Journal of the American Heart Association

Job Strain as a Risk Factor for Peripheral Artery Disease: A Multi-Cohort Study

Katriina Heikkilä (iD), PhD; Jaana Pentti, MSc; Ida E. H. Madsen, PhD; Tea Lallukka, PhD;
Marianna Virtanen, PhD; Lars Alfredsson, MD, PhD; Jakob Bjorner, PhD; Marianne Borritz, MD, PhD;
Eric Brunner, PhD; Hermann Burr, PhD; Jane E. Ferrie, PhD; Anders Knutsson, MD; Aki Koskinen, MSc;
Constanze Leineweber, PhD; Linda L. Magnusson Hanson, PhD; Martin L. Nielsen, MD, PhD;
Solja T. Nyberg, PhD; Tuula Oksanen, MD, PhD; Jan H. Pejtersen, PhD; Olli Pietiläinen, MSc; Ossi Rahkonen, PhD;
Reiner Rugulies, PhD; Archana Singh-Manoux, PhD; Andrew Steptoe, DSci; Sakari Suominen, MD, PhD;
Töres Theorell, PhD; Jussi Vahtera, MD, PhD; Ari Väänänen, PhD; Hugo Westerlund, PhD; Mika Kivimäki, PhD

BACKGROUND: Job strain is implicated in many atherosclerotic diseases, but its role in peripheral artery disease (PAD) is unclear. We investigated the association of job strain with hospital records of PAD, using individual-level data from 11 prospective cohort studies from Finland, Sweden, Denmark, and the United Kingdom.

METHODS AND RESULTS: Job strain (high demands and low control at work) was self-reported at baseline (1985–2008). PAD records were ascertained from national hospitalization data. We used Cox regression to examine the associations of job strain with PAD in each study, and combined the study-specific estimates in random effects meta-analyses. We used τ^2, I^2, and subgroup analyses to examine heterogeneity. Of the 139 132 participants with no previous hospitalization with PAD, 32 489 (23.4%) reported job strain at baseline. During 1 718 132 person-years at risk (mean follow-up 12.8 years), 667 individuals had a hospital record of PAD (3.88 per 10 000 person-years). Job strain was associated with a 1.41-fold (95% CI, 1.11–1.80) increased average risk of hospitalization with PAD. The study-specific estimates were moderately heterogeneous (τ^2=0.0427, I^2: 26.9%). Despite variation in their magnitude, the estimates were consistent in both sexes, across the socioeconomic hierarchy and by baseline smoking status. Additional adjustment for baseline diabetes mellitus did not change the direction or magnitude of the observed associations.

CONCLUSIONS: Job strain was associated with small but consistent increase in the risk of hospitalization with PAD, with the relative risks on par with those for coronary heart disease and ischemic stroke.

Key Words: epidemiology ■ job strain ■ meta-analysis ■ peripheral artery disease ■ risk factors

Peripheral artery disease (PAD) is a manifestation of atherosclerotic cardiovascular disease, characterized by intermittent claudication or atypical leg pain.[1] In 2010, this disease affected >200 million people worldwide, reflecting a 13.1% increase in its prevalence in high income countries between 2000 and 2010.[1] With the population agiing, larger numbers of people are living with PAD for longer, a trend which is reflected by the wider uptake of secondary preventive treatments, such as statins, antiplatelets, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.[2] Given the scale of the disease and the effort of keeping PAD at bay by means of secondary preventive measures, it is not surprising that the costs of PAD to patients (in terms of decreased quality of life and years of life lost, disability, sickness absence, and loss of income) and healthcare systems (in terms of medical, endovascular, and surgical management) are now comparable with those incurred by coronary heart disease and stroke.[3,4]

CLINICAL PERSPECTIVE

What Is New?

- Job strain, a marker of psychosocial stress at work, was associated with small but consistent increase in the risk of hospitalization with peripheral artery disease.
- The strength of the association was similar to that of job strain with coronary heart disease and ischemic stroke.

What Are the Clinical Implications?

- Physicians in occupational health and primary care need to recognize work-related stress as a risk factor for many cardiovascular disease outcomes, including peripheral artery disease.

Nonstandard Abbreviations and Acronyms

DWECS	Danish Work Environment Cohort Study
FPS	Finnish Public Sector study
HHS	Helsinki Health Study
IPD-WORK	Individual-Participant Data Meta-Analysis in Working Populations
PAD	peripheral artery disease
SHR	sub-distribution hazard ratio
WOLF S	Work, Lipids and Fibrinogen Stockholm

Despite the considerable burden of PAD, the evidence on specific risk factors, including potential primary preventive targets, for this disease is scarce.[5] Advanced age, type 2 diabetes mellitus and elevated blood pressure, circulating lipids, and clotting are important risk factors for all atherosclerotic cardiovascular diseases, including PAD.[1,5] In addition, recent large-scale observational "mega-studies" have shown that stress is associated with many cardiovascular outcomes, most strongly as a trigger or a prognostic factor for major cardiac events in high-risk populations and in those with pre-existing cardiovascular disease.[6] Reflecting this evidence, European clinical guidelines now recognize psychosocial stress as an important clinical target in the management of heart disease and stroke.[5] However, in contrast to the extensive research into the associations of various stress exposures with myocardial infarction, stroke, atrial fibrillation, and venous thromboembolism,[7,8] few studies have examined the relationship between stress and PAD.

The Individual-Participant Data Meta-Analysis in Working Populations (IPD-Work) Consortium is among the world's largest collaborations using harmonized individual-participant data on work stress and health outcomes in adults.[9] Here we have used data from >139 000 men and women from the Consortium's studies to investigate the association between work-related stress, operationalized as job strain, and hospital-treated PAD.

METHODS

Data Availability

This study used data from 11 independent studies, which all have different data sharing policies. Our data protection agreements with the participating cohort studies do not allow IPD-Work Consortium to share individual-level data from these studies to third parties. Requests for individual study data can be addressed to each study's executive committee. Syntax for the main analyses is provided in Data S2.

Studies and Participants

The analyses presented here are based on data from 11 prospective cohort studies, which had available data on job strain and hospital-treated PAD. Eight of the 19 Consortium studies were not included in the analyses because of missing exposure or outcome data. The analyses were based on data from Copenhagen Psychosocial Questionnaire versions I and II,[10,11] DWECS (Danish Work Environment Cohort Study),[12,13] FPS (Finnish Public Sector) study,[14] Health and Social Support,[15] HHS (Helsinki Health Study),[16] Intervention Project on Absence and Well-Being,[17,18] Swedish Longitudinal Occupational Survey of Health,[19] Still Working,[20,21] Whitehall II,[22] and Work, Lipids and Fibrinogen Stockholm (WOLF S).[23] All studies were approved by local and/or national ethics committees and participants gave informed consent to take part. Details of the studies have been published previously and are provided in Data S1. Participants were included in the analyses if they had baseline data available on job strain, age, sex, and socioeconomic position, and follow-up data on hospitalizations. Those with a hospital record of PAD at or before baseline were excluded.

Measurements

The main exposure in our analyses was job strain, the most extensively used operationalization of work-related psychosocial stress, was ascertained from baseline questionnaires in all studies.[24,25] A detailed description of the harmonization of job strain has been published previously.[26] Briefly, participants were asked to rate statements describing psychosocial aspects of their job on a Likert-type scale. Mean response scores were calculated for job demands items (eg, "my job

Table. Study and Participant Characteristics

Study	Country	Baseline, y	Setting (Occupational vs Population-Based)	n, Participants	Mean (Range*) Baseline Age (y)	n (%) Men	n (%) Job Strain at Baseline	Mean (SD) Follow-Up (y)	n With PAD (Incidence Per 10 000 Person-Years)
COPSOQ-I[10]	Denmark	1997	Population	1769	40.7 (23–57)	908 (51.3)	363 (20.5)	11.7 (1.6)	16 (7.71)
COPSOQ-II[11]	Denmark	2004 to 2005	Population	3424	42.8 (25–58)	1630 (47.6)	486 (14.2)	5.0 (0.4)	12 (7.71)
DWECS[12,13]	Denmark	2000	Population	5563	41.8 (23–59)	2963 (53.3)	1239 (22.3)	8.8 (1.2)	37 (7.53)
FPS[14]	Finland	2000 to 2004	Occupational	65 495	43.7 (17–69)	13 104 (20.0)	17 859 (27.3)	9.8 (1.8)	110 (1.72)
HeSSup[15]	Finland	1998 and 2003	Population	18 465	38.6 (20–59)	7760 (42.0)	5203 (28.2)	13.1 (2.2)	55 (2.28)
HHS[16]	Finland	2000 to 2002	Occupational	6448	49.2 (39–60)	1397 (21.7)	1001 (15.5)	14.4 (1.8)	41 (4.41)
IPAW[17,18]	Denmark	1996 to 1997	Occupational	2025	41.2 (24–57)	672 (33.1)	355 (17.5)	12.8 (1.9)	25 (9.66)
SLOSH[19]	Sweden	2006 to 2008	Population	10 974	47.7 (19–68)	5063 (46.1)	2223 (20.3)	6.5 (1.2)	16 (2.23)
Still Working[20,21]	Finland	1986	Occupational	9154	40.9 (18–65)	7071 (77.2)	1424 (15.6)	21.7 (4.0)	161 (8.11)
Whitehall II[22]	United Kingdom	1985 to 1988	Occupational	10 153	44.4 (34–56)	6799 (70.0)	1417 (14.0)	26.8 (4.6)	159 (5.82)
WOLF S[23]	Sweden	1992	Occupational	5662	41.5 (19–70)	3216 (56.8)	919 (16.2)	15.5 (2.2)	35 (3.98)

