Work Schedules and 11-Year Progression of Carotid Atherosclerosis in Middle-Aged Finnish Men

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Objectives *This study investigated the relationship between different work schedules and progression of carotid atherosclerosis, an early indicator of cardiovascular disease (CVD).*
Methods *We studied 621 men, aged 42–60 years, in the prospective Kuopio Ischemic Heart Disease Risk Factor Study cohort. Using multivariable regressions adjusting for 22 covariates including total time worked during follow-up, we evaluated the associations of baseline work schedules with 11-year progression of ultrasonographically assessed carotid intima-media thickness (IMT), and their variation by preexisting CVD.*
Results *Standard daytime work, weekend shifts, and evening/night/rotating shifts were associated with 31%, 37%, and 33% increases in IMT, respectively. Compared to daytime workers, weekend workers experienced a faster progression of carotid atherosclerosis [relative change ratio (RCR) = 1.05, 95% CI: 1.00–1.09)]. This ratio was higher among men who had preexisting CVD.*
Conclusions *Weekend shifts, more than standard daytime work, appear to accelerate carotid atherosclerosis progression among middle-aged Finnish men, especially those with pre-existing CVD.* Am. J. Ind. Med. 58:1–13, 2015. © 2014 Wiley Periodicals, Inc.

KEY WORDS: occupational health; overtime work; prospective study; weekend shift; work-life balance

INTRODUCTION

Shift work, specifically when including evenings, nights or weekends, has been shown to disturb circadian rhythms, sleep, and social life [Garde et al., 2009] and to be associated with various chronic diseases [Kolstad, 2008; Wang et al., 2011; Vyas et al., 2012]. Among the 11 previous published prospective cohort studies assessing shift work and vascular or coronary events, two found a relative risk of more than 2, four found a relative risk between 1 and 2, and five did not find an increased risk. The reasons for such inconsistency partly lie in varying methods, populations, and definitions of shift work and vascular or coronary events, as suggested in a recent review [Vyas et al., 2012].

Using the general population as reference, as done in some studies, is not appropriate because healthier people self-select into the work force and thus dilute any work-related risks in comparisons between a working population and the general population. Shift workers also differ substantially from daytime workers with regard to risk profiles for cardiovascular disease (CVD). For example, shift workers are more likely to be smokers and at a worse socioeconomic

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Accepted 13 August 2014
DOI 10.1002/ajim.22388. Published online 27 October 2014 in Wiley Online Library (wileyonlinelibrary.com).

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position than daytime workers [Møller et al., 1991; Knutsson and Nilsson, 1998]. Without proper adjustment for confounders, it is difficult to determine whether shift work is a real cause of CVD or a marker for an underlying cause when daytime workers are used as reference. In addition, shift workers who cannot tolerate shift schedules or develop disease may be forced to move to regular daytime work, or to stop working. Research on long-term health effects of shift work can easily suffer from misclassification of shift work as well as selection bias if symptomatic chronic CVD are used as the study endpoint.

To address these methodological issues, the current study, a secondary analysis of data collected for the prospective Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), accounted for an extensive list of confounders and aimed to assess the association of different work schedules with progression of carotid atherosclerosis, an early asymptomatic pre-clinical manifestation of chronic CVD among middle-aged Finnish men. Based on the hemodynamic theory of atherosclerosis [Glagov et al., 1988] and previous findings that suggested men with preexisting CVD experienced faster progression of atherosclerosis associated with standing at work [Krause et al., 2000], occupational physical activity [Krause et al., 2007], and duration of work time [Krause et al., 2009], we also investigated whether non-standard work schedules were more strongly associated with progression of atherosclerosis among men with preexisting ischemic heart disease (IHD) or carotid artery stenosis (CAS) than among men without these conditions.

METHODS

Study Design, Setting and Population

Participants were part of the age-stratified, random, population-based sample of the prospective KIHD, which enrolled 1,516 Finnish men aged 42, 48, 54, or 60 years in August 1986. Women were also recruited in this study recently but were not included in current analyses due to the short follow-up period. Ultrasound measurements of IMT of both common carotid arteries were conducted beginning in February 1987 on 1,229 participants. Only 854 participants remained in the cohort at the 11-year follow-up. Reasons for loss to follow-up included death or being severely ill (14%), having moved or could not be contacted (5%), refusal (11%), or other (0.4%). We excluded 223 men from this sample because they had not worked at all during the follow-up period, and 10 because they had missing values on outcome or exposure, leaving 621 men for analyses. Missing values for one or more covariates were replaced by sample mean values in 11 (<1.8%) observations. Follow-up time between ultrasound examinations ranged from 9.23–13.82 years (mean: 11.13 years). All participants provided written informed consent. This study has been approved by the UCLA Institutional Review Board (UCLA IRB).

Outcomes, Exposures, Modifiers, and Covariates

Outcome assessment—carotid atherosclerotic progression

The primary outcome for this study was 11-year change of carotid IMT, an indicator of progression of atherosclerosis. Ultrasound measurement of IMT in carotid arteries has been shown to be reliable [Espeland et al., 1996; Kanters et al., 1997], and to relate to the extent of disease in the coronary arteries, and to have predictive validity with regard to risk of coronary events [Salonen et al., 1993; Salonen and Salonen, 1993; Persson et al., 1994; Selmaoui et al., 1997; Lorenz et al., 2010, 2007; Bots and Sutton-Tyrrell, 2012]. IMT was assessed at baseline and 11-year-follow-up using high-resolution B-mode ultrasonography recording on average 100 estimates of the distance between the lumen-intima and media-adventitia interfaces of a 1.0–1.5 cm section of the left and right common carotid artery (CCA) below the carotid bulbs. Additional technical details are published elsewhere [Salonen and Salonen, 1993]. In our analysis, we calculated maximum IMT, defined as the average of the maximum IMT in the right and left CCA. Our natural-log-transformed outcome measure was then defined as the natural log of maximum IMT at 11 years minus the natural log of maximum IMT at baseline.

