baseline	131.4 (14.4)	127.1 (14.7)	0.015
Proportion of follow-up time under lipid-lowering medication	0.01 (0.07)	0.04 (0.14)	0.059
Proportion of follow-up time under blood pressure lowering medication	0.17 (0.31)	0.34 (0.41)	0.001

Behavioral Factors				
Alcohol consumption				
average[2] (g/week)		77.6 (97.1)	80.6 (108.7)	0.805
Smoker				
no		203 (37.9%)	28 (36.4%)	
former		155 (29.0%)	23 (29.9%)	
irregular	40	(7.5%)	7 (9.1%)	
current		137 (25.6%)	19 (25.7%)	0.957
Conditioning LTPA (average[2] hours/year)		118.9 (99.3)	119.4 (90.7)	0.968
Cardiorespiratory fitness (ml 0_2/kg/min)		34.2 (7.0)	28.3 (6.9)	0.001
Socioeconomic Status				
Personal income (average2 1000 FIM/yr)		12.0 (6.7)	9.4 (4.5)	0.001
Psychosocial Job Factors				
Social support at work		6.0 (2.5)	5.7 (2.4)	0.245
Mental strain at work index		11.8 (5.2)	13.4 (5.4)	0.021
Stress from work deadlines		0.35 (0.48)	0.40 (0.49)	0.364
Energy Expenditure				
Kcal per typical work day at baseline		2020 (844)	2224 (842)	0.048
Total amount of kcal during follow-up		3,862,574 (2,668,618)	2,983,855 (2,415,210)	0.012
Kcal per 8 hours actually worked during follow-up		1800 (565)	1968 (642)	0.013
Kcal per potential 8-hour standard work day during follow-up		1499 (1028)	1167 (950)	0.014
Relative aerobic strain (%VO_2max) at baseline		28.0 (11.3)	37.8 (15.5)	0.001
Percent oxygen uptake reserve (%$V0_2$Res) at baseline		21.2 (12.9)	31.0 (17.9)	0.001

1) All ultrasound examinations were performed by the same sonographer at baseline
2) Average of baseline, 4-year and 11-year values

Table 3: Work time measures at baseline and by follow-up time.
Kuopio Ischemic Heart Disease Risk Factor Study 1984-2001

Work time Measure	N	Median	Mean	SD	Min- Max
Days per week					
baseline'	621	5	5.2	0.6	3- 7
4-year	487	5	5.1	0.7	1 - 7
11-year	606	5	5.2	0.8	1 - 7
Hours per day					
baseline'	621	7.5	8.0	1.5	3.5 - 14.5
4-year	490	7.5	7.9	1.5	3.0-14.0
11-year[2]	253	7.5	7.8	1.5	2.0-13.0
Hours per week					
baseline'	621	37.5	42.2	11.7	16.0-91.(
4-year	485	37.5	41.2	11.6	8.0-98.0
11-year[2]	253	37.9	40.4	11.7	10.0-86.9
Employment Intensity					
between baseline and 4-year	621	1.00	0.87	0.23	0-1.00
between 4-year and 11-year	621	0.60	0.57	0.41	0 - 1.00
between baseline and 11-year'	621	0.74	0.68	0.32	0.02-1.0(
Average hours per year employed3					
between baseline and 4-year	621	1679	1670	624	0 -4023
between 4-year and 11-year	618	1191	1095	874	0-3862
between baseline and 11-year'	621	1340	1305	717	23 -3922

1) This measure was used for regression analyses

2) N at 11-year is small because it is based on occupational interview data among active employees only in contrast to days per week assessed by questionnaire for current job or last job if not working at 11-year.

3) weighted average of yearly work hours per year employed during follow-up

Table 4: Percentage of men exceeding Finnish work time standards by work time measure

Work Time Measure	**Work Time Standard**	**Percent of Men Exceeding Standard**
Days per week		
Baseline	5	18.2%
4-year	5	16.2%
11-year	5	20.8%
Hours per day		
Baseline	8	30.8%
4-year	8	28.2%
11-year	8	30.4%
Hours per week		
Baseline	40	33.3%
4-year	40	31.3%
11-year	40	33.6%
Average hours per year employed'		
Between baseline and 4-year	1840	26.6%
Between 4-year and 11-year	1840	15.9%
Between baseline and 11-year	1840	17.4%

1) Weighted average of yearly work hours per year employed during follow-up

Table 5: Ratio of relative change' in maximum IMT during 11 year follow-up, by measure of work time: regression analyses with incremental adjustment for covariates (All men, N=621)

Work Time Measure	**Model 1:** Adjusted for age and technical factors	**Model** 2: Model 1 plus adjustment for biological factors	**Model 3:** Model 2 plus adjustment for behavioral factors	**Model 4:** Model 3 plus adjustment for SES and psychosocial job factors2
Days per week at baseline	1.12 (1.03 – 1.22) p=.008	1.11 (1.02-1.21) p=.016	1.14 *(1.05-1.25)* p=.002	1.14 (1.04-1.24) p=.003
Hours per day at baseline	1.02 (0.92-1.13) p=.665	1.02 (0.92-1.12) p=.743	1.01 (0.92-1.12) p=.815	1.01 (0.92 –1.12) p=.781
Hours per week at baseline	1.07 (0.98-1.67) p=.123	1.06 (0.97 – 1.16) p=.171	1.07 (0.98-1.17) p=.105	1.07 (0.98-1.17) p=.118
Employment intensity after baseline	1.00 (0.95 – 1.06) p=.863	1.00 (0.95 – 1.06) p=.864	1.01 (0.96 – 1.07) p=.630	1.02 (0.96 – 1.08) p=.501
Average hours per year employed after baseline	1.09 (1.00 – 1.19) p=.041	1.07 (0.99 – 1.17) p=0.098	1.09 (1.00 – 1.19) p=0.047	1.10 (1.01-1.20) p=0.038

1) Relative Change Ratio (RCR) per unit change in IMT where unit is the observed range (max – min) in work time (with 95% confidence intervals)

