**Effect of Physical Activity on the Relation between Psychosocial Factors and
Cardiovascular Events (From the Multi-Ethnic Study of Atherosclerosis [MESA])**

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Abstract

Depression, chronic stress and low levels of social support have known associations with cardiovascular disease (CVD). Physical activity has been shown to promote psychological health, reduce the frequency of depressive symptoms and is associated with fewer cardiovascular events in depressed subjects with known CVD. The purpose of the present study was to test the hypothesis that physical activity attenuates the association between psychosocial factors and incident CVD. The MESA cohort includes 6,814 participants free of clinical CVD at baseline. Complete data on physical activity were available for 6,795 subjects (mean age 62 years; 47% male). Psychosocial factors were assessed using standardized questionnaires. Cox proportional hazard models were used to evaluate the association between psychosocial factors and CVD events, and its modulation by physical activity. In models adjusted for age, gender and race/ethnicity, both depression and chronic burden were associated with CVD events [HR=1.38 (1.04-1.84), $p=0.028$ for depression; HR=1.15 (1.05-1.24), $p=0.001$ for chronic burden]. Adjusting for physical activity, the relationship between depression, chronic burden and CVD events was not significantly reduced [HR=1.35 (1.02-1.80), $p=0.039$ for depression; HR=1.14 (1.05-1.23), $p=0.001$ for chronic burden]. Although physical activity is an important component of physical and psychological health and well-being, it did not significantly attenuate the strong relationship between depression or chronic burden and incident CVD.

Key words: psychosocial factors, physical activity, cardiovascular disease

Introduction

Psychosocial factors such as depression, chronic stress and low levels of social support have known associations with cardiovascular disease outcomes (1). Pathophysiologic mechanisms linking psychosocial dysfunction with elevated CVD risk include vascular inflammation, platelet activation and autonomic dysfunction (2). Depression, perceived stress and anxiety have also been associated with a variety of negative health behaviors such as poor diet, physical inactivity and smoking (3-4). Health behaviors have also been shown to mediate the association between psychosocial factors and CVD events. In over 4,000 patients with established coronary heart disease, Ye and colleagues observed a significant association between depressive symptoms and subsequent myocardial infarction. This relationship, however, became non-significant after adjusting for negative health behaviors (5). Health promoting behaviors, such as leisure-time physical activity, are known to be cardio-protective and inversely associated with cardiovascular events (6). Among adults with depression, physical activity interventions have been shown to significantly reduce the burden of depressive symptoms in patients with baseline CVD (7). Studies have also demonstrated a positive “buffering” effect of exercise on stress-induced blood pressure changes and telomere length (8-9). The extent to which participation in physical activity attenuates the association between negative psychosocial factors and subsequent CVD has not been well-defined. Thus, the purpose of the present study is to test the hypothesis that physical activity attenuates the association between psychosocial factors and incident CVD events in a large, ethnically diverse population without baseline CVD.

Methods

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal, population-based study of 6,814 men and women, initially free of clinical cardiovascular disease, aged 45-84 years

at baseline, and recruited from 6 field centers: Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN. Specific racial/ethnic groups enrolled included non-Hispanic white/Caucasian, Black/African American, Hispanic and Chinese-American. Approximately 50% of the participants enrolled were female. The baseline visit took place between July 2000 and September 2002. MESA was approved by institutional review boards at each site, and all participants gave written informed consent. The details of the MESA study design and recruitment strategy have been described in detail previously (10).

Information was obtained by questionnaire at the baseline exam in 2000-2002 regarding age, sex, race/ethnicity, medical history, and medication use. Current smoking was defined as having smoked in the last 30 days, whereas former smoker was defined as an individual who is not currently smoking but had smoked ≥ 100 cigarettes in his or her lifetime. Diabetes was defined as a fasting glucose ≥ 126 mg/dL or on hypoglycemic medication. Use of antihypertensive and other medications was based on clinic staff entry of prescribed medications. Resting blood pressure was measured 3 times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL), and the average of the second and third readings was recorded. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of medications together with a self-reported diagnosis of high blood pressure. Total and high-density lipoprotein cholesterol and triglyceride levels were measured from blood samples obtained after a 12-hour fast. Low-density lipoprotein cholesterol was calculated with the Friedewald equation (11).

Psychosocial factors were assessed using standardized questionnaires which were available in English, Spanish or Chinese. The presence of depressive symptoms was assessed by the Center for Epidemiologic Studies – Depression Scale (CES-D) (12). Scores range from 0-60,

with higher scores indicating higher levels of depressive symptoms. Scores were dichotomized into < 16 and ≥ 16 . Any depression was considered to be present if the CES-D score was ≥ 16 , while participants with CES-D scores ≥ 27 were considered to have moderate-severe depression (13). Those who used anti-depressant medication and were not previously designated as depressed by their CES-D score were also considered to have depression, and this was assessed by the standard MESA medication inventory.

