Journal of Physical Activity and Health, 2011, 8, 994-1003

Ambulatory Activity Associations With Cardiovascular and Metabolic Risk Factors in Smokers

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Background: We examined the association between ambulatory activity and biological markers of health in smokers. ***Methods:*** Baseline data from 985 subjects enrolled in a pharmacologic smoking cessation trial were examined. Body size, blood pressure, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), total and small LDL particles, LDL size, high density lipoprotein cholesterol, triglycerides (TG), C-reactive protein (CRP), creatinine, fasting glucose, and hemoglobin A1c were assessed in relation to pedometer-assessed ambulatory activity, as was the odds of metabolic syndrome and CRP > 3 mg/L. Effect modification by gender was examined. ***Results:*** Only waist circumference was lower with greater steps/day in the men and women combined ($P_{trend} < 0.001$). No other significant relationships were noted in men, while women with ≥ 7500 steps/day had lower weight, BMI, CRP, TG, total, and small LDL particles compared with those with < 7500 steps/day. These women also had 62% and 43% lower odds of metabolic syndrome and elevated CRP, respectively, compared with the less active women. Adjustment for BMI attenuated all the associations seen in women. ***Conclusions:*** Greater ambulatory activity is associated with lower levels of metabolic and cardiovascular risk factors in female smokers which may, in part, be mediated by a reduction in BMI.

Keywords: physical activity, walking, smoking, biomarkers, body mass index

Approximately, 43.4 million adults in the United States are current cigarette smokers.[1] Cigarette smoking is associated with increased risk of several diseases including cancer, cardiovascular, and respiratory disease. Adverse health effects of cigarette smoking account for an estimated 438,000 or nearly 1 of every 5 deaths/year in the United States.[2]

It is clear that smokers are at risk for multiple negative health outcomes.[3] It is also clear that smokers differ in the expression of such risk, so it is important to identify factors that are associated with especially negative health outcomes among smokers. Such factors could be used to focus health risk assessments on at-risk populations and perhaps also to motivate quit attempts among those at highest risk. Moreover, it is of theoretical interest to identify factors that may modulate risk. Risk factors identified in general populations may not translate directly to populations of smokers since smoking may interact with such factors to modify the relationships.

Physical activity may effectively predict health risk among smokers. There is clear evidence that in the general population physical inactivity is an important risk factor for multiple negative health outcomes,[4] and conversely, physical activity produces many beneficial health effects including reduced total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG),[5] inflammation,[6] and blood pressure,[7] and improved high density lipoprotein cholesterol (HDL-C)[8] and glycemic control.[9] It has also been shown to reduce levels of atherogenic lipoproteins including total LDL particles, small LDL particles, and to increase LDL size.[10] Physical activity is also associated with a reduced risk of metabolic syndrome, which is a clustering of cardiovascular and metabolic risk factors.[11,12] It is unknown, however, whether physical activity similarly affects these factors among smokers who typically manifest more negative biomarker profiles and who tend to be more sedentary than nonsmokers,[13,14] nor if the relationships are similar in male and female smokers.

Previous research suggests a possible association between physical activity and health status in smokers. Epidemiological studies have consistently demonstrated associations between low physical activity and all-cause mortality risk while controlling for smoking.[15-17] Additionally, physical activity is associated with a reduced risk of cardiovascular disease in male and female smokers,[18,19] and with a decreased risk of many cancers including lung cancer, although this latter relationship may represent residual confounding by cigarette smoking.[20,21] We hypothesized that smokers who took more steps per day

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would have a better profile of biomarkers that are related to these various outcomes compared with smokers who took fewer steps per day. Specifically, we evaluated the relationship between objectively measured ambulation and body size, blood pressure, TC, HDL-C, LDL-C, LDL particle number and size, TG, C-reactive protein (CRP), hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and creatinine in Wisconsin smokers participating in a pharmacologic smoking cessation clinical trial.

