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Effect of Physical Activity Level on Biomarkers of Inflammation and Insulin Resistance Over 5 Years in Outpatients with Coronary Heart Disease (*From the Heart and Soul Study*)

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Abstract

Higher levels of physical activity are associated with lower rates of coronary heart disease (CHD). Prior studies suggest this is partly due to lower levels of inflammation and insulin resistance. We sought to determine whether physical activity level was associated with inflammation or insulin resistance during a 5-year period in outpatients with known CHD. We evaluated 656 participants from the Heart and Soul Study, a prospective cohort study of outpatients with documented CHD. Self-reported physical activity frequency was assessed at baseline and after 5 years of follow-up. Participants were classified as low versus high activity at each visit, yielding 4 physical activity groups: stable low activity, decreasing activity (high at baseline to low at Year 5), increasing activity (low at baseline to high at Year 5), and stable high activity. We compared Year 5 markers of inflammation (C-reactive protein [CRP], interleukin-6, and fibrinogen) and insulin resistance (insulin, glucose, and A1c) across the 4 activity groups. After 5-years of follow-up, higher activity was associated with lower mean levels of all biomarkers. In the fully adjusted regression models CRP, interleukin-6, and glucose remained independently associated with physical activity frequency (log CRP p-trend across activity groups = 0.03; log interleukin-6 p-trend = 0.01; log glucose p-trend = 0.003). Individuals with Stable High Activity typically had the lowest levels of biomarkers. In conclusion, in this novel population of outpatients with known CHD followed for 5 years, higher physical activity frequency was independently associated with lower levels of CRP, interleukin-6, and glucose.

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Keywords

Physical Activity; Coronary Heart Disease; Inflammation; Insulin Resistance

Introduction

To date, most studies examining the effect of physical activity on inflammation or insulin resistance have been limited by cross-sectional design or short duration. One exception is a prospective study of British adults aged 35-55, which found that regular physical activity was associated with lower inflammation over a 10-year interval.[1] However, it is unclear whether the results from this younger sample apply to patients with existing CHD. Patients with CHD may be less likely to participate in more vigorous physical activity, which may attenuate the effect of physical activity on biomarker levels. In addition, medications such as statins, which are highly prevalent among patients with CHD, may decrease baseline levels of inflammation. Understanding the effects of physical activity on inflammation and insulin resistance in CHD patients is important as this population is at greatest cardiovascular risk and most likely to benefit from preventive interventions. Therefore, we conducted a prospective cohort study of outpatients with existing CHD to examine profiles of 5-year change in physical activity as predictors of inflammation and insulin resistance.

Methods

Participants were enrolled in the Heart and Soul Study, a cohort of outpatients with known CHD recruited between 2000 and 2002 from the San Francisco VA Medical Center, VA Palo Alto Health Care System, the University of California, San Francisco Medical Center, and 9 public health clinics in the Community Health Network of San Francisco, California.[2] A total of 1024 participants were enrolled in the original cohort. Eligible participants had documented CHD, defined as a history of myocardial infarction, coronary revascularization, angiographic evidence of at least a 50% stenosis in 1 or more coronary vessels, or evidence of exercise-induced ischemia on a prior treadmill or nuclear stress test. Participants were excluded if they reported a myocardial infarction in the previous 6 months, were unable to walk 1 block, or were planning to move out of the local area within 3 years. Participants attended a baseline examination, which included a fasting blood draw, physical examination, questionnaires, echocardiogram, and maximal exercise treadmill test. At 5 years, 667 participants (80% of the 829 survivors) completed a 5-year follow-up examination that repeated the baseline protocol, including a fasting blood draw. The current study was limited to 656 participants who had physical activity and biomarker assessments from both time points. The study was approved by the appropriate institutional review boards and all participants provided informed consent prior to enrollment.