Chronic burden was assessed using the chronic burden scale which measures ongoing difficulty in five life domains (personal health, health of a close contact, job, finances, and relationships) lasting greater than six months (14). Scores range from 0-5 with higher scores reflecting greater degrees of chronic burden. Moderate chronic burden was defined as the presence of three or more life stressors lasting at least six months in duration.

Social support was assessed using the ENRICH Social Support Inventory (ESSI) which consists of six questions pertaining to the availability of emotional support (scores range from 6-30; Cronbach's alpha 0.87) (15). Higher scores reflect greater availability of emotional support. A score of ≤ 12 was consistent with low levels of social support (16).

Race/ethnicity was characterized using participant responses to questions based on the 2000 U.S. Census. Family annual income and education were obtained from the baseline MESA questionnaire and categorized using the following categories: for income, $< \$20,000$, $\$20,000$ - $\$49,000$ and $\geq \$50,000$, and for education, less than high school, completed high school, technical school certificate or associate degree and completed college or more.

Self-reported physical activity was obtained at baseline exam 1 using the MESA Typical Week Physical Activity Survey which assesses the time spent in and frequency of various physical activities over the past month (17). Metabolic equivalents (METs) were assigned to

each physical activity, and the total MET-minutes per week of physical activity was determined for each participant. Additional categories of physical activity were created, including intentional physical activity which includes the sum of walking for exercise, sports, dancing and other conditioning activities that are typically associated with physical activity guidelines. For analysis purposes, the log of intentional physical activity was used.

At the time of analysis, the cohort had been followed for incident CVD events for a median of 10 years. At intervals of 9-12 months, a telephone interviewer contacted each participant to inquire about interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. Trained personnel abstracted medical records suggesting possible cardiovascular events. Two physicians independently classified the events and assigned incidence dates. If, after review and adjudication, disagreements persisted, a full mortality and morbidity review committee made the final classification. For the purposes of this study, we used all CVD events as the endpoint. Specifically, the endpoint included myocardial infarction, CHD death, resuscitated cardiac arrest, angina, stroke, stroke death, or other CVD death for total CVD events.

Baseline descriptive statistics were reported as means and standard deviations for continuous variables and frequencies and percentages for discrete variables. Unadjusted comparisons were tested using the chi squared test and one-way ANOVA. Cox proportional hazard models for CVD events were used to estimate the hazard ratios of the groups defined by psychosocial variables while adjusting for potential confounders. Model 1 adjusted for age, gender, and race. Model 2 further adjusted for education level, income level, smoking, systolic blood pressure, cholesterol (total and high-density), diabetes, body mass index and medication use (aspirin, statin and anti-hypertensive). We also tested for two-way interactions between

categories of physical activity and depression, chronic burden and social support, after fully adjusting as in Model 2. The proportional hazards assumption was evaluated by testing Schoenfeld's residuals. Statistical significance was set at a two-sided $p < 0.05$. Analyses were performed in Stata version 11.2 (StataCorp LP, College Station, TX).

Results

A total of 6,795 subjects had complete data on physical activity at baseline (exam 1), thus comprising the study cohort for this analysis (mean age 62 years, 47% male). The prevalence of depression and/or antidepressant medication use was 18.4%, of moderate or greater chronic burden 12.2%, and of low social support 3.9%. Tables 1A and 1B show the characteristics of the study participants at MESA exam 1 according to the presence or absence of depression, chronic burden and social support. Psychosocial factors were found to be negatively although weakly correlated with physical activity ($r = -0.046$, $p < 0.001$ for physical activity and any depression; $r = -0.029$, $p = 0.017$ for physical activity and chronic burden; $r = -0.039$, $p = 0.001$ for physical activity and low social support).

Over a median follow-up period of 10 years there were 499 CVD events. Figures 1 and 2 show cumulative risk of incident CVD among participants with any or moderate/severe depression, chronic burden and low social support respectively, adjusted for mean age and log of physical activity. In multivariate adjusted models, negative psychosocial factors were associated with CVD events, except low social support, while higher physical activity level was inversely associated with CVD events (Table 2).

As shown in Table 3, physical activity level did not attenuate the association between moderate/severe depression, chronic burden and CVD events. All tests for interactions between physical activity and each psychosocial variable were non-significant.

Discussion

The main finding in our study was that higher level of physical activity, although associated with lower risk of incident CVD, did not attenuate the associations between negative psychosocial factors, specifically depression and chronic burden, and CVD events.