2) Adjusted for a total of 21 covariates including technical, biological, behavioral, socioeconomic, and psychosocial factors listed in table 1

Table 6: 11 year percent change in maximum IMT, and ratio of relative change (RCR)[1] by work time measure during 11 year follow-up: results from multiple regression analyses with adjustment for all 21 covariates[2] **(All** *men, N=621)*

Work Time Measure	**Min**	**Median**	**Max**	**RCR**	**P-value**
Days per week at baseline	23.1 (16.1 - 30.4)	31.3 (27.6-35.2)	40.2 (33.9-46.7)	1.14 (1.04-1.24)	.003
Hours per day at baseline	32.0 (25.5-38.8)	32.7 *(29.0-36.5)*	33.9 *(25.4-43.0)*	1.01 (0.92 - 1.12)	.781
Hours per week at baseline	29.5 (24.1 - 35.1)	32.1 (28.3-36.0)	38.9 (30.4-47.9)	1.07 (0.98-1.17)	.118
Employment intensity after baseline	31.1 (25.0 - 37.4)	33.0 (29.2 - 36.8)	33.6 (29.3 - 38.2)	1.02 (0.96 - 1.08)	.501
Average hours per year employed after baseline	28.8 (23.7 - 34.1)	32.8 (29.1 -36.6)	41.1 (32.4 - 50.4)	1.10 (1.01 - 1.20)	.038

1) Relative change ratio (RCR) per unit change in IMT where unit is the observed range (max - min) in work time

2) Same covariates as in model 4 of Table 5, including 21 technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table 1

Table 7: 11 year percent change in maximum IMT at minimum, median, and maximum levels of work time; measures of association between work time and IMT progression (RCR)[1]; and interactions of work time with baseline ischemic heart disease (IHD): results from multiple regression analyses with adjustment for 21 covariates[2] (N=621)

	Men w/o IHD at baseline (n=542)					Men with IHD at baseline (n=79)					RCR Ratio	Inter-action
Work Time Measure	**Min**	**Median**	**Max**	**RCR[1]**	**p-value**	**Min**	**Median**	**Max**	**RCR[1]**	**p-value**	**RCR1nu / RCRNOIHD**	**p-value**
Days per week at baseline	24.8 (17.4 - 32.8)	30.7 (27.0 - 34.6)	36.9 (30.3 - 43.8)	1.10 (1.00 - 1.21)	.057	16.9 (3.7-31.8)	35.6 (29.3 - 42.4)	57.4 (43.2 - 73.1)	1.35 (1.11 - 1.63)	.003	1.23 (0.99 - 1.52)	.058
Hours per day at baseline	33.5 (26.6-40.7)	32.0 (28.3-35.9)	29.5 (20.8-38.8)	0.97 (0.87 - 1.08)	.580	20.9 (6.9-36.7)	36.5 (30.0-43.2)	68.9 (42.6 - 100.0)	1.40 (1.06 -1.84)	.018	1.44 (1.07 - 1.94)	.016
Hours per week at bl.	30.6 (24.9-36.5)	31.5 *(27.7-35.4)*	33.7 (25.1 - 43.0)	1.02 (0.93 - 1.13)	.620	22.6 (11.8 - 34.4)	35.3 (28.9-42.1)	73.1 (49.1 - 101.0)	1.41 (1.13- 1.76)	.002	1.38 (1.09 -1.75)	.008
Employment intensity after baseline	28.9 *(22.7-35.4)*	32.2 (28.4-36.0)	33.4 (28.9-38.0)	1.03 (0.98-1.10)	.259	41.3 (30.5-53.1)	36.9 (29.9-44.4)	36.9 *(26.0-45.6)*	0.96 (0.85-1.08)	.480	0.95 (0.87-1.03)	.225
Average hours per year empl. after baseline	28.2 (22.9-33.7)	31.9 (28.2-35.8)	39.7 (30.6-49.4)	1.09 (0.99 - 1.20)	.066	32.8 (23.6-42.7)	39.6 (32.8-46.6)	53.8 (31.0-81.0)	1.16 (0.94 -1.43)	.166	1.06 (0.85-1.33)	.589

1) Relative change ratio (RCR) per unit change in IMT where unit is the observed range (max - min) in work time (with 95% confidence intervals)

2) Same covariates as in model 4 of Table 5, including 21 technical, biological, socioeconomic, behavioral, and psychosocial factors listed in Table 1

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Table 8: 11 year percent change in maximum IMT at minimum, median, and maximum levels of work time; measures of association between work-time intensity and IMT progression (RCR)'; and interactions of work time with baseline carotid artery stenosis: results from multiple regression analyses with adjustment for 21 covariates[2] (N=621)

	Men w/o carotid stenosis at baseline (n=492)					Men with carotid stenosis at baseline (n=129)					RCR	Inter-
Work Time Measure	**Min**	**Median**	**Max**	RCR'	p-value	**Min**	**Median**	**Max**	RCR	p-value	RCRs, / RCRaOS(flwi,	I)-value
Days per week at baseline	23.1 (15.2-31.5)	30.9 (27.1 - 34.9)	39.3 (32.3 - 46.7)	1.13 (1.02 - 1.26)	.019	26.1 (14.5-39.0)	35.0 (29.1 - 41.2)	44.5 (33.8-56.0)	1.15 (0.99 1.33)	.078	1.01 (0.85 1.21)	.897
Hours per day at baseline	34.9 *(27.6-42.5)*	32.6 (28.9 - 36.5)	28.8 (19.7-38.6)	0.96 (0.85 1.07)	.435	25.5 (14.0-38.1)	35.4 (29.5 41.5)	54.6 (35.8-76.0)	1.23 (1.00 1.52)	.049	1.29 (1.02 1.64)	.036

1) Relative change ratio (RCR) per unit change in IMT where unit is the observed range (max - min) in work time (with 95% confidence intervals)

2) Same covariates as in model 4 of Table 5, including 21 technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table 1

Table 9: Associations of covariates with yearly change in in-transformed maximum IMT in multivariate[1] regression analyses including average hours worked per year employed as the main predictor variable. Kuopio Ischemic Heart Disease Risk Factor Study 1984-2001 (N=621 men).