Physical activity frequency was determined by self-report using the question, “Which of the following statements best describes how physically active you have been during the last month, that is, done activities such as 15-20 minutes of brisk walking, swimming, general conditioning, or recreational sports?” Possible responses included: not at all active, a little active (1-2 times per month), fairly active (3-4 times per month), quite active (1-2 times per

week), very active (3-4 times per week), or extremely active (5 or more times per week). Participants who answered “not at all active” or “a little active” were grouped into the Low Activity group, whereas those who reported being “fairly active,” “quite active,” “very active,” and “extremely active” were grouped into the High Activity group. This is consistent with prior classifications of physical activity in this cohort and has been shown to be a strong predictor of incident CHD events.[2] Single-item self-report measures of physical activity have also been shown to be valid and reliable measures of cardiovascular fitness.[3-8] We used data from baseline and Year 5 to categorize participants into 4 groups: (1) Stable Low Activity included participants reporting low activity frequency at baseline and Year 5, (2) Decreasing Activity included those with high activity frequency at baseline and low activity frequency at Year 5, (3) Increasing Activity included those with low activity frequency at baseline and high activity frequency at Year 5, and (4) Stable High Activity included those with high activity frequency at baseline and Year 5.

Using baseline data, we also assessed the extent to which participants engaged in activities of different intensities within the last month for at least 15-20 minutes per episode, such as light-intensity activity (walking at an average pace, sweeping, vacuuming), moderate-intensity activity (brisk walking, lawn mowing, golf, dancing, light cycling), or heavy-intensity activity (swimming laps, basketball, jogging, vigorous cycling, hiking, or weight lifting). Possible responses were “Not at all,” “Less than 1 time per week,” “1-2 times per week,” or “3 or more times per week.”

Blood samples were collected after an overnight fast. High-sensitivity C-reactive protein (CRP) was measured using the Roche Integra assay (Indianapolis, IN, USA) for the first 229 participants or (due to a change in the laboratory) the Beckman Extended Range assay (Galway, Ireland). Results from the two assays were highly correlated ($r = 0.99$) in a sample of 189 participants. The inter-assay coefficient of variation for the Roche Integra assay was 3.2% and 6.7% for the Beckman Extended Range assay. A Quantikine High Sensitivity Immunoassay kit was used to assess interleukin-6 serum concentration (R&D Systems, Minneapolis, MN, USA). The interleukin-6 coefficient of variation ranged from 6.5% to 9.6%. Fibrinogen was measured using the Clauss assay with a coefficient of variation of <3%. Fasting serum samples were used to measure glucose, insulin, hemoglobin A1c, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations. Low-density lipoprotein (LDL) cholesterol concentrations were calculated.[9]

Age, gender, race and ethnicity, smoking status, highest educational achievement, and income level were determined by self-report. Comorbidities were determined by asking if participants had ever received a diagnosis from a list of medical conditions. Blood pressure, height, and weight were measured. Body mass index (BMI) was calculated. All participants were instructed to bring in their current medication bottles for study personnel to record. Physical fitness was assessed by maximal exercise treadmill testing using a standard or modified Bruce protocol to determine maximal exercise capacity in metabolic equivalent tasks (METs).[10] Rest and peak exercise 2-dimensional echocardiograms were obtained. Inducible ischemia was defined as the presence of new wall motion abnormalities at maximum exercise by an expert echocardiographer.

Other covariates were evaluated by self-report. Medication non-adherence was defined as taking medications ≤ 75% of the time. Depressive symptoms were assessed using the 9-item Patient Health Questionnaire (PHQ-9), and standard cut-point of ≥10 points was used to define depression.[11] Posttraumatic Stress Disorder (PTSD) was evaluated using the Computerized Diagnostic Interview Schedule (CDIS) for DSM-IV.[12]

