Associations of Work Hours, Job Strain, and Occupation With Endothelial Function

The Multi-Ethnic Study of Atherosclerosis (MESA)

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Objective: To investigate associations of work hours, job control, job demands, job strain, and occupational category with brachial artery flow-mediated dilation (FMD) in 1499 Multi-Ethnic Study of Atherosclerosis participants. **Methods:** Flow-mediated dilation was obtained using high-resolution ultrasound. Mean values of FMD were examined across categories of occupation, work hours, and the other exposures using regression analyses. **Results:** Occupational category was significantly associated with FMD overall, with blue-collar workers showing the lowest mean values—management/professional = 4.97 ± 0.22%; sales/office = 5.19 ± 0.28%; services = 4.73 ± 0.29%; and blue-collar workers = 4.01 ± 0.26% (adjusted $P < 0.001$). There was evidence of effect modification by sex (interaction $P = 0.031$)—significant associations were observed among women (adjusted $P = 0.002$) and nearly significant results among men (adjusted $P = 0.087$). Other exposures were not significantly associated with FMD. **Conclusions:** Differences in endothelial function may account for some of the variation in cardiovascular disease across occupational groups.

The vascular endothelium is involved in numerous critical functions, including maintaining vascular homeostasis, regulating vascular tone, controlling coagulation through the production of factors that regulate platelet activity and the fibrinolytic system, and producing cytokines and adhesion molecules that regulate and direct the inflammatory process.[1,2] Endothelial dysfunction occurs when a chronic inflammatory process is initiated, resulting in loss of vasodilator and prothrombotic products.[2] Endothelial dysfunction is observed in the early stages of atherosclerosis and is associated with increased plaque rupture in myocardial infarction and other adverse outcomes.[2–5] Flow-mediated dilation (FMD) of the brachial artery is a commonly used and reproducible approach to measuring endothelial function in conduit arteries.[5–7]

A large body of literature has documented the links between occupation and cardiovascular outcomes.[8–10] Effects of occupation on endothelial function could be one of the mediating pathways, but few studies have investigated how various aspects of occupation are related to endothelial function.[11] According to Cooper and colleagues,[11] participants perceiving themselves to be of lower social status in their communities exhibited reduced endothelial function (ie, lower FMD). Nevertheless, the authors did not find a significant association between objective socioeconomic status measures (including education/occupation) and FMD.

Other aspects of occupation that could be associated with endothelial dysfunction include shift work and work hours and psychosocial characteristics like job strain. Night-shift work has been shown to be associated with endothelial dysfunction in persons of various occupations.[12–14] Long work hours are known to be associated with multiple health conditions, including cardiovascular risk factors and cardiovascular disease (CVD),[15–20] but to our knowledge associations with endothelial function have not been investigated.

Job strain has been shown to be associated with CVD outcomes.[21–24] Results from a large ($n = 197,473$) meta-analytical study show that job strain is significantly associated with a small, but consistent, increased risk of CVD events.[23] Alterations of FMD could be one of the mechanisms through which job strain affects CVD risk[25,26]; however, to our knowledge no studies have directly investigated whether job strain affects endothelial function.

The primary aim of this study was to determine whether long work hours, job control, job demands, job strain, and occupational categories are associated with endothelial dysfunction. Both the degree of endothelial dysfunction and work characteristics differ by sex and race.[27–29] In addition, the effect of occupational exposures on health may be modified by sex and race/ethnicity. Assessment of effect modification by these variables might help to identify the most vulnerable subgroups, where the negative health effect of long work hours would be most severe. Therefore, a secondary exploratory aim of this study was to assess whether any of the relationships with FMD are modified by sex and race/ethnicity. We hypothesized that long work hours, low job control, high job demands, job strain, and being in the lower occupational categories would be positively associated with endothelial dysfunction.

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METHODS

Study Design and Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) was initiated in July 2000, and details of the study design and protocol have been previously published.[30] The original cohort of 6814 men and women aged 45 to 84 years consisted of participants from various racial and ethnic backgrounds (whites, African Americans, Hispanics, and Chinese Americans). The participants were recruited from six US communities (Forsyth County, North Carolina; Northern Manhattan and the Bronx, New York; Baltimore City and Baltimore County, Maryland; St Paul, Minnesota; Chicago, Illinois; and Los Angeles, California). Persons were excluded from participating in MESA if they had any physician-diagnosed CVD or cerebrovascular disease, cancer or any serious medical condition, pregnancy, poor cognitive function, weight more than 300 lb (more than 136 kg), language barrier (unable to understand English, Spanish, Cantonese, or Mandarin), and if they lived in a nursing home or had plans to leave the community within 5 years. Written informed consent was obtained from participants. The institutional review boards of the six field centers and the National Heart, Lung, and Blood Institute approved the study protocol. Approval was also obtained by the institutional review board of the National Institute for Occupational Safety and Health for secondary analysis of the study data.