Exposure assessment—work schedules

Baseline work schedules were assessed by self-administered questionnaire including the following categories: (a) daytime, (b) evening, (c) night, (d) 2-shift schedule, (e) 3-shift schedule, (f) swing shift, and (g) work on demand. Participants also reported the number of days worked per week. Given the previously found positive association between work time and progression of atherosclerosis [Krause et al., 2009], we separated people who did standard daytime work (worked during weekdays) from those who also worked on weekends (i.e., >5 days). We further categorized work schedules into the following categories: (i) *standard daytime work*—people who reported working during daytime and working less or equal to five days per week; (ii) *weekend shifts*—people who worked during daytime and more than five days per week; (iii) *evening/night/rotating shifts*—including work schedules b, c, and e above, regardless of the number of days worked per week; (iv) *other shift work*—including work schedules d, f, and g above, regardless the number of days worked per week. We

initially investigated evening, night, and rotating shifts separately; however, given the few men working evening shifts (n = 1) or night shifts (n = 3), we combined them into one category for this analysis.

Assessment of Covariates

Details of the measurement of these variables have been described previously [Lynch et al., 1997b, 1996]. In summary, the following groups of covariates were measured:

Demographic and technical factors: age, baseline IMT, and sonographer.

Biological factors: blood samples were drawn to determine serum high-density lipoprotein cholesterol (HDL), serum low-density lipoprotein cholesterol (LDL), plasma fibrinogen, and blood glucose. Height and weight were measured and body mass index was calculated by dividing the subject's weight by the square of his height (kg/m^2).

Behavioral factors: Smoking, alcohol, and lack of leisure-time physical activity are established risk factors for CVD and were assessed by questionnaire. Smoking was classified as "never smoked", "former smoker", "irregular smoker", and "current smoker." Alcohol consumption was a continuous measure (grams per week) that accounted for both frequency of drinking and amount of drinks per occasion for each type of alcoholic beverage (beer, wine, spirits) for the last 12 months. Conditioning leisure-time physical activity, in hours per year, was measured using a modified version of the Minnesota Leisure Time Physical Activity questionnaire [Taylor et al., 1978]. Cardiorespiratory fitness (VO_2 max) was measured with a maximal, symptom-limited exercise-tolerance test on a bicycle ergometer.

Socioeconomic status was measured using annual income (in 1,000 FIM).

Psychosocial job factors were measured by questionnaire including stress from work deadlines, mental strain at work (11 items of psychological demands), and social support at work (three items). These factors have been associated with progression of atherosclerosis and an increased risk for myocardial infarction and mortality in this study population and showed satisfactory Cronbach's α coefficients [Lynch et al., 1997a,b].

Work time: An occupational interview was administered by trained interviewers at baseline and 11-year follow-up assessing current work status, work and break time per day, days worked per week, and number of months absent from work during the past year. This information was combined into a cumulative measure of total time at work (excluding breaks) during follow-up [Krause et al., 2009].

Assessment of Modifiers—Ischemic Heart Disease and Carotid Artery Stenosis at Baseline

We considered IHD and CAS as potential effect-measure modifiers. The participants with existing IHD at baseline were those who (i) had a history of prior myocardial infarction or angina pectoris, (ii) currently used anti-angina medication, or (iii) had positive findings of angina according to the London School of Hygiene cardiovascular questionnaire [Rose et al., 1982]. Based on participants' baseline IMT recordings, they were classified as having preexisting CAS if there was a plaque that obstructed more than 20% of the lumen diameter [Salonen and Salonen, 1993; Krause et al., 2000]. The participants were not informed about these ultrasound results except for a limited number of examinees who were judged to require medical attention.

Statistical Analysis

We used appropriate descriptive statistics to summarize the characteristics of the participants by their baseline IHD or CAS status. Next, we used multiple linear regression analysis with incremental adjustment of covariates listed in Tables I and II. We also added work schedule by IHD status or by CAS status product terms into the model to examine potential heterogeneity (i.e., effect measure modification, or statistical interaction) of the relationships between work schedules and progression of atherosclerosis by IHD or CAS status on the multiplicative scale.

The outcome for all analyses was $[\ln(Y_F)\text{-}\ln(Y_I)]/\Delta t$, where *ln* was the natural logarithm, Y_I was the initial maximum IMT at baseline and Y_F was the final maximum IMT at the follow-up examination, and Δt the years since baseline examination. The maximum IMT values at baseline and follow-up were ln-transformed because doing so normalized the original skewed maximum IMT measurements. The division by Δt handled the variation from the nominal follow-up time of 11 years by expressing change on a per-year basis. All continuous covariates were centered at the mean and, when appropriate, rescaled so that 1-unit increase amounted to a meaningful span of the variable.