Methods

Study Population

Study participants were enrolled in the Wisconsin Smokers' Health Study (WSHS), a 3-year smoking cessation trial examining specific pharmacotherapies (nicotine lozenge, nicotine patch, sustained-release buproprion, and various combinations of the therapies), conducted in Madison and Milwaukee, WI in 2005.[22] The long-term objective of the WSHS was to reveal how successful and unsuccessful quit attempts are related to important physiological and psychosocial outcomes, with consideration for individual differences and other modifiable risk factors such as physical activity. Exercise was not a part of the cessation trial, but subject physical activity levels were measured. Data for this analysis (performed in 2008–2009) came from baseline data (2005–2007) of WSHS participants (n = 1504). Participants were recruited through television, radio, and newspaper ads; flyers; earned media, and television and radio interviews. Inclusion criteria included smoking > 9 cigarettes/day on average for at least the past 6 months, having an alveolar carbon monoxide level greater than 9 ppm, and being motivated to quit smoking (≥8 on a 1-to-10-point scale where 10 is 'highly motivated to quit'). Exclusion criteria included using other noncigarette forms of tobacco, taking buproprion, having current psychosis or schizophrenia, as well as contraindications to the various pharmocotherapies including high alcohol consumption (6 drinks/day on 6 or 7 days of the week), a history of seizure, high blood pressure (>160/100 mmHg), bipolar disorder, an eating disorder, a recent cardiac event or allergies to any of the medications. This study was approved by the University of Wisconsin-Madison Human Subjects Institutional Review Board and subjects gave their informed consent to participate.

Ambulatory Activity Assessment

Subjects wore a Yamax Digiwalker SW-701 pedometer for at least 7 consecutive days within 1 month of their quit date. Subjects had prequit data, postquit data, or both. Subjects were fitted with the pedometer on their waistband over their right, midthigh, and accuracy of the placement was checked with a 20-step test. Placement was altered (moved closer to the hip) to achieve 20 ± 1 steps on the test. Subjects were asked to wear the pedometer during all waking hours, except for water-based activities such as bathing or swimming, and to record their wear times and steps taken daily. Pedometers and logs were returned at their next clinic visit. The data were cleaned and scored using several criteria: days with < 10 hours of wear time or days with > 50,000 steps or < 500 steps were excluded; subjects with < 3 valid days of wear were excluded, as < 3 days of wear is not a reliable measure of normal ambulatory activity level;[23] and subjects with < 2000 steps/day who also reported malfunctioning pedometers were excluded. After these exclusions, 960 of the study's 1504 participants had valid prequit data and 1032 had valid baseline data from either pre- or postquit. An average steps/day was calculated for each subject, with subjects placed into sedentary, low active, somewhat active, and active categories based on recently published guidelines, corresponding to < 5000, 5000–7499, 7500–9999, and ≥ 10,000 steps/day.[24] Analysis using a Wilcoxon Signed Rank test showed there was no significant difference in steps taken between prequit and total baseline pedometry data ($P = .47$). In addition, results were unchanged when limited to the 960 with prequit data; therefore, our analysis initially included the 1032 subjects who had valid pre- or postquit baseline data (69% of the subjects enrolled in WSHS).

Health Status Assessment

Blood samples were collected after a 12-hour fast during which subjects refrained from smoking. Blood was processed and plasma was stored at –70°C for the analysis of the lipids and lipoproteins. All other assays were performed on fresh samples. Nuclear magnetic resonance spectroscopy (LipoScience, Inc., Raleigh, NC) was used to measure very low density lipoprotein (VLDL), LDL, HDL and mean particle sizes, and from these, total TC, TG, HDL-C, and LDL-C were estimated. Coefficients of variation (% cv) were as follows: VLDL (4.3%), LDL (3.7%), HDL (1.5%), TG (1.1%), HDL-C (1.1%), small LDL particles (9.1%), and mean LDL particle size (0.6%). Assays for high-sensitivity CRP, creatinine, FPG, and HbA1c were performed at the University of Wisconsin-Madison Hospital and Clinics Laboratory, and % cv's were 2.5%–4.2%, 1.1%–7.8%, 1.6%–2.5%, 1.1%–1.6%, respectively. Standard sphygmomanometry methodology was used for blood pressure assessment. Weight and height were measured while barefoot or in stocking feet. Waist circumference was measured at the midpoint between the lower rib margin and the iliac crest. We created categories to indicate presence of metabolic syndrome and high risk CRP. Metabolic syndrome was defined using the National Cholesterol Education Program Adult Treatment Panel III guidelines (NCEP ATP III)[25] updated in 2004[26] which defines metabolic syndrome as having 3 or more of the following conditions: WC ≥ 102 cm in men or ≥ 88 cm in women; TG ≥ 150 mg/dL or drug treatment for elevated levels; HDL-C < 40 mg/dL in men and < 50 mg/dL in women or drug treatment for reduced levels; BP ≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic or drug treatment for elevated levels; or FPG ≥ 100 mg/dL or drug treatment for diabetes mellitus. High risk CRP was defined as > 3 mg/L.