Most of the data for this study were taken from the first examination (July 2000 to July 2002). Participants were excluded from the FMD examination if they had uncontrolled hypertension ($n = 158$), a history of the Raynaud phenomenon ($n = 55$), a congenital abnormality of the arm or hand ($n = 12$), a radical mastectomy on either side ($n = 100$), or blood pressures (BPs) in the left and right arms that differed by more than 15 mm Hg ($n = 307$, not mutually exclusive), resulting in 6489 participants who underwent the brachial artery FMD examination. Participants were included in these analyses if they answered "yes" to the question "do you work to earn money" ($n = 3700$). Even though 6489 participants had FMD measured, for cost and data quality reasons, only a subset had their tapes read and were included in the analytical data set ($n = 3025$). Selection of participants for FMD reading, from those who completed the procedure at examination I, was performed using a case-cohort design. This included random selection of participants who completed the procedure, and some of these randomly selected participants met the case definition—CVD (myocardial infarction, resuscitated cardiac arrest, or coronary heart disease (CHD) death, stroke, angina [definite angina or probable angina followed by revascularization]) or congestive heart failure event prior to selection (personal communication, MESA Coordinating Center, October 27, 2005). As a result, each participant had a different probability of being selected, and this was accounted for during statistical analyses. We included participants if they kept the same job in both examinations I and II ($n = 2801$) and had complete values on job control, job demands, occupational category, and brachial artery FMD. The final sample size consisted of 1499 participants, 667 women and 832 men.

Hours of Work

Participants completed questions on occupational activities. They were asked about the amount of time spent in all jobs. The number of days and hours worked per week were assessed from the question "How many days per week and hours per day do you work in all jobs?" The total number of hours of work per week was calculated by multiplying the two responses.

Occupational Categories

Occupational information was collected by questionnaire.[31] Four open-ended questions modeled on the US Census occupational questions were used to determine the respondent's current occupation—For whom do/did you work? What type of business or industry is/was this? What kind of work do/did you do? What was your job title? Participants who were no longer working were asked to respond for their last main occupation. The responses were coded using the Census 2000 Occupational Codes and categorized as follows: (1) management/professional; (2) service; (3) sales/office; (4) farming, fishing, and forestry; (5) construction, extraction, and maintenance; and (6) production, transportation, and material moving.[31] The last three categories included a small number of participants in this sample so they were combined into one category of "blue-collar jobs."

Job Demands, Job Decision Latitude, and Job Strain

At examination II (2002 to 2004), data were obtained for job demands and job decision latitude (a measure of job control) from the Job Content Questionnaire[32] for a subsample of participants ($n = 6233$) who were working at the time of data collection.[31] After straight and reverse coding, the scores were calculated following the original formulation.[33] The job control scores ranged from 24 to 96, whereas the job demands scores ranged from 12 to 48. Both scales had an acceptable level of internal consistency within the study sample (the Cronbach $\alpha = 0.70$ for job demands and 0.84 for job control).[31] Job demands and job control, originally continuous variables, were both dichotomized at the sample median to create binary variables, which were then combined to create the following: high job control/high job demands, high job control/low job demands, low job control/high job demands, and low job control/low job demands. Analyses were also performed using these variables in the continuous form.

Brachial Artery FMD

To assess endothelial function, brachial artery FMD was performed as one component of the first examination of the MESA cohort. Participants were required to fast for at least 6 hours before undergoing the brachial artery FMD measurement.[5,34] A detailed description of the scanning and reading protocol can be found at the MESA Web site (www.mesa-nhlbi.org). Participants were allowed to rest for 15 minutes in the supine position. A standard BP cuff was positioned around the right arm, two inches below the antecubital fossa, and the artery was imaged 5 to 9 cm above the antecubital fossa. An automated sphygmomanometer (Dinamap device, Critikon, Milwaukee, WI) was used to monitor BP and pulse in the left arm at 5-minute intervals throughout the examination. Blood pressure at baseline was measured in the left arm, before inflation of the right arm cuff, immediately before release of the occluding cuff, at 1 minute and then at 3 minutes after release of the occluding cuff. Blood pressure was measured in both arms to confirm no significant gradients (ie, 15 mm Hg or less). This was to ensure that the maneuver did not cause a change in BP that might have affected the resting tone (diameter) of the artery.

The right brachial artery was imaged with high-resolution ultrasound at the elbow, 5 to 9 cm above the antecubital fossa, where it formed a straight segment, free of major branches. After obtaining baseline images of the right brachial artery over a 30-second period, the cuff was inflated for 5 minutes (pressure was 200 mm Hg or BP +50 mm Hg if the systolic BP was more than 150 mm Hg). Frame rate was fixed at 32 frames per second. Images of the right brachial artery were captured continuously for 105 seconds after cuff deflation. Videotapes of the acquired images of the brachial artery were analyzed at the Wake Forest University Cardiology Image Processing Laboratory using a previously validated semiautomated system. The readings of the digitized images generated the baseline and maximum diameters of the brachial artery from which the absolute change from baseline diameter and percentage brachial artery FMD was computed. Flow-mediated dilation was computed with the following formula: 100 (maximum − baseline diameter)/baseline diameter and expressed as a percentage.

Intrareader reproducibility was evaluated by comparing an original and a blinded quality control reread of ultrasounds from 40 MESA participants. The intraclass correlation coefficients were 0.99 for baseline diameter, 0.99 for maximum diameter, and 0.93 for % FMD. Technicians performed duplicate examinations on 19 participants on 2 days separated by 1 week to evaluate intrasubject variability. The intraclass correlation coefficients were as follows: baseline diameter (0.90), maximum diameter (0.90), and % FMD (0.54). The percentage technical error of measurement for baseline diameter, maximum diameter, and % FMD measurement was 1.39%, 1.47%, and 28.4%, respectively.[5]

Covariates

Self-administered questionnaires provided information on demographic and lifestyle variables, which included age, self-identified race/ethnicity, educational attainment, annual household income, pack-years of smoking for current and former smokers, and current smoking status. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Cigarette smoking was defined as current, former, or never. Pack-years of smoking were calculated.

