

Association of Physical Activity and Body Mass Index With Novel and Traditional Cardiovascular Biomarkers in Women

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PHYSICAL INACTIVITY AND OVER-weight/obesity are major public health epidemics.¹ More than half of the US population does not meet recommended levels of physical activity, while 65% are overweight or obese, with women being more at risk than men.^{1,2} Overweight and obesity continue to substantially increase in the United States and worldwide, affecting women and men of all ages and ethnic groups.^{1,3,4} Both increased body weight and low levels of physical activity have been shown consistently to be powerful predictors of cardiovascular disease, diabetes, and all-cause mortality.⁵⁻¹⁰ Both are also associated with increased prevalence of traditional cardiovascular risk factors and they often occur together. This has led to some controversy over the relative contributions of each to cardiovascular risk.¹¹

Few studies have directly compared the effects of physical activity and body weight on cardiovascular biomarkers, and these studies have been mostly limited to men¹²⁻¹⁵ or small numbers of women.¹⁶⁻¹⁸ A previous study examining inflammatory biomarkers in an elderly cohort found an inverse association between physical activity and inflammatory markers, with the association being attenuated after adjust-

Context There are few data directly comparing the effects of physical activity and body weight on cardiovascular biomarkers.

Objective To examine the association of physical activity and body mass index (BMI, defined as weight in kilograms divided by the square of height in meters) alone and in combination with cardiovascular biomarkers.

Design, Setting, and Participants Cross-sectional analysis of 27 158 apparently healthy US women (mean age, 54.7 years) at the time of enrollment (1992-1995) in the Women's Health Study, a randomized, double-blind, placebo-controlled trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer.

Main Outcome Measures The association of physical activity and BMI with high-sensitivity C-reactive protein (CRP), fibrinogen, soluble intracellular adhesion molecule 1 (ICAM-1), homocysteine, low- and high-density lipoprotein (LDL and HDL) cholesterol, total cholesterol, apolipoprotein A-1 and B₁₀₀, lipoprotein(a), and creatinine.

Results Lower levels of physical activity and higher levels of BMI were independently associated (*P* for trend <.001) with adverse levels of nearly all lipid and inflammatory biomarkers. High BMI showed stronger associations with these biomarkers than physical inactivity. For example, using the reference group of physically active, normal weight women (energy expenditure \geq 1000 kcal/week; BMI, 18.5-24.9) and adjusting for age, race, smoking, blood pressure, diabetes, menopausal status, and hormone use, the odds ratios (95% confidence intervals [CIs]) for having CRP >3 mg/L were: for inactive, normal weight women 1.26 (1.15-1.37); active, overweight 2.68 (2.41-2.98); inactive, overweight 3.11 (2.84-3.41); active, obese 8.25 (7.15-9.51); and inactive, obese 9.86 (8.84-10.99). In similar analyses, the odds ratios (95% CIs) for having HDL cholesterol <50 mg/dL were 1.20 (1.11-1.30); 2.25 (2.04-2.49); 2.62 (2.41-2.85); 4.21 (3.68-4.81); and 5.27 (4.77-5.84), respectively, and for having apolipoprotein B₁₀₀ >120 mg/dL they were 1.21 (1.11-1.33); 1.86 (1.66-2.08); 2.06 (1.88-2.67); 2.35 (2.04-2.70); and 2.33 (2.09-2.59). Fibrinogen, ICAM-1, apolipoprotein A1, total cholesterol, and LDL cholesterol showed similar associations. By contrast, homocysteine, lipoprotein (a), and creatinine showed weak or nonsignificant associations.

Conclusions High BMI was more strongly related to adverse cardiovascular biomarker levels than physical inactivity. However, within BMI categories, physical activity was generally associated with more favorable cardiovascular biomarker levels than inactivity.

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ing for body mass index (BMI, defined as weight in kilograms divided by the square of height in meters).¹⁹

To provide more information, we measured levels of 11 novel and traditional biomarkers that have been related to cardiovascular risk and may play a role in the development of atherosclerosis (high-sensitivity C-reactive protein [CRP], fibrinogen, soluble intracellular adhesion molecule 1 [ICAM-1], homocysteine, low- and high-density lipoprotein [LDL and HDL] cholesterol, total cholesterol, apolipoprotein A-1 and B₁₀₀, lipoprotein [a], and creatinine) in a large cohort of middle-aged healthy women.^{20,21} We sought to compare the association of physical activity and BMI, alone and in combination, with these cardiovascular biomarkers.