We computed the percentage change based on the relative change (RC) from a fully adjusted model for all 621 men, and for sub-populations classified by their IHD or CAS status. Relative change was calculated as $RC = Y_F/Y_I$, and the outcome measure became $\ln(RC)/\Delta t$. Consequently, for any specified values of covariates, the fitted model estimated the conditional mean of $\ln(RC)/\Delta t$, symbolized as $E[\ln(RC)/\Delta t]$,

TABLE I. Characteristics of the Study Sample and Distribution of Exposure and Covariates by Ischemic Heart Disease (IHD) Status at Baseline, Kuopio Ischemic Heart Disease Risk Factor Study, 1986–2001 (N = 621)

	Men without IHD (n = 542)				Men with IHD (n = 79)			
Variable	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**
Age and technical factors								
Age at baseline (years)	49.1	5.9			52.3	5.5		
Ln of maximum IMT at baseline (ln mm)	−0.128	0.194			−0.052	0.25		
Sonographer at 11-year follow-up[a]								
Sonographer A			19	3.5			2	2.5
Sonographer B			6	1.1			0	0.0
Sonographer C			517	95.4			77	97.5
Participation in lipid-lowering drug trial								
Placebo group			37	6.8			6	7.6
Treatment group			34	6.3			6	7.6
Biological factors								
Blood glucose level (mmol/L)[b]	4.9	0.9			4.9	0.7		
Plasma fibrinogen level (g/L)[b]	3.0	0.5			3.1	0.5		
BMI at baseline (kg/m^2)	26.5	3.2			26.8	3.3		
LDL cholesterol at baseline (mmol/L)	3.8	0.9			3.9	1.0		
HDL cholesterol at baseline (mmol/L)	1.3	0.3			1.3	0.3		
SBP at baseline (mmHg)	131.4	14.6			127.2	14.6		
Proportion of follow-up time taking lipid-lowering medication	0.01	0.07			0.04	0.13		
Proportion of follow-up time taking	0.17	0.32			0.33	0.41		
blood pressure-lowering medication								
Behavioral factors								
Alcohol consumption (g/week)[b]	77.3	96.6			84.5	110.2		
Smoking status								
Nonsmoker			204	37.6			28	35.4
Former smoker			157	29.0			23	29.1
Irregular smoker			41	7.6			7	8.9
Current smoker			140	25.8			21	26.6
Conditioning LTPA (hr/year)[b]	120.7	102.8			120.5	93.3		
Cardiorespiratory fitness (ml O_2/kg/min)[b]	34.3	7.0			28.4	6.8		
Socioeconomic status								
Annual income (1,000 FIM)[b]	12.0	6.8			9.2	4.5		
Psychosocial job factors								
Social support at work score	6.0	2.3			5.7	2.4		
Mental strain at work index	11.8	5.2			13.5	5.4		
Stress from work deadlines[c]								
Stress at one time point			109	20.1			12	15.2
Stress at both time points			82	15.1			21	26.6
Total time at work during follow-up, excluding breaks (hr/year)	1350.7	707.6			993.2	711.2		
Work schedules								
Standard daytime work			387	71.4			43	54.4
Weekend shifts			75	13.8			17	21.5
Evening/night/rotating shifts			18	3.3			6	7.6
Other shifts			62	11.4			13	16.5

SD, standard deviation; IMT, intima-media thickness; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; LTPA, leisure-time physical activity; FIM, Finnish markka.

[a]Follow-up ultrasound examination for each participant was performed by the same sonographer at baseline.

[b]Weighted average of baseline, 4-year, and 11-year values.

[c]Stress from work was measured at both baseline and 4-year follow-up.

TABLE II. Characteristics of the Study Sample and Distribution of Exposure and Covariates by Carotid Artery Stenosis (CAS) Status at Baseline, Kuopio Ischemic Heart Disease Risk Factor Study, 1986–2001 (N = 621)

	Men without CAS (n = 492)				Men with CAS (n = 129)			
Variable	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**
Age and technical factors								
Age at baseline (years)	48.4	5.6			53.7	5		
Ln of maximum IMT at baseline (ln mm)	−0.154	0.179			0.021	0.230		
Sonographer at 11-year follow-up[a]								
Sonographer A			16	3.3			5	3.9
Sonographer B			3	0.6			3	2.3
Sonographer C			473	96.1			121	93.8
Participation in lipid-lowering drug trial								
Placebo group			33	6.7			10	7.8
Treatment group			29	5.9			11	8.5
Biological factors								
Blood glucose level (mmol/L)[b]	4.9	0.8			5.0	0.8		
Plasma fibrinogen level (g/L)[b]	3.0	0.5			3.2	0.4		
BMI at baseline (kg/m^2)	26.6	3.2			26.4	3.2		
LDL cholesterol at baseline (mmol/L)	3.8	0.9			4.0	0.9		
HDL cholesterol at baseline (mmol/L)	1.3	0.3			1.3	0.3		
SBP at baseline (mmHg)	130.5	14.4			132.4	15.6		
Proportion of follow-up time taking lipid-lowering medication	0.01	0.06			0.04	0.13		
Proportion of follow-up time taking	0.16	0.31			0.3	0.4		
blood pressure-lowering medication								
Behavioral factors								
Alcohol consumption (g/week)[b]	79.6	96.9			72.9	104.1		
Smoking status								
Nonsmoker			199	40.5			33	25.6
Former smoker			136	27.6			44	34.1
Irregular smoker			40	8.1			8	6.2
Current smoker			117	23.8			44	34.1
Conditioning LTPA (hr/year)[b]	118.7	100.3			128.1	106.5		
Cardiorespiratory fitness (ml O_2/kg/min)[b]	34.4	7.1			30.2	6.9		
Socioeconomic status								
Annual income (1,000 FIM)[b]	12.2	6.9			9.7	5.0		
Psychosocial job factors								
Social support at work score	5.9	2.2			12.2	5.9		
Mental strain at work index	12.0	5.0			6.0	2.6		
Stress from work deadlines[c]								
Stress at one time point			100	20.3			21	16.3
Stress at both time points			74	15.0			29	22.5
Total time at work during follow-up, excluding breaks (hr/year)	1383.6	696.8			1006.2	719.3		
Work schedules								
Standard daytime work			352	71.5			78	60.5
Weekend shifts			68	13.8			24	18.6
Evening/night/rotating shifts			20	4.1			4	3.1
Other shifts			52	10.6			23	17.8

SD, standard deviation; IMT, intima-media thickness; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; LTPA, leisure-time physical activity; FIM, Finnish markka.