Measurement of Covariates

Age, gender, race, marital status, income, education level, smoking history, and alcohol use were measured with questionnaires. Saturated fat and sodium intake were measured using the Willett Food Frequency Questionnaire and adjusted for total caloric intake. All medications used were recorded, and any use of blood pressure, lipid lowering, diabetes, or anti-inflammatory medication was noted. Leisure-time and total moderate-vigorous physical activity was measured using the long form of the International Physical Activity Questionnaire (IPAQ).[27] Chronic conditions (cardiovascular disease, hypertension, diabetes/high blood sugar, and chronic lung disease) were assessed with the National Comorbidity Survey-Replication Composite International Diagnostic Interview (NCS-R-CIDI), a modified version of the World Health Organization's CIDI.[28]

Statistical Analysis

Data were tested for normality and log-transformed when necessary for parametric statistical analysis. Variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Analysis of covariance and general linear models was used to calculate least-squared means across category of steps/day, and tests for linear trend were performed using an ordered categorical variable. Odds ratios were calculated using logistic regression to estimate the odds of having metabolic syndrome or high risk CRP by ambulatory activity category. We used stepwise modeling, considering relevant covariates with and without adjustment for BMI, which could be a mediator of some of the associations. Marital status, education level, income, alcohol use, sodium intake, moderate-vigorous physical activity, pedometer wear-time, and saturated fat intake were not included in the final models as these variables did not change the significance of the biological marker terms or reduce the magnitude of the difference appreciably between high and low ambulatory activity categories. Of the 1032 subjects with valid pedometry data, we further excluded 47 subjects who were missing covariates of interest including age, sex, race, smoking history, chronic conditions, and body mass index (BMI), leaving 985 subjects for analysis. In an attempt to further control potential confounding, models excluding those individuals with a history of specific diseases or those taking relevant medications were also run. To examine effect modification by gender, ambulatory activity was collapsed into < 7500 or ≥ 7500 steps/day, and the cross-product term of the activity category and gender were tested in models. In addition, models stratified by gender were run, and if effect modification appeared present, then the stratified models are presented. We also examined effect modification using the median steps/day in men and women separately as the cutpoints, but results were not different from the 7500 step/day cutpoint presented here. Spearman correlations were used to examine the association between steps/day and self-reported moderate-vigorous activity, and separately, leisure time activity from the IPAQ. All analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC). We present specific p-values, and make note of associations at the $\alpha = 0.05$, 0.01, and 0.001 levels due to the multiple comparisons made.

Results

Characteristics of the 985 subjects from the WSHS included and excluded in the current analysis are presented in Table 1. The 519 subjects from the WSHS without valid pedometry data were similar to the 985 subjects included in our analysis in regards to age, gender, race, pack-years of smoking, BMI, and moderate-vigorous physical activity. Characteristics of the 985 subjects included in the analysis, stratified by gender, are shown in Table 2. On average, the women fell into the "low active" category while the men on average were "somewhat active." Median laboratory values were within their normal ranges, with the exception of HDL, which tended to be low.

Table 1 Characteristics of Wisconsin Smokers' Health Study Participants Who Were Included and Excluded From the Current Analysis

	Included[a] (n = 985)	Excluded[b] (n = 519)
Age, y, mean ± SD	44.5 ± 11.2	45.0 ± 10.9
Female, %	57	60
White, %	85	83
Body mass index, kg/m^2, mean ± SD	29.0 ± 6.3	28.9 ± 6.9
Pack-years, median (IQR)	25 (15–39)	26 (15–39)
Mod-vig physical activity, Met-hr/wk, median (IQR)	63 (21–167)	56 (19–173)

[a] Number of included participants missing by variable: mod-vig physical activity (n = 9).