Baseline characteristics were compared among the four physical activity groups using Chi-square tests for categorical variables and t-tests for continuous variables. Biomarkers with abnormal distributions were log-transformed. Multivariate linear regression models were constructed with the 4 categories of physical activity as the independent variable and follow-up (Year 5) inflammatory and insulin resistance biomarkers as the dependent variables. A test for trend was conducted across these models with Stable Low Activity as the reference group, followed by Decreasing Activity, Increasing Activity, and Stable High Activity. Adjustments were made for all variables that differed by physical activity status at $p \leq 0.10$. Smoking was also added to the models ($p = 0.11$) because of the known association with the predictor and the outcomes. Models were adjusted sequentially for baseline biomarker levels (Model 1), then adding gender, education, chronic obstructive pulmonary disease, and aspirin use (Model 2), followed by diabetes, use of any diabetes medications (specifically metformin, insulin, sulfonylureas, and thiazolidinediones), BMI, and smoking (Model 3), and finally depression and PTSD (Model 4). All values entered into the models were baseline values as covariates did not substantially change within activity groups from baseline to Year 5 (see Results). Statistical testing was 2-sided, at a significance level of 0.05. All analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 656 participants were included in the study, with a mean age of 66.1 ± 10.2 years. Sixty percent of participants were white and 83% were male. Baseline characteristics by physical activity group are shown in Table 1. Cardiovascular medication use was similar across groups. Use of diabetes medications differed across activity groups despite a non-significant difference in rates of diabetes. Notably, mean measured exercise capacity corresponded well with self-reported activity status. Reported levels of light, moderate, and heavy-intensity activity at baseline are shown in Supplemental Figure 1. The majority of all activities reported were of light and moderate-intensity. Even among the Stable High Activity group, less than 20% reported engaging in heavy-intensity activity 3 or more times per week. Among the entire cohort, only 73 participants (11%) reported engaging in heavy-intensity activities 3 or more times per week.

Median values of biomarkers at baseline and after 5 years of follow-up in each physical activity group are shown in Table 2. There were significant inverse trends between inflammation and insulin resistance biomarkers and physical activity group at both baseline and 5-year follow-up. Nearly all groups were observed to have decreasing or unchanged levels of biomarkers at 5 years, with the exception of interleukin-6. The groups with the lowest activity had the largest increase in interleukin-6.

The relation between change in physical activity over time and levels of biomarkers at the 5-year follow-up are shown in Tables 3 and 4. Log CRP remained inversely associated with activity level in the fully adjusted model (p-value for trend across activity groups = 0.03, Table 3). Similar results were seen for log interleukin-6 (p-trend = 0.01). Of the markers for insulin resistance, only glucose achieved significance and remained so in the fully adjusted model (p-trend = 0.003; Table 4).

For the covariates adjusted for in the regression analysis, we evaluated for differences in baseline and 5-year follow-up rates within each of the four activity groups. No significant differences were seen in rates of depression, aspirin use, or in BMI between baseline and the 5-year follow-up within any activity group. Differences in other covariates were modest and occurred in a minority of the activity groups. Smoking decreased at 5-year follow up in the Stable High Activity group (13.5% to 10.8%, p=0.03), and rates of diabetes increased in the Decreasing Activity group (29.1% to 37.3%, p = 0.02) and the Stable High Activity group (19.7% to 25.7%, p = <0.001). Higher rates of chronic obstructive pulmonary disease were also reported at the 5-year follow-up in the Decreasing Activity group (20.0% to 25.7%, p = 0.04).

Discussion

In a prospective study of outpatients with known CHD and high rates of statin and aspirin use, higher frequency of physical activity was independently associated with lower levels of CRP, interleukin-6, and glucose at the 5-year follow-up. Overall, levels of vigorous physical activity were low, with few patients reporting participation in moderate or heavy-intensity physical activity 3 or more times per week. These data suggest that even light-intensity activity may be beneficial for reducing or maintaining lower levels of inflammation in a medically complex population.

Our results expand upon prior studies examining the biological impact of physical activity. Using a community-based sample, the Whitehall II cohort study[1] followed more than 4000 apparently healthy middle-aged men and women over 10 years and monitored self-reported adherence to physical activity guidelines and markers of inflammation (i.e. CRP and interleukin-6). They found that the high adherence group had lower log CRP levels and lower log interleukin-6 at follow-up. However, these patients were generally disease-free and were on average almost 20 years younger than our study cohort.