METHODS

Study Population

Study participants were selected from individuals enrolled in the Women's Health Study, a recently completed randomized, double-blind, placebo-controlled clinical trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer in 39 876 women followed through February 2005.²²⁻²⁴ The study was approved by the institutional review boards of the Brigham and Women's Hospital (Boston, Mass). Participants were apparently healthy female health care professionals, aged 45 years or older, who were free of self-reported cardiovascular disease and cancer at study entry (1992-1995). Participants gave written informed consent and completed questionnaires at time of enrollment on demographics, medical history, medications, and lifestyle factors. Participants self-reported race/ethnic status in 1 of 6 categories (white, Hispanic, black, Asian/Pacific Islander, American Indian/Alaskan Native, and other). Participants also were asked to provide a blood sample, if they were willing; 28 345 (71.1%) did and of these, 546 samples could not be analyzed due to technical limitations. For the purposes of

this report, we additionally excluded women with missing BMI or physical activity data (n=543) and missing information on the biomarkers of interest (n=98), leaving 27 158 women for analysis.

Assessment of BMI and Physical Activity

Self-reported body height and weight were obtained from the baseline questionnaires and used to calculate BMI.⁴ Physical activity was assessed by using a questionnaire that has been shown to be valid and reliable, with test-retest correlation of 0.59 in a random sample of nurses from another study.^{25,26} The correlation of physical activity reported on the questionnaires as compared with activity diaries kept for 4 weeks over a year was 0.62.^{25,26} Participants were asked on the questionnaire to estimate the average time per week over the past year spent on 8 groups of recreational activities (walking/hiking, jogging, running, bicycling, aerobic exercise/dance, lap swimming, tennis/squash/racquetball, and lower-intensity exercise) and also to report the number of flights of stairs climbed daily. A metabolic equivalent task (MET) score was assigned to each activity based on the energy cost of that activity (1-MET is equivalent approximately to 1 kcal of energy expended/kg of body weight/hour). We estimated the energy expended on each of the above activities, and summed over all activities to estimate the total energy expended on physical activity (kcal/week).

Inflammatory and Lipid Biomarker Measurements

Blood samples (collected in EDTA) were obtained at the time of enrollment and stored in vapor phase liquid nitrogen (-170°C). In a core laboratory certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization program, samples were thawed and analyzed for a panel of inflammatory biomarkers. High-sensitivity CRP and lipoprotein (a) were

measured using immunoturbidimetric assays on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, Ind), using reagents and calibrators from Denka Seiken (Tokyo, Japan). Fibrinogen was measured using an immunoturbidimetric assay (Kamiya Biomedical, Seattle, Wash) and ICAM-1 was measured using an enzyme-linked immunosorbent assay (R & D Systems, Minneapolis, Minn). An enzymatic assay was used to measure homocysteine (Catch Inc, Seattle, Wash). Total, LDL, and HDL cholesterol were assayed directly using reagents from Genzyme Corporation (Cambridge, Mass) and Roche Diagnostics. Apolipoproteins A1 and B₁₀₀ were measured using an immunoturbidimetric assay (DiaSorin, Stillwater, Minn). Creatinine was measured by a rate-blanked method that is based on the Jaffé reaction.

Statistical Methods

Statistical analyses were performed using STATA version 8.2 (STATA Corporation, College Station, Tex). We calculated Spearman rank correlation coefficients (r_s) for continuous values of the biomarkers. We used the non-parametric Cuzick extension to the Wilcoxon rank-sum test for trend to compare median biomarker levels across quintiles of physical activity or BMI.

Next, biomarkers were divided into quintiles based on the distribution among women not taking hormone therapy, using guidelines from the Department of Health and Human Services for lipid standardization.²⁷ The highest quintile cutpoint was then used to define elevated levels of that biomarker for all participants. Associations of physical activity and BMI with elevated biomarker levels were examined using logistic regression models that adjusted for age, race, smoking (never, past, current), systolic blood pressure, diabetes mellitus, postmenopausal status, and hormone therapy. The association of physical activity with biomarkers was examined with and without adjusting for BMI, while models examining the association of BMI with biomarkers were examined with

Table 1. Baseline Characteristics of Women (N = 27 158)

Variable	Data
Age, mean (SD), y	54.7 (7.1)
White, %	95.5
Body mass index, mean (SD)*	25.9 (5.0)
Physical activity, median (IQR), kcal/wk	601 (199-1353)
Medical history, %	
Hypertension	25.0
Current smoking	11.5
Diabetes	2.8
Postmenopausal	54.2
Postmenopausal hormone use	43.6
Laboratory values, median (IQR)	
C-reactive protein, mg/L	2.0 (0.8-4.4)
Fibrinogen, mg/dL	351 (308-403)
ICAM-1, ng/mL	343 (301-395)
Homocysteine, μmol/L	10.5 (8.7-12.9)
LDL cholesterol, mg/dL	121.4 (100.5-144.3)
HDL cholesterol, mg/dL	51.9 (43.2-62.3)
Total cholesterol, mg/dL	208 (184-235)
Apolipoprotein A-1, mg/dL	148.9 (132.4-167.9)
Apolipoprotein B ₁₀₀ , mg/dL	100.1 (83.9-121.2)
Lipoprotein(a), mg/dL	10.6 (4.4-32.7)
Creatinine, mg/dL	0.71 (0.63-0.80)

Abbreviations: HDL, high-density lipoprotein; ICAM-1, soluble intracellular adhesion molecule-1; IQR, interquartile range (25th percentile-75th percentile); LDL, low-density lipoprotein.