Blood was drawn from participants after they had fasted for a minimum of 12 hours, and aliquots were prepared for analysis and for storage at $-70°F$ at the University of Vermont and the University of Minnesota. Laboratory analysis was performed for lipids. Low-density lipoprotein cholesterol was calculated by the Friedewald equation.[35]

Resting BP was measured three times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Wipro GE Healthcare, Waukesha, Wisconsin). The average of the last two measurements was used in the analysis. Hypertension was defined as systolic pressure of 140 mm Hg or higher, diastolic pressure of 90 mm Hg or higher, or the current use of antihypertensive medication.

The MESA Typical Week Physical Activity Survey, adapted from the Cross-Cultural Activity Participation Study,[36] was used to obtain the time and frequency spent in various physical activities during a typical week in the previous month. The survey has 28 items in categories of activity as follows: household chores, yard/lawn/garden work, care of others (children or adults), transportation, nonoccupational walking, team sports and dancing, leisure activities (eg, reading, and watching TV), work (occupational or volunteer), and intentional exercise. Participants reported the average number of days per week and time per day engaged in the activities, as well as the intensity level (light, moderate, or heavy). Minutes of activity were summed for each discrete activity type and multiplied by metabolic equivalent level to derive composite physical activity levels.

Statistical Methods

Descriptive statistics were obtained for all variables by sex, and differences between men and women were tested using the chi-squared test and regression analysis. We also investigated the associations of several covariates with the independent variables (hours of work, job control, job demands, and occupation) and also with the dependent variable (brachial FMD) using regression analysis. Four categories of total hours worked per week (less than 40, 40, 41 to 49, and 50 or more hours) were selected by placing participants who worked 40 hours per week into one group and then dividing the remaining hours worked to obtain reasonable and fairly equal sample sizes in each group. Job demands and job control, originally continuous variables, were both dichotomized at the sample median to create high and low categories of each variable. Mean values of brachial FMD were obtained across these categories of hours worked, job control/job demands, and occupational category. Because the sampling for FMD was not random, the inverse of the probability of selection was used as weights to account for the sampling scheme. The survey procedures in Statistical Analysis System were used to generate percentages, test association between categorical variables, and estimate unadjusted and adjusted means for continuous variables. P values for trend were obtained using the continuous form of the exposure of interest. Effect modification was assessed for sex and race/ethnicity. Formal tests of effect modification were performed by including interaction terms in the fully adjusted models. Potential confounders included in the models were age, sex, race/ethnicity, educational level, and the potentially mediating (and/or confounding) variables waist circumference, high-density lipoprotein (HDL) cholesterol, total cholesterol, BMI, systolic BP, diastolic BP, physical activity, cigarette smoking status, and pack-years of smoking. Three variables, diabetes, glucose level, and the use of antihypertensive medications, when included in the multivariate models, did not change the results so they were omitted from the final models. Statistical Analysis System (SAS) version 9.2 (Cary, NC) was used to analyze these data.[37]

RESULTS

The mean age ± SEM of participants in this analysis was 56.1 ± 0.21 years (Table 1). Slightly more than half of the participants were men (n = 832; 55.5%). The largest racial/ethnic group was whites (41.2%), followed by African Americans (23.1%), Hispanics (22.5%), and Chinese Americans (13.2%). A total of 31% of participants worked 40 hours per week; 20.8% worked more than 50 or more hours per week. Participants were in occupations classified as management/professional (47.9%); 20.4% were in sales/office, 16.2% in service, and 15.5% in blue-collar occupational categories. Men had significantly lower mean brachial artery FMD (4.24 ± 0.09% vs 5.47 ± 0.13%; $P < 0.001$) than women.

The age-adjusted mean values of FMD across selected variables are shown in Table 2. Flow-mediated dilation was significantly associated with race/ethnicity (lowest in African Americans and highest in whites) and smoking status (lowest in current smokers and highest in never smokers). Flow-mediated dilation was negatively and significantly correlated with waist circumference, physical activity, and systolic BP and diastolic BP, and it was positively and significantly correlated with HDL and total cholesterol. Analyses were also conducted to determine the associations of demographic, lifestyle, and other characteristics with work hours, occupational categories, job demands, and job control (see Supplemental Digital Content Table, available at http://links.lww.com/JOM/A173).

In Table 3, mean values of FMD are shown across categories of work hours per week, occupational categories, and job strain. There was a positive association between work hours and FMD before any risk-factor adjustment ($P = 0.001$), but the association was no longer significant after adjustment for age and sex ($P = 0.413$). After adjustment for several confounders and CVD risk factors, the association remained statistically insignificant ($P = 0.157$). Flow-mediated dilation was significantly associated with occupational category before and after risk-factor adjustment. Employees in management/professional and sales/office categories had the highest mean FMD values, 4.97 ± 0.22% and 5.19 ± 0.28%, respectively, followed by services (4.73 ± 0.29%) and blue-collar workers (4.01 ± 0.26%) after full adjustment ($P < 0.001$). Post hoc comparisons revealed that the differences between management/professional and blue-collar workers were statistically significant ($P < 0.001$), as were those between sales/office and blue-collar workers ($P < 0.001$), and services and blue-collar workers ($P = 0.012$). Flow-mediated dilation was not significantly associated with job strain, job control, or job demands after full risk-factor adjustment.