Within our study, patients with greater frequency of physical activity over time had lower mean levels of insulin resistance biomarkers, although associations with insulin and A1c were not significant after adjusting for baseline values. Observations from prior studies have shown that regular physical activity improves insulin resistance through multiple metabolic and vascular processes[13,14] and that these pathways often work in concert to improve an individual's cardiovascular risk. However, observations from obese children have shown that the benefits are short-lived after the cessation of regular physical activity, lasting only weeks to months.[15] This may explain why participants whose physical activity decreased over 5 years had insulin resistance biomarker levels similar to those in the Stable Low Activity group.

In contrast to prior studies, which have shown a rise in inflammatory biomarkers with age, CRP and fibrinogen were lower at follow up in our population.[16] Participants in our study had known CHD, and therapies aimed at reducing their risk of further events could have lowered inflammatory levels. For example, statin trials have shown that CRP declines over time with continued statin therapy,[17] and our findings could reflect the long-term effect of high statin use in our population. It is also possible that statin therapy was intensified during the study period, as the timeline corresponds with updated guidelines recommending more aggressive LDL goals.[18]

Although this is the first study of its kind in outpatients with CHD, there are several limitations that should be considered. First, given that only those participants who survived to the 5-year follow-up were included, our study population may have been healthier than the full baseline cohort, although we would expect this to diminish the variability in inflammation and insulin resistance. Second, physical activity data were self-reported and may have been susceptible to recall or response biases. However, self-reported physical activity has been shown to correspond to objective measures[3,5,7] and it correlated highly with objectively measured physical fitness within this study. Third, this cohort had stable CHD and was predominantly male, thereby limiting generalizability to women and other populations. Finally, dietary patterns have been shown to influence levels of inflammatory biomarkers and risk of incident diabetes,[19,20] but no diet information was obtained in this study. The interaction of diet and physical activity and their effect on biomarkers would be an important topic for future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Outpatients with known CHD were separated into activity categories.
- Participants were followed for 5-years.
- We compared inflammation and insulin resistance at baseline and 5-years.
- Higher activity was associated with lower mean levels of inflammation.
- CRP, interleukin-6, and glucose were inversely associated with activity.

Table 1

Baseline characteristics by 5-year change in physical activity

Variable	Activity				P-value
	Stable Low (N=151)	Decreasing (N=110)	Increasing (N=60)	Stable High (N=335)	
Age, Mean ± SD	65.4 ± 10.4	67.1 ± 10.8	64.7 ± 10.3	66.4 ± 9.8	0.36
Women	31 (21%)	21 (19%)	16 (27%)	44 (13%)	0.03
White	84 (56%)	65 (59%)	35 (58%)	210 (63%)	0.51
Graduated High School	124 (82%)	94 (86%)	48 (81%)	309 (92%)	<0.01
Diabetes Mellitus	41 (27%)	32 (29%)	11 (18%)	66 (20%)	0.09
Congestive Heart Failure	25 (17%)	19 (17%)	7 (12%)	45 (14%)	0.63
Myocardial Infarction	79 (52%)	55 (50%)	28 (47%)	179 (54%)	0.74
Chronic Obstructive Pulmonary Disease	28 (20%)	22 (21%)	8 (14%)	34 (11%)	0.02
Smoker	32 (21%)	23 (21%)	11 (18%)	45 (13%)	0.11
Medication Non-adherence	10 (7%)	10 (9%)	8 (13%)	18 (5%)	0.13
Body Mass Index (kg/m^2), Mean ± SD	30.1 ± 5.9	28.9 ± 5.7	28.3 ± 4.7	27.7 ± 4.3	<0.001
LDL (mg/dL), Mean ± SD	104.6 ± 33.1	106.3 ± 35.6	102.9 ± 32.6	103.6 ± 32.9	0.89
HDL (mg/dL), Mean ± SD	45.3 ± 14.4	46.6 ± 13.5	46.5 ± 16.2	47.1 ± 14.1	0.66
Systolic Blood Pressure (mmHg), Mean ± SD	134.1 ± 21.8	131.2 ± 19.7	136.3 ± 18.6	131.6 ± 20.0	0.26
Diastolic Blood Pressure (mmHg), Mean ± SD	75.1 ± 11.8	73.0 ± 11.7	77.2 ± 10.9	74.9 ± 10.6	0.11
Depression	49 (32%)	18 (16%)	16 (27%)	30 (9%)	<0.001
Posttraumatic Stress Disorder	27 (17.9%)	17 (15.5%)	8 (13.3%)	33 (9.9%)	0.08
Left Ventricular Ejection Fraction <40%	20 (13%)	7 (6%)	5 (8%)	34 (10%)	0.31
Fitness (METs), Mean ± SD	6.5 ± 2.5	6.7 ± 2.8	7.2 ± 3.1	9.1 ± 3.2	<0.001
Inducible Ischemia	30 (21%)	25 (26%)	8 (15%)	56 (17%)	0.248
Aspirin	101 (68%)	87 (80%)	41 (69%)	254 (76%)	0.10
Statins	97 (65%)	76 (70%)	42 (71%)	237 (71%)	0.62
Renin Angiotensin System Inhibitor	80 (54%)	54 (50%)	23 (39%)	173 (52%)	0.26
Beta Blockers	88 (59%)	68 (62%)	34 (58%)	190 (57%)	0.78
* Any Diabetes Medication	35 (23%)	27 (25%)	11 (18%)	42 (13%)	0.01