[a]Follow-up ultrasound examination for each participant was performed by the same sonographer at baseline.

[b]Weighted average of baseline, 4-year, and 11-year values.

[c]Stress from work was measured at both baseline and 4-year follow-up.

all other covariates held constant. A corresponding estimate of $E(RC)$ over K years instead of per year was obtained from $E(RC)_K = \varphi \cdot \exp\{E[\ln(RC) \cdot K/\Delta t]\}$ where φ was the back-transformation correction factor [Duan, 1983], which with our data, was so close to 1 that it had no effect. Accordingly, the average percentage change (PC) for K years was $E(RC)_K\% = 100 \cdot [E(RC)_K - 1]$.

We used the relative change ratio (RCR), defined as the ratio of the relative change comparing different work schedules to standard daytime work, to provide a summary measure of the associations between work schedule and IMT progression. A detailed description of the outcome measure, PC, and RCR can be found in an earlier publication [Krause et al., 2009]. In current analyses, we chose $K = 11$ when presenting all RCs and RCRs.

Sensitivity Analyses

In order to test the robustness of our result in terms of covariate selection, we performed sensitivity analysis where we adjusted for a relative cardiorespiratory fitness measure that accounted for individual's physical work demands (relative aerobic strain) instead of the absolute cardiorespiratory fitness measure (VO_2 max). Relative aerobic strain was predictive of IMT progression in this cohort, as found in a previous study [Krause et al., 2007]. We also conducted a drop-out analysis to assess whether the distribution of exposure and covariates was different among our analytical sample (N = 621) and the eligible sample (N = 1006).

All analyses were performed using Stata version 13.0 (StataCorp LP, College Station, Texas).

RESULTS

Characteristics of the Study Sample

In our sample, 31% of men reported doing any type of shift work, including work during weekend (n = 92), evening (n = 1), night (n = 3), 2 shifts (n = 31), 3 shifts (n = 20), swing shifts (n = 30), or work on demand (n = 14). At baseline, 79 men had IHD, 129 had CAS and 32 of them had both conditions. Compared to men without IHD at baseline, men with IHD were slightly older, had higher values of maximum IMT at baseline, were more likely to take blood pressure lowering medication, had lower levels of cardiorespiratory fitness, earned less money, worked less time during follow-up, and were more likely to work non-standard daytime work schedules (Table I). Similar differences were found between men with and without CAS at baseline except that men with CAS were more likely to be former or current smokers, had higher social support at work, and reported less mental strain at work than did men without CAS (Table II).

Associations Between Work Schedules and Progression of Carotid Atherosclerosis

The RCR in maximum IMT during the 11-year follow-up period was positively associated with weekend shifts in all five models but not associated with the other two types of shifts (Table III). The effect estimates varied little with incremental adjustment for covariates.

Men with standard daytime work schedule experienced a 31% increase in maximum IMT, those who worked evening, night, or rotating shifts experienced a 33% increase, and those who worked "other" shifts experienced a 33% increase (Table IV). The highest PC was 37%, observed among men who did daytime work including weekends. Compared to standard daytime workers, men with weekend shifts experienced a faster progression of carotid atherosclerosis (RCR = 1.05, 95% CI: 1.00–1.09, $P = 0.042$) after adjusting for total hours worked during follow-up and all other covariates.

Effect-measure Modification of Work Schedule—Progression of Atherosclerosis Association by Baseline IHD or CAS Status

Men with preexisting IHD experienced a higher percentage change of IMT than men without IHD except among men who worked evening, night, or rotating shifts (Table V). Among men with IHD at baseline, men who reported doing weekend shifts had a higher rate of percentage change of IMT than those who reported standard daytime work (RCR = 1.11, 95% CI: 1.01–1.23, $P = 0.029$). Effect measure modification on the multiplicative scale was observed between weekend shifts and preexisting IHD status (P value for interaction = 0.121).

Men with CAS at baseline had a higher percentage change of IMT than men without CAS (Table VI). Among men with CAS at baseline, weekend shift workers had a higher rate of percentage change of IMT than those who reported standard daytime work (RCR = 1.09, 95% CI: 1.00–1.18, $P = 0.039$). Effect measure modification on the multiplicative scale might exist between weekend shifts and preexisting CAS status (P value for interaction = 0.236).