COPSOQ-I and –II indicates Copenhagen Psychosocial Questionnaire versions I and II; DWECS, Danish Work Environment Cohort Study; FPS, Finnish Public Sector study; HeSSup, Health and Social Support; HHS, Helsinki Health Study; IPAW, Intervention Project on Absence and Well-being; PAD, peripheral artery disease; SLOSH, Swedish Longitudinal Occupational Survey of Health; and WOLF S, Work, Lipids and Fibrinogen Stockholm.

*5th and 95th percentiles are presented for COPSOQ-II, COPSOQ-II, DWECS, and IPAW for data security reasons.

requires working very fast") and job control items or (eg, "my job allows me to learn new things") for each participant. Using the original and most commonly used categorization, we defined high demands as having a job demand score above the study-specific median and low control as having a job control score below the study-specific median. According to the original model, a combination of high demands and low control was defined as job strain, and all other demand-control combinations as no strain.[25] To minimize investigator bias, we validated the job strain measure before linking exposure and covariate data to outcome data.

Covariates in our analyses were participant age, sex, socioeconomic position (harmonized into 3 categories: low, intermediate and high), body mass index (BMI: weight in kilograms divided by height in meters squared, harmonized into underweight [<18.5 kg/m^2], normal weight [18.5 to <25 kg/m^2], overweight [25 to <30 kg/m^2] and obese [≥30 kg/m^2]), smoking (harmonized into never, former and current), alcohol consumption (harmonized into none, moderate and heavy), leisure-time physical activity (sedentary or active) and baseline diabetes mellitus (yes or no). Details of ascertainment of these covariates are provided in Data S1.

PAD outcomes were ascertained by linking participants' study records (with the participants' consent, using national identification numbers in the Nordic studies and the National Health Service number in Whitehall II) to national hospitalization registers (Nordic studies) and administrative hospitalization data (Whitehall II). Any episode of hospital care with a record of an *International Classification of Diseases, Eighth Revision (ICD-8), Ninth Revision (ICD-9),* or *Tenth Revision (ICD-10)* code indicating PAD either as primary or secondary diagnostic code[27] (Table S1) was counted as a PAD event. Deaths from any cause were ascertained by linking participants' study records to national death registers.

Statistical Analyses

We used Cox proportional hazards regression to examine the associations between job strain and hospital-treated PAD events during follow-up. Time to the outcome of interest was defined as time from the baseline assessment to the first hospital record of PAD, death of the participant or the end of study-specific follow-up, whichever occurred first. Examination of log(–log) plots and Schoenfeld test provided no evidence for violation of the proportional hazards assumption.

First, we examined the associations of job strain with hospital-treated PAD in each study, using harmonized individual-participant data. This approach

was chosen because of ethical and data protection regulations, only study-level results from the studies conducted in Sweden and Denmark could be used in the combined analyses. Second, we combined the study-specific hazard ratios (HRs) and their 95% CIs in random effects meta-analyses, using empirical Bayes (EB) estimator for between-study variance. Sensitivity analyses were conducted using DerSimonian and Laird and restricted maximum likelihood estimators for between-studies variance. Random effects approach was chosen to estimate the mean of the associations between job strain and PAD, which are likely to differ in different countries and work settings. We calculated I^2 and τ^2 to estimate relative and absolute heterogeneity, respectively, among the study-specific estimates. In addition to the random effects, overall HR and its 95% CI (which estimate the average association between job strain and PAD and uncertainty about this average), we calculated a 95% prediction interval to estimate the range of associations of job strain with PAD across different study settings. The calculation of the prediction interval is based on the assumptions that the study-specific estimates in a meta-analysis represent a random, normally distributed sample from an underlying distribution of estimates.[28,29] Whilst these assumptions cannot be formally checked in the available data, our use of previously unpublished, harmonized data reassures us that the studies included in our analyses are unlikely to be severely biased by publication or other reporting biases. To help meet the normality assumption of the study-specific estimates, the calculations for the prediction interval were performed on the log-scale and results back-transformed to ratio-scale for ease of interpretation. Stratified meta-analyses and random effects meta-regression were used to explore potential sources for heterogeneity. Analyses in the Nordic studies were conducted using SAS 9.4 (Cary, NC, USA) and in Whitehall II using Stata IC 15 (Stata Corporation, College Station, TX, USA), with user-written Stata packages *ipdmetan*[30] and *metareg.*[31]

RESULTS

In all, 139 132 men and women had baseline data available on job strain, age, sex, and socioeconomic position, and had no previous hospital record relating to PAD (Table).[10–23] The study-specific mean age ranged from 38.6 to 49.2 years. Overall, 50 583 (36.4%) of the participants were men, with the study-specific proportions of men ranging from 20% in FPS to 77% in Still Working. Just under a quarter of participants reported job strain at baseline (n=32 489, 23.4%). The study-specific distributions of the baseline characteristics are

shown in Table S2. The number of PAD patients included in the unadjusted, age- and sex-adjusted and multivariable-adjusted models was different in HHS, Swedish Longitudinal Occupational Survey of Health, and Whitehall II because a small proportion of participants in these studies had incomplete data on relevant covariates.

During 1 718 132 person-years at risk, 667 men and women (0.2%–1.8% of participants, depending on the study) had a hospital record of PAD during the follow-up. The overall incidence of PAD per 10 000 person-years of follow-up was 3.88, ranging from 1.72 (FPS) to 8.11 (Still Working) (Table).

The unadjusted associations between job strain and hospital-treated PAD, calculated using empirical Bayes between-study variance estimator, suggested that the average risk of hospitalization with PAD was higher in participants reporting job strain compared with those with no strain (HR: 1.25, 95% CI, 1.04–1.50) (Figure 1).[10–23] Adjustment for age and sex increased the point estimate and widened its CI (HR: 1.46, 95% CI, 1.17–1.83) and further adjustment for lifestyle-related covariates decreased it only slightly (HR: 1.41, 95% CI, 1.11–1.80). Additional adjustment for baseline diabetes mellitus attenuated the overall point estimate and narrowed its CI (HR: 1.31, 95% CI, 1.07–1.59).

All unadjusted study-specific estimates were consistent with each other (all I^2 <0.1%) but the covariate-adjusted estimates were moderately heterogeneous. In the multivariable-adjusted meta-analyses, τ^2 of 0.0427 indicated that the study-specific estimates were somewhat dispersed around their mean (ie, the overall random-effects HR). The corresponding I^2 denoted that 26.9% of this variation was attributable to differences beyond chance variation in the association of job strain with PAD in different cohort studies (Table S3). Accordingly, the 95% prediction interval from the multivariable-adjusted meta-analyses (0.82–2.44) crossed the null-value, suggesting that though the average association of job strain with hospitalization for PAD was firmly positive, in some contexts job strain can be associated with over 2-fold increase in this risk and in others with a decreased risk (Figure 1).