Physical activity has been shown to be an effective treatment strategy for depression in subjects with and without baseline CVD. Dunn et al. observed a 47% reduction in the Hamilton Rating Scale for Depression in subjects randomized to moderate physical activity (18). Among subjects with baseline CVD, Blumenthal et al. observed significant reductions in depressive symptoms among participants in the UPBEAT trial randomized to 4 months of moderate-intensity aerobic exercise (7). Of note, individuals in the exercise arm experienced reductions in depressive symptoms similar to that of medical therapy with sertraline, as well as greater improvements in heart rate variability. Finally, in a meta-analysis of 28 studies, physical activity was found to be associated with a 33% reduction in depressive symptoms (19). Despite this consistent body of literature, few studies to date have investigated the relationship between depression, physical activity and CVD outcomes. In the Heart and Soul Study, CVD events were substantially higher in those with depression, but adjustment for physical activity largely accounted for this association (20). That study sampled patients with stable CHD, while MESA excluded patients with clinical CVD at baseline, which may be a possible explanation for the difference between that study and our findings. Conversely, when physical activity was examined as a risk-reducing strategy, Blumenthal and colleagues observed a 38% reduction in mortality and a 28% reduction in non-fatal MI among subjects in the ENRICHD Trial who engaged in regular physical activity (21). More recently, Al Mheid et al. observed significant attenuating effects of regular physical activity on subclinical vascular disease biomarkers among

subjects with depressive symptoms (22). However, these studies did not directly examine effect modification by exercise level of the relationship between depression and CVD risk.

Chronic burden, a measure of chronic stress, was directly associated with incident CVD. These findings are consistent with the literature which have shown strong associations between chronic psychological stress and CVD events (23), often mediated by physical inactivity (24). Conversely, in a meta-analysis of studies involving individuals participating in acute or chronic exercise activities, Petruzzello and colleagues found a significant buffering effect of exercise on anxiety-related symptoms (25). In the MESA study physical activity, although protective, did not attenuate the relationship between chronic burden and CVD events.

Although low levels of social support have been consistently associated with a variety of health outcomes, including vascular inflammation (16) and mortality (1), we did not observe any direct association between low levels of social support and CVD events in the MESA study. However, only 4% of the MESA cohort were categorized as having low levels of social support.

Conditions such as depression and chronic stress have been associated with a variety of pathophysiologic responses, including shortened telomere length (9), decreased hippocampal volume and impaired memory (26), increased inflammatory markers, endothelial dysfunction and heightened sympathetic tone (2). Conversely, exercise has been found to promote memory (27), enhance coping and levels of perceived stress (28-29), have anti-inflammatory effects, improve vascular health and promote heart rate variability (30-31). Given these biological effects, it is possible that only higher levels of physical activity induce these positive physiological changes, and therefore modify the relationship between depression, chronic burden

and CVD events. Furthermore, perhaps the risk-reducing effects of physical activity are more pronounced and effective among populations with baseline CVD.

Although our study is among the first to report the associations of physical activity, psychosocial factors and incident CVD in adults without baseline CVD, it is not without limitations. First, our study is observational in nature and as such we are unable to make causal inferences based on study findings alone. Second, although we controlled for the baseline use of medications in our multivariate models, we were not able to account for other possible interventions over the study period which could have positively impacted disease severity, and therefore outcomes. Third, physical activity measures were self-reported in MESA. Self-reported measures of physical activity are prone to recall as well as social desirability bias, both of which could over estimate amounts of physical activity (32).

Increasing evidence supports a relationship between psychosocial factors such as depression, chronic stress, low social support and CVD events. We observed in a large, multi-ethnic population that physical activity, although protective, did not attenuate the association between depression, chronic burden and incident CVD. Additional research is needed to further characterize the impact of physical activity interventions on health outcomes among individuals with depression and chronic burden.

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Figure titles and legends

Figure 1. Kaplan-Meier survival estimates by depression status adjusted for mean age and log of physical activity
CVD: cardiovascular disease

Figure 2. Kaplan-Meier survival estimates by chronic burden and social support status adjusted for mean age and log of physical activity
CVD: cardiovascular disease