Race did not modify any of the associations between the occupational exposures and FMD (data not shown). The association between FMD and occupational category was stratified by sex, and the results are shown in Table 4. Sex significantly modified the

TABLE 1. Demographic, Lifestyle, and Other Characteristics of the Study Sample

Characteristics	All (N = 1,499) n (%)	Women (n = 667) n (%)	Men (n = 832) n (%)	P
Hours of work per week				<0.001
<40	504 (34.2)	268 (40.5)	236 (28.8)	
40	463 (31.0)	215 (32.3)	248 (29.9)	
41–49	211 (14.0)	78 (11.9)	133 (15.9)	
≥50	321 (20.8)	106 (15.4)	215 (25.4)	
Race/ethnicity				0.512
White	569 (41.2)	252 (41.4)	317 (40.9)	
Chinese American	256 (13.2)	105 (11.9)	151 (14.3)	
African American	339 (23.1)	160 (24.2)	179 (22.2)	
Hispanic	335 (22.5)	150 (22.4)	185 (22.5)	
Educational status				<0.001
≤High school graduate/General Education Development	387 (25.5)	187 (27.5)	200 (23.8)	
Some college/technical school	440 (30.2)	231 (35.5)	209 (25.6)	
Bachelor's degree	293 (19.4)	123 (18.3)	170 (20.4)	
Graduate/professional	379 (24.9)	126 (18.7)	253 (30.2)	
Annual household income ($)				<0.001
<20 k	164 (10.9)	82 (11.9)	82 (10.0)	
20–50 k	514 (34.9)	276 (41.6)	238 (28.8)	
50–75 k	316 (21.5)	144 (21.7)	172 (21.3)	
>75 k	483 (32.8)	161 (24.8)	322 (39.9)	
Occupational categories				<0.001
Management/professional	722 (47.9)	288 (43.4)	434 (51.8)	
Sales/office	294 (20.4)	185 (28.7)	109 (13.2)	
Service	249 (16.2)	139 (20.0)	110 (12.8)	
Blue-collar	234 (15.5)	55 (7.8)	179 (22.2)	
Smoking status				<0.001
Never	801 (51.4)	419 (59.6)	382 (44.3)	
Former	507 (35.1)	171 (27.5)	336 (41.7)	
Current	191 (13.5)	77 (12.9)	114 (14.0)	
Job control/demand				<0.001
High control/high demand	334 (22.5)	122 (19.1)	212 (25.4)	
High control/low demand	340 (24.0)	112 (18.0)	228 (29.2)	
Low control/high demand	437 (28.4)	262 (38.0)	175 (20.0)	
Low control/low demand	381 (25.2)	166 (24.9)	215 (25.4)	
	Mean ± SEM	Mean ± SEM	Mean ± SEM	
Age, yr	56.1 ± 0.21	55.4 ± 0.30	56.7 ± 0.30	0.002
Body mass index (kg/m^2)	28.2 ± 0.14	28.6 ± 0.25	27.8 ± 0.15	0.008
Waist circumference (cm)	96.8 ± 0.37	95.0 ± 0.64	98.3 ± 0.41	<0.001
Physical activity (MET) (min/wk)	14,109.0 ± 179.6	14,196.0 ± 259.5	14,035.0 ± 248.8	0.654
Pack-years of smoking (ever smokers)	10.3 ± 0.67	7.5 ± 0.64	12.6 ± 1.13	<0.001
Systolic blood pressure (mm Hg)	120.8 ± 0.50	118.7 ± 0.79	122.7 ± 0.62	<0.001
Diastolic blood pressure (mm Hg)	72.4 ± 0.27	68.4 ± 0.39	75.8 ± 0.31	<0.001
HDL cholesterol (mg/dL)	50.4 ± 0.39	56.7 ± 0.63	45.0 ± 0.39	<0.001
Total cholesterol (mg/dL)	193.9 ± 0.90	198.1 ± 1.34	190.2 ± 1.21	<0.001
Work hours (h/wk)	40.4 ± 0.40	38.5 ± 0.58	42.0 ± 0.54	<0.001
Baseline brachial artery diameter (mm)	4.28 ± 0.02	3.69 ± 0.02	4.80 ± 0.02	<0.001
Maximum brachial artery diameter (mm)	4.48 ± 0.02	3.88 ± 0.02	4.99 ± 0.02	<0.001
Brachial FMD (absolute)	0.20 ± 0.01	0.19 ± 0.01	0.20 ± 0.01	0.522
Brachial FMD (%)	4.81 ± 0.08	5.47 ± 0.13	4.24 ± 0.09	<0.001

All values were weighted.
P values are for differences between men and women and were obtained from the chi-square tests (categorical values) and the *t* tests (continuous values).
Results for continuous variables are mean ± SEM.
FMD, flow-mediated dilation; HDL, high-density lipoprotein; MET, metabolic equivalent (units are in thousands); SEM, standard error of mean.