We explored sex, socioeconomic position, and smoking as potential sources for the observed heterogeneity (Figure 2). The subgroup associations were consistent in direction, all indicating an increased risk, but the sizes of the estimated average associations varied. Job strain was associated with an increased average risk of hospitalization with PAD in men (HR: 1.59, 95% CI, 1.12–2.28), individuals with a high socioeconomic position (HR: 2.77, 95% CI, 1.35–5.71), and baseline smokers (HR: 1.52, 95% CI, 1.10–2.09). The estimates were directionally consistent but
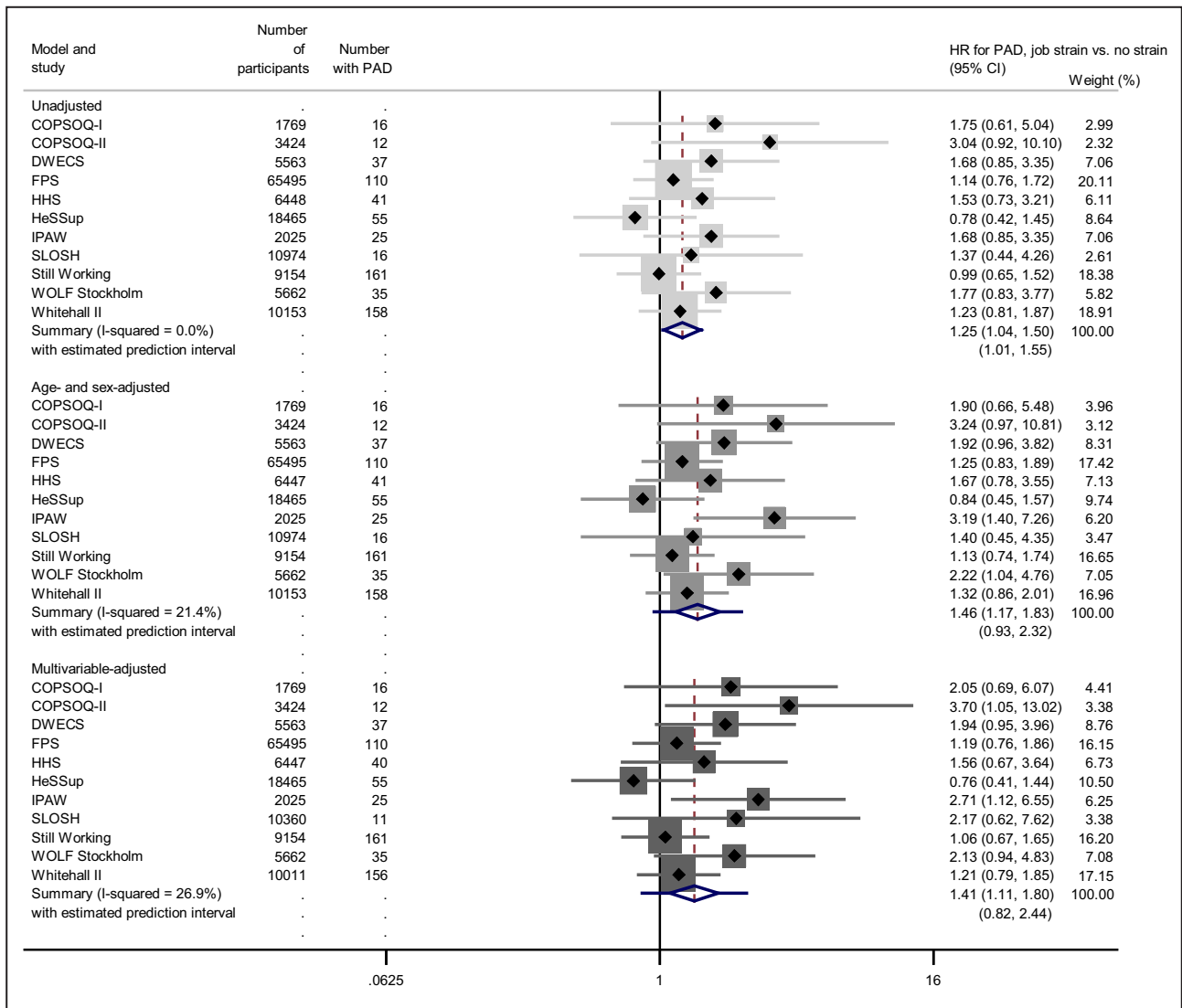
Figure 1. **Job strain and hospital record of peripheral artery disease.** [10–23]

COPSOQ-I and –II indicates Copenhagen Psychosocial Questionnaire versions I and II; DWECS, Danish Work Environment Cohort Study; FPS, Finnish Public Sector study; HeSSup, Health and Social Support; HHS, Helsinki Health Study; IPAW, Intervention Project on Absence and Well-Being; PAD, peripheral artery disease; SLOSH, Swedish Longitudinal Occupational Survey of Health; and WOLF S, Work, Lipids and Fibrinogen Stockholm.

imprecise in women, people from low or intermediate socioeconomic positions, ex-smokers, and those who had never smoked. Neither the 95% prediction intervals from the stratified meta-analyses nor the meta-regression analyses provided evidence for differences by sex (P=0.3) or trend by baseline smoking status (P=0.7) beyond chance variation. There was some indication of the association between job strain and hospital-treated PAD being stronger in the high socioeconomic group than in the low socioeconomic group (P=0.046) but no evidence for a linear trend across the socioeconomic groups (P=0.3). Because of overall low numbers of PAD cases in the subgroups the power in the subgroup analyses, however, was limited.

The findings from sensitivity analyses excluding men and women with a hospital record of PAD during the first year of follow-up, as well as from those using DerSimonian and Laird and restricted maximum likelihood variance estimators in the meta-analyses, were similar in direction and magnitude to our main findings (Tables S3 and S4).

Analysis of absolute risks showed that in our study population of working-age men and women, the incidence of PAD per 10 000 person-years ranged from 1.72 (FPS) to 9.66 (Intervention Project on Absence and Well-Being) (Table). The average difference in the absolute risks between the job strain and no strain groups was firmly positive (3.28, 95% CI, 0.78–5.78) but the study-specific estimates varied (Table S5).
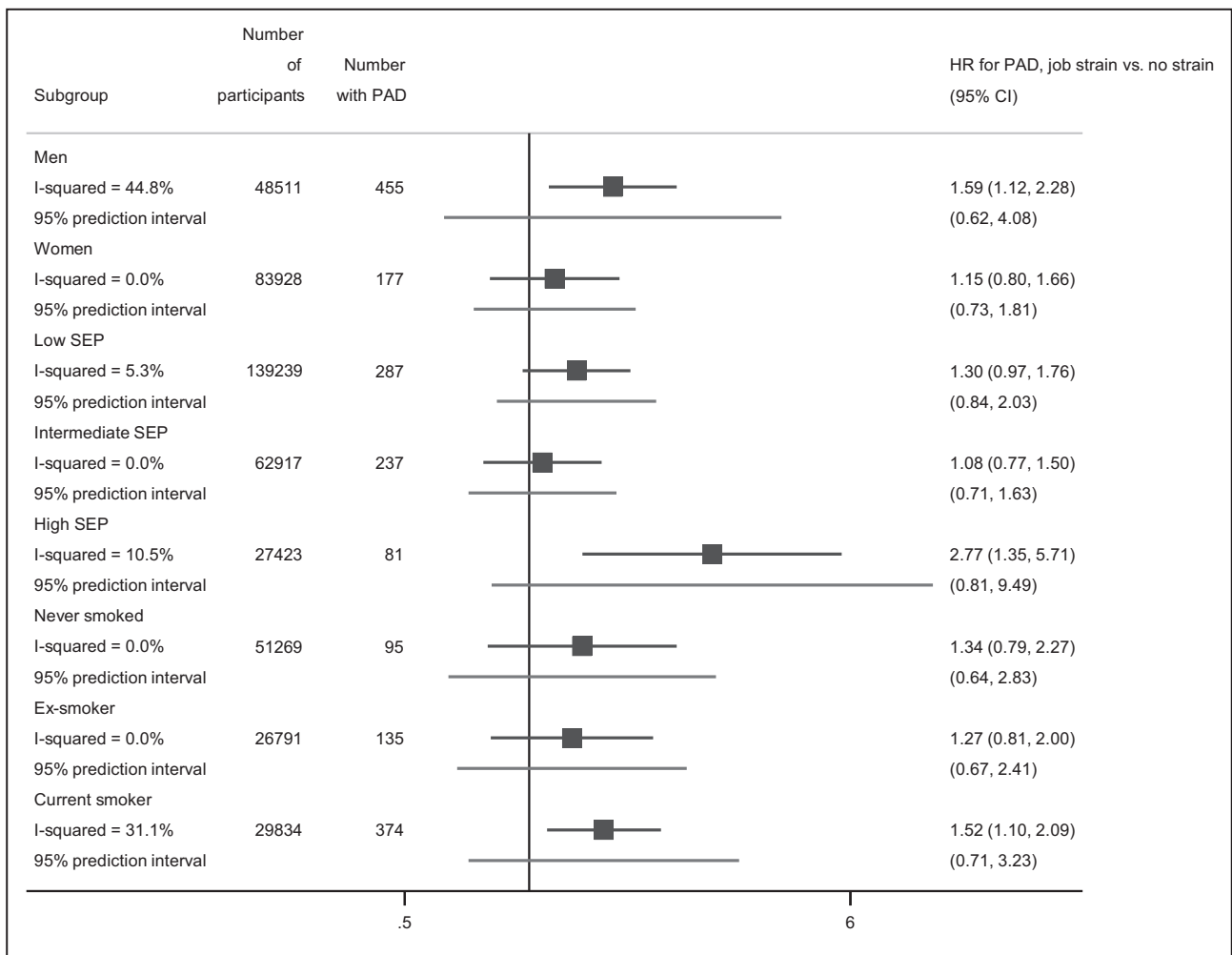
Subgroup	Number of participants	Number with PAD		HR for PAD, job strain vs. no strain (95% CI)
Men				
I-squared = 44.8%	48511	455		1.59 (1.12, 2.28)
95% prediction interval				(0.62, 4.08)
Women				
I-squared = 0.0%	83928	177		1.15 (0.80, 1.66)
95% prediction interval				(0.73, 1.81)
Low SEP				
I-squared = 5.3%	139239	287		1.30 (0.97, 1.76)
95% prediction interval				(0.84, 2.03)
Intermediate SEP				
I-squared = 0.0%	62917	237		1.08 (0.77, 1.50)
95% prediction interval				(0.71, 1.63)
High SEP				
I-squared = 10.5%	27423	81		2.77 (1.35, 5.71)
95% prediction interval				(0.81, 9.49)
Never smoked				
I-squared = 0.0%	51269	95		1.34 (0.79, 2.27)
95% prediction interval				(0.64, 2.83)
Ex-smoker				
I-squared = 0.0%	26791	135		1.27 (0.81, 2.00)
95% prediction interval				(0.67, 2.41)
Current smoker				
I-squared = 31.1%	29834	374		1.52 (1.10, 2.09)
95% prediction interval				(0.71, 3.23)