Independent Variables	**Multiple Regression Results Adjusted for All Covariates' Coefficient**	**e**
Work time: Average hours per year employed after baseline	.00214X	.038
Age and Technical Factors		
Age at baseline (years)	.000506	.001
Log of maximum IMT at baseline (log mm)	-.035111	.001
Sonographer at 11-year[2]		
A	Ref	
B	-.000717	.834
C	.001979	.761
Participant in placebo group of lipid lowering drug trial	-.005981	.024
Participant in treatment group of lipid lowering drug trial	-.005172	.054
Biological Factors		
Blood glucose average[3] (mmol/1)	.000385	.619
Plasma fibrinogen average[3] (g/1)	.000466	.754
Bodymass-Index baseline	.000358	.121
LDL-cholesterol baseline (mmol/1)	.002739	.001
HDL-cholesterol baseline (mmol/1)	.000667	.774
Systolic blood pressure at baseline (mm Hg)	.000099	.035
Proportion of follow-up time under lipid-lowering medication	-.017354	.035
Proportion of follow-up time under blood pressure lowering medication	-.000299	.887
Behavioral Factors		
Alcohol consumption average[3] (g/week)	-.000003	.679
Smoker		
no	Ref	
former	.001566	.315
irregular	.002313	.356
current	.007601	.001
Conditioning LTPA (average[3] hours/year)	-.000006	.351
Cardiorespiratory fitness (ml 0_2/kg/min)	-.000059	.584

Socioeconomic Status		
Personal income (average[3] FIM per year)	-.000159	.101
Psychosocial job factors		
Social support at work (average[3] score)	-.000099	.715
Mental strain at work index (average[3])	-.000114	.369
Stress from work deadlines[4]	-.000047	.973
Model Constant	.022928	.001

1) Multiple linear regression with average hours worked per year employed after baseline and all covariates listed in this table entered simultaneously into one model.
2) All ultrasound examinations were performed by the same sonographer at baseline
3) Average of baseline, 4-year and 11-year values
4) Combination of baseline and 4-year follow-up, not assessed at 11-year follow-up

Table 10: Absolute and relative measures of energy expenditure by time of assessment and age-cohort. Kuopio Ischemic Heart Disease Risk Factor Study 1984-2001 (N=612)

Energy Expenditure	N	Mean	SD	Min	Max
Kcal per typical work day at baseline					
age 42	203	2071	834		616-5066
age 48	184	1983	831		664-5418
age 54	167	2109	893		792-5292
age 60	58	1974	799		684-4661
total	612	2046	846		616-5418
Kcal per typical work day at 4-year follow-up					
age 42	191	2132	886		758-4809
age 48	175	1942	720		857-4172
age 54	104	2045	946		439-4705
age 60	20	1801	749		811-3571
total	490	2032	842		439-4809
Kcal per typical work day at 11-year follow-up					
age 42	166	1963	645		455-4152
age 48	84	1825	711		599-5232
age 54	3	1915	1022		751-2664
age 60	0	-	-		
total	253	1916	672		455-5232
Total amount of kcal spent between baseline and 11-year (in 1000 kcal)					
age 42	204	4954	235		721-16507
age 48	186	3940	2124		365-14586
age 54	164	2830	2988		36-16469
age 60	58	1608	1665		62–8933
total	612	3759	2645		36-16469
Kcal per potential standard 8-hour workday between baseline and 11-year					
age 42	204	1905	900		273-5209
age 48	186	1529	826		141-5691
age 54	164	1121	1173		15-6403
age 60	58	643	665		27-3638
total	612	1461	1023		15-6403

Relative aerobic strain ($\%VO_2max$) at baseline					
age 42	203	27.0%	11.5	12.4-	95.5
age 48	184	27.1%	10.2	12.5-	83.6
age 54	167	32.5%	14.9		119.
age 60	58	34.1%	10.1	13.1-	56.2
total	612	29.2%	12.4		119.
Percent oxygen uptake reserve ($\%VO_2Res$) at baseline					
age 42	203	20.6%	12.8		100.3
age 48	184	20.3%	11.4	5.8-	61.8
age 54	167	25.6%	17.5	6.8 -	142.2
age 60	58	25.9%	11.2	6.7-	52.4
total	612	22.4%	14.0		142.2

Note: age refers to age-cohort, i.e. age at baseline regardless of time of follow-up

Table** 11: **Proportion** of **men exceeding recommended levels** of **relative aerobic strain at baseline by age-cohort, baseline ischemic heart disease (IHD) status, and method to define maximum allowable levels

Method and Age Group	All Men (n=612)	Men without IHD (n=535)	Men with IHD (n=77)
Method 1			
Age 42	19.7%	18.7%	40.0%
Age 48	26.6%	23.8%	45.8%
Age 54	36.5%	33.1%	51.6%
Age 60	53.5%	50.0%	66.7%
Total	29.6%	26.5%	50.7%
Method 2			
Age 42	21.7%	20.7%	40.0%
Age 48	27.7%	25.6%	41.7%
Age 54	38.9%	34.6%	58.0%
Age 60	53.5%	50.0%	66.7%
Total	31.2%	28.2%	52.0%

Method 1: For men working less or more than 8 hours during a typical workday, relative aerobic strain was calculated as if they worked only 8 hours disregarding the extra energy expenditure and ignoring the fact that recommended levels for relative aerobic strain change with work time [99]. The threshold for excessive relative aerobic strain was set to 33% for an 8-hour day based on the literature [99, 106].

Method 2: Thresholds for excessive aerobic strain calculated based on formula provided by Wu and Wang [101] which gives the maximal allowable work time (MAWT) based on $\%V0_2max$: MAWT=95.33e 7 2gvo2max)*boo The formula can be solved to yield maximum allowable relative aerobic strain =(ln(95.33)-ln(work time))* 100/7.28. For 8 hours of work this formula sets the maximum allowable level of aerobic strain to 34 %.