SI conversions: to convert LDL, HDL, and total cholesterol to mmol/L, multiply by 0.0259; to convert creatinine to μmol/L, multiply by 88.4.

*Body mass index is calculated as weight in kilograms divided by the square of height in meters.

and without adjusting for physical activity. Additional models not including blood pressure or diabetes were also used to examine the associations of physical activity and BMI, since these 2 variables may represent intermediate variables in the causal pathway. Dietary intake of fruits, vegetables, red meat, alcohol use, and multivitamin use were not included in the final logistic regression models because none of these dietary factors or education, geographic location, and income affected the findings.

Finally, we examined the joint associations of physical activity and BMI with elevated biomarker levels. To simplify these analyses, instead of using quintile cutpoints for physical activity and BMI, we now used clinical cutpoints on an a priori basis. Physical activity was categorized into 2 groups (≥ 1000 or <1000 kcal/wk of energy expenditure, or approximately 2.5 hours of moderate-intensity physical activity/week) based on current recommendations from the Centers for Disease Control and Prevention, the American College of Sports Medicine, and the US surgeon general, which recommend a minimum energy expenditure of 30 minutes per day most days of the week or the equivalent of approximately 1000 kcal/wk.^{28,29} BMI was categorized into 3 groups according to the Clinical Guidelines on the Identifi-

cation, Evaluation, and Treatment of Overweight and Obesity in Adults: normal weight (BMI, 18.5-24.9), overweight (BMI, 25.0-29.9), and obese (BMI, ≥ 30).⁴ P values were 2-tailed with a $<.05$ level of significance.

RESULTS

The mean age of the participants was 54.7 years (TABLE 1). The prevalence of overweight and obesity was 30.7% and 17.6%, respectively, with the mean BMI being 25.9. For weekly physical activity expenditure, the median level was 601 kcal/wk (interquartile range, 199-1353 kcal/wk). The median levels of biomarkers were as expected for a healthy cohort of middle-aged women.

Physical activity and BMI were only weakly and inversely correlated (r_s , -0.10) (TABLE 2). BMI was positively correlated with the inflammatory markers, LDL cholesterol, total cholesterol, and apolipoprotein B₁₀₀, and inversely correlated with HDL cholesterol and apolipoprotein A1. Physical activity was correlated with the biomarkers in the opposite direction of BMI and showed smaller correlations. Homocysteine, lipoprotein (a) and creatinine were only minimally correlated with either physical activity or BMI.

When we examined median levels of the biomarkers (TABLE 3), lower quintiles of physical activity and higher quin-

Table 2. Spearman Correlation Coefficients for Cardiovascular Biomarkers

	CRP	Fibrinogen	ICAM-1	Homocysteine	LDL-C	HDL-C	TC	Apo A-1	Apo B ₁₀₀	Lp(a)	Creatinine	BMI
Fibrinogen	.41											
ICAM-1	.29	.27										
Homocysteine	-.01	.12	.11									
LDL-C	.08	.20	.13	.11								
HDL-C	-.18	-.23	-.22	-.04	-.04							
Total cholesterol	.16	.14	.12	.11	.88	.16						
Apo A-1	.03	-.16	-.13	-.03	-.07	.79	.20					
Apo B ₁₀₀	.25	.27	.23	.10	.79	-.32	.74	-.10				
Lp(a)	-.01*	.12	<.01*	.02	.17	<.01*	.14	-.03	.14			
Creatinine	-.01	.02	-.01†	.27	.18	.15	.24	.01†	.03	.03		
BMI	.47	.33	.21	.05	.15	-.38	.10	-.25	.26	.01*	-.01	
Physical activity	-.10	-.09	-.10	-.05	-.05	.10	-.04	.07	-.08	.01*	.04	-.10

Abbreviations: Apo A-1, apolipoprotein A-1; Apo B₁₀₀, apolipoprotein B₁₀₀; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CRP, C-reactive protein; HDL-C, high-density lipoprotein; ICAM-1, soluble intracellular adhesion molecule 1; LDL-C, low-density lipoprotein; Lp(a), lipoprotein (a).