[b] Number of excluded participants missing by variable: race (n = 4); body mass index (n = 29); pack-years (n = 5); mod-vig physical activity (n = 3).

Table 2 Subject Characteristics (N = 985)

Variable	Men (N = 420)[a]	Women (N = 565)[b]
Age, y, mean ± SD	45.0 ± 11.6	44.2 ± 10.9
White, %	85	84
Marital status, %		
Married/living with partner	60	54
Divorced/separated/widowed	23	29
Never married	17	17
Education, %		
<High school	5	5
High school	21	28
Some college/tech school	50	48
College degree or more	24	20
Household income, %		
<$25,000/yr	16	26
$25,000–$49,999/yr	33	35
$50,000–$74,999/yr	26	21
$75,000+ /yr	24	18
Alcohol intake, %		
0 gm/d	32	41
1–30 gm/d	45	49
>30 gm/d	23	10
Saturated fat intake (% kcals), mean ± SD	11.7 ± 2.7	11.9 ± 2.6
Sodium intake (mg/1000 kcals), mean ± SD	1184 ± 232	1250 ± 293
Weight, kg, mean ± SD	90.8 ± 17.9	78.5 ± 19.8
Body mass index, kg/m^2, mean ± SD	28.9 ± 5.4	29.0 ± 6.9
Waist circumference, cm, mean ± SD	101 ± 14	92 ± 16
Pack-years, median (IQR)	28 (16–45)	23 (14–36)
Ambulatory activity, steps/day, median (IQR)	8306 (6018–11376)	6239 (4312–8585)
Mod-vig physical activity, Met-hr/wk, median (IQR)	98 (27–260)	51 (18–123)
Laboratory values, median (IQR)		
Systolic blood pressure, mm Hg	122 (112–132)	118 (108–126)
Diastolic blood pressure, mm Hg	77 (68–83)	74 (66–80)
Total cholesterol, mg/dL	181.3 (156.4–205.2)	185.1 (162.6–209.0)
LDL cholesterol, mg/dL	117.5 (98.1–139.9)	117.6 (98.9–140.7)
HDL cholesterol, mg/dL	34.4 (28.0–42.3)	44.0 (36.7–53.7)
Total LDL particles, nmol/L	1329 (1107–1617)	1230 (1038–1488)
Small LDL particles, nmol/L	817.7 (531.6–1160.7)	641.0 (401.4–905.9)
Mean LDL particle size, µmol/L	20.9 (20.3–21.5)	21.3 (20.8–21.8)
TC/HDL ratio	5.2 (4.1–6.6)	4.0 (3.4–5.1)
Triglycerides, mg/dL	130.1 (90.0–203.6)	104.3 (76.0–160.1)
C-Reactive protein, mg/L	0.72 (0.20–2.70)	0.70 (0.20–2.57)
Creatinine, mg/dL	1.0 (0.9–1.1)	0.8 (0.8–0.9)
Fasting glucose, mg/dL	95 (89–101)	90 (85–96)
HbA1c, %	5.5 (5.3–5.8)	5.5 (5.2–5.7)

[a] Number of men missing by variable: Saturated fat, Sodium intake (n = 20); Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Total LDL Particles, Small LDL Particles, Mean LDL Particle Size, TC/HDL Ratio, Triglycerides, (n = 15); Alcohol intake (n = 13); C-Reactive Protein (n = 10); Hemoglobin A1c (n = 9), Creatinine, Fasting Glucose (n = 8), Waist Circumference (n = 6), Moderate-Vigorous Physical Activity (n = 4), Income (n = 3).

[b] Number of women missing by variable: Alcohol intake (n = 57); Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Total LDL Particles, Small LDL Particles, Mean LDL Particle Size, TC/HDL Ratio, Triglycerides (n = 18); Saturated fat, sodium intake (n = 15); Hemoglobin A1c (n = 8); C-Reactive Protein (n = 7), Fasting Glucose, Waist Circumference, Moderate-Vigorous Physical Activity (n = 5); Creatinine (4); Education, Income (n = 3).