Table 12: Ratio of relative change' in maximum IMT during 11 year follow-up with 95% confidence intervals, by measure of energy expenditure: Results from multiple regression analyses with incremental adjustment for covariates (All men, n=612)

Energy Expenditure	**Model 1:** Adjusted for age and technical factors	**Model** 2: Model 1 plus adjustment for biological factors	**Model 3:** Model 2 plus adjustment for behavioral factors	**Model 4:** Model 3 plus adjustment for SES and psychosocial job factors2
Absolute Measures				
Kcal per typical work day at baseline	1.14 (1.05– 1.23) p=.001	1.12 (1.03 –1.21) *p=.008*	1.13 (1.05 –1.23) p=.002	1.13 (1.04 –1.23) p=.005
Total amount of kcal during follow-up	1.17 (1.07-1.29) p=.001	1.14 *(1.04-1.25)* p=.005	1.18 (1.07-1.30) p=.001	1.17 (1.06-1.29) p=.001
Relative Measures				
Kcal per potential 8-hour standard work day during follow-up	1.19 (1.09-1.31) p=.001	1.16 (1.06-1.27) p=.002	1.19 (1.09-1.31) p=.001	1.18 (1.08-1.30) p=.001
Relative aerobic strain (%VO_2max) at baseline	1.20 (1.06 – 1.35) p=.003	1.18 (1.04 – 1.33) p=.010	1.24 (1.07-1.43) p=.004	1.23 (1.06-1.44) p=.008
Percent oxygen uptake reserve (%VO_2Res) at baseline	1.21 (1.06-1.39) p=.005	1.20 (1.04 –1.37) p=.010	1.25 (1.7-1.45) p=.004	1.24 (1.05 –1.46) p=0.010

1) Relative Change Ratio (RCR) per unit change in IMT where unit is the observed range (max – min) in energy expenditure measure
2) Adjusted for a total of 21 covariates including technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table 1

Table 13: 11-year percent change in maximum IMT, and ratio of *relative change (RCR/ by level* of *energy expenditure during 11 year follow-up: Results from multiple regression analyses with adjustment for all 21 covariates[2] (All men, n=612)*

Energy Expenditure	**11-Year Percent Change in Maximum IMT**				
	Min	**Median**	**Max**	**RCR1**	**P-value**
Absolute Measures					
Kcal per typical work day at baseline	27.6 (22.7 - 32.6)	31.6 (27.8 - 35.4)	44.3 (35.1-54.1)	1.13 (1.04-1.23)	.005
Total amount of kcal during follow-up	28.0 (23.1 - 32.4)	31.7 (28.0 - 35.5)	49.4 (38.3-61.4)	1.17 (1.06 - 1.29)	.001
Relative Measures					
Kcal per potential 8-hour standard work day during follow-up	30.2 (26.9 - 33.5)	34.9 (32.9 - 36.9)	55.3 (44.4-67.1)	1.18 (1.08-1.30)	.001
Relative aerobic strain ($\%VO_2max$) at baseline	28.1 (23.3 - 33.1)	31.6 (27.9 - 35.4)	57.9 (38.3 - 80.4)	1.23 (1.06 -1.44)	.008
Percent oxygen uptake reserve ($\%VO_2Res$) at baseline	29.0 (24.5 - 33.6)	31.6 (27.9 - 35.4)	60.0 (38.4 - 85.0)	1.24 (1.05 - 1.46)	.010

1) Relative change ratio (RCR) per unit change in IMT where unit is the observed range (max - min) in energy expenditure

2) Same covariates as in model 4 of Table 12, including 21 technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table 1

Table 14: 11 year percent change in maximum IMT at minimum, median, and maximum levels of energy expenditure; measures of association between energy expenditure and IMT progression (RCR)'; and interactions of energy expenditure with baseline ischemic heart disease (IHD) status: Results from multiple regression analyses with adjustment for 21 covariates[2] (N=612)

Energy Expenditure	Men without IHD (N=535)					Men with IHD (N=77)					Rate Ratio	Interaction
	Min	Median	Max	RCR'	P-value	Min	Median	Max	RCR'	P-value	RCRJHD / RCRNOIHD	P-value
Absolute Measures												
Kcal per typical work day at baseline	27.9 (22.9-33.1)	32.8 (26.7-39.2)	40.0 (30.6-50.1)	1.09 (1.00 - 1.20)	.052	24.6 (14.0 - 36.2)	34.9 (28.2 - 41.8)	70.9 (46.5-99.4)	1.37 (1.10 - 1.71)	.005	1.25 (0.99 - 1.59)	.060
Total amount of kcal during follow-up	27.1 (22.4-31.9)	31.0 (27.3-34.9)	48.1 (36.7-60.5)	1.17 (1.06 1.29)	.003	32.1' (23.1 - 41.8)	37.2 (30.1 - 43.9)	59.5 (28.2-98.4)	1.21 (0.93 1.57)	.164	1.04 (0.79 1.37)	.802
Kcal per potential 8-hour standard work day during follow-up	26.7 (22.1 - 31.5)	30.9 (27.3-34.7)	49.1 (37.7-61.5)	1.18 (1.07 1.30)	.001	31.6 (22.7 - 41.2)	37.3 (30.9-44.0)	62.1 (30.8 - 101.0)	1.23 (0.95 1.60)	.117	1.05 (0.80 1.37)	.741
Relative Measures												
Relative aerobic strain (%VO_2max) at baseline	29.0 (24.0-34.2)	31.1 (27.4-35.0)	46.3 (26.4-69.4)	1.13 (0.96 1.35)	.150	27.1 (17.6-37.3)	33.9 (26.9-41.3)	90.0 (52.9 - 136.1)	1.50 (1.14 1.96)	.004	1.36 (1.00 1.83)	.067
Percent oxygen uptake reserve %VO_2Res) at baseline	29.6 (25.0-34.4)	31.2 (27.4-35.0)	47.1 (25.2-72.9)	1.14 (0.95 -1.36)	.170	28.9 (20.1 - 38.3)	35.2 (28.0 -42.7)	98.3 *(54.2-155.0)*	1.54 (1.14-2.08)	.005	1.35 (0.97-1.88) (	.071