Table 1A. Baseline demographics by depression categories

Variable	Any Depression			Moderate/Severe Depression		
	N (%) or Mean $\pm$ SD		p-value	N (%) or Mean $\pm$ SD		p-value
	0 (n=5537)	+ (n=1244)		0 (n=6096)	+ (n=685)	
Age (years)	62.4 $\pm$ 10.2	61.0 $\pm$ 10.4	< 0.001	62.4 $\pm$ 10.2	60.1 $\pm$ 10.0	< 0.001
Male	2810 (51%)	386 (31%)	< 0.001	2997 (49%)	199 (29%)	< 0.001
Ethnicity			< 0.001			< 0.001
European American	2084 (38%)	524 (42%)		2244 (37%)	364 (53%)	
Chinese American	721 (13%)	83 (7%)		768 (13%)	36 (5%)	
African American	1600 (29%)	273 (22%)		1749 (29%)	124 (18%)	
Hispanic American	1132 (20%)	364 (29%)		1335 (22%)	161 (24%)	
Education Level (% > HS ^a degree)	3599 (65%)	721 (58%)	< 0.001	3871 (64%)	449 (66%)	0.260
Income Level (% High Income ^b)	2225 (42%)	360 (30%)	< 0.001	2348 (40%)	237 (36%)	0.025
Smoker			0.001			0.001
Never	2806 (51%)	604 (49%)		3103 (51%)	307 (45%)	
Former	2044 (37%)	437 (35%)		2223 (37%)	258 (38%)	
Current	683 (12%)	201 (16%)		766 (13%)	118 (17%)	
Systolic Blood Pressure (mmHg)	126.6 $\pm$ 21.3	126.2 $\pm$ 22.3	0.576	126.8 $\pm$ 21.5	124.3 $\pm$ 20.9	0.004
Total Cholesterol (mg/dL)	193.8 $\pm$ 35.5	195.8 $\pm$ 36.9	0.078	193.9 $\pm$ 35.6	196.6 $\pm$ 36.7	0.062
HDL Cholesterol (mg/dL)	50.5 $\pm$ 14.7	52.7 $\pm$ 15.1	< 0.001	50.7 $\pm$ 14.8	53.0 $\pm$ 14.9	< 0.001
Body Mass Index (kg/M ²)	28.2 $\pm$ 5.4	29.0 $\pm$ 5.9	< 0.001	28.2 $\pm$ 5.4	29.3 $\pm$ 6.1	< 0.001
Diabetes Mellitus	673 (12%)	182 (15%)	0.016	764 (13%)	91 (13%)	0.557
Aspirin	1398 (25%)	296 (24%)	0.288	1520 (25%)	174 (25%)	0.796
Statin	884 (16%)	213 (17%)	0.319	958 (16%)	139 (20%)	0.002
Hypertension medication	2024 (37%)	496 (40%)	0.029	2243 (37%)	277 (40%)	0.062
Anti-depressant medication	0 (0%)	500 (40%)	< 0.001	0 (0%)	500 (73%)	< 0.001
Physical Activity ^c	1574 $\pm$ 2355	1478 $\pm$ 2287	0.196	1560 $\pm$ 2344	1520 $\pm$ 2328	0.670

^a High school^b High income is defined as at least \$50,000 total gross family income.^c Intentional physical activity is analyzed.