When adjusting for relative aerobic strain instead of VO_2 max, we observed nearly identical estimates and patterns of PC and RCR among all men, among men with or without IHD at baseline, and among men with or without CAS at baseline as that observed in the main analyses, but P-values for interaction between weekend shifts and both IHD and CAS were now below 0.2. (Appendices Tables AI.1–AI.3). The distribution of work schedule and other covariates did not

TABLE III. Relative Change Ratio (RCR) in Maximum Intima-media Thickness by Work Schedule During 11-year Follow-up, Kuopio Ischemic Heart Disease Risk Factor Study, 1986–2001 (N = 621)

	Model 1[a]			Model 2[b]			Model 3[c]			Model 4[d]			Model 5[e]		
Work schedule	**RCR**	**95% CI**	***P* value**	**RCR**	**95% CI**	***P* value**	**RCR**	**95% CI**	***P* value**	**RCR**	**95% CI**	***P* value**	**RCR**	**95% CI**	***P* value**
Standard day work	1.00			1.00			1.00			1.00			1.00		
Weekend shifts	1.05	1.01–1.09	0.022	1.04	1.00–1.08	0.037	1.06	1.02–1.10	0.005	1.06	1.01–1.10	0.008	1.05	1.00–1.09	0.042
Evening / night / rotating shifts	1.00	0.93–1.07	0.950	1.00	0.93–1.07	0.946	1.01	0.94–1.08	0.826	1.01	0.94–1.08	0.802	1.01	0.94–1.08	0.790
Other shifts	1.04	0.99–1.08	0.107	1.03	0.98–1.07	0.232	1.02	0.98–1.06	0.405	1.02	0.98–1.06	0.386	1.01	0.97–1.06	0.500

95% CI, 95% confidence interval.
[a]Model 1: adjust for age and technical factors (listed in Table I).
[b]Model 2: Model 1 with additional adjustment for biological factors (Table I).
[c]Model 3: Model 2 with additional adjustment for behavioral factors (Table I).
[d]Model 4: Model 3 with additional adjustment for socioeconomic status and psychosocial job factors (Table I).
[e]Model 5: Model 4 with additional adjustment for total time at work during follow-up (total of 22 covariates in Table I).

TABLE IV. Fully Adjusted[a] Percentage Change (PC) in Maximum Intima-media Thickness and Relative Change Ratio (RCR) by Work Schedule During 11-year Follow-up, Kuopio Ischemic Heart Disease Risk Factor Study, 1986–2001 (N = 621)

Work schedule	**PC (%)**	**95% CI**	**RCR**	**95% CI**	***P* value**
Standard day work	31.3	27.4–35.2	1.00		
Weekend shifts	37.2	31.4–43.3	1.05	1.00–1.09	0.042
Evening / night / rotating shifts	32.5	23.6–42.2	1.01	0.94–1.08	0.790
Other shifts	33.2	27.2–39.6	1.01	0.97–1.06	0.500

95% CI, 95% confidence interval.
[a]Results are from multiple regression analysis that adjusted for all 22 covariates listed in Table I (equal to model 5 in Table III).

differ much between the analytical sample and the eligible sample (Appendices Table AII).

DISCUSSION

Despite its relatively small sample size, our study provided a methodologically sound examination on the relationship between shift work and progression of carotid atherosclerosis. First, we observed faster progression of carotid atherosclerosis when comparing weekend shifts to standard daytime work. Second, when we looked at sub-groups of men with IHD or CAS at baseline, the positive associations between progression of atherosclerosis and weekend shifts became even stronger, as expected based on the hemodynamic theory of atherosclerosis [Glagov et al., 1988]. However, we found no substantial difference in atherosclerosis progression when comparing people who did evening/night/rotating shifts or other shifts to standard daytime workers among all men or among the sub-groups of men with IHD or CAS at baseline.

A comparison with similar studies of IMT progression and weekend shifts is difficult. Work during weekends has received little attention and almost all cohort studies on shiftwork examining cardiovascular health used broad work schedule categories and also symptomatic clinical CVD outcomes in contrast to our asymptomatic IMT measure. Our definition of weekend shifts is also an indicator of overtime work or extended work hours during weekends. In this case, our finding about weekend shifts is in line with a previous study done in this cohort where work time, measured by days worked per week, was predictive of progression of carotid atherosclerosis [Krause et al., 2009]. However, in this study of work schedules this positive association between weekend shifts and progression of atherosclerosis persisted even when we additionally adjusted for other work schedules and the total time at work during follow-up, our most comprehensive cumulative measure of work time (combining hours worked per day, days worked per week, weeks worked per year, and

TABLE V. Fully Adjusted[a] 11-year Percentage Change (PC) in Maximum Intima-media Thickness and Relative Change Ratio (RCR) Associated With Work Schedules by Baseline Ischemic Heart Disease (IHD) Status, Kuopio Ischemic Heart Disease Risk Factor Study, 1986–2001 (N = 621)

	Men without IHD at baseline (n = 542)					Men with IHD at baseline (n = 79)					*P* value for
Work schedule	**PC (%)**	**95% CI**	**RCR**	**95% CI**	***P* value**	**PC (%)**	**95% CI**	**RCR**	**95% CI**	***P* value**	**interaction**
Standard day work	31.1	27.3–35.1	1.00			36.4	28.7–44.5	1.00			
Weekend shifts	34.5	28.4–40.8	1.03	0.98–1.07	0.294	51.9	39.1–65.8	1.11	1.01–1.23	0.029	0.121
Evening/night/rotating shifts	34.9	24.6–46.2	1.03	0.95–1.11	0.484	26.1	10.2–44.3	0.93	0.80–1.07	0.284	0.200
Other shifts	32.7	26.2–39.4	1.01	0.97–1.06	0.631	39.3	26.6–53.3	1.02	0.92–1.13	0.687	0.866

95% CI, 95% confidence interval.
[a]Results are from multiple regression analysis that adjusted for all 22 covariates listed in Table I (equal to model 5 in Table III).

years worked during 11-year follow-up) that predicted progression of atherosclerosis in this population [Krause et al., 2009]. In fact, to our knowledge this is the first paper on shift-work schedules adjusting for total work time and reporting the independent effect of weekend work on CVD.