1) Relative change ratio (RCR) per unit change in IMT where unit is the observed range (max - min) in energy expenditure or relative aerobic strain

2) Same covariates as in model 4 of Table 12, including 21 technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table I

***Table 15:** 11 year percent change in maximum IMT at minimum, median, and maximum levels of energy expenditure; measures of association between energy expenditure and IMT progression (RCR)'; and interactions of energy expenditure with baseline status of carotid artery stenosis: Results from multiple regression analyses with adjustment for 21 covariates[2] (N=612)*

Energy Expenditure	Men without Carotid Stenosis (N=485)					Men with Carotid Stenosis (N=127)				Rate Ratio		Interaction
	Min	Median	Max	RCR'	P-value	Min	Median	Max	RCR'	P-value	RCRs,e„ / RCRrrosje,	P-value
Absolute Measures												
Kcal per typical work day at baseline	27.9 (22.7-33.3)	31.1 (27.4-35.0)	41.3 (31.3- 52.1)	1.11 (1.00 1.22)	.045	29.1 (20.1 - 38.0)	35.3 (29.4 - 41.4)	55.6 (38.3-75.0)	1.20 (1.03 1.41)	.022 (0.91	1.09 1.31)	.348
Total amount of kcal during follow-up	28.4 (23.6-33.4)	31.4 (27.7-35.3)	44.5 (32.8-57.2)	1.13 (1.01 1.25)	.027	28.9 (21.6-36.6)	36.4 (30.5-42.6)	71.6 (45.8 - 101.9)	1.33 (1.10 1.62)	.004 (0.95	1.18 1.47)	.124
Kea] per potential 8-hour standard work day during follow-up	27.8 (23.1 - 32.8)	31.2 (27.6-35.0)	45.7 *(34.0-58.4)*	1.14 (0.97 1.21)	.014	28.8 (21.5 - 36.5)	36.2 (30.4-42.4)	70.4 (45.2 - 99.8)	1.32 (1.09 1.60)	.004 (0.94	1.16 1.43)	.168
Relative Measures												
Relative aerobic strain (%VO_2max) at baseline	28.2 *(23.2-33.5)*	31.1 *(27.4.-*35.0)	52.2 (30.8-77.2)	1.19 (0.99 1.42)	.058	30.4 (22.6-38.9)	35.2 *(29.2-41.5)*	71.6 (41.2- 108.6)	1.32 (1.04 1.66)	.022 (0.85	1.11 1.46)	.440
Percent oxygen uptake reserve %VO_2Res) at baseline	29.2 (24.5 -34.0)	31.2 (27.4 -35.0)	52.0 (28.6 -79.6)	1.18 (0.97-1.42)	.090	31.0 (23.7 - 38.8)	35.0 (29.0 - 41.3)	80.0 (43.7-125.5)	1.37 (1.06-1.78)	.016	1.17 (0.87 -1.57) (	.301

1) Relative change ratio (RCR) per unit change in IMT where unit is the observed range (max - min) in energy expenditure

2) Same covariates as in model 4 of Table 12 including 21 technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table I

Table 16: Distribution of the duration of work postures (in minutes per typical workday and as percent of daily work time). Kuopio Ischemic Heart Disease Risk Factor Study 1984-2001 (N=612)

Work Posture by Survey time and age	N	Mean	SD	Min –Max	Percent Work Day
Sitting at baseline					
age 42	203	206	147	0-645	39.3%
age 48	184	247	157	30-660	46.3%
age 54	167	210	138	0-630	38.9%
age 60	58	216	169	0-720	39.9%
total	612	221	151	0-720	41.4%
Sitting at 4-year					
age 42	191	238	169	0-780	44.4%
age 48	175	257	162	0-720	48.7%
age 54	104	235	156	0-600	44.8%
age 60	20	258	161	0-510	50.3%
total	490	245	163	0– 780	46.2%
Sitting at 11-year					
age 42	166	241	167	0-720	45.0%
age 48	84	261	168	30-660	49.2%
age 54	3	190	200	60-420	39.7%
age 60	0	0	0	0	0%
total	253	247	168	0-720	46.3%
Standing at baseline					
age 42	203	102	126	0-540	18.9%
age 48	184	65	90	0-500	12.3%
age 54	167	119	139	0-555	21.0%
age 60	58	115	134	0-540	20.9%
total	612	97	123	0-555	17.7%
Standing at 4-year					
age 42	191	79	122	0-600	14.3%
age 48	175	57	97	0-570	10.4%
age 54	104	90	133	0-540	15.9%
age 60	20	60	80	0-240	10.5%
total	490	73	115	0-600	13.1%
Standing at 11-year					
age 42	166	89	100	0-420	16.9%
age 48	84	84	113	0-430	16.4%
age 54	3	185	256	15-480	26.4%
age 60	0	0	0	0	0%
total	253	89	107	0-480	16.9%

ground at baseline					
age 42	203	143	104	0-600	26.8%
age 48	184	137	98	0-480	26.2%
age 54	167	144	107	*0-550*	25.9%
age 60	58	159	111	0-480	28.9%
total	612	143	104	0-600	26.6%
Walking on level ground at 4-year					
age 42	191	128	101	-570	24.2%
age 48	175	139	104	0-480	26.9%
age 54	104	134	100	*0-450*	24.7%
age 60	20	122	124	*0-450*	22.7%
total	490	133	103	*0-570*	25.2%
Walking on level ground at 11-year					
age 42	166	131	97	0-480	24.8%
age 48	84	125	111	0-540	24.5%
age 54	3	125	95	*15-180*	20.9%
age 60	0	0	0	0	0%
total	253	129	102	0-540	24.6%
Walking on uneven ground at baseline					
age 42	203	56	86	0-420	9.9%
age 48	184	55	87	0-420	9.9%
age 54	167	53	81	0-420	8.8%
age 60	58	46	75	0-360	7.8%
total	612	54	84	0 – 420	9.4%
Walking on uneven ground at 4-year					
age42	191	64	88	0-360	11.8%
age 48	175	54	85	0-360	10.0%
age 54	104	62	96	0-360	10.9%
age 60	20	50	62	0-180	10.3%
total	490	59	88	0-360	10.9%
Walking on uneven ground at 11-year					
age 42	166	39	88	0-450	7.4%
age 48	84	24	77	0-480	4.2%
age 54	3	40	69	0-120	7.8%
age 60	0	0	0	0	0%
total	253	34	85	0 -480	6.3%