TABLE 2. Age-Adjusted Mean Values of Flow-Mediated Dilation (%) Across Selected Characteristics

Characteristics	FMD (%) Mean ± SEM
Race/ethnicity	
White	5.37 ± 0.13
Chinese American	4.94 ± 0.17
African American	3.96 ± 0.15
Hispanic	4.79 ± 0.14
*P**	<0.001
Educational status	
≤ High school graduate/General Education Development	4.64 ± 0.13
Some college/technical school	4.87 ± 0.15
Bachelor's degree	4.89 ± 0.17
Graduate/professional	5.02 ± 0.15
P†	0.071
Smoking status	
Never	4.93 ± 0.10
Former	4.95 ± 0.14
Current	4.30 ± 0.20
*P**	0.014
Body mass index (kg/m^2)	−0.0236, 0.098
Waist circumference (cm)	−0.0126, 0.029
Physical activity (MET min/wk)	−0.00002, 0.025
Pack-years of smoking (ever-smokers)	−0.0041, 0.061
Systolic Blood Pressure (mm Hg)	−0.0182, <0.001
Diastolic Blood Pressure (mm Hg)	−0.0418, <0.001
High-density lipoprotein cholesterol (mg/dL)	0.0185, 0.001
Total cholesterol (mg/dL)	0.0058, 0.007

Results for continuous variables are regression coefficients and *P* values.
**P* values obtained from analysis of covariance tests of differences between mean values.
†*P* values obtained from analysis of covariance linear contrasts.
FMD, flow-mediated dilation; SEM, standard error of mean.

association between occupational category and FMD (interaction $P = 0.031$) but did not modify any of the other associations with FMD. Women in the management/professional and sales/office categories had the highest mean FMD values, whereas those in the blue-collar group had the lowest value, and these effects were robust to various adjustments. After full risk-factor adjustment, the results among women remained statistically significant ($P = 0.002$). The association between FMD and occupational category was statistically significant among men after adjustment for age ($P = 0.042$) but not in the more fully adjusted models. Post hoc comparisons revealed that, among women, the differences between management/professional and blue-collar workers were statistically significant ($P = 0.008$) as were those between sales/office and blue-collar workers ($P = 0.001$).

DISCUSSION

In this community-based sample of employed individuals, we examined the association of work hours, job demands, job control, job strain, and occupational category with brachial artery FMD. Occupational category was significantly associated with FMD; blue-collar workers had the lowest mean FMD value and those in the management/professional and services categories had the highest mean values. After stratification by sex, the pattern remained but the association was only significant among women.

We did not find any published studies that investigated the association between occupational category and endothelial function, but Cooper and colleagues[11] found that participants perceiving themselves to be of lower social status in their communities exhibited reduced endothelial function (ie, lower FMD). This association remained significant after adjusting for objective socioeconomic status measures such as income, education/occupation, and other covariates, although they did not find a significant association between objective socioeconomic status measures and FMD. The authors posited that endothelial dysfunction could be a pathway through which psychosocial factors, such as subjective social status, are linked to CVD. In contrast, among a healthy group of British civil servants, several markers of socioeconomic status such as lower employment grade, educational qualifications, and income showed no relationship to any measure of vascular function, including FMD.[38] We found that blue-collar workers have significantly worse endothelial function than management/professional workers. Nevertheless, this association was stronger in women than in men, suggesting the need for further research on differential effects of occupational conditions by sex.

In this study, neither job demands, job control, nor job strain were found to be significantly associated with FMD. Studies investigating the association between job strain and endothelial function were not found, but numerous articles investigating the relationship between job strain and CHD are available. One study examined the relationship between job strain, job insecurity, and incident CVD more than 10 years among 22,086 participants in the Women's Health Study.[24] Women with high job strain (high demands and low control) and active jobs (high demands and high control) were 38% more likely to experience a CVD event than those who reported low job strain. Results from the Whitehall II study, a prospective cohort study, show that men and women with low job control had a higher-risk CHD during the follow-up than those with high job control.[21] Kivimaki and colleagues[23] conducted a meta-analysis of published and unpublished studies and reported that job strain was significantly associated with a small, but consistent, increased risk of CVD events. Nevertheless, we found no evidence that job strain is related to endothelial function. Our results suggest that the effect of job strain on endothelial function is not an important pathway through which job strain is linked to cardiovascular events.

No published studies have been identified that investigated the association between work hours and FMD. Nevertheless, a recent systematic review conducted by Virtanen and colleagues[39] reported significant positive associations between longer work hours and CHD in seven of 12 studies and positive but not significant associations in the remaining five studies. Other studies have reported that night or irregular shift work, but not extended work hours, negatively affects vascular function.[14,39] We found no evidence that work hours are related to FMD.

In a recent study conducted on the MESA participants, significant positive associations were observed between work hours and common carotid intima-media thickness among women only, after adjustment for age, race/ethnicity, education, annual household income, and CVD-related risk factors.[40] In addition, longer hours of work were significantly associated with lower levels of ankle-brachial index among men but not among women.[40] Carotid intima-media thickness and ankle-brachial index are used to estimate the burden of atherosclerosis, whereas endothelial function measured by FMD is a marker of subclinical vascular function, which is believed to precede and accompany development of atherosclerosis.[2] We have no compelling explanation for why longer work hours was associated with subclinical disease but not with FMD in MESA. Nevertheless, the smaller sample size for FMD analyses may have hampered our ability to detect small effects.