*All pairwise P values $<.05$ except for Lp(a) with CRP (P = .15), ICAM-1 (P = .97), HDL-C (P = .80), physical activity (P = .18), and BMI (P = .12).

†Creatinine with Apo A-1 and ICAM-1 had nonsignificant correlations (P = .10 and 0.30, respectively).

tiles of BMI were linearly associated (*P* for trend <.001) with adverse levels of nearly all biomarkers in the expected direction, with greater differences in median levels of biomarkers across quintiles of BMI compared with physical activity. For women in the lowest quintile of physical activity, unadjusted median values of biomarkers were higher than those in the highest quintile by 43% for CRP, 5% to 8% for fibrinogen, ICAM-1, homocysteine, LDL cholesterol, and apolipoprotein B₁₀₀, and 3% to 8% lower for HDL cholesterol and apolipoprotein A1, with linear associations for quintiles 2-4. For women in the highest quintile of BMI, median biomarker levels were higher than those in the lowest quintile by 4-fold for CRP, 22% for fibrinogen, 14% for ICAM-1, 5% for homocysteine, 12% for LDL cholesterol,

and 23% for apolipoprotein B₁₀₀, while HDL cholesterol and apolipoprotein A1 were lower by 26% and 13%, respectively. Linear associations were also found for the intermediate BMI quintiles.

After adjusting for age, race, smoking, systolic blood pressure, diabetes, menopausal status, hormone use, and either BMI or physical activity, both physical activity and BMI remained significantly associated in a linear manner with most biomarker levels, with greater odds ratios (ORs) for BMI compared with physical activity (TABLE 4). For example, after adjusting for risk factors and BMI, the lowest quintile of physical activity, compared with the highest, was associated with ORs (95% confidence intervals [CIs]) for elevated CRP, fibrinogen, and ICAM-1 of

1.37 (95% CI, 1.24-1.51); 1.26 (95% CI 1.13-1.40); and 1.59 (95% CI, 1.43-1.76), respectively. A similar analysis of the highest compared with the lowest quintile of BMI that adjusted for the same risk factors and physical activity was associated with ORs of 10.79 (95% CI, 9.63-12.08); 5.81 (95% CI, 5.13-6.59); and 2.33 (95% CI, 2.09-2.60), respectively. Intermediate quintiles (2-4) of both physical activity and BMI also showed significant associations when compared with the reference quintiles, with little overlap in the CIs for BMI quintiles.

Analyses that did and did not adjust for BMI resulted in only minimal changes in the ORs for physical activity. Similarly, analyses of BMI that did and did not adjust for physical activity also resulted in almost identical find-

Table 3. Median Biomarker Levels According to Quintiles of Physical Activity and Body Mass Index

	Quintiles of Physical Activity, kcal/wk					<i>P</i> Value*
	5 (>1574) (Highest)	4 (>844-1574)	3 (>412-844)	2 (>144-412)	1 (≤144) (Lowest)	
CRP, mg/L	1.78	1.78	1.90	2.11	2.54	<.001
Fibrinogen, mg/dL	345	346	349	354	362	<.001
ICAM-1, ng/mL	337	337	339	346	358	<.001
Homocysteine, μmol/L	10.4	10.3	10.3	10.5	10.8	<.001
LDL-C, mg/dL	119.2	120.1	121.1	122.1	124.6	<.001
HDL-C, mg/dL	53.5	53.1	52.5	51.1	49.3	<.001
Total cholesterol, mg/dL	207	206	208	209	211	<.001
Apo A-1, mg/dL	151.1	150.8	150.0	147.5	146.1	<.001
Apo B ₁₀₀ , mg/dL	97.9	98.1	99.6	103.7	105.8	<.001
Lp(a), mg/dL	10.4	10.9	10.5	11.0	10.2	.12
Creatinine, mg/dL	0.72	0.71	0.71	0.71	0.70	<.001

	Quintiles of Body Mass Index†					<i>P</i> Value*
	1 (≤21.9) (Lowest)	2 (>21.9-23.8)	3 (>23.8-25.8)	4 (>25.8-29.3)	5 (>29.3) (Highest)	
CRP, mg/L	0.87	1.31	1.85	2.64	4.49	<.001
Fibrinogen, mg/dL	322	335	350	363	393	<.001
ICAM-1, ng/mL	325	331	339	350	371	<.001
Homocysteine, μmol/L	10.3	10.3	10.4	10.5	10.8	.001
LDL-C, mg/dL	112.7	118.4	123.7	126.0	125.9	<.001
HDL-C, mg/dL	59.5	55.7	52.5	48.7	43.9	<.001
Total cholesterol, mg/dL	201	206	210	213	211	<.001
Apo A-1, mg/dL	157.7	153.8	149.6	145.7	138.0	<.001
Apo B ₁₀₀ , mg/dL	90.0	95.6	103.4	108.0	110.9	<.001
Lp(a), mg/dL	10.1	10.4	10.9	11.0	10.7	.13
Creatinine, mg/dL	0.71	0.71	0.71	0.71	0.70	.08

Abbreviations: Apo A-1, apolipoprotein A-1; Apo B₁₀₀, apolipoprotein B₁₀₀; CRP, C-reactive protein; HDL-C, high-density lipoprotein; ICAM-1, soluble intracellular adhesion molecule 1; LDL-C, low-density lipoprotein; Lp(a), lipoprotein (a).