• Climbing stairs at baseline					
age 42	203	29	**58**	0-300	5.1%
age 48	184	29	62	0-300	5.4%
age 54	167	32	61	0-240	5.3%
age 60	58	18	46	0-180	2.6%
total	612	29	59	0-300	5.0%
Climbing stairs at 4-year					
age42	191	29	70	-420	**5.3%**
age48	175	21	53	-390	3.9%
age 54	104	22	45	0-180	3.7%
age 60	20	29	51	0-120	6.2%
total	490	24	59	0-420	4.5%
Climbing stairs at 11-year					
age42	166	12	25	0-150	2.2%
age 48	84	13	29	0-180	2.3%
age 54	3	0	0	0	0%
age 60	0	0	0	0	0%
total	253	12	26	0 - 180	2.2%
Upright postures at baseline					
age 42	203	333	172	0-720	61.2%
age 48	184	284	160	0-660	53.5%
age 54	167	349	176	30-690	61.0%
age 60	58	336	185	0-690	60.0%
total	612	323	172	0-720	*58.7%*

Note: 11-year percentages do not add up to 100% because about 3.7% of time was spent in other activities not otherwise classified and not listed in this table. Such other activities were not recorded at baseline and 4 years.

Table 17: Work postures at baseline and ratio of relative change' in maximum IMT during 11 year follow-up with 95% confidence intervals: Regression analyses with incremental adjustment for covariates (N=612)

Work posture at baseline	**Model 1:** Adjusted for age and technical factors	**Model 2:** Model 1 plus adjustment for biological factors	**Model 3:** Model 2 plus adjustment for behavioral factors	**Model** 4: Model 3 plus adjustment for psychosocial job factors2
Sitting	0.97 (0.91 - 1.04) p=.421	0.98 (0.92 - 1.05) p=.617	0.98 (0.91 - 1.04) p=.704	0.99 (0.93 - 1.05) p=.704
Standing	1.01 (0.95 - 1.07) p=.777	1.00 (0.94 - 1.06) p=.896	0.99 (0.93 - 1.05) p=.632	0.98 (0.92 - 1.04) p=.535
Walking on level ground	0.96 (0.89 - 1.04) p=.304	0.96 (0.89 - 1.04) p=.287	0.96 (0.88 - 1.03) p=.243	0.94 (0.86 - 1.02) p=.136
Walking on uneven ground	1.08 (1.01 - 1.15) p=.033	1.07 *(1.00-1.15)* p=.038	1.08 (1.01 - 1.16) p=.022	1.07 *(1.00-1.15)* p=.048
Climbing stairs	1.12 (1.04 - 1.20) p=.002	1.12 (1.05 - 1.20) p=.001	1.14 (1.07 -1.23) p=.001	1.14 (1.06 - 1.23) p=.001
Upright work posture	1.05 (0.99- 1.12) p=.080	1.04 (0.98 - 1.10) p=.155	1.04 (0.98 - 1.10) p=.165	1.03 (0.97 - 1.10) p=.350

1) Relative Change Ratio (RCR) per unit change in IMT where unit is the observed range (max - min) in energy expenditure measure
2) Adjusted for a total of 21 covariates including technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table 1

Table 18: Weighted[1] averages of baseline, 4-year and 11 year work postured, intensity of upright work posture, and ratio of relative change[2] in maximum IMT during 11 year follow-up with 95% confidence intervals: Regression analyses with incremental adjustment for covariates (N=621)

Working posture (weighted average)'	**Model 1:** Adjusted for age and technical factors	**Model** 2: Model 1 plus adjustment for biological factors	**Model 3:** Model 2 plus adjustment for behavioral factors	**Model 4:** Model 3 plus adjustment for psychosocial job factors3
Sitting	0.98 (0.91 - 1.04) p=.488	0.98 (0.92 - 1.05) p=.574	0.98 (0.91 - 1.04) p=.450	0.99 (0.92 - 1.07) p=.832
Standing	1.00 (0.93 - 1.07) p=.973	1.00 (0.93 - 1.07) p=.965	1.00 (0.93 - 1.07) p=.965	0.99 (0.93 - 1.06) p=.849
Walking on level ground	0.97 (0.90 - 1.05) p=.466	0.96 (0.89 - 1.04) p=.290	0.97 (0.89 - 1.05) p=.389	0.95 (0.88 -1.03) p=.230
Walking on uneven ground	1.10 (1.04-1.18) p=.002	1.09 (1.02-1.16) p=.007	1.09 (1.02-1.16) p=.006	1.08 (1.02-1.16) p=.016
Climbing stairs	1.14 (1.03-1.26) p=.009	1.15 *(1.05-1.27)* p=.004	1.18 (1.07-1.30) p=.001	1.18 (1.06 -1.30) p=.002
Intensity of upright work posture	1.04 (0.98 - 1.09) p=.172	1.03 (0.98 - 1.08) p=.279	1.03 (0.98 -1. 09) p=.194	1.02 (0.97 - 1.08) p=.414
Proportion of time upright at work	1.12 (1.04-1.21) p=.003	1.11 (1.03-1.19) p=.008	1.13 (1.05-1.22) p=.001	1.13 (1.04-1.22) p=.004

1) Weights were assigned to baseline (4/22), 4-year (11/22) and 11-year (7/22) values and missing values at one survey time were replaced by values form adjacent survey dates with appropriate change in weights.
2) Relative Change Ratio (RCR) per unit change in IMT where unit is the observed range (max - min) in energy expenditure measure
3) Adjusted for a total of 21 covariates including technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table 1