Gender significantly affected the relationship between ambulatory activity and many of the biological markers examined. Table 3 presents the results for analyses in which no effect modification was noted. Waist circumference was significantly lower with greater steps/day among the men and women combined, and there were lower levels of DBP and TC/HDL with greater steps/day that were attenuated with BMI adjustment. No

Table 3 Mean Level of Health Indices By Steps/Day Level in Men and Women Combined

	Physical activity (steps/day)				
	Sedentary (<5000)	Low active (5000–7499)	Somewhat active (7500–9999)	Active (≥10,000)	*P*-trend
Waist circumference (cm)					
Sample size	246	287	216	225	
Model 1[a]	101	96***	95***	92***	<0.001
Model 2[b]	97	96	96	95***	<0.001
Systolic blood pressure (mmHg)					
Sample size	249	291	217	228	
Model 1[a,c]	121	119*	120	119	0.26
Model 2[b,c]	121	119	121	120	0.83
Diastolic blood pressure (mmHg)					
Model 1[a,c]	76	74	75	74*	0.04
Model 2[b,c]	75	74	75	74	0.22
Creatinine (mg/dL)					
Sample size	247	287	215	224	
Model 1[a]	0.92	0.92	0.93	0.90	0.64
Model 2[b]	0.92	0.92	0.94	0.90	0.71
Fasting glucose (mg/dL)[d]					
Sample size	245	287	216	224	
Model 1[a,c]	94	93	95	91*	0.09
Model 2[b,c]	93	93	95	92	0.47
Hemoglobin A1c (%)[d]					
Sample size	247	285	214	222	
Model 1[a,c]	5.5	5.5	5.6	5.5	0.54
Model 2[b,c]	5.5	5.5	5.6*	5.5	0.10
Lipids					
Sample size	239	284	209	220	
HDL-C (mg/dL)					
Model 1[a,c]	41.8	41.0	42.0	43.3	0.16
Model 2[b,c]	42.9	41.0	41.5	42.5	0.95
TC/HDL-C (mg/dL)[d]					
Model 1[a,c]	4.7	4.6	4.6	4.3*	0.04
Model 2[b,c]	4.6	4.6	4.7	4.4	0.51
LDL Mean Particle Size (μmol/L)					
Model 1[a,c]	21.1	21.1	21.0	21.2	0.11
Model 2[b,c]	21.1	21.1	21.0	21.2	0.45

* $P < .05$ vs. Q1 (<5000 steps/d).

** $P < .01$ vs. Q1 (<5000 steps/d).

*** $P < .001$ vs. Q1 (<5000 steps/d).

[a] Adjusted for age, gender, race, pack years, cardiovascular disease, diabetes, hypertension, and chronic lung disease.

[b] Additionally adjusted for BMI.

[c] Specific medication use added to models: Systolic and Diastolic Blood Pressure (blood pressure medication); CRP (anti-inflammatory medication); Fasting Glucose and HbA1c (diabetes medication); HDL-C, TC/HDL-C, and LDL Mean Particle Size (lipid-lowering medication).

[d] Values are presented as geometric means.

dose-response relationship was seen for SBP, creatinine, FPG, HbA1c, HDL, the TC/HDL ratio, or LDL particle size. After removing subjects with self-reported hypertension or those taking blood pressure medications, the relationship between ambulatory activity and SBP was somewhat stronger (P_{trend} = 0.03), while that for DBP was substantially stronger (P_{trend} < 0.01), with a 3 mmHg difference in DBP from < 5000 to ≥ 10,000 steps/day.

Results for biomarkers in which effect modification by gender was present are shown in Table 4. Women taking at least 7500 steps/day had significantly lower weight, BMI, CRP, triglycerides, total and small LDL particles compared with those with < 7500 steps/day, but this was not true in men. Further adjustment for BMI attenuated the CRP, triglyceride, and LDL particle relationships in the women. Removal of subjects reporting nonsteroidal anti-inflammatory use or chronic lung disease attenuated the CRP relationship in women, but the number of women left in the analysis was substantially reduced. Removal of subjects with other relevant conditions or medication use did not alter any of the other results presented in Tables 3 or 4.