SI conversions: to convert LDL, HDL, and total cholesterol to mmol/L, multiply by 0.0259; to convert creatinine to μmol/L, multiply by 88.4.

**P* values obtained from Cuzick's nonparametric test for trend across ordered groups for median biomarker levels across quintiles of physical activity or BMI.

†Body mass index is calculated as weight in kilograms divided by the square of height in meters.

ings. Excluding systolic blood pressure and diabetes from the multivariable models did not change our findings.

We then proceeded to examine the joint associations of physical activity and BMI with biomarker levels using established clinical cutpoints when available (FIGURE). High BMI showed stronger associations with these biomarkers than physical inactivity, but within BMI categories, physical activity was generally associated with more favorable cardiovascular biomarker levels than inactivity. For example, using the reference group of physically active, normal weight (energy expenditure ≥ 1000 kcal/wk; BMI, 18.5-24.9)

and adjusting for age, race, smoking, systolic blood pressure, diabetes, menopausal status, and hormone use, the ORs for having CRP higher than 3 mg/L were: for inactive, normal weight women 1.26 (95% CI, 1.15-1.37); active, overweight 2.68 (95% CI, 2.41-2.98); inactive, overweight 3.11 (95% CI, 2.84-3.41); active, obese 8.25 (95% CI, 7.15-9.51); and inactive, obese 9.86 (95% CI, 8.84-10.99); all $P < .001$.

In similar analyses, the ORs for having HDL cholesterol less than 50 mg/dL were 1.20 (95% CI, 1.11-1.30); 2.25 (95% CI, 2.04-2.49); 2.62 (95% CI, 2.41-2.85); 4.21 (95% CI, 3.68-4.81); and 5.27 (95% CI, 4.77-5.84), respectively,

and for having apolipoprotein B₁₀₀ higher than 120 mg/dL, they were 1.21 (95% CI, 1.11-1.33); 1.86 (95% CI, 1.66-2.08); 2.06 (95% CI, 1.88-2.67); 2.35 (95% CI, 2.04-2.70); and 2.33 (95% CI, 2.09-2.59), respectively. Fibrinogen, ICAM-1, total and LDL cholesterol, and apolipoprotein A1 showed similar associations (Figure). By contrast, homocysteine, lipoprotein (a), and creatinine showed weak or nonsignificant associations.

COMMENT

In this cross-sectional analysis of 27 158 healthy women, lower levels of physical activity and higher levels of BMI were

Table 4. Adjusted Odds Ratios for the Association of Quintiles of Physical Activity and Quintiles of Body Mass Index With Elevated Biomarker Levels*

	Quintiles of Physical Activity, kcal/wk†					P for Linear Trend
	5 (>1574) (Highest)	4 (>844-1574)	3 (>412-844)	2 (>144-412)	1 (≤144) (Lowest)	
CRP	1.00	1.14 (1.03-1.26)	1.19 (1.07-1.31)	1.23 (1.12-1.36)	1.37 (1.24-1.51)	<.001
Fibrinogen	1.00	1.11 (0.99-1.24)	1.08 (0.97-1.21)	1.18 (1.05-1.32)	1.26 (1.13-1.40)	<.001
ICAM-1	1.00	1.04 (0.93-1.16)	1.18 (1.06-1.31)	1.37 (1.24-1.52)	1.59 (1.43-1.76)	<.001
Homocysteine	1.00	0.89 (0.81-0.99)	0.88 (0.79-0.97)	1.00 (0.90-1.10)	1.06 (0.96-1.17)	.49
LDL-C	1.00	1.05 (0.95-1.17)	1.09 (0.99-1.21)	1.15 (1.04-1.27)	1.14 (1.03-1.26)	.002
HDL-C	1.00	0.88 (0.81-0.96)	0.86 (0.79-0.94)	0.78 (0.71-0.85)	0.78 (0.71-0.86)	<.001
Total cholesterol	1.00	1.00 (0.91-1.10)	1.06 (0.96-1.17)	1.07 (0.98-1.18)	1.09 (0.99-1.20)	.04
Apo A-1	1.00	0.92 (0.85-1.00)	0.90 (0.83-0.98)	0.82 (0.75-0.89)	0.79 (0.73-0.87)	<.001
Apo B ₁₀₀	1.00	1.05 (0.95-1.17)	1.12 (1.02-1.24)	1.15 (1.04-1.27)	1.20 (1.09-1.32)	<.001
Lp(a)	1.00	1.03 (0.94-1.13)	0.98 (0.89-1.08)	1.05 (0.95-1.15)	0.97 (0.88-1.07)	.86
Creatinine	1.00	0.85 (0.77-0.93)	0.90 (0.82-0.99)	0.86 (0.79-0.95)	0.84 (0.76-0.92)	<.001