Table 19: Working posture (weighted average of baseline, 4-year and II year)', percent change in maximum IMT, and relative change ratio (RCR)[2] during 1I year follow-up for all men: Regression analyses with adjustment for all covariates[3] (N=621)

Working posture (weighted average')	11-Year Percent Change in Maximum IMT				
	Min	Median	Max	RCR2	P-value
Sitting	33.2 (28.5 - 38.0)	32.9 (29.2 - 36.7)	32.1 (24.7 - 40.0)	0.99 (0.92 - 1.07)	.832
Standing	33.0 (29.0-37.1)	32.9 (29.2 - 36.7)	32.1 (23.8 - 40.9)	0.99 (0.93 - 1.06)	.849
Walking on level ground	34.6 *(29.9-39.5)*	33.1 (29.4-37.0)	28.1 (19.9-36.8)	0.95 (0.88-1.03)	.230
Walking on uneven ground	31.0 (27.0-35.0)	31.1 *(27.2-35.1)*	42.0 (33.6-50.9)	1.08 (1.02-1.16)	.016
Climbing stairs	31.1 (27.3 - 34.9)	31.1 (27.3 - 34.9)	54.1 (39.8-69.8	1.18 (1.06 - 1.30)	.002
Intensity of upright work posture	31.0 25.3 -26.9)	32.9 (29.2-36.7)	34.1 29.4-39.0)	1.02 (0.97 - 1.08)	.414
Proportion of time upright at work	28.9 (24.5 - 33.4)	31.9 (28.2 - 35.7)	45.1 *(35.9-54.9)*	1.13 (1.04 - 1.22)	.004

1) Weights were assigned to baseline (4/22), 4-year (11/22) and 11-year (7/22) values. Missing values at one survey time were replaced by values form adjacent survey dates with appropriate change in weights.
2) Relative change ratio (RCR) per unit change in IMT where unit is the observed range (max - nun) in work posture exposure.
3) Same covariates as in model 4 of Table 18, including 21 technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table 1.

Table 20: Working posture (weighted average of baseline, 4-year and 11 year)', percent change in maximum IMT, and relative change ratio (RCR)[2] during 11 year follow-up, ***by ischemic heart disease at baseline:*** *Regression analyses with adjustment for all covariates[3] (N=621)*

Working posture (weighted average')	Men without IHD (N=535) Min	Median	Max	RCRZ	P-value	Men with IHD (N=77) Min	Median	Max	RCRZ	P-value	Rate Ratio RCR,,rp / RCRN.1HD	Interaction P-value
Sitting	31.6 (26.9-36.6)	31.9 (28.2-35.8)	32.8 (25.1 - 41.0)	1.01 (0.94 - 1.09)	.821	42.0 (31.9 - 52.8)	38.6 (32.3-45.2)	29.6 (1.09 - 54.5)	0.91 (0.73 - 1.14)	.429	0.91 (0.72 - 1.15)	.406
Standing	32.4 (28.4- 36.6)	32.2 (28.4 - 36.1)	30.1 (21.3 -39.5)	0.98 (0.91 - 1.06)	.648	38.0 (30.3 - 46.1)	38.4 (31.7 - 45.4)	41.9 (22.8-63.9)	1.03 (0.87 - 1.22)	.746	1.05 (0.87 - 1.26)	.630
Walking on level ground	34.6 (29.8-39.6)	32.5 (28.7-36.3)	25.2 (16.9-34.1)	0.93 (0.85 - 1.01)	.097	43.1 (24.3-44.6)	38.1 (31.7 - 44.8)	53.2 (28.3-82.9)	1.14 (0.91 - 1.44)	258	1.23 (0.96 - 1.57)	.099
Walking on uneven ground	30.5 (26.6-34.6)	30.6 (26.7-34.7)	38.2 (29.5-47.4)	1.06 (0.99-1.14)	.110	32.7 (25.2-40.7)	33.1 (25.8-40.9)	66.1 (43.1 -94.0	1.26 (1.05-1.50)	.014	1.19 (0.98 - 1.44)	.082
Climbing stairs	30.3 (26.5 - 34.2)	30.3 (26.5-34.2)	54.8 (38.7-72.8)	1.19 (1.06 - 1.33)	.003	37.4 (30.4-44.8)	37.4 (30.4-44.8)	47.8 (21.3-80.0)	1.08 (0.87 - 1.34)	.509	0.91 (0.71 - 1.15)	.421
Intensity of upright work posture	31.7 (25.8-37.8)	32.0 (28.3-35.8)	32.2 (27.3 - 37.2)	1.00 (0.95- 1.07)	.897	25.7 (11.1 - 42.0)	38.0 (31.7 - 44.6)	45.8 (35.5-56.9)	1.16 (0.98 - 1.37)	.085	1.16 (0.97 - 1.38)	.107
Proportion of time upright at work	28.9 (24.4-33.5)	31.3 (27.6-35.1)	41.6 (32.3-51.6)	1.10 (1.01 - 1.19)	.026	29.7 (21.2-38.7)	36.7 (30.7 - 43.6)	72.0 (44.6 - 104.7)	1.33 (1.07 - 1.65)	.010	1.21 (0.96 - 1.51)	.101

1) Weights were assigned to baseline (4/22), 4-year (11/22) and 11-year (7/22) values. Missing values at one survey time were replaced by values form adjacent survey dates with appropriate change in weights.

2) Relative change ratio (RCR) per unit change in IMT where unit is the observed range (max - min) in work posture exposure.

3) Same covariates as in model 4 of Table 18, including 21 technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table 1.