There are plausible mechanisms through which occupational category may be associated with endothelial function, and they

TABLE 3. Mean Values of Brachial FMD (%) by Hours of Work per Week, Occupational Categories, and job Strain

	n	Model 1*	Model 2†	Model 3‡	Model 4§
Hours of work per week					
<40	504	4.44 ± 0.13	4.65 ± 0.13	4.65 ± 0.13	4.61 ± 0.24
40	463	5.07 ± 0.15	4.94 ± 0.14	4.95 ± 0.14	4.95 ± 0.25
41–50	211	4.96 ± 0.23	4.91 ± 0.22	4.87 ± 0.22	4.91 ± 0.34
≥50	321	4.96 ± 0.16	4.88 ± 0.16	4.87 ± 0.16	4.88 ± 0.28
P‖		0.001	0.413	0.289	0.157
Occupational categories¶					
Management/professional		4.93 ± 0.12	4.99 ± 0.11	4.96 ± 0.12	4.97 ± 0.22
Sales/office	722	5.29 ± 0.20	5.35 ± 0.19	5.16 ± 0.18	5.19 ± 0.28
Services	294	4.69 ± 0.18	4.66 ± 0.17	4.79 ± 0.19	4.73 ± 0.29
Blue-collar	249	3.96 ± 0.17	3.96 ± 0.15	3.96 ± 0.16	4.01 ± 0.26
P#	234	<0.001	<0.001	<0.001	<0.001
Job strain					
HC/HD		5.18 ± 0.16	5.12 ± 0.15	4.92 ± 0.15	4.90 ± 0.26
HC/LD	334	4.35 ± 0.15	4.71 ± 0.16	4.66 ± 0.16	4.67 ± 0.26
LC/HD	340	5.21 ± 0.16	4.87 ± 0.16	4.97 ± 0.16	4.95 ± 0.26
LC/LD	437	4.47 ± 0.15	4.61 ± 0.14	4.69 ± 0.14	4.71 ± 0.24
P#	381	<0.001	0.088	0.388	0.518
Job control		− 0.002, 0.673	0.008, 0.115	0.001, 0.875	− 0.002, 0.673
Job demands		0.058, <0.001	0.024, 0.026	0.017, 0.104	0.016, 0.132

*Model 1: Unadjusted.
†Model 2: Adjusted for age and sex.
‡Model 3: Adjusted for age, sex, race/ethnicity, educational level, waist circumference, HDL cholesterol, and total cholesterol.
§Model 4: Adjusted for age, sex, race/ethnicity, educational level, waist circumference, HDL cholesterol, total cholesterol, BMI, diastolic blood pressure, systolic blood pressure, physical activity, smoking status, and pack-years of smoking.
‖*P* values were obtained from linear regression models.
¶Occupational categories, Model 4:
Management/professional versus sales/office: $P = 0.801$.
Management/professional versus services: $P = 0.771$.
Management/professional versus blue-collar: $P < 0.001$.
Services versus sales/office: $P = 0.293$.
Services versus blue-collar: $P = 0.012$.
Sales/office versus blue-collar: $P < 0.001$.
Sex was not included in any of the models for “occupational categories” because sex is a significant effect modifier in the association between occupational categories and FMD % (see Table 4).
#*P* values were obtained from the analysis of variance/analysis of covariance models.
Results for the categorical variables are mean ± SEM.
Results for “job control” and “job demands” are β-coefficients and *P* values.
FMD, flow-mediated dilation; HC, high control; HD, high demands; LC, low control; LD, low demands.

include psychological stress and unhealthy lifestyle behaviors such as physical inactivity.[41–43] In our analyses, associations of blue-collar work with endothelial dysfunction persisted after controlling for waist circumference, HDL cholesterol, total cholesterol, BMI, diastolic BP, systolic BP, physical activity, smoking status, and pack-years of smoking, suggesting that other mediators may be involved.

This study has some limitations. Because of the cross-sectional study design, we are not able to determine causality or the temporal sequence of the association involving occupational category and brachial artery FMD. Exclusion of participants with uncontrolled hypertension, which is associated with both job strain and endothelial dysfunction, may have resulted in some selection bias. The bias would be toward the null value if participants with both higher levels of endothelial dysfunction and adverse occupational exposures were excluded.

Nevertheless, this study also has several strengths. The MESA data set provided a rich resource in which to examine associations of long work hours, job control, job demands, and occupation with endothelial function and included information on multiple factors that could potentially modify or confound the associations of interest. All technicians were centrally trained and were required to demonstrate competency in relevant procedures before being certified to perform MESA examinations. The large sample size, the geographically and ethnically diverse population, and utilization of internal and external quality control programs for all study measurements are additional strengths of this study. Other strengths include adjusting for traditional risk factors for CVD such as physical activity, BP, total and HDL cholesterol, BMI, and waist circumference.

CONCLUSIONS

We found a significant association between occupational category and endothelial function; blue-collar workers had slightly worse endothelial function, whereas workers in management/professional and services groups had slightly better endothelial function. Our results suggest that alterations of endothelial function may be one of the pathways linking occupational categories to FMD.