	Quintiles of Body Mass Index‡					P for Linear Trend
	1 (≤21.9) (Lowest)	2 (>21.9-23.8)	3 (>23.8-25.8)	4 (>25.8-29.3)	5 (>29.3) (Highest)	
CRP	1.00	1.66 (1.47-1.87)	2.44 (2.17-2.73)	4.25 (3.80-4.75)	10.79 (9.63-12.08)	<.001
Fibrinogen	1.00	1.52 (1.33-1.75)	1.86 (1.63-2.13)	2.73 (2.40-3.10)	5.81 (5.13-6.59)	<.001
ICAM-1	1.00	0.95 (0.85-1.06)	1.06 (0.95-1.19)	1.42 (1.28-1.58)	2.33 (2.09-2.60)	<.001
Homocysteine	1.00	0.94 (0.85-1.04)	0.94 (0.85-1.04)	0.99 (0.89-1.10)	1.14 (1.03-1.27)	.001
LDL-C	1.00	1.39 (1.24-1.56)	1.71 (1.53-1.90)	1.98 (1.78-2.21)	1.87 (1.67-2.10)	<.001
HDL-C	1.00	0.67 (0.62-0.72)	0.41 (0.38-0.45)	0.27 (0.24-0.29)	0.15 (0.13-0.16)	<.001
Total cholesterol	1.00	1.26 (1.13-1.40)	1.45 (1.31-1.61)	1.64 (1.48-1.81)	1.46 (1.31-1.63)	<.001
Apo A-1	1.00	0.72 (0.66-0.78)	0.54 (0.50-0.59)	0.43 (0.40-0.47)	0.26 (0.23-0.28)	<.001
Apo B ₁₀₀	1.00	1.51 (1.34-1.70)	2.13 (1.90-2.38)	2.68 (2.40-3.00)	2.93 (2.61-3.28)	<.001
Lp(a)	1.00	1.09 (0.99-1.20)	1.12 (1.01-1.23)	1.16 (1.05-1.28)	1.07 (0.97-1.19)	.23
Creatinine	1.00	1.00 (0.91-1.10)	1.01 (0.92-1.11)	1.02 (0.93-1.13)	1.02 (0.92-1.13)	.59

Abbreviations: Apo A-1, apolipoprotein A-1; Apo B₁₀₀, apolipoprotein B₁₀₀; CRP, C-reactive protein; HDL-C, high-density lipoprotein; ICAM-1, soluble intracellular adhesion molecule 1; LDL-C, low-density lipoprotein; Lp(a), lipoprotein (a).

*All data are presented as odds ratios (95% confidence intervals). Elevated biomarker level was defined as the highest quintile of that biomarker in women not taking hormone therapy, with values as follows: CRP 4.2 mg/L, fibrinogen 428 mg/dL, ICAM-1 411 ng/mL, homocysteine 14.0 μmol/L, LDL-C 153.9 mg/dL, HDL-C 61.5 mg/dL, total cholesterol 242 mg/dL, apolipoprotein A-1 160 mg/dL, apolipoprotein B₁₀₀ 126 mg/dL, lipoprotein(a) 45.3 mg/dL, creatinine 0.83 mg/dL.

†Obtained from logistic regression analysis that adjusted for age, race, smoking status, systolic blood pressure, diabetes mellitus, menopausal status, and hormone use, with models for physical activity quintiles additionally adjusted for body mass index as a continuous variable and models for body mass index additionally adjusted for physical activity as a continuous variable.

‡Body mass index is calculated as weight in kilograms divided by the square of height in meters.