.5   6

Figure 2.   Job strain and hospital record of peripheral artery disease, by subgroup.
PAD indicates peripheral artery disease; and SEP, socioeconomic position.

DISCUSSION

Our analysis of individual-participant data from >139 000 men and women suggest that job strain is associated with an ≈1.4-fold average increase in the risk of having a hospital record of PAD. This association was observed in all participant subgroups, and the findings were robust to additional adjustment for baseline diabetes mellitus and uncertainty deriving from different ways of estimating between-study variation.

A large and increasing evidence shows that psychosocial stress is implicated in the development of various forms of atherosclerotic cardiovascular disease.[6] However, we are unaware of previous investigations of work-related stress and the risk of PAD, and must discuss our findings in relationship to previous studies of other stress measures and other cardiovascular disease outcomes. Our findings support those of previous studies, pointing to a role of life stress in atherosclerotic

disease. A pooled analysis of the Health Survey for England and Scottish Health Survey, for example, suggests that psychological distress is associated with some 3-fold increase in the risk of peripheral vascular disease during an average follow-up of 9.5 years.[32] Meta-analyses of large, prospective individual-level data sets, have also shown that the general population of adults who reported stress at work or in private life had an 1.1- to 1.6-fold increased risk of coronary heart disease or stroke.[6]

One possible explanation for the elevated risk of hospitalization with PAD among individuals reporting job strain is that stress has a role in the development of PAD, independently of the known risk factors of age, male sex, low socioeconomic position, smoking, heavy alcohol intake, obesity, and physical inactivity. The associations observed in our investigation were in line with those observed for other atherosclerotic cardiovascular diseases in the IPD-Work Consortium and other studies: job strain has shown robust

associations with hospitalization for ischemic stroke (average relative risk: 1.18, 95% CI, 1.00–1.39),[33] coronary heart disease overall (average relative risk: 1.23, 95% CI, 1.10–1.27)[9] as well as among those with pre-existing cardiovascular disease (average relative risk: 1.61, 95% CI, 1.14–2.28).[34] While there is limited evidence directly linking stress to atherosclerosis per se, stress response is associated with increased systemic inflammation and elevated blood glucose, which may contribute to exacerbations and complications of PAD.[6] In addition to this worsening effect of work-related stress on pre-existing artery disease, our findings could reflect other mechanisms, such as stress symptoms lowering the threshold for visiting a physician and subsequently delaying referral and diagnosis.

We conducted sensitivity analyses excluding individuals with a hospital record of PAD during the first year of follow-up, but we cannot completely eliminate the possibility of early stage, undiagnosed, or subclinical PAD influencing our findings. As less severe manifestations of PAD can be managed medically in primary care, it is possible that the group of participants with no record of hospital-treated PAD includes individuals with subclinical, early stage, or mild PAD. If this is the case, the association between job strain and hospitalization for PAD may reflect work-related stress triggering a PAD event among those with existing peripheral artery atherosclerosis. Previous research in high-risk populations and in adults who already have some form of cardiovascular disease suggests that stress incurs an ≈2- to 5.6-fold increased risks of death.[6] Results of a small case-control study, in which women with coronary vascular dysfunction experienced more peripheral vasoconstriction after a mental stress test than control women,[35] may provide a mechanistic explanation for the ability of stress to induce cardiovascular events in general and PAD events specifically in individuals with pre-existing cardiovascular disease.

PAD is a multifactorial disease, with a large number of risk factors making a relatively modest contribution to its pathogenesis. Smoking, hypertension and type 2 diabetes mellitus have been consistently shown to be associated with an increased risk of developing PAD.[1,2] For instance, a meta-analysis of 22 published studies showed that current smoking was associated with a 2.72 -fold (95% CI, 2.39–3.09), history of previous cardiovascular disease with 2.55-fold (95% CI, 2.16–3.02) and diabetes mellitus with 1.88-fold average odds (95% CI, 1.66–2.14) of PAD.[1] The odds ratios were lower for hypertension (1.55, 95% CI, 1.42–1.71) and hypercholesterolemia (1.19, 95% CI, 1.07–1.33).[1] The hazard ratios from our meta-analyses suggest that the risk associated with job strain is not as large as that deriving from smoking or history of cardiovascular disease but is on par with the relative risks associated with hypertension and hypercholesterolemia.

The I^2 and τ^2 pointed to moderate heterogeneity among the study-specific hazard ratios in our meta-analyses. The 95% prediction interval from the multivariable-adjusted meta-analysis (0.82–2.44) suggests that though on average, job strain is associated with an increase in the relative risk of hospitalization with PAD, true relative risks vary from about one fifth decrease to >2-fold increase in different study settings. This variation could reflect differences in diagnostic and referral practices over time and across healthcare systems. The absolute risk differences varied between studies, pointing to different baseline risks of PAD in the study populations. However, the 95% prediction interval should be interpreted with caution: although the studies in our analyses had a low risk of publication or reporting biases, it is possible that the prediction interval reflects heterogeneity derived from other, unknown sources of bias.

The point-estimates for the subgroup associations between job strain and PAD were consistent in direction, all indicating an increased risk in individuals reporting job strain; however, their magnitude varied by sex, socioeconomic position, and baseline smoking status and the subgroup differences did not conclusively explain the observed heterogeneity among the study-specific findings.

The main strength of our analyses is that they were based on previously unpublished, harmonized, prospective data (including pre-defined job strain exposure and objectively assessed PAD outcomes) from 3 Nordic and 1 Western European countries. The analytical strategies we used to pool their results aimed to reduce the risk of biases arising from publication preferences, differential exposure, or outcome reporting, and data dredging. We ascertained PAD events from routinely collected hospitalization data, which cover a range of severities of this disease, from intermittent claudication to gangrene and tissue loss. However, early stages of PAD can often be managed in primary care, and although participants with a previous hospital record of PAD were excluded from our analyses, some PAD patients who were treated in primary care may have been included in the comparison group. Thus, the hospital-treated PAD in our analyses represents the severe end of the disease spectrum and the findings reported here are possibly not generalizable to less severe manifestations of PAD. Unfortunately, we had no access to primary care data and were unable to explore this further.

Data on lipids and blood pressure were not available in all the cohorts included in our analyses, and we

were thus unable to examine their roles in the association between job strain and PAD. However, previous research suggests that additional adjustment for lipids and blood pressure is unlikely to have a major effect on the association between job strain and PAD. Our previous work in the IPD-Work Consortium data has shown that job strain is not associated with either systolic or diastolic blood pressure or circulating cholesterol,[36] and that the association between job strain and coronary heart disease (another atherosclerotic outcome) was robust to adjustment for the Framingham Cardiovascular Risk Score, including conventional biological risk factors (eg, diabetes mellitus, lipids, and blood pressure).[9]

Ours was a sample of studies from an existing research collaboration, and it is possible that other studies, particularly from parts of the world other than Northern Europe, would produce different estimates of the association between job strain and PAD. We also recognize that although well-conducted, large prospective observational epidemiological studies can indicate temporal relationships between risk factors and disease outcomes, such as PAD, no judgement on the causality of such associations can be made based on longitudinal observational findings alone. Furthermore, although all study-specific analyses were adjusted for a number of harmonized covariates, we cannot exclude the possibility that residual confounding from imprecisely measured, unmeasured, or unknown confounders has impacted on our estimates. For instance, we were unable to adjust the analyses for sedentary work (eg, large proportion of working time spent sitting), which might confound the association between job strain and PAD.