Irregular work schedules could lead to work-life imbalance [Jansen et al., 2004; Albertsen et al., 2008]. Even after accounting for the amount of weekly working hours, working on weekends was found to be associated with poorer work-life balance [Wirtz et al., 2011]. Workers who engage in weekend work can experience considerable disruption of weekend family and social activities such as sporting events and religious activities [Harrington, 2001]. Apart from disturbance of the work-life balance among these workers, our finding may also be attributed to not being able to recover from work. Employees who seldom rested from work during free weekends were reported to have an increased risk of death due to heart disease [Kivimäki et al., 2006]. Older workers are in greater need of recovery after work compared to younger ones [Kiss et al., 2008; Mohren et al., 2010]. Work during weekends can also act as a "circadian" psychosocial stressor that is relevant for CVD [Puttonen et al., 2010].

One prospective cohort study conducted among Japanese male workers found that rotating shift work increases the risk of death due to ischemic heart disease or circulatory system diseases but has almost no effect on death due to cerebrovascular disease [Fujino et al., 2006]. In order to test whether the null finding of evening/night/rotating work category in our study is due to the mixing of different work schedule categories, we excluded four men who reported evening or night shifts at baseline from this category. Both PC and RCR increased slightly but the conclusion did not change (PC for rotating shift only = 35.5%, 95% CI: 25.5–46.2%; RCR = 1.03, 95% CI: 0.96–1.12, $P = 0.393$). Due to limited sample size, we were not able to assess the effects of evening or night shifts alone on progression of atherosclerosis. Comparison between our study and other prospective cohort studies that examined the effect of rotating or night shift on vascular events may not be meaningful as the other studies were conducted in a very different population (i.e., among female nurses). The prevalence of any shift work, or night shift, or rotating shift among our sample is relatively low compared to studies among Copenhagen men [Boggild et al., 1999] or a general population in Germany [Haupt et al., 2008] but similar to the prevalence found in the Finnish twin study [Hublin et al., 2010]. This indicates that our sample may be a survivor population or the difference may be explained by the variation of shift work prevalence between

TABLE VI. Fully Adjusted[a] 11-year Percentage Change (PC) in Maximum Intima-media Thickness and Relative Change Ratio (RCR) Associated With Work Schedules by Baseline Carotid Artery Stenosis (CAS) Status, Kuopio Ischemic Heart Disease Risk Factor Study, 1986–2001 (N = 621)

	Men without CAS at baseline (n = 492)					Men with CAS at baseline (n = 129)					*P* value for
Work schedule	**PC (%)**	**95% CI**	**RCR**	**95% CI**	***P* value**	**PC (%)**	**95% CI**	**RCR**	**95% CI**	***P* Value**	**interaction**
Standard day work	31.2	27.3–35.3	1.00			33.8	27.4–40.5	1.00			
Weekend shifts	35.3	29.1–41.8	1.03	0.98–1.08	0.205	45.7	34.8–57.4	1.09	1.00–1.18	0.039	0.236
Evening/night/rotating shifts	31.1	21.5–41.5	1.00	0.93–1.08	0.984	41.5	19.7–67.2	1.06	0.89–1.25	0.522	0.553
Other shifts	32.7	25.9–39.8	1.01	0.96–1.06	0.669	35.7	25.7–46.5	1.01	0.94–1.10	0.735	0.955

95% CI, 95% confidence interval.
[a]Results are from multiple regression analysis that adjusted for all 22 covariates listed in Table I (equal to model 5 in Table III).

populations. Men who reported to be shift workers in their middle age may be the ones who remained shift workers for years and can manage the consequences of non-standard work schedules. However, selection bias is unlikely to account for the null finding as the distribution of exposure and covariates were comparable between our eligible sample and our analytical sample that excluded drop-outs.

In our study, men did not differ much in terms of biological factors and behavioral factors but those with preexisting IHD or CAS were slightly older, worked less time, and were more likely to work non-standard schedules. These men who have IHD or CAS at baseline also experienced a higher rate of progression of atherosclerosis associated with weekend shifts. As these workers age, they may experience both faster progression of atherosclerosis and higher CVD mortality associated with non-standard daytime work. We plan to investigate the latter in a follow-up study. Our current results indicate that for men with preexisting CVD, standard daytime work could be a safer work schedule than daytime work including weekends, though more studies are needed to confirm our findings.

To our knowledge, there are no other prospective studies examining shift work and atherosclerosis. Only two cross-sectional studies have examined the associations of shift work with atherosclerosis, indicated by higher mean and maximum carotid IMT. One study among the general population defined (former) shift work as "ever worked in shift and night work" and reported a positive association between former shift work and atherosclerosis [Haupt et al., 2008]. Yet, former shift workers could be people who cannot tolerate such work and selected themselves out of shift work. The other study among young adults defined shift work as "any 2- or 3-shift work or regular evening or night work during the last 12 months" and also reported a positive association between shift work and atherosclerosis [Puttonen et al., 2009]. Both of these studies used a dichotomous shift work indicator and mixing of effects in different shift categories was possible. Direct comparisons of our findings with these results are impossible due to the different shift work and outcome measures, and slightly different populations. We need additional prospective studies that have repeated measures of IMT, can differentiate between different shift work schedules, and examine shift work-atherosclerosis relationship with greater power.