Table 1B. Baseline demographics by psychosocial factor levels

	Chronic Burden N (%) or Mean $\pm$ SD				Low Social Support N (%) or Mean $\pm$ SD		
	0 (n=2583)	1-2 (n=3282)	3 or more (n=818)	p-value	0 (n=6506)	+ (n=262)	p-value
Age (years)	63.4 $\pm$ 10.0	62.1 $\pm$ 10.3	58.0 $\pm$ 9.5	< 0.001	62.1 $\pm$ 10.2	62.2 $\pm$ 10.4	0.893
Male	1388 (54%)	1467 (45%)	305 (37%)	< 0.001	3073 (47%)	116 (44%)	0.347
Ethnicity				< 0.001			0.416
European American	923 (36%)	1347 (41%)	312 (38%)		2505 (39%)	98 (37%)	
Chinese American	459 (18%)	291 (9%)	51 (6%)		779 (12%)	25 (10%)	
African American	641 (25%)	912 (28%)	276 (34%)		1795 (28%)	72 (28%)	
Hispanic American	560 (22%)	732 (22%)	179 (22%)		1427 (22%)	67 (26%)	
Education Level (% > HS ^a degree)	1572 (61%)	2122 (65%)	564 (69%)	< 0.001	4160 (64%)	153 (58%)	0.065
Income Level (% High Income ^b)	995 (40%)	1288 (41%)	278 (35%)	0.006	2523 (40%)	56 (22%)	< 0.001
Smoker				< 0.001			0.056
Never	1367 (53%)	1606 (49%)	386 (47%)		3287 (51%)	118 (45%)	
Former	930 (36%)	1244 (38%)	272 (33%)		2377 (37%)	98 (37%)	
Current	284 (11%)	430 (13%)	160 (20%)		838 (13%)	46 (18%)	
Systolic Blood Pressure (mmHg)	127.2 $\pm$ 21.2	126.4 $\pm$ 21.5	124.8 $\pm$ 22.0	0.026	126.6 $\pm$ 21.5	124.8 $\pm$ 20.1	0.186
Total Cholesterol (mg/dL)	193.4 $\pm$ 34.5	194.6 $\pm$ 36.3	195.5 $\pm$ 37.0	0.261	194.1 $\pm$ 35.7	195.2 $\pm$ 36.6	0.641
HDL Cholesterol (mg/dL)	50.2 $\pm$ 14.6	51.4 $\pm$ 14.9	51.3 $\pm$ 15.1	0.008	50.9 $\pm$ 14.8	51.1 $\pm$ 14.4	0.833
Body Mass Index (kg/M ²)	27.6 $\pm$ 4.9	28.5 $\pm$ 5.6	29.7 $\pm$ 6.0	< 0.001	28.3 $\pm$ 5.5	28.4 $\pm$ 5.7	0.748
Diabetes Mellitus	271 (11%)	445 (14%)	128 (16%)	< 0.001	820 (13%)	32 (12%)	0.853
Aspirin	674 (26%)	821 (25%)	176 (22%)	0.032	1628 (25%)	63 (24%)	0.732
Statin	439 (17%)	524 (16%)	118 (14%)	0.199	1060 (16%)	35 (13%)	0.205
Hypertension medication	946 (37%)	1207 (37%)	328 (40%)	0.172	2399 (37%)	112 (43%)	0.054
Anti-depressant medication	103 (4%)	278 (9%)	110 (14%)	< 0.001	467 (7%)	29 (11%)	0.017
Physical Activity ^c	1597 $\pm$ 2289	1522 $\pm$ 2340	1553 $\pm$ 2494	0.480	1557 $\pm$ 2340	1541 $\pm$ 2450	0.913

^a High school

^b High income is defined as at least \$50,000 total gross family income.

^c Intentional physical activity is analyzed.

Table 2. Relationship between each psychosocial or physical activity variable and cardiovascular events

	Model 1			Model 2		
	HR	95% CI	p-value	HR	95% CI	p-value
Any Depression	1.36	1.08-1.70	0.008	1.25	0.99-1.57	0.061
Moderate/Severe Depression	1.38	1.04-1.84	0.028	1.34	1.00-1.80	0.047
Chronic Burden	1.15	1.05-1.24	0.001	1.10	1.01-1.20	0.023
Low Social Support	1.32	0.87-2.00	0.197	1.36	0.88-2.09	0.164
Physical Activity (log)	0.94	0.92-0.97	<0.001	0.96	0.94-0.99	0.008

Model 1 adjusted for age, gender, and race.

Model 2 further adjusted for education level, income level, smoking, systolic blood pressure, cholesterol (total and HDL), diabetes, body mass index and medication use (aspirin, statin, anti-hypertensive).

CVD = cardiovascular disease. CI = confidence interval. HR = hazard ratio.

Table 3. Relationship between cardiovascular events, physical activity, and each psychosocial variable

	Model 1			Model 2		
	HR	95% CI	p-value	HR	95% CI	p-value
Any Depression	1.33	1.07-1.67	0.012	1.24	0.98-1.56	0.068
Physical Activity (log)	0.95	0.92-0.97	<0.001	0.96	0.94-0.99	0.009
Moderate/Severe Depression	1.35	1.02-1.80	0.039	1.34	1.00-1.79	0.052
Physical Activity (log)	0.95	0.92-0.97	<0.001	0.96	0.94-0.99	0.009
Chronic Burden	1.14	1.05-1.23	0.001	1.10	1.01-1.19	0.028
Physical Activity (log)	0.95	0.92-0.97	<0.001	0.96	0.94-0.99	0.014
Low Social Support	1.26	0.83-1.92	0.281	1.32	0.86-2.03	0.211
Physical Activity (log)	0.94	0.92-0.97	<0.001	0.96	0.93-0.99	0.005

Model 1 adjusted for age, gender, and race.

Model 2 further adjusted for education level, income level, smoking, systolic blood pressure, cholesterol (total and HDL), diabetes, body mass index and medication use (aspirin, statin, anti-hypertensive).

CVD = cardiovascular disease. CI = confidence interval. HR = hazard ratio.

Figure 1

Figure 1: Kaplan-Meier survival estimates by depression status adjusted for mean age and log of physical activity

Figure 2

Figure 2: Kaplan-Meier survival estimates by burden status adjusted for mean age and log of physical activity