CONCLUSIONS

Findings of this multi-national multi-cohort study show that that job strain is associated with a small but consistent increase in the risks of hospitalization with PAD. The strength of the observed association is approximately the same as that of job strain with other atherosclerotic diseases, such as coronary heart disease and ischemic stroke.

ARTICLE INFORMATION

Affiliations

From the Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom (K.H.); Finnish Institute of Occupational Health, Tampere, Helsinki and Turku, Finland (K.H., T.L., M.V., A. Koskinen, T.O., A.V.); Department of Public Health, University of Turku and Turku University Hospital, Turku, Finland (J.P., S.S., J.V.); Department of Public Health, University of Helsinki, Finland (J.P., T.L., S.T.N., O.P., O.R., M.K.); National Research Centre for the Working Environment, Copenhagen, Denmark (I.E.H.M., J.B., R.R.); Department of Public Health and Caring Sciences, University of Uppsala, Sweden (M.V.); Stress Research Institute, University of Stockholm, Sweden (M.V., C.L., L.L.M.H., T.T., H.W.); Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden (L.A.); Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden (L.A.); Department of Occupational and Environmental Medicine, Bispebjerg Hospital, Copenhagen University, Copenhagen, Denmark (M.B.); Federal Institute for Occupational Safety and Health, Berlin, Germany (H.B.); Department of Epidemiology and Public Health, University College London, London, United Kingdom (E.B., J.E.F., A.S.-M., A.S., M.K.); Bristol Medical School: Population Health Sciences, University of Bristol, United Kingdom (J.E.F.); Department of Health Sciences, Mid Sweden University, Sundsvall, Sweden (A. Knutsson); Lægekonsulenten, AS3 Companies, Århus, Denmark (M.L.N.); VIVE, The Danish Center for Social Science Research, Copenhagen, Denmark (J.H.P.); Department of Public Health and Department of Psychology, University of Copenhagen, Denmark (R.R.); Department of Public Health, University of Skövde, Sweden (S.S.).

Acknowledgments

Sources of Funding

Disclosures

None.

Supplementary Materials

Data S1–S2
Tables S1–S5
References 10-23

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329–1340.

2. Cea-Soriano L, Fowkes FGR, Johansson S, Allum AM, Garcia Rodriguez LA. Time trends in peripheral artery disease incidence, prevalence and secondary preventive therapy: a cohort study in The Health Improvement Network in the UK. *BMJ Open*. 2018;8:e018184.

3. Hirsch AT, Hartman L, Town RJ, Virnig BA. National health care costs of peripheral arterial disease in the Medicare population. *Vasc Med*. 2008;13:209–215.

4. Mahoney EM, Wang K, Keo HH, Duval S, Smolderen KG, Cohen DJ, Steg G, Bhatt DL, Hirsch AT; Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. *Circ Cardiovasc Qual Outcomes*. 2010;3:642–651.

5. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other

Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J*. 2016;37:2315–2381.

6. Kivimaki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol*. 2018;15:215–229.

7. Fransson EI, Stadin M, Nordin M, Malm D, Knutsson A, Alfredsson L, Westerholm PJM. The association between job strain and atrial fibrillation: results from the Swedish WOLF Study. *Biomed Res Int*. 2015;2015:371905.

8. Kivimaki M, Nyberg ST, Batty GD, Madsen IEH, Tabak AG; IPD-Work Consortium. Long working hours and risk of venous thromboembolism. *Epidemiology*. 2018;29:e42–e44.

9. Kivimaki M, Nyberg ST, Batty GD, Fransson E, Heikkila K, Alfredsson L, Bjorner JB, Borritz M, Burr H, Casini A, et al. Job strain as a risk factor for future coronary heart disease: collaborative meta-analysis of 2358 events in 197,473 men and women. *Lancet*. 2012;380:1491–1497.

10. Kristensen TS, Hannerz H, Hogh A, Borg V. The Copenhagen Psychosocial Questionnaire—a tool for the assessment and improvement of the psychosocial work environment. *Scand J Work Environ Health*. 2005;31:438–449.

11. Pejtersen JH, Kristensen TS, Borg V, Bjorner JB. The second version of the Copenhagen Psychosocial Questionnaire. *Scand J Public Health*. 2010;38:8–24.

12. Burr H, Bjorner JB, Kristensen TS, Tüchsen F, Bach E. Trends in the Danish work environment in 1990–2000 and their associations with labor-force changes. *Scand J Work Environ Health*. 2003;29:270–279.

13. Feveile H, Olsen O, Burr H, Bach E. Danish work environment cohort study 2005: from idea to sampling design. *Stat Transit*. 2007;8:441–458.

14. Kivimaki M, Lawlor DA, Smith GD, Kouvonen A, Virtanen M, Elovainio M, Vahtera J. Socioeconomic position, co-occurrence of behavior-related risk factors, and coronary heart disease: the Finnish Public Sector study. *Am J Public Health*. 2007;97:874–879.

15. Korkeila K, Suominen S, Ahvenainen J, Ojanlatva A, Rautava P, Helenius H, Koskenvuo M. Non-response and related factors in a nation-wide health survey. *Eur J Epidemiol*. 2001;17:991–999.

16. Lahelma E, Aittomaki A, Laaksonen M, Lallukka T, Martikainen P, Piha K, Rahkonen O, Saastamoinen P. Cohort profile: the Helsinki health study. *Int J Epidemiol*. 2013;42:722–730.

17. Nielsen M, Kristensen T, Smith-Hansen L. The Intervention Project on Absence and Well-Being (IPAW): design and results from the baseline of a 5-year study. *Work Stress*. 2002;16:191–206.

18. Nielsen ML, Rugulies R, Christensen KB, Smith-Hansen L, Bjorner JB, Kristensen T. Impact of the psychosocial work environment on registered absence from work: a two-year longitudinal study using the IPAW cohort. *Work Stress*. 2004;18:323–335.

19. Magnusson Hanson LL, Leineweber C, Persson V, Hyde M, Theorell T, Westerlund H. Cohort profile: the Swedish Longitudinal Occupational Survey of Health (SLOSH). *Int J Epidemiol*. 2018;47:691–692.

20. Kalimo R, Toppinen S. *Organizational well-being: ten years of research and development: in a forest industry corporation*. In: Kompier M, Cooper C, eds. *Preventing Stress, Improving Productivity: European Case Studies in the Workplace*. London: Routledge; 1999:52–85.

21. Vaananen A, Murray M, Koskinen A, Vahtera J, Kouvonen A, Kivimaki M. Engagement in cultural activities and cause-specific mortality: prospective cohort study. *Prev Med*. 2009;49:142–147.

22. Marmot M, Brunner E. Cohort profile: the Whitehall II study. *Int J Epidemiol*. 2005;34:251–256.

23. Peter R, Alfredsson L, Hammar N, Siegrist J, Theorell T, Westerholm P. High effort, low reward, and cardiovascular risk factors in employed Swedish men and women: baseline results from the WOLF Study. *J Epidemiol Community Health*. 1998;52:540–547.

24. Karasek R, Brisson C, Kawakami N, Houtman I, Bongers P, Amick B. The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics. *J Occup Health Psychol*. 1998;3:322–355.

25. Karasek R, Theorell T. *Healthy Work: Stress, Productivity, and the Reconstruction of Working Life*. New York: Basic Books; 1990.

26. Fransson EI, Nyberg ST, Heikkila K, Alfredsson L, de Bacquer D, Batty GD, Bonenfant S, Casini A, Clays E, Goldberg M, et al. Comparison of alternative versions of the job demand-control scales in 17 European cohort studies: the IPD-Work Consortium. *BMC Public Health*. 2012;12:62.

27. Batty GD, Gale CR, Kivimaki M, Bell S. Aetiological utility of different placements of cause of mortality on death certificates in multiple cohort studies comprising 700,000 individuals. *JAMA Netw Open*. 2019;2:e198024.

28. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ*. 2011;342:d549.

29. Serghiou S, Goodman SN. Random-effects meta-analysis: summarizing evidence with caveats. *JAMA*. 2019;321:301–302.

30. Fisher DJ. Two-stage individual participant data meta-analysis and generalized forest plots. *Stata J*. 2015;15:369–396.

31. Harbord RM, Higgins JPT. Meta–regression in Stata. *Stata J*. 2008;8:493–519.

32. Batty GD, Russ TC, Stamatakis E, Kivimaki M. Psychological distress and risk of peripheral vascular disease, abdominal aortic aneurysm, and heart failure: pooling of sixteen cohort studies. *Atherosclerosis*. 2014;236:385–388.