We also saw effect modification by gender for the relationships between ambulatory activity and metabolic syndrome (P_{intxn} < 0.001) and high-risk CRP (P_{intxn} = 0.06). There was no relationship between ambulatory activity and either of these conditions in men. Among the women, those with ≥ 7500 or more steps/day had a 62% lower odds of metabolic syndrome compared with those with < 7500 steps day, that was still statistically

Table 4 Mean Level of Health Indices By Steps/Day Level Stratified By Gender

	Men: Physical activity (steps/day)			Women: Physical activity (steps/day)			
	<7500	≥7500	P_{diff}	<7500	≥7500	P_{diff}	P_{intxn}
Weight (kg)							
Sample size	174	246		366	199		
Model 1[a]	92.0	90.0	0.24	81.4	73.3	<0.001	0.02
BMI (kg/m2)							
Sample size	174	246		366	199		
Model 1[a]	29.1	28.8	0.52	30.0	27.2	<0.001	<0.01
CRP (mg/L)[d]							
Sample size	169	241		363	195		
Model 1[a,c]	0.63	0.78	0.17	0.78	0.52	<0.01	<0.01
Model 2[b,c]	0.62	0.78	0.13	0.72	0.60	0.23	0.04
Total cholesterol (mg/dL)							
Sample size	168	237		355	192		
Model 1[a,c]	178.6	184.8	0.07	188.0	184.5	0.28	<0.01
Model 2[b,c]	178.5	184.8	0.07	187.7	185.1	0.44	0.01
LDL-C (mg/dL)							
Model 1[a,c]	117.4	121.4	0.18	121.5	117.6	0.16	<0.01
Model 2[b,c]	117.3	121.5	0.16	120.9	118.7	0.44	0.02
Triglycerides (mg/dL)[d]							
Model 1[a,c]	135.7	136.5	0.92	116.0	101.0	<0.01	0.01
Model 2[b,c]	135.3	136.8	0.84	114.3	103.8	0.04	0.05
Total LDL particles (nmol/L)							
Model 1[a,c]	1360.9	1402.4	0.31	1303.2	1227.2	0.02	<0.01
Model 2[b,c]	1358.8	1403.9	0.26	1291.1	1249.7	0.21	0.03
Small LDL particles (nmol/L)							
Model 1[a,c]	870.8	892.9	0.65	712.9	631.0	0.03	0.09
Model 2[b,c]	868.3	894.7	0.57	700.0	654.9	0.24	0.28

[a] Adjusted for age, race, pack years, cardiovascular disease, diabetes, hypertension, and chronic lung disease.

[b] Additionally adjusted for BMI.

[c] Specific medication use added to models: CRP (anti-inflammatory medication); Total Cholesterol, LDL-C, Triglycerides, Total LDL Particles, and Small LDL Particles (lipid-lowering medication).

[d] Values are presented as geometric means.

significant (45% lower) with further BMI adjustment (Table 5). Higher ambulatory activity was also associated with a reduced odds of having high risk CRP, with women taking ≥ 7500 steps/day having a statistically significant 43% lower odds of the condition compared with those with < 7500 steps/day. This relationship was attenuated after adjustment for BMI (OR = 0.80, 95% CI = 0.48–1.31).

Self-reported pedometer wear-time was somewhat longer in the men than the women (878 ± 91 vs. 848 ± 81 min/day, respectively), but its inclusion in the models did not change the results. We examined how total steps/day were associated with self-reported activity in men and women separately. Associations were weak for leisure-time activity ($r = .10$, $P = .05$ in men; $r = .19$, $P < .001$ in women), while total moderate-vigorous activity was more strongly associated with steps/day in men ($r = .38$, $P < .001$) than in women ($r = .22$, $P < .001$).

Discussion

In this cross-sectional analysis of individuals enrolled in the WSHS, greater ambulatory activity was associated with lower waist circumference, and a tendency toward lower DBP and TC/HDL-C ratio in both men and women. Solely among women, a higher level of steps/day was associated with lower body weight, BMI, CRP, triglycerides, total LDL, and small LDL particle concentration, but these associations were explained in part by the lower BMIs of the active individuals. Similarly, women taking ≥ 7,500 steps/day had a 62% lower odds of metabolic syndrome and a 43% lower odds of high CRP, that was attenuated after adjustment for BMI, and not present in the men. Although other studies have examined the relationship between physical activity and biological markers of health, to our knowledge this is the first study to examine this relationship specifically in smokers.