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TABLE 4. Mean Values of Brachial FMD (%) by Four Occupational Categories, Stratified by Sex*

	Occupational Categories				
	Management /Professional	**Sales/Office**	**Services**	**Blue-Collar**	***P*†**
Women	***n* = 288**	***n* = 185**	***n* = 139**	***n* = 55**	
Model 1‡	5.77 ± 0.21	5.75 ± 0.27	4.90 ± 0.24	4.23 ± 0.36	<0.001
Model 2§	5.76 ± 0.20	5.92 ± 0.26	4.91 ± 0.24	4.39 ± 0.32	<0.001
Model 3‖	5.71 ± 0.22	5.82 ± 0.26	5.17 ± 0.26	4.28 ± 0.35	0.002
Model 4¶#	5.73 ± 0.34	5.83 ± 0.40	5.21 ± 0.40	4.27 ± 0.44	0.002
Men	***n* = 434**	***n* = 109**	***n* = 110**	***n* = 179**	
Model 1‡	4.31 ± 0.12	4.41 ± 0.24	4.40 ± 0.27	3.88 ± 0.19	0.176
Model 2§	4.40 ± 0.12	4.41 ± 0.23	4.37 ± 0.26	3.83 ± 0.18	0.042
Model 3‖	4.32 ± 0.13	4.43 ± 0.23	4.53 ± 0.28	3.87 ± 0.20	0.092
Model 4¶**	4.32 ± 0.28	4.41 ± 0.33	4.48 ± 0.40	3.83 ± 0.33	0.087

*Results are mean ± SEM.
†*P* values were obtained from the analysis of variance/analysis of covariance models.
‡Model 1: Unadjusted.
§Model 2: Adjusted for age.
‖Model 3: Adjusted for age, race/ethnicity, educational level, waist circumference, high-density lipoprotein cholesterol, and total cholesterol.
¶Model 4: Adjusted for age, race/ethnicity, educational level, waist circumference, high-density lipoprotein cholesterol, total cholesterol, BMI, diastolic blood pressure, systolic blood pressure, physical activity, smoking status, and pack-years of smoking.
#Model 4 (women):
Management/professional versus sales/office: $P = 0.993$.
Management/professional versus services: $P = 0.513$.
Management/professional versus blue-collar: $P = 0.008$.
Services versus sales/office: $P = 0.320$.
Services versus blue-collar: $P = 0.100$.
Sales/office versus blue-collar: $P = 0.001$.
**Model 4 (men):
Management/professional versus sales/office: $P = 0.989$.
Management/professional versus services: $P = 0.969$.
Management/professional versus blue-collar: $P = 0.257$.
Services versus sales/office: $P = 0.997$.
Services versus blue-collar: $P = 0.165$.
Sales/office versus blue-collar: $P = 0.209$.
Interaction by sex ($P = 0.031$) in the association between FMD% and occupational categories.

manuscript has been reviewed by the MESA investigators for scientific content, and consistency of data interpretation with previous MESA publications and significant comments have been incorporated prior to submission for publication. We thank the other MESA investigators, staff, and study participants for their contribution. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

REFERENCES

1. Gonzalez MA, Selwyn AP. Endothelial function, inflammation, and prognosis in cardiovascular disease. *Am J Med*. 2003;115(suppl 8A):99S–106S.
2. Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol*. 2003;42:1149–1160.
3. Gupta AK, Ravussin E, Johannsen DL, Stull AJ, Cefalu WT, Johnson WD. Endothelial dysfunction: an early cardiovascular risk marker in asymptomatic obese individuals with prediabetes. *Br J Med Med Res*. 2012;2:413–423.
4. Toda N, Tanabe S, Nakanishi S. Nitric oxide-mediated coronary flow regulation in patients with coronary artery disease: recent advances. *Int J Angiol*. 2011;20:121–134.
5. Yeboah J, Folsom AR, Burke GL, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation*. 2009;120:502–509.
6. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol*. 2002;39:257–265.
7. Kapuku GK, Harshfield GA, Davis HC, Treiber FA. Early markers of cardiovascular disease. *Vascul Pharmacol*. 2006;45:277–280.
8. Hart JE, Garshick E, Smith TJ, Davis ME, Laden F. Ischaemic heart disease mortality and years of work in trucking industry workers. *Occup Environ Med*. 2013;70:523–528.
9. Jeong I, Rhie J, Kim I, et al. Working hours and cardiovascular disease in Korean workers: a case-control study. *J Occup Health*. 2014;55:385–391.
10. Shin SY, Lee CG, Song HS, et al. Cardiovascular disease risk of bus drivers in a city of Korea. *Ann Occup Environ Med*. 2013;25:34.
11. Cooper DC, Milic MS, Mills PJ, Bardwell WA, Ziegler MG, Dimsdale JE. Endothelial function: the impact of objective and subjective socioeconomic status on flow-mediated dilation. *Ann Behav Med*. 2010;39:222–231.
12. Amir O, Alroy S, Schliamser JE, et al. Brachial artery endothelial function in residents and fellows working night shifts. *Am J Cardiol*. 2004;93:947–949.
13. Kubo T, Fukuda S, Hirata K, et al. Comparison of coronary microcirculation in female nurses after day-time versus night-time shifts. *Am J Cardiol*. 2011;108:1665–1668.
14. Suessenbacher A, Potocnik M, Dorler Je, et al. Comparison of peripheral endothelial function in shift versus nonshift workers. *Am J Cardiol*. 2011;107:945–948.
15. Holtermann A, Mortensen OS, Burr H, Sogaard K, Gyntelberg F, Suadicani P. Long work hours and physical fitness: 30-year risk of ischaemic heart disease and all-cause mortality among middle-aged Caucasian men. *Heart*. 2010;96:1638–1644.
16. Kang MY, Park H, Seo JC, et al. Long working hours and cardiovascular disease: a meta-analysis of epidemiologic studies. *J Occup Environ Med*. 2012;54:532–537.
17. Kivimaki M, Batty GD, Hamer M, et al. Using additional information on working hours to predict coronary heart disease: a cohort study. *Ann Intern Med*. 2011;154:457–463.
18. Tuchsen F, Hannerz H, Spangenberg S. Mortality and morbidity among bridge and tunnel construction workers who worked long hours and long