33. Fransson EI, Nyberg ST, Heikkila K, Alfredsson L, Bjorner JB, Borritz M, Burr H, Dragano N, Geuskens GA, Goldberg M, et al. Job strain and the risk of stroke: an individual-participant data meta-analysis. *Stroke*. 2015;46:557–559.

34. Li J, Zhang M, Loerbroks A, Angerer P, Siegrist J. Work stress and the risk of recurrent coronary heart disease events: a systematic review and meta-analysis. *Int J Occup Med Environ Health*. 2015;28:8–19.

35. Mehta PK, Hermel M, Nelson MD, Cook-Wiens G, Martin EA, Alkhoder AA, Wei J, Minissian M, Shufelt CL, Marpuri S, et al. Mental stress peripheral vascular reactivity is elevated in women with coronary vascular dysfunction: results from the NHLBI-sponsored Cardiac Autonomic Nervous System (CANS) study. *Int J Cardiol*. 2018;251:8–13.

36. Nyberg ST, Fransson EI, Heikkila K, Alfredsson L, Casini A, Clays E, De Bacquer D, Dragano N, Erbel R, Ferrie JE, et al. Job strain and cardiovascular disease risk factors: meta-analysis of individual-participant data from 47,000 men and women. *PLoS One*. 2013;8:e67323.

SUPPLEMENTAL MATERIAL

Data S1. Study Descriptions.

Copenhagen Psychosocial Questionnaire version I (COPSOQ-I), Denmark

The COPSOQ-I is a prospective cohort study of a random sample of Danish residents selected from the Danish population register. The participants were aged 20-60 years of age and were in paid employment at the study baseline in 1997. A baseline questionnaire and an invitation to take part was posted to 4 000 people and 2 454 individuals agreed to participate. [10] In Denmark, questionnaire- and register-based studies do not require approval from the Danish National Committee on Biomedical Research Ethics (Den Centrale Videnskabetiske komité). COPSOQ-I was approved by and registered with the Danish Data protection agency (registration number: 2008 - 54 - 0553).

Copenhagen Psychosocial Questionnaire version II (COPSOQ-II), Denmark

COPSOQ-II was carried out in 2004-2005. It included a follow up of respondents from COPSOQ I and also a representative sample of Danish residents aged 20-60 at study baseline. The questionnaire was sent to 8 000 individuals from the random sample and 4 732 individuals responded, returning the questionnaire by post or via the internet. [11] In Denmark, questionnaire- and register-based studies do not require ethics committee approval. COPSOQ-II was approved by and registered with the Danish Data protection agency (registration number: 2004-54-1493).

Danish Work Environment Cohort Study (DWECS), Denmark

DWECS is a split panel survey of working age Danish people. The cohort was established in 1990, when a simple random sample of men and women, aged 18-59, was drawn from the Danish population register. The participants have been followed up at five-year intervals and data from the year 2000 were used for the IPD-Work. That year 11 437 individuals were invited to participate and 8 583 agreed to do so. [12, 13] In Denmark, questionnaire- and register-based studies do not require ethics committee approval. DWECS was approved by and registered with the Danish Data protection agency (registration number: 2007-54-0059).

Finnish Public Sector study (FPS), Finland

The Finnish Public Sector study is a prospective cohort study comprising the entire public sector personnel of 10 towns or municipalities, and 21 hospitals in the same geographical areas. Participants were recruited from employers' records in 2000-2002 and 2004. [14] At either time of recruitment (2000-2002 or 2004), a total of 66 430 individuals aged 17 to 65 responded to the baseline questionnaire. Ethical approval was obtained from the Helsinki and Uusimaa hospital district ethics committee.

Health and Social Support (HeSSup), Finland

The Health and Social Support (HeSSup) study is a prospective cohort study of a stratified random sample of the Finnish population in the following four age groups: 20–24, 30–34, 40–44 and 50–54 years. The participants were identified from the Finnish population register and posted an invitation to participate in 1998. In all, 25 898 individuals responded and returned the baseline questionnaire. [15] Turku University Central Hospital Ethics Committee approved the study.

Helsinki Health Study (HHS), Finland

The Finnish Helsinki Health Study (HHS) is a prospective cohort study comprising all employees of the City of Helsinki, who turned 40, 45, 50, 55, or 60 years in 2000-2002.[16] We included in this study all participants who responded to the baseline survey (n=8 960, response rate 67%, 80% women) and provided an informed written consent to combine their survey responses with retrospective and prospective register based follow-up data on different diseases and mortality (n=6 605). Ethical approvals for this study were obtained from the ethics committees of the health authorities of the City of Helsinki, and the Department of Public Health, University of Helsinki.

Intervention Project on Absence and Well-being (IPAW), Denmark

IPAW is a 5-year psychosocial work environment intervention study including 22 intervention and 30 control workplaces in three organisations (a large pharmaceutical company, municipal technical services and municipal nursing homes) in Copenhagen, Denmark. [17, 18] The baseline questionnaire was posted to all the employees at the selected work sites between 1996 and 1997. Interventions took place at 22 workplaces during 1996-98 at the organisational and interpersonal level. Of the 2 721 employees who worked at the IPAW sites, 2 068 men and women completed the baseline questionnaire. IPAW was approved by and registered with the Danish Data Protection Agency (registration number: 2000-54-0066).

Swedish Longitudinal Occupational Survey of Health (SLOSH), Sweden

Swedish Longitudinal Occupational Survey of Health (SLOSH) is an on-going prospective cohort study following up individuals who participated in the Swedish Work Environment Survey (SWES) between 2003 and 2011 [19]. SWES, conducted biennially by Statistics Sweden (commissioned by the Swedish Work Environment Authority), is based on a sample of gainfully employed people aged 16-64 years drawn from the Labour Force Survey (LFS). These

individuals were first sampled into LFS through stratification by county, sex, citizenship and inferred employment status.

Still Working

Still Working is an ongoing prospective cohort study. [20, 21] In 1986, the employees (n = 12 173) at all Finnish centres of operation of Enso Gutzeit (a forestry products manufacturer) were invited to participate in a questionnaire survey on demographic, psychosocial and health-related factors and 9 282 individuals participated. The study was approved by the ethics committee of the Finnish Institute of Occupational Health.

Whitehall II, United Kingdom

Whitehall II is a prospective cohort study set up to investigate socioeconomic determinants of health. At study baseline in 1985-1988, 10 308 civil service employees aged 35-55 and working in 20 civil service departments in London were invited to participate in the study.[22] Data on weekly working hours were collected in study phase 3, in 1991-94, which was used as an analytical baseline in our investigation. The Whitehall II study protocol was approved by the University College London Medical School committee on the ethics of human research. Written informed consent was obtained at each data collection wave.

Work, Lipids, and Fibrinogen Stockholm (WOLF S), Sweden

WOLF Stockholm study is a prospective cohort study of 5 698 people (3 239 men and 2 459 women) aged 19–70 and working in companies in Stockholm county. [23] At study baseline the participants underwent a clinical examination and completed a set of health questionnaires at 20 occupational health units in 1992-95. The Regional Research Ethics Board in Stockholm and the ethics committee at Karolinska Institutet, Stockholm, Sweden, approved the study.

Data S2. SAS and Stata Commands.

Study-specific Analyses

<u>**SAS**</u>

```
proc phreg data=pad1;
    model futime_pad*PAD_inc(0) = strain / rl;
    by study;
    ods output ParameterEstimates=pe;
    data res; set pe; by study; if parameter='strain';
    keep study Estimate StdErr ProbChiSq HazardRatio HRLowerCL HRUpperCL;
    proc print data=res;
run;
proc phreg data=pad1;
    model (age_beginning,age_end)*PAD_inc(0)= sex strain / rl;
    by study;
    ods output ParameterEstimates=pe;
    data res; set pe; by study; if parameter='strain';
    keep study Estimate StdErr ProbChiSq HazardRatio HRLowerCL HRUpperCL;
    proc print data=res;
run;
proc phreg data=pad1;
    class sex smokerex alcocl ses inactive wgcl2;
    model (age_beginning,age_end)*PAD_inc(0)= sex smokerex alcocl ses inactive diabetes wgcl2
strain / rl;
    by study;
    ods output ParameterEstimates=pe;
    data res; set pe; by study; if parameter='strain';
    keep study Estimate StdErr ProbChiSq HazardRatio HRLowerCL HRUpperCL;
    proc print data=res;
run;
```

<u>**Stata**</u>

```
stset yexit, failure(PAD_inc) origin(byear) id(id)
xi:stcox job_strain, nohr

stset yexit, failure(PAD_inc) enter(byear) origin(yob) id(id)
xi:stcox sex job_strain, nohr
xi:stcox sex i.ses i.wgcl2 i.smokerex i.alcocl inactive diabetes strain, nohr
```

Meta-analyses

<u>Stata</u>

use H:\studyspecific_results.dta, clear

sort model Study
admetan logHR logse2 if model==1 | model==2| model==3, re(eb) rfdist eform by(model) ///
      lcols(Study Nallfollowup NPADfollowup) ///
      sgwt nograph nooverall saving(H:\admetan_results_eb.dta, replace)

use H:\admetan_results_eb.dta, clear

replace _LABELS="Unadjusted" if _LABELS=="1" & _ES==.
replace _LABELS="Multivariable-adjusted" if _LABELS=="3" & _ES==.