Our results regarding the association between ambulatory activity and the various health markers are reasonably consistent with prior work. Physical activity, including ambulatory activity, has been shown to be inversely related to BMI, LDL-C, TC/HDL-C, LDL lipoproteins, triglycerides, and blood pressure.[10,29–36] We found very strong relationships between ambulatory activity and metabolic syndrome, consistent with what has been seen in a population of older adults,[33] and for physical activity in general.[12] The relationship between ambulatory activity and inflammation was also strong, consistent with previous studies.[37,38] Overall, the associations we saw in this group of smokers were similar to what has previously been seen in other populations.

The differential associations we noted for women vs. men are somewhat surprising, but may be attributed to measurement issues. Although we objectively measured ambulatory activity, we cannot determine characteristics of that activity such as the intensity or pattern of steps. A previous Australian study noted that men who accumulated ≥ 10,000 steps day were more likely to report vigorous work activity or blue-collar occupations compared with less active men, while in women, the 10,000 steps/day goal was more likely to be met among those participating in ≥ 150 minutes of leisure-time activity/week.[39] Our data are consistent with this finding in that the steps/day were more strongly associated with total moderate-vigorous activity in men than in women. Although correlations with total leisure-time activity were weak overall, they were somewhat stronger in

Table 5 Odds Ratios for Metabolic Syndrome and High Risk CRP by Level of Physical Activity and Gender

	Men		Women		
	Physical activity (steps/day)		Physical activity (steps/day)		
	<7500	≥7500	<7500	≥7500	P_{intxn}
Metabolic Syndrome[a]					
Sample size (cases/controls)	79/95	98/148	173/193	40/159	
Model 1[b]	1.0	0.86 (0.57–1.29)	1.0	0.38 (0.25–0.57)	0.001
Model 2[c]	1.0	0.98 (0.61–1.59)	1.0	0.55 (0.34–0.90)	
High-risk CRP (>3.0mg/L)					
Sample size	37/132	58/183	93/270	32/163	
Model 1[b,d]	1.0	1.18 (0.73–1.90)	1.0	0.57 (0.36–0.92)	0.06
Model 2[c,d]	1.0	1.21 (0.75–1.95)	1.0	0.80 (0.48–1.31)	

[a] Metabolic Syndrome was defined using the NCEP ATP III Guidelines (≥ 3 of the following): WC ≥ 102 cm in men or ≥ 88 cm in women; TG ≥150 mg/dL or drug treatment for elevated levels; HDL-C < 40 mg/dL in men and <50 mg/dL in women or drug treatment for reduced levels; BP ≥130 mm Hg systolic or ≥85 mm Hg diastolic or drug treatment for elevated levels; or FPG ≥100 mg/dL or drug treatment for Diabetes Mellitus.

[b] Adjusted for age, race, and pack years.

[c] Additionally adjusted for BMI.

[d] Anti-inflammatory medication use was added to model.

women. Although strong inferences cannot be made as to the intensity of the actual steps recorded, these results suggest that the intensity and/or quality of the steps may have been different, such that a step in the men was not equivalent to a step in the women. In addition, our men recorded substantially more steps/day than the women such that far fewer men were considered low active than the women. Although these measurement differences may underlie our results, it is also possible that there are biological reasons that explain the differences we saw among male and female smokers, and this appears worthy of further investigation.

After adjustment for BMI, the associations between greater ambulatory activity and many of the biological markers were attenuated; however, this was not unexpected as excess body weight may actually mediate some of these relationships. The interrelationship of activity and body fatness is complex and not always able to be clarified by linear regression modeling. Various studies have found that the relationship between physical activity and inflammation is attenuated after adjustment for fatness.[40,41] Increased body size has also been shown to be associated with lipid biomarkers, with higher BMI more strongly associated with higher LDL-C, TC, and lower HDL-C than physical inactivity.[40] In our study, greater ambulatory activity was related to a better LDL lipoprotein profile, which was in part related to BMI as was expected. Our results suggest that body fatness is an important mediator of the relationships we examined.