LDL = low density lipoprotein, HDL = high density lipoprotein, CRP = C-reactive protein

* Includes: sulfonylureas, insulin, metformin, thiazolidinediones

Table 2

Median levels of biomarkers by activity group at baseline and 5-year follow up

Biomarker	Activity				P-value for trend
	Stable Low	Decreasing	Increasing	Stable High	
CRP (mg/L)					
Baseline	3.08	1.75	2.37	1.63	<0.001
Follow-up	2.16	1.93	1.65	1.15	<0.001
5-year change (% change)	-0.92 (-30%)	0.18 (+10%)	-0.72 (-30%)	-0.48 (-29%)	
Interleukin-6 (pg/mL)					
Baseline	2.90	2.44	2.73	2.11	<0.001
Follow-up	4.18	4.23	3.46	2.83	<0.001
5-year change (% change)	1.28 (+44%)	1.79 (+73%)	0.73 (+27%)	0.72 (+34%)	
Fibrinogen (RU/mL)					
Baseline	393	376	389	363	<0.01
Follow-up	382	372	373	357	0.01
5-year change (% change)	-11 (-3%)	-4 (-1%)	-16 (-4%)	-6 (-2%)	
Insulin (pg/mL)					
Baseline	296	286	272	269	0.25
Follow-up	255	250	228	215	0.08
5-year change (% change)	-41 (-14%)	-36 (-13%)	-44 (-16%)	-54 (-20%)	
Glucose (mg/dL)					
Baseline	108	108	107	105	0.23
Follow-up	106	108	102	104	0.01
5-year change (% change)	-2 (-2%)	0 (0)	-5 (-5%)	-1 (-1%)	
Hemoglobin A1c (%)					
Baseline	5.8	5.8	5.7	5.6	0.02
Follow-Up	5.8	5.7	5.6	5.6	0.01
5-year change (% change)	0 (0)	-0.1 (-2%)	-0.1 (-2%)	0 (0)	

CRP = C-reactive protein

Table 3

Differences in Year 5 inflammatory biomarker levels as compared with the stable low group