*Table 21: Working posture (weighted average of baseline, 4-year and 11 year)', percent change in maximum IMT, and relative change ratio (RCR)[2] during 11 year follow-up, by carotid artery stenosis at baseline: Regression analyses with adjustment for all **covariates**[3] (N=621)*

Working posture (weighted average')	Men without Carotid Stenosis (N=485) Min	Median	Max	RCRZ	P-value	Men with Carotid Stenosis (N=127) Min	Median	Max	RCRZ	P-value	Rate Ratio RCRIxo I RCRNOInn	Interaction P-value
Sitting	31.6 (26.9 - 36.6)	31.9 (28.2 - 35.9)	32.8 (25.1 41.0))	1.00 (0.92- 1.08)	.821	42.0 (31.9-52.8)	38.6 (32.3 - 45.2)	29.6 (1.09 - 54.5)	0.99 (0.85 - 1.16)	.429	1.00 (0.85 - 1.18)	.406
Standing	32.4 (28.4- 36.6)	32.2 (28.4 - 36.1)	30.1 (21.3 - 39.5)	1.01 (0.92- 1.10)	.648	38.0 (30.3-46.1)	38.4 (31.7-45.4)	41.9 (22.8-63.9)	0.95 (0.85 - 1.06)	.746	0.94 (0.82 -1.08)	.630
Walking on level ground	34.6 (29.8-39.6)	32.5 (28.7-36.3)	25.2 (16.9-34.1)	0.93 (0.85- 1.24)	.097	43.1 (24.3 - 44.6)	38.1 (31.7-44.8)	53.2 (28.3-82.9)	1.05 (0.89 - 1.24)	258	1.12 (0.93 - 1.35)	.099
Walking on uneven ground	30.5 (26.6-34.6)	30.6 (26.7-34.7)	38.2 (29.5-47.4)	1.06 (0.99- 1.15)	.110	32.7 *(25.2-40.7)*	33.1 (25.8 - 40.9)	66.1 (43.1 -94.0	1.13 (1.00 - 1.29)	.014	1.07 (0.92 - 1.23)	.082
Climbing stairs	30.3 (26.5-34.2)	30.3 (26.5-34.2)	54.8 (38.7-72.8)	1.15 (1.03 -- 1.29)	.003	37.4 (30.4-44.8)	37.4 (30.4-44.8)	47.8 (21.3-80.0)	1.22 (0.99 - 1.49)	.509	1.06 (0.84 1.33)	.421
Intensity of upright work posture	31.7 (25.8-37.8)	32.0 (28.3 - 35.8)	32.2 (27.3 - 37.2)	1.01 (0.95- 1.08)	.897	25.7 (11.1 - 42.0)	38.0 (31.7-44.6)	45.8 (35.5-56.9)	1.06 (0.95 - 1.18)	.085	1.05 (0.93 - 1.18)	.107
Proportion of time upright at work	28.9 (24.4-33.5)	31.3 (27.6-35.1)	41.6 (32.3-51.6)	1.08 (0.99-1.18)	.026	29.7 (21.2-38.7)	36.7 (30.7-43.6)	72.0 (44.6-104.7)	1.28 (1.10-1.51)	.010	1.19 (1.00-1.42)	.101

1) Weights were assigned to baseline (4/22), 4-year (11/22) and 11-year (7/22) values. Missing values at one survey time were replaced by values form adjacent survey dates with appropriate change in weights.

2) Relative change ratio (RCR) per unit change in IMT where unit is the observed range (max - min) in work posture exposure.

3) Same covariates as in model 4 of Table 18, including 21 technical, biological, behavioral, socioeconomic, and psychosocial factors listed in Table 1.

PUBLICATIONS

Manuscripts

One manuscript has been accepted for publication:

(1) Krause, N, Brand, RJ, Kaplan, GA, Kauhanen, J, Malla, S, Tuomainen, TP Salonen, JT, Occupational physical activity, energy expenditure, and 11-year progression of carotid atherosclerosis, Scand J Work Environ Health, 2007 (in press)

This manuscript addresses aims la, 3a, 3b, and 5 of the original proposal.

Abstracts

Four abstracts have been presented at international conferences:

(1) Dasinger LK, Krause N, Brand RJ, Kaplan GA, Salonen JT. "Percent Time at Work in an Upright Posture Associated with 11 Year Change in Systolic Blood Pressure." 4th International Conference on Work Environment and Cardiovascular Diseases, Newport Beach, California, March 9-11, 2005
This abstract addresses aim 2b, 3a, 3b, and 5 of the proposal.

(2) Krause N, Dasinger LK, Brand RJ, Kaplan GA, Salonen JT. "Standing, Walking and Climbing Stairs at Work Associated with 11 Year Progression of Atherosclerosis." 4th International Conference on Work Environment and Cardiovascular Diseases, Newport Beach, California, March 9-11, 2005
This abstract addresses aims 2b, 3a, 3b, and 5 of the proposal.

(3) Krause N, Brand RJ, Kaplan GA, Malla S, Salonen JT,"Working posture and 11-year progression of carotid atherosclerosis," 28th International Congress on Occupational Health, Milan, Italy, June 11-16, 2006
This abstract addresses aims 2b, 3a, 3b, and 5 of the proposal.

(4) Krause N, Brand RJ, Kaplan GA, Malla S, Salonen JT,"Work intensity, energy expenditure, relative aerobic strain, and 11-year progression of carotid atherosclerosis," 28th International Congress on Occupational Health, Milan, Italy, June 11-16, 2006 This abstract addresses aims lb, 3a, 3b, 5, and 6 of the proposal.

INCLUSION OF GENDER AND MINORITY STUDY SUBJECTS

This Finnish study population has been selected for this research project because no other population-based sample of comparable sample size and sufficient follow-up time provides such comprehensive data on the full range of predictor variables and possible confounders necessary to clarify the unresolved issues in this area of research.

For historical and economic reasons, the study was designed to only include men. At the time of inception in the early 1980s cardiovascular morbidity and mortality was substantially (about 2-fold) higher in men than in women, and considerations of statistical power and costs precluded a study of both genders.

In the collection of the KIHD data, no exclusions were made based on race or ethnicity. The population under study may be considered 100% "white." Although descendents from different people in the Baltic region make up the local population, people in Finland typically do not identify themselves in such categories, and Finnish institutions do not routinely collect data on the ethnic mix of the population. For these reasons, there is no further information on minority issues available.

INCLUSION OF CHILDREN

Children were not included in this study. The sample was restricted to middle age persons (at least 42 years old at baseline) because ischemic heart disease typically manifests in middle or old age.