We saw statistically significant associations with many of the biomarkers even though the participants had reasonably healthy biomarker profiles. Participants in the WSHS were recently compared with nonsmokers, former smokers, and current smokers who participated in the National Health and Nutrition Examination Survey (NHANES) in 2005 to 2006.[42] Smokers in the WSHS had lower levels of TC (183.8 mg/dL vs. 202.5 mg/dL; $P < .05$), TG (142.2 mg/dL vs. 158.0 mg/dL; $P < .05$), and FG (94.9 ± vs. 102.3; $P < .05$) compared with smokers in NHANES, suggesting that smokers seeking cessation treatment may have a different health profile than current smokers in the general population. Consequently, it is possible that the association between greater ambulatory activity and health status would be stronger in a population of smokers not seeking treatment.

Understanding how much ambulatory activity is related to improved biomarkers of health is an important public health issue. Although limited by the observational nature of our study, we can still examine what level of ambulatory activity is associated with an improved biomarker profile. Waist circumference was significantly lower with ambulatory activity > 5000 steps/day; however, other significant relationships were only seen with higher levels of activity. DBP, FG, and TC/HDL-C were significantly lower in men and women with > 10,000 steps/day vs. those with < 5000 steps/day. Among the women only, where we used the 7500 step/day cutpoint, that level of activity was associated with significantly lower weight, BMI, CRP, TC, LDL particles, and small LDL particles. In addition, this level of activity was related to substantial and significant reductions in the risk of metabolic syndrome and high-risk levels of CRP. These associations with what is considered to be the "somewhat active" category are consistent with prior studies, although relationships with specific biomarkers have varied.[43–45] This suggests that ambulatory activity may not need to be > 10,000 steps/day for health benefits to be accrued.

The main limitation of this study is its cross-sectional design, which does not allow us to make strong causal inferences about the observed relations. In addition, reactivity to wearing the pedometer, in which subjects will increase their activity when they know they are being monitored, may also be a problem. A recent study suggested that pedometer reactivity was greatest when participants used an unsealed pedometer and recorded their steps/day as our subjects did.[46] Therefore, it's possible we overestimated subjects' normal activity levels which would have attenuated predictive relations. However, it's also possible we underestimated activity as pedometers cannot capture nonambulatory activities like swimming and cycling. As mentioned previously, another limitation is that we could not measure the intensity or duration of the steps taken. Finally, only 69% of the subjects enrolled in the WSHS had valid pedometry data, and therefore our results could be subject to selection bias. However, we did compare those with and without valid pedometry data and the subjects appeared to have similar demographic characteristics. Although it seems low, this 69% figure is similar to the proportion of samples with valid pedometry data seen in prior population-based studies in Colorado (68%)[47] and Australia (70%).[39]

Strengths of this study include the objective measurement of ambulatory activity to assess daily physical activity. Most prior studies have usually measured physical activity through self-report, which is subject to validity issues and recall bias.[48] Also, our study measures cumulative ambulatory activity, not just purposeful exercise, which has great translatable potential. With further work, the potential recommendations for a steps/day level has great public health appeal in that walking is a very common activity, people can accumulate steps throughout a day, and pedometers are reasonably cheap and easy to use for personal measurement.

Conclusions

This study suggests that the relations between ambulatory activity and health outcomes observed in smokers are similar to those observed in nonsmokers. Greater activity was associated with lower waist circumference, diastolic blood pressure, and TC/HDL-C in the total sample, as well as lower weight, BMI, CRP, triglycerides, total LDL and small LDL particle concentration, and metabolic syndrome in women. These associations were mediated, in part, by a reduction in body mass index. These results suggest that the benefits of physical activity are not negated by smoking; however, these findings do not in any way suggest that physical activity neutralizes the harms of smoking. Quitting smoking will always be the most beneficial action a smoker can take regardless of his/her activity level.

Acknowledgments

Our thanks to Megan Piper and Paul Kohn of the Center for Tobacco Research and Intervention at the University of Wisconsin for their assistance with data management. This work was supported in part by grant P50 DA019706 from the National Institute on Drug Abuse and by 1UL1RR025011 from the National Center for Research Resources, NIH, to the University of Wisconsin-Center for Tobacco Research and Intervention. Medications for the study were provided by GlaxoSmithKline. This study is registered at www.clinicaltrials.gov (No. NCT00332644).

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