The current study extends the existing literature on work time and progression of atherosclerosis in the same population [Krause et al., 2009]. It has a number of strengths, including the use of change in asymptomatic IMT outcome measure instead of CVD symptoms or clinical events. Using this pre-clinical indicator allowed us to examine the relationship between work schedule and atherosclerosis before most disease-based selections occur [Crouse and Thompson, 1993; Salonen and Salonen, 1993]. We were also able to adjust for an extensive list of factors that were either probable confounders of the association between work schedule and progression of atherosclerosis, or predictors of such progression that were not consequences of work schedule. Both work time duration and weekend shifts were independently predictive of IMT progression. Using information on both work schedule and work time allowed us to make more sensible comparisons. If men who have regular daily working hours but also work during weekends have elevated risk for IMT progression or CVD events, the choice of a reference group that mixes these workers with standard daytime workers will increase the background risk in this group and thus result in a reduced contrast between shift workers and daytime workers. This may explain some of the inconsistent findings in the previous literature. Finally, investigation of the sub-population with preexisting IHD or CAS could help identify those more or most vulnerable to IMT progression when exposed to non-standard work schedules.

A limitation of our study is the lack of data on the full history of work schedules and the precise duration of exposures to different work shifts. There can be misclassification of self-reported work schedule exposure as men who reported doing daytime work at baseline may in fact have non-standard daytime work shifts prior to baseline and vice versa. However, unlike young adults who may change their jobs frequently, job stability was quite high among middle-aged men in Finland when this study was carried out [Rokkanen and Uusitalo, 2010]. It is less likely that these workers would later switch to other work schedules during follow-up. Thus, one-time assessment of work schedules among these men was assumed to be reflective of their typical work schedule for an extended period of time during the 11-year follow-up. Furthermore, the outcome of interest is an asymptomatic manifestation of CVD so that misclassification of work schedule is likely to be non-differential with regard to IMT, possibly attenuating our estimates. We were not able to identify workers who worked during weekends but no more than 5 days per week and therefore cannot make inferences about all weekend work per se. Future studies should investigate possible modifying effects of schedules that combine weekend work with rest days during weekdays.

In conclusion, weekend shifts appear to accelerate the progression of carotid atherosclerosis compared to standard daytime work among middle-aged Finnish men, even after controlling for total work time, socioeconomic status, and an extensive list of other potential confounders. Men with pre-existing IHD or CAS were especially vulnerable to the atherogenic effects of weekend shifts. We could neither demonstrate nor rule out any association between non-daytime work shifts and progression of carotid atherosclerosis.

ACKNOWLEDGMENTS

This research was partially funded by the Finnish Academy of Science through the University of Eastern

Finland (Grant Number 132552). The authors thank Kimmo Ronkainen for managing and updating of underlying KIHD databases. Aolin Wang was supported by a doctoral scholarship from the China Scholarship Council (CSC) and a scholarship from the Chinese-American Engineers and Scientists Association of Southern California (CESASC). This project was also supported by the Southern California NIOSH Education and Research Center, Grant Agreement Number 5T42OH008412-09 from the Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of CDC.

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Disclosure Statement: The authors report no conflicts of interests.

List of Contributions of Each Author: Aolin Wang conceived this study, performed all analyses, and wrote the manuscript assisted by Niklas Krause. Jussi Kauhanen served as liaison with KIHD study data management at the University of Eastern Finland, provided access to data for this study, and reviewed the final manuscript. Onyebuchi Arah provided biostatistical advice for model building and the interpretation of results, and reviewed and edited the final manuscript draft.

APPENDICES (Results from sensitivity analyses)

Sensitivity analysis: using relative aerobic strain to account for cardiorespiratory fitness instead of VO_2 max.
Tables AI.1–AI.3

TABLE AI.1. Fully Adjusted[a] Percentage Change (PC) in Maximum Intima-media Thickness and Relative Change Ratio (RCR) by Work Schedule During 11-year Follow-up, Kuopio Ischemic Heart Disease Risk Factor Study, 1986–2001 (N = 612)

Work schedule	PC (%)	95% CI	RCR	95% CI	*P* value
Standard day work	31.4	27.6–35.4	1.00		
Weekend shifts	36.2	30.2–42.4	1.04	0.99–1.09	0.121
Evening / night / rotating shifts	33.2	24.2–42.8	1.01	0.95–1.09	0.711
Other shifts	33.7	27.6–40.1	1.02	0.97–1.06	0.433

95% CI = 95% confidence interval.
[a]Results are from multiple regression analysis that adjusted for all 22 covariates listed in Table I but using relative aerobic strain as measure of cardiorespiratory fitness relative to energy expenditure at work instead of the absolute fitness measure VO_2 max.

TABLE AI.2. Fully Adjusted[a] 11-year Percentage Change (PC) in Maximum Intima-media Thickness and Relative Change Ratio (RCR) Associated With Work schedules by Baseline Ischemic Heart Disease (IHD) Status, Kuopio Ischemic Heart Disease Risk Factor Study, 1986–2001 (N = 612)

	Men without IHD at baseline (n = 542)					Men with IHD at baseline (n = 79)					
Work schedule	PC (%)	95% CI	RCR	95% CI	*P* value	PC (%)	95% CI	RCR	95% CI	*P* value	*P* value for interaction
Standard day work	31.4	27.5–35.4	1.00			35.6	27.9–43.8	1.00			
Weekend shifts	33.8	27.6–40.2	1.02	0.97–1.7	0.466	51.4	37.8–66.3	1.12	1.01–1.24	0.034	0.198
Evening/night/ rotating shifts	35.7	25.3–46.9	1.03	0.95–1.12	0.427	26.5	10.6–44.7	0.93	0.81–1.08	0.339	0.221
Other shifts	33.1	26.6–39.9	1.01	0.97–1.06	0.596	39.3	26.6–53.3	1.03	0.93–1.14	0.612	0.807

95% CI, 95% confidence interval.