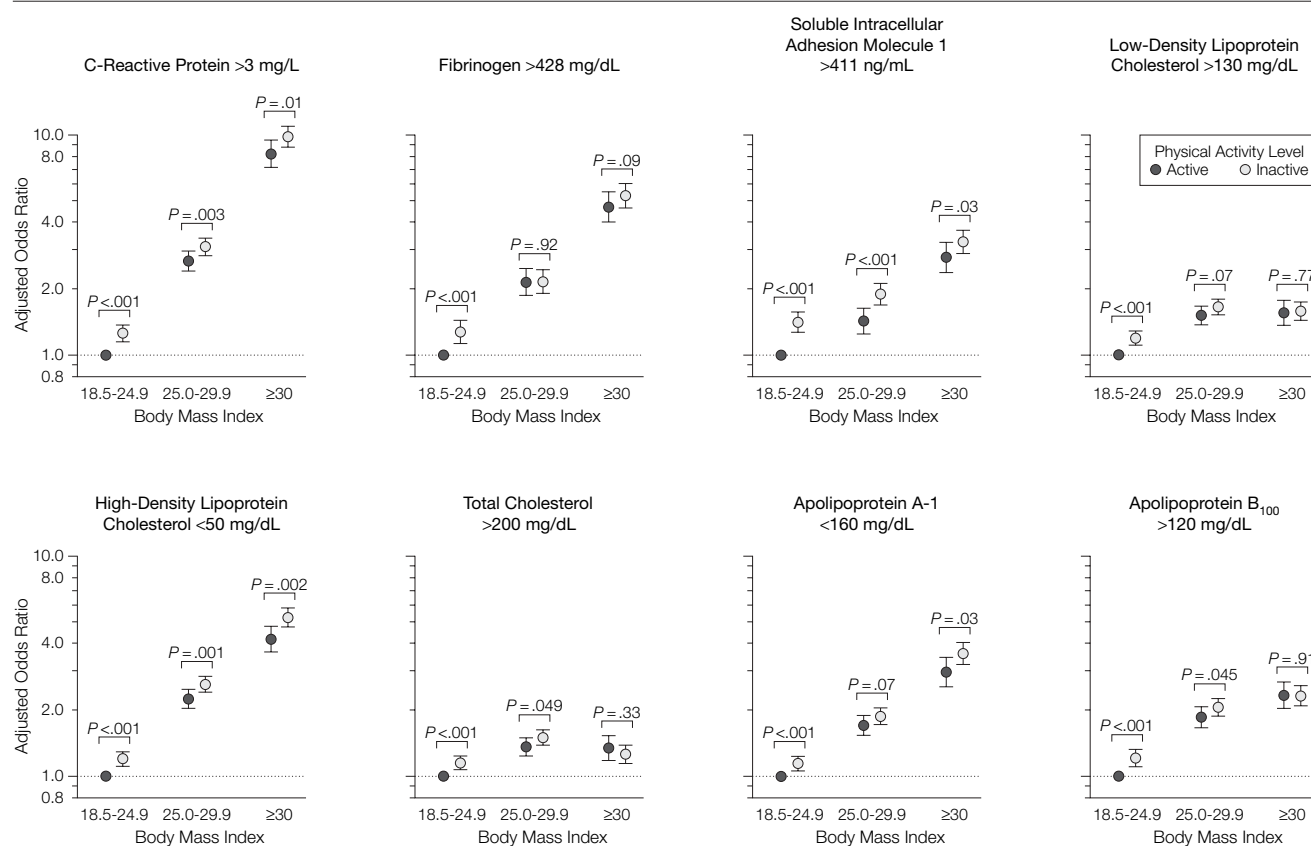
both independently associated with nearly all inflammatory and lipid biomarkers, with stronger associations seen for BMI compared with physical activity in combined analyses. The strength of the association between BMI and biomarker levels did not noticeably change after adjustment for physical activity, and vice versa. There was no threshold effect but, rather, a linear relationship between physical activity or BMI and cardiovascular biomarkers. These observations suggest that both physical activity and BMI have significant independent associations with inflammatory and lipid factors that may be related to the development of atherosclerosis and cardiovascular disease.

Although we observed greater ORs for cardiovascular biomarkers associated with high BMI compared with physical inactivity, being physically active was associated with more favorable cardiovascular biomarker levels within BMI categories. The most favorable biomarker values were found in women who had an optimal BMI (18.5-24.9) and who met current guidelines for physical activity expenditure (30 min/d of moderate intensity activity most days of the week or a total of 1000 kcal/wk).