days constructing the Great Belt Fixed Link. *Scand J Work Environ Health*. 2005;31(suppl 2):22–26.

19. Virtanen M, Ferrie JE, Singh-Manoux A, et al. Overtime work and incident coronary heart disease: the Whitehall II prospective cohort study. *Eur Heart J*. 2010;31:1737–1744.
20. Yang H, Schnall PL, Jauregui M, Su TC, Baker D. Work hours and self-reported hypertension among working people in California. *Hypertension*. 2006;48:744–750.
21. Bosma H, Marmot MG, Hemingway H, Nicholson AC, Brunner E, Stansfeld SA. Low job control and risk of coronary heart disease in Whitehall II (prospective cohort) study. *BMJ*. 1997;314:558–565.
22. Emeny RT, Zierer A, Lacruz ME, et al. Job strain-associated inflammatory burden and long-term risk of coronary events: findings from the MONICA/KORA Augsburg case-cohort study. *Psychosom Med*. 2013;75:317–325.
23. Kivimaki M, Nyberg ST, Batty GD, et al. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet*. 2012;380:1491–1497.
24. Slopen N, Glynn RJ, Buring JE, Lewis TT, Williams DR, Albert MA. Job strain, job insecurity, and incident cardiovascular disease in the Women's Health Study: results from a 10-year prospective study. *PLoS One*. 2012;7:e40512.
25. Landsbergis PA, Dobson M, Koutsouras G, Schnall P. Job strain and ambulatory blood pressure: a meta-analysis and systematic review. *Am J Public Health*. 2013;103:e61–e71.
26. Quyyumi AA, Patel RS. Endothelial dysfunction and hypertension: cause or effect? *Hypertension*. 2010;55:1092–1094.
27. Adler NE, Rehkopf DH. U.S. disparities in health: descriptions, causes, and mechanisms. *Annu Rev Public Health*. 2008;29:235–252.
28. Kalinowski L, Dobrucki IT, Malinski T. Race-specific differences in endothelial function: predisposition of African Americans to vascular diseases. *Circulation*. 2004;109:2511–2517.
29. Skaug EA, Aspenes ST, Oldervoll L, et al. Age and gender differences of endothelial function in 4739 healthy adults: the HUNT3 Fitness Study. *Eur J Prev Cardiol*. 2013;20:531–540.
30. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol*. 2002;156:871–881.
31. Fujishiro K, Diez Roux AV, Landsbergis P, et al. Associations of occupation, job control and job demands with intima-media thickness: the Multi-Ethnic Study of Atherosclerosis (MESA). *Occup Environ Med*. 2011;68: 319–326.
32. 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.
33. Theorell T, Karasek RA, Eneroth P. Job strain variations in relation to plasma testosterone fluctuations in working men—a longitudinal-study. *J Int Med*. 1990;227:31–36.
34. Nguyen TT, Islam FM, Farouque HM, et al. Retinal vascular caliber and brachial flow-mediated dilation: the Multi-Ethnic Study of Atherosclerosis. *Stroke*. 2010;41:1343–1348.
35. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
36. Bertoni AG, Whitt-Glover MC, Chung H, et al. The association between physical activity and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2009;169:444–454.
37. SAS. *SAS/STAT 9.2 User's Guide*. Cary, NC: SAS Institute Inc; 2008.
38. Hemingway H, Shipley M, Mullen MJ, et al. Social and psychosocial influences on inflammatory markers and vascular function in civil servants (the Whitehall II study). *Am J Cardiol*. 2003;92:984–987.
39. Virtanen M, Heikkila K, Jokela M, et al. Long working hours and coronary heart disease: a systematic review and meta-analysis. *Am J Epidemiol*. 2012;176:586–596.
40. Charles LE, Fekedulegn D, Burchfiel CM, et al. Associations of work hours with carotid intima-media thickness and ankle-brachial index: the Multi-Ethnic Study of Atherosclerosis (MESA). *Occup Environ Med*. 2012;69: 713–720.
41. Mausbach BT, Chattillion E, Roepke SK, et al. A longitudinal analysis of the relations among stress, depressive symptoms, leisure satisfaction, and endothelial function in caregivers. *Health Psychol*. 2012;31: 433–440.
42. Pahkala K, Heinonen OJ, Simell O, et al. Association of physical activity with vascular endothelial function and intima-media thickness. *Circulation*. 2011;124:1956–1963.
43. Siasos G, Chrysohoou C, Tousoulis D, et al. The impact of physical activity on endothelial function in middle-aged and elderly subjects: the Ikaria study. *Hellenic J Cardiol*. 2013;54:94–101.