[a]Results are from multiple regression analysis that adjusted for all 22 covariates listed in Table I but using relative aerobic strain as measure of cardiorespiratory fitness relative to energy expenditure at work instead of the absolute fitness measure VO_2 max.

TABLE AI.3. Fully Adjusted[a] 11-year Percentage Change (PC) in Maximum Intima-Media Thickness and Relative Change Ratio (RCR) Associated With Work Schedules by Baseline Carotid Artery Stenosis (CAS) Status, Kuopio Ischemic Heart Disease Risk Factor Study, 1986–2001 (N = 612)

	Men without CAS at baseline (n = 492)					Men with CAS at baseline (n = 129)					
Work schedule	PC (%)	95% CI	RCR	95% CI	*P* value	PC (%)	95% CI	RCR	95% CI	*P* value	*P* value for interaction
Standard day work	31.4	27.5–35.4	1.00			34.1	27.6–40.8	1.00			
Weekend shifts	34.0	27.7–40.6	1.02	0.97–1.07	0.434	45.9	34.7–58.0	1.09	1.00–1.18	0.046	0.160
Evening/night/ rotating shifts	31.7	22.1–42.1	1.00	0.93–1.08	0.950	42.3	20.4–68.1	1.06	0.90–1.26	0.491	0.547
Other shifts	33.1	26.3–40.3	1.01	0.96–1.07	0.621	36.2	26.1–47.1	1.02	0.94–1.10	0.692	0.946

95% CI, 95% confidence interval.

[a]Results are from multiple regression analysis that adjusted for all 22 covariates listed in Table I but using relative aerobic strain as measure of cardiorespiratory fitness relative to energy expenditure at work instead of the absolute fitness measure VO_2 max.

Drop-out analysis: compare exposure/covariate distribution among eligible sample (N = 1006) and among analytical sample (N = 621).

Table AII

TABLE AII. Distribution of Exposure and Covariates of the Eligible Sample and the Analytical Sample, Kuopio Ischemic Heart Disease Risk Factor Study, 1986–2001

	Eligible sample (n = 1006)[a]				Analytical sample (n = 621)			
Variable	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**
Age and technical factors								
Age at baseline (years)	51.4	6.5			49.5	5.9		
Ln of maximum IMT at baseline (ln mm)	−0.077	0.221			−0.118	0.203		
Ln of maximum IMT at 4-year follow-up (ln mm)	0.161	0.205			0.137	0.188		
Sonographer at 11-year follow-up[b]								
Sonographer A			22	3.5			21	3.4
Sonographer B			6	1.0			6	1.0
Sonographer C			598	95.5			594	95.7
Participation in lipid-lowering drug trial								
Placebo group			68	6.8			43	6.9
Treatment group			68	6.8			40	6.4
Biological factors								
Blood glucose level (mmol/L)[c]	5.0	1.3			4.9	0.8		
Plasma fibrinogen level (g/L)[c]	3.1	0.5			3.0	0.5		
BMI at baseline (kg/m^2)	26.7	3.5			26.5	3.2		
LDL cholesterol at baseline (mmol/L)	3.9	1.0			3.8	0.9		
HDL cholesterol at baseline (mmol/L)	1.3	0.3			1.3	0.3		
SBP at baseline (mmHg)	132.7	16.2			130.9	14.7		
Proportion of follow-up time taking lipid-lowering medication	0.01	0.08			0.02	0.08		
Proportion of follow-up time taking blood pressure-lowering medication	0.21	0.37			0.19	0.33		
Behavioral factors								
Alcohol consumption (g/week)[c]	85.4	122.0			78.2	98.4		
Smoking status								
Nonsmoker			233	37.2			232	37.4
Former smoker			181	28.9			180	29.0
Irregular smoker			51	8.1			48	7.7
Current smoker			162	25.8			161	25.9
Conditioning LTPA (hr/year)[c]	124.7	129.0			120.7	101.6		
Cardiorespiratory fitness (ml O_2/kg/min)[c]	31.3	7.7			33.5	7.2		
Socioeconomic status								
Annual income (1,000 FIM)[c]	10.1	6.5			11.7	6.6		
Psychosocial job factors								
Social support at work score	6.1	2.4			5.9	2.3		
Mental strain at work index	12.6	6.1			12.0	5.2		
Stress from work deadlines[d]								
Stress at one time point			122	12.1			121	19.5
Stress at both time points			113	11.2			103	16.6
Total time at work during follow-up, excluding breaks (hr/year)	1302.5	718.3			1305.2	717.5		
Work schedules								
Standard daytime work			665	66.3			430	69.2
Weekend shifts			33	3.3			24	3.9
Evening/night/rotating shifts			169	16.8			92	14.8
Other shifts			136	13.6			75	12.1

SD, standard deviation; IMT, intima-media thickness; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SBP, systolic blood pressure; LTPA, leisure-time physical activity; FIM, Finnish markka.

[a]Due to missing values in some of the variables, the total may not add up to 1006.

[b]Follow-up ultrasound examination for each participant was performed by the same sonographer at baseline.

[c]Weighted average of baseline, 4-year, and 11-year values.

[d]Stress from work was measured at both baseline and 4-year follow-up.