The current study examined the combined and separate associations of physical activity and BMI with a comprehensive panel of novel and tradi-

tional cardiovascular biomarkers in women. Previous studies have been limited in the sample size of women and the number and variety of biomarkers examined, with most studies focusing on fibrinogen, CRP, or traditional lipids. A recent small study in men that examined fibrinogen, lipids, and other hemostatic factors but not CRP, homocysteine, or ICAM-1, also found that increased body weight was more closely related to adverse risk factors than physical inactivity.¹⁵ Other studies that examined physical activity and body weight have reported significant associations, predominantly with fibrinogen and CRP,^{19,30-33} with the present analysis extending these findings to a

Figure. Association of Physical Activity and Body Mass Index Categories With Cardiovascular Biomarkers



Odds ratios (95% confidence intervals) for women categorized by their physical activity level (active or inactive, \geq or $<$ 1000 kcal/wk) and body mass index (normal weight, overweight, obese [calculated as weight in kilograms divided by the square of height in meters]) were adjusted for age, race, smoking status, systolic blood pressure, diabetes mellitus, menopausal status, and hormone use. All comparisons were with the reference group of normal weight, active women ($P < .001$). The bracketed P values are from serial logistic regression models using as reference the active group within each BMI group to test for the significance of the association of physical inactivity with adverse cardiovascular biomarker levels within each BMI group. Established clinical cutpoints for biomarker levels in women were used when available. Top quintile values were used to define the cutpoints for ICAM-1 and fibrinogen. Cutpoints for apolipoprotein B₁₀₀ and A-1 corresponded to top quintile as well as clinical cutpoints.

range of other inflammatory and lipid biomarkers. The magnitude of the association between physical activity and biomarker levels was similar to that seen in previous reports, including those from the National Health and Nutrition Examination Survey³⁴ and the Cardiovascular Health Study,¹⁹ both of which also found that CRP showed the most striking association with physical activity, compared with other biomarkers such as fibrinogen.

It is well known that increased body weight is associated with inflammatory and lipid biomarkers. Adipose tissue, particularly visceral adipose tissue, is metabolically active, promoting a thrombotic and inflammatory state,^{32,35,36} as well as an atherogenic lipoprotein state with predominance of high triglycerides and low HDL cholesterol.³⁷ It is less clear why physical activity would be associated with inflammatory or lipid biomarkers independent of body weight, as our results demonstrate.³⁸ It has been postulated that physical activity may modulate levels of inflammation both locally by regular muscle movement that may suppress inflammation, and systemically via muscle-derived cytokines or leptin, which may be reduced with physical activity independent of BMI.³⁸⁻⁴⁰ Physical activity is also associated with improved endothelial function and nitric oxide synthesis and has been recently found to increase endothelial progenitor cell activation and mobilization.^{38,41,42}

There are several limitations of this study. The study was cross-sectional in design, and hence causal relationships cannot be inferred. We only had data on women, although to our knowledge there are no data to suggest substantial sex differences with respect to inflammation and lipids after taking into account menopausal status and hormone use, as we did in our adjusted analyses. While our study included health care professionals who were mostly white, apparently healthy, recruited from a variety of geographic locations across the United States, it is unclear if our results would be appli-

cable to other populations. The data on physical activity and body weight were self-reported. Nonetheless, the physical activity questionnaire that we used has been shown to be reliable and valid in a population such as the one in this study,^{25,26} and reported body weight correlates well with measured body weight.⁴³ Finally, if physical activity were much less precisely reported than body weight, this might partially account for the stronger associations seen for BMI.

Strengths of the present study include a large number of healthy women participants with comprehensive measurements of both novel and traditional cardiovascular biomarkers. Additionally, detailed information on cardiovascular risk factors was available, allowing for the control for potential confounding by these factors. Finally, few previous studies have examined physical activity and BMI jointly with regard to their influence on cardiovascular biomarkers.

In sum, both lower levels of physical activity and higher levels of BMI were strongly and independently associated with adverse inflammatory and lipid biomarker levels in a large population of healthy women. While BMI showed greater magnitude of association with the biomarkers, a modest level of physical activity (at least 1000 kcal/wk or approximately 2.5 hours of modest physical activity/week as recommended by guidelines) was significantly associated with more favorable biomarker profiles, even in overweight or obese individuals. However, the most favorable inflammatory and lipid levels were found in women who had at least moderate physical activity levels and were normal weight. With the growing epidemics of overweight/obesity and physical inactivity, which are particularly rising in women and are expected to continue to grow in the 21st century, an optimal prevention strategy for diseases linked to inflammation and lipids, such as cardiovascular disease and diabetes, should emphasize a healthy lifestyle that includes regular physical ac-

tivity and a healthy diet, which are important for attaining and maintaining an optimal BMI.

Author Contributions: Drs Mora and Ridker had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mora, Buring, Ridker.

Acquisition of data: Lee, Buring, Ridker.

Analysis and interpretation of data: Mora, Lee, Ridker.

Drafting of the manuscript: Mora.

Critical revision of the manuscript for important intellectual content: Mora, Lee, Buring, Ridker.

Statistical analysis: Mora.

Obtained funding: Buring, Ridker.

Administrative, technical, or material support: Lee, Ridker.

Study supervision: Lee, Ridker.

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I shall tell you a great secret, my friend. Do not wait for the last judgment, it takes place every day.
—Albert Camus (1913-1960)