/* changed "subgroup" to "summary" in a string var used for labelling the figure */
gen n = "Summary" if substr(_LABELS,1,8) == "Subgroup"
replace _LABELS= n + substr(_LABELS,9,20) if substr(_LABELS,1,8) == "Subgroup"

label var _LABELS "Model and study"
drop n

tostring Nallfollowup, replace
tostring NPADfollowup, replace

forestplot, hr plotid(_BY) lcols(Nallfollowup NPADfollowup)   ///
      box1opts(mcolor(gs13)) ci1opts(lcolor(gs13)) ///
      box2opts(mcolor(gs9)) ci2opts(lcolor(gs9)) ///
      box3opts(mcolor(gs6)) ci3opts(lcolor(gs6)) ///
      graphregion(color(white)) noadjust rfdist(_rfLCI _rfUCI)

Table S1. International Classification of Diseases (ICD) versions 8, 9 and 10 codes to identify lower limb peripheral arterial disease (PAD).

Coding system Code	Description
ICD-10	
I702	Atherosclerosis of arteries of extremities (including atherosclerotic gangrene)
I738	Other specified peripheral vascular disease
I739	Peripheral vascular disease, unspecified (including intermittent claudication)
I743	Embolism and thrombosis of arteries of lower extremities
I744	Embolism and thrombosis of arteries of extremities, unspecified
I745	Embolism and thrombosis of iliac artery
E105, E115, E125, E135, E145	Diabetes with peripheral circulatory complications
ICD-9	
2507	Diabetes with peripheral circulatory disorders
4402	Atherosclerosis of native arteries of the extremities
4404	Chronic total occlusion of artery of the extremities (including complete occlusion of artery of the extremities, total occlusion of artery of the extremities)
4438	Other specified peripheral vascular disease
4439	Peripheral vascular disease, unspecified (including intermittent claudication NOS, peripheral angiopathy or vascular disease NOS, spasm of artery)
4442	Arterial embolism or thrombosis of extremities
44481	Arterial embolism or thrombosis of iliac artery
ICD-8	
4402	Arteriosclerosis of arteries of the extremities
4438	Other peripheral vascular disease, other
4444	Embolism and thrombosis of arteries of the extremities

NOS: not otherwise specified

Table S2. Baseline covariates by study.

Study	Socioeconomic position	N (%)	Smoking	N (%)	Alcohol consumption	N (%)	Physical activity	N (%)	Body mass index	N (%)	Diabetes N (%)
COPSOQ_I	Low	759 (43.95)	Never	681 (38.67)	None	-*	Active	-*	<18.5	-*	16 (0.9)
	Intermediate	494 (28.60)	Ex-	429 (24.36)	Moderate	-	Inactive	-	18.5 to 24.9	-	
	High	474 (27.45)	Current	651 (36.97)	Heavy	-	All	-	25.0 to 29.9	-	
	All	1727 (100.0)	All	1 761 (100.0)	All	-			>=30.0	-	
									All	-	
COPSOQ-II	Low	1445 (42.45)	Never	1 424 (41.86)	None	601 (17.71)	Active	1 757 (51.91)	<18.5	49 (1.45)	<5 (<0.1)
	Intermediate	971 (28.53)	Ex-	886 (26.04)	Moderate	2 464 (72.62)	Inactive	1 628 (48.09)	18.5 to 24.9	1 814 (53.80)	
	High	988 (29.02)	Current	1 092 (32.10)	Heavy	328 (9.67)	All	3 385 (100.0)	25.0 to 29.9	1 118 (33.16)	
	All	3404 (100.0)	All	3 402 (100.0)	All	3 393 (100.0)			>=30.0	391 (11.60)	
									All	3 372 (100.0)	
DWECS	Low	2372 (43.33)	Never	2 222 (39.96)	None	3 109 (55.99)	Active	2 325 (41.86)	<18.5	93 (1.69)	51 (0.9)
	Intermediate	1659 (30.31)	Ex-	1 280 (23.02)	Moderate	2 134 (38.43)	Inactive	3 229 (58.14)	18.5 to 24.9	3 209 (58.22)	
	High	1443 (26.36)	Current	2 058 (37.01)	Heavy	310 (5.58)	All	5 554 (100.0)	25.0 to 29.9	1 786 (32.40)	
	All	5474 (100.0)	All	5 560 (100.0)	All	5 553 (100.0)			>=30.0	424 (7.69)	
									All	5 512 (100.0)	
FPS	Low	11 807 (18.2)	Never	39 777 (63.4)	None	8 884 (13.8)	Active	51 292 (80.2)	<18.5	810 (1.3)	1 438 (2.2)
	Intermediate	34 282 (52.8)	Ex-	11 446 (18.3)	Moderate	48 746 (75.9)	Inactive	12 632 (19.8)	18.5 to 24.9	35 488 (55.4)	
	High	18 872 (29.1)	Current	11 506 (18.3)	Heavy	6 593 (10.3)	All	63 924 (100.0)	25.0 to 29.9	20 311 (31.7)	
	All	64 961 (100.0)	All	62 729 (100.0)	All	64 223 (100.0)			>=30.0	7 423 (11.6)	
									All	64 032 (100.0)	
HeSSup	Low	4 180 (22.7)	Never	7 772 (42.4)	None	2 526 (13.7)	Active	14 606 (79.6)	<18.5	291 (1.6)	331 (1.8)
	Intermediate	9 828 (53.5)	Ex-	6 193 (33.8)	Moderate	14 188 (76.9)	Inactive	3 748 (20.4)	18.5 to 24.9	10 472 (57.0)	
	High	4 375 (23.8)	Current	4 374 (23.9)	Heavy	1 734 (9.4)	All	18 354 (100.0)	25.0 to 29.9	5 793 (31.5)	
	All	18 383 (100.0)	All	18 339 (100.0)	All	18 448 (100.0)			>=30.0	1 812 (9.9)	
									All	18 368 (100.0)	

*Body mass index was not measured in Still Working; Body mass index, physical activity and alcohol consumption were not measured in COPSOQ-I; the quality of the alcohol consumption measure was questionable in SLOSH.