	Activity			
Variable	**Decreasing**	**Increasing**	**Stable High**	**P-value for trend**
Log CRP		**β (95% CI)**		
Model 1	-0.07 (-0.34, 0.20)	-0.24 (-0.57, 0.08)	-0.25 (-0.46, -0.03)	0.01
Model 2	-0.07 (-0.34, 0.21)	-0.24 (-0.57, 0.09)	-0.24 (-0.46, -0.02)	0.02
Model 3	-0.05 (-0.33, 0.22)	-0.21 (-0.54, 0.13)	-0.24 (-0.46, -0.02)	0.02
Model 4	-0.05 (-0.33, 0.23)	-0.20 (-0.53, 0.14)	-0.23 (-0.46, -0.001)	0.03
Log Interleukin-6		**β (95% CI)**		
Model 1	0.09 (-0.05, 0.24)	-0.08 (-0.25, 0.10)	-0.14 (-0.26, -0.03)	0.003
Model 2	0.08 (-0.07, 0.23)	-0.08 (-0.26, 0.10)	-0.15 (-0.27, -0.03)	0.002
Model 3	0.08 (-0.06, 0.23)	-0.07 (-0.25, 0.11)	-0.14 (-0.26, -0.02)	0.01
Model 4	0.09 (-0.06, 0.24)	-0.06 (-0.24, 0.12)	-0.13 (-0.25, -0.003)	0.01
Fibrinogen		**β (95% CI)**		
Model 1	-14.40 (-33.67, 4.87)	-17.44 (-40.52, 5.63)	-16.82 (-31.88, -1.76)	0.04
Model 2	-13.70 (-33.26, 5.87)	-16.78 (-40.4, 6.84)	-16.86 (-32.30, -1.43)	0.05
Model 3	-14.34 (-33.94, 5.26)	-15.42 (-39.18, 8.34)	-15.15 (-30.90, 0.60)	0.09
Model 4	-12.51 (-32.30, 7.29)	-14.52 (-38.33, 9.29)	-12.32 (-28.61, 3.97)	0.16

CI = confidence interval; CRP = C-reactive protein

Model 1 = Adjusted for baseline biomarker level

Model 2 = Adjusted for above + gender, baseline education, chronic obstructive pulmonary disease, and aspirin use

Model 3 = Adjusted for above + baseline diabetes, BMI, diabetes medications, and smoking

Model 4 = Adjusted for above + baseline depression, and posttraumatic stress disorder

Table 4

Differences in Year 5 insulin resistance biomarker levels as compared with the stable low group

	Activity			
Variable	**Decreasing**	**Increasing**	**Stable High**	**P-value for trend**
Log Insulin		**β (95% CI)**		
Model 1	-0.10 (-0.26, 0.05)	-0.13 (-0.32, 0.06)	-0.10 (-0.22, 0.03)	0.14
Model 2	-0.12 (-0.28, 0.03)	-0.15 (-0.34, 0.04)	-0.10 (-0.23, 0.02)	0.12
Model 3	-0.07 (-0.22, 0.08)	-0.08 (-0.27, 0.10)	-0.05 (-0.18, 0.07)	0.40
Model 4	-0.08 (-0.23, 0.07)	-0.09 (-0.27, 0.10)	-0.07 (-.19, 0.06)	0.32
Log Glucose		**β (95% CI)**		
Model 1	-0.01 (-0.06, 0.03)	-0.08 (-0.13, -0.02)	-0.04 (-0.08, -0.003)	0.005
Model 2	-0.01 (-0.06, 0.03)	-0.07 (-0.13, -0.01)	-0.05 (-0.08, -0.01)	0.003
Model 3	-0.01 (-0.06, 0.03)	-0.07 (-0.12, -0.01)	-0.04 (-0.08, -0.01)	0.005
Model 4	-0.02 (-0.06, 0.03)	-0.07 (-0.12, -0.01)	-0.05 (-0.08, -0.009)	0.003
Hemoglobin A1c		**β (95% CI)**		
Model 1	0.13 (-0.06, 0.32)	-0.01 (-0.24, 0.22)	-0.04 (-0.19, 0.11)	0.32
Model 2	0.13 (-0.06, 0.33)	-0.01 (-0.24, 0.23)	-0.03 (-0.19, 0.12)	0.38
Model 3	0.15 (-0.03, 0.34)	0.04 (-0.19, 0.27)	0.02 (-0.13, 0.17)	0.82
Model 4	0.15 (-0.04, 0.33)	0.03 (-0.19, 0.26)	0.003 (-0.15, 0.16)	0.70

CI = confidence interval

Model 1 = Adjusted for baseline biomarker level

Model 2 = Adjusted for above + gender, baseline education, chronic obstructive pulmonary disease, and aspirin use

Model 3 = Adjusted for above + baseline diabetes, BMI, and smoking

Model 4 = Adjusted for above + baseline depression, and posttraumatic stress disorder