Table S2, continued. Baseline covariates by study

Study	Socioeconomic position	N (%)	Smoking	N (%)	Alcohol consumption	N (%)	Physical activity	N (%)	Body mass index	N (%)	Diabetes N (%)
HHS	Low	917 (14.2)	Never	3 394 (53.0)	None	421 (6.6)	Active	1 272 (19.8)	<18.5	61 (1.0)	171 (2.7)
	Intermediate	2 216 (34.4)	Ex-	1 529 (23.9)	Moderate	5 712 (89.0)	Inactive	1 700 (26.5)	18.5 to 24.9	3 172 (49.6)	
	High	3 314 (51.4)	Current	1 482 (23.1)	Heavy	285 (4.4)	All	6 413 (100.0)	25.0 to 29.9	2 229 (34.9)	
	All	6 447 (100.0)	All	6 405 (100.0)	All	6 418 (100.0)			>=30.0	934 (14.6)	
									All	6 396 (100.0)	
IPAW	Low	1367 (67.51)	Never	601 (29.83)	None	336 (17.01)	Active	814 (41.55)	<18.5	57 (2.91)	40 (2.0)
	Intermediate	288 (14.22)	Ex-	464 (23.03)	Moderate	1 502 (76.05)	Inactive	1 145 (58.45)	18.5 to 24.9	1182 (60.34)	
	High	370 (18.27)	Current	950 (47.15)	Heavy	137 (6.94)	All	1 959 (100.0)	25.0 to 29.9	556 (28.38)	
	All	2 025 (100.0)	All	2 015 (100.0)	All	1 975 (100.0)			>=30.0	164 (8.37)	
									All	1 959 (100.0)	
Still Working	Low	6 332 (69.2)	Never	3 185 (35.2)	None	434 (4.8)	Active	1 742 (19.5)	<18.5	-*	86 (0.9)
	Intermediate	2 162 (23.6)	Ex-	2 881 (31.8)	Moderate	8 162 (90.4)	Inactive	7 216 (80.6)	18.5 to 24.9	-	
	High	660 (7.2)	Current	2 988 (33.0)	Heavy	249 (4.8)	All	8 958 (100.0)	25.0 to 29.9	-	
	All	9 154 (100.0)	All	9 054 (100.0)	All	9 025 (100.0)			>=30.0	-	
									All	-	
WOLF-S	Low	1 711 (30.9)	Never	2 571 (46.3)	None	212 (3.8)	Active	1 321 (23.4)	<18.5	82 (1.5)	73 (1.3)
	Intermediate	2 932 (52.9)	Ex-	1 563 (28.1)	Moderate	4 864 (87.9)	Inactive	4 325 (76.6)	18.5 to 24.9	3 270 (58.0)	
	High	899 (16.2)	Current	1 422 (25.6)	Heavy	457 (8.3)	All	5 646 (100.0)	25.0 to 29.9	1 853 (32.9)	
	All	5 542 (100.0)	All	5 556 (100.0)	All	5 533 (100.0)			>=30.0	433 (7.7)	
									All	5 638 (100.0)	
SLOSH	Low	2 315 (21.5)	Non-smoker	9 145 (84.0)	None	-*	Active		<18.5 to 24.9	5 341 (50.2)	310 (2.9)
	Intermediate	5 315 (49.4)	Smoker	2 743 (16.0)	Moderate	-	Inactive	2 075 (19.1)	25.0 to 29.9	4 101 (38.5)	
	High	3 126 (29.1)			Heavy	-	All	8 781 (80.9)	>=30.0	1 208 (11.3)	
	All	10 756 (100.0)	All	10 888 (100.0)	All	-		10 650 (100.0)	All	10 650 (100.0)	
Whitehall II	Low	2 287 (22.5)	Never	4 997 (49.6)	None	1 926 (19.0)	Active	8 382 (82.9)	<18.5	142 (1.4)	92 (0.9)
	Intermediate	4 864 (47.9)	Ex-	3 227 (32.1)	Moderate	6 647 (65.5)	Inactive	1 735 (17.2)	18.5 to 24.9	6 025 (59.5)	
	High	3 002 (29.6)	Current	1 843 (18.3)	Heavy	1 580 (15.6)	All	10 117 (100.0)	25.0 to 29.9	3 260 (32.2)	
	All	10 153 (100.0)	All	10 067 (100.0)	All	10 153 (100.0)			>=30.0	705 (7.0)	
									All	10 132 (100.0)	

*Body mass index was not measured in Still Working; Body mass index, physical activity and alcohol consumption were not measured in COPSOQ-I; the quality of the alcohol consumption measure was questionable in SLOSH.

Table S3. Associations of job strain with incident peripheral artery disease (PAD).

Study	N with PAD	HR (95 % CI) for PAD	N with PAD	HR (95 % CI) for PAD	N with PAD	HR (95 % CI) for PAD
	Unadjusted		**Age- and sex-adjusted**		**Multivariable-adjusted***	
COPSOQ_I	16	1.75 (0.61 to 5.04)	16	1.90 (0.66 to 5.48)	16	2.05 (0.69 to 6.07) [†]
COPSOQ-II	12	3.04 (0.92 to 10.10)	12	3.24 (0.97 to 10.81)	12	3.70 (1.05 to 13.03)
DWECS	37	1.68 (0.85 to 3.35)	37	1.92 (0.96 to 3.82)	37	1.94 (0.95 to 3.96)
FPS	110	1.14 (0.76 to 1.72)	110	1.25 (0.83 to 1.89)	110	1.19 (0.76 to 1.86)
HeSSup	55	0.78 (0.42 to 1.45)	55	0.84 (0.45 to 1.57)	55	0.76 (0.41 to 1.44)
HHS	41	1.53 (0.73 to 3.21)	41	1.67 (0.78 to 3.56)	40	1.67 (0.78 to 3.55)
IPAW	25	2.63 (1.16 to 5.94)	25	3.82 (1.40 to 7.26)	25	2.71 (1.12 to 6.55)
SLOSH	16	1.37 (0.44, 4.26)	16	1.40 (0.45 to 4.35)	11	2.17 (0.62 to 7.62) [†]
Still Working	161	0.99 (0.65 to 1.52)	161	1.13 (0.74 to 1.74)	161	1.06 (0.68 to 1.66) [†]
Whitehall II	159	1.23 (0.81 to 1.87)	158	1.32 (0.86 to 2.01)	156	1.21 (0.79 to 1.85)
WOLF S	35	1.77 (0.83 to 3.77)	35	2.22 (1.04 to 4.76)	35	2.13 (0.94 to 4.83)
	Random effects summary estimates					
		HR (95% CI)		**HR (95% CI)**		**HR (95% CI)**
	EB	1.25 (1.04 to 1.50)		1.46 (1.17 to 1.82)		1.41 (1.11 to 1.80)
	τ^2	<0.00001		0.0285		0.0427
	I^2	<0.01%		21.8%		26.9%
	DL	1.25 (1.04 to 1.50)		1.46 (1.18 to 1.81)		1.41 (1.11 to 1.78)
	τ^2	<0.00001		0.0241		0.0357
	I^2	<0.01%		18.7%		23.6%
	REML	1.25 (1.04 to 1.50)		1.44 (1.18 to 1.77)		1.40 (1.11 to 1.76)
	τ^2	<0.00001		0.0136		0.0291
	I^2	<0.01%		11.5%		20.1%

[*] Adjusted for baseline age, sex, socioeconomic position, smoking, alcohol consumption, body mass index and physical activity.

[†] Still Working estimates not adjusted for body mass index; COPSOQ-I estimates not adjusted for body mass index, physical activity and alcohol consumption; SLOSH estimates not adjusted for alcohol consumption.

Abbreviations: EB: empirical Bayes; DL: DerSimonian and Laird; REML: restricted maximum likelihood

Table S4. Associations of job strain with incident peripheral artery disease (PAD), with cases during the 1st year of follow-up excluded.

Study	N (%) PAD	Multivariable-adjusted* HR (95 % CI) for PAD
COPSOQ_I	15	2.31 (0.77 to 6.99) [†]
COPSOQ-II	10	3.20 (0.77 to 13.32)
DWECS	33	2.11 (0.99 to 4.49)
FPS	102	1.25 (0.79 to 1.98)
HeSSup	53	0.72 (0.38 to 1.39)
HHS	40	1.56 (0.77 to 3.16)
IPAW	24	2.71 (1.12 to 6.55)
SLOSH	7	2.80 (0.61 to 12.78) [†]
Still Working	160	1.01 (0.64 to 1.60) [†]
Whitehall II	156	1.21 (0.79 to 1.85)
WOLF S	34	1.86 (0.78 to 4.40)

Random effects summary estimates		HR (95 % CI)
	EB	
	HR (95% CI)	**1.40 (1.10 to 1.79)**
	τ^2	0.0423
	I^2	26.2%
	DL	**HR (95 % CI)**
	HR (95% CI)	1.39 (1.10 to 1.77)
	τ^2	0.0357
	I^2	23.1%
	REML	**HR (95 % CI)**
	HR (95% CI)	1.39 (1.10 to 1.75)
	τ^2	0.0291
	I^2	19.6%

[*] Adjusted for baseline age, sex, socioeconomic position, smoking, alcohol consumption, body mass index and physical activity.

[†] Still Working estimates not adjusted for body mass index; COPSOQ-I estimates not adjusted for body mass index, physical activity and alcohol consumption; SLOSH estimates not adjusted for alcohol consumption.

Abbreviations: EB: empirical Bayes; DL: DerSimonian and Laird; REML: restricted maximum likelihood

Table S5. Absolute risk of PAD, by job strain.

Study	Incidence of PAD (per 10,000 person-years)		Difference in incidence per 10,000 person-years (95% CI)
	Job strain	*No strain*	
COPSOQ-I	11.7	6.7	5.0 (1.4 to 8.6)
COPSOQ-II	16.7	5.5	11.2 (7.8 to 14.6)
DWECS	11.0	6.6	4.4 (2.5 to 6.3)
FPS	1.9	1.7	0.2 (0.01 to 0.5)
HeSSup	1.9	2.4	-0.5 (-1.0 to -0.1)
HHS	6.3	4.1	2.2 (0.6 to 3.8)
IPAW	19.8	7.5	12.3 (8.0 to 16.6)
SLOSH	2.1	2.7	0.6 (-0.1 to 1.4)
Still Working	8.1	8.1	-0.1 (-1.6 to 1.5)
Whitehall II	6.9	5.6	1.3 (-0.1 to 2.7)
WOLF S	6.3	3.5	2.8 (1.1 to 4.4)