Nonexercise Physical Activity and Inflammatory and Oxidative Stress Markers in Women

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Abstract

Background: Leisure time exercise has been linked to lower circulating levels of inflammatory markers. Few studies have examined the association of nonexercise physical activity with markers of inflammation and oxidative stress.

Methods: This cross-sectional analysis included 1005 Chinese women aged 40–70 years. Usual physical activity was assessed through in-person interviews using a validated physical activity questionnaire. Plasma proinflammatory cytokines and urinary F₂-isoprostanes were measured. Multivariable linear models were used to evaluate the association of inflammatory and oxidative stress markers with nonexercise physical activity and its major components.

Results: Nonexercise physical activity accounted for 93.8% of overall physical activity energy expenditure. Levels of nonexercise physical activity were inversely associated with circulating concentrations of interleukin (IL)-6 ($P_{\text{trend}}=0.004$), IL-1 β ($P_{\text{trend}}=0.03$) and tumor necrosis factor- α (TNF- α) ($P_{\text{trend}}=0.01$). Multivariable-adjusted concentrations of these cytokines were 28.2% for IL-6, 22.1% for IL-1 β , and 15.9% for TNF- α lower in the highest quartile of nonexercise physical activity compared with the lowest quartile. Similar inverse associations were found for two major components of nonexercise physical activity, walking and biking for transportation, and household activity. No significant associations were observed between nonexercise physical activity and oxidative stress markers.

Conclusion: Daily nonexercise physical activity is associated with lower levels of systemic inflammation. This finding may have important public health implications because this type of activity is the main contributor to overall physical activity among middle-aged and elderly women.

Introduction

AN ACTIVE LIFESTYLE WITH REGULAR EXERCISE has been associated with decreased risk of many chronic diseases and increased longevity.^{1,2} Current public health recommendations for physical activity call for adults to have at least 30 min per day of moderate-intensity exercise on most days of the week.^{3,4} Nevertheless, only about one half of adults in the United States and less than a fifth of adults in East Asian countries meet this recommendation.^{3,5} On the other hand, nonexercise physical activity, any form of physical activity in a nonstructured period, such as housework and activity associated

with domestic responsibilities, is the primary source of physical activity-related energy expenditure among middle-aged and elderly women.^{6,7} Nonexercise activity thermogenesis, defined by Levine *et al.*^{8,9} as all physical activity energy expenditure except that from structured exercise, was found to play a significant role in resistance to fat gain in humans.⁸ This form of daily physical activity at home and in the workplace, which is likely to be a light-to-moderate level of exercise intensity, has been associated with reduced risk of many chronic diseases, including cardiovascular disease, cancer, diabetes, and obesity.¹⁰

Chronic inflammation and oxidative stress are important in the pathogenesis of many chronic diseases.^{11–13} A hallmark

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of inflammation is increased production of proinflammatory cytokines.¹⁴ Greater levels of physical activity have been associated with lower circulating concentrations of inflammatory biomarkers such as C-reactive protein (CRP) and interleukin (IL)-6 in epidemiological studies, most of which have been conducted in Western societies^{15–18} and focused on leisure time exercise.^{16–18} The influence of nonexercise physical activity such as household and other daily physical activity has not been adequately examined.^{18,19} Only two published studies reported that increases in walking and/or other daily life activity were inversely associated with blood concentrations of IL-6 and CRP.^{18,19} In addition, 15-F_{2t}-isoprostanes (F₂-IsoPs), a class of free radical-catalyzed lipid peroxidation products of arachidonic acid, are considered the accurate and reliable biomarker of endogenous oxidative stress in humans.^{20,21} Mixed results have been reported with respect to effects of physical activity on oxidative stress,^{22–24} with exercise both reducing²² and failing to reduce oxidative stress in previous studies.^{23,24} To our knowledge, no study to date has directly evaluated the association between non-exercise physical activity and oxidative stress.

In this study, we measured a panel of inflammatory markers (CRP, proinflammatory cytokines and their soluble receptors) and oxidative stress markers F₂-IsoPs and their major metabolite in 1005 Chinese women aged 40–70 years, to examine whether low- to moderate-intensity daily non-exercise physical activity is inversely associated with levels of systemic inflammation and oxidative stress.

Methods

Subjects

This analysis used data from a nested case-control study of colorectal cancer,²⁵ in which 1005 women were selected from the Shanghai Women's Health Study (SWHS). Both selected cases and controls were cancer-free at baseline. The SWHS is an ongoing prospective cohort study in Shanghai, China. Details of the study design and methods have been described elsewhere.^{26,27} Briefly, at the baseline survey conducted from 1997 to 2000, 74,941 women aged 40–70 years from seven urban communities of Shanghai were recruited (participation rate: 92%). All women completed a detailed baseline survey that collected information on demographic characteristics, lifestyle and dietary habits, medical history, and other exposures. Habitual dietary intake data over the preceding 12 months were collected during in-person interviews using a validated food-frequency questionnaire.²⁶ Anthropometric measurements, including current weight, height, and circumferences of the waist and hips, were also taken according to a standard protocol.²⁸ The study was approved by the relevant institutional review boards for human research in both China and the United States. Written informed consent was obtained from all study participants.

At study enrollment, resting blood and urine samples were collected after completion of questionnaire surveys. Seventy-six percent of cohort members donated a 10-mL blood sample and 88% donated a urine sample (76% at baseline and 12% during the first follow-up approximately 2 years later).²⁷ After collection, samples were kept at 0°C–4°C and processed within 6 hr. Immediately after processing, all samples were stored at –70°C until laboratory analyses were conducted.

Assessment of physical activity

A validated physical activity questionnaire (Supplementary Appendix 1; Supplementary material is available online at www.liebertpub.com/jwh) was used to assess physical activity related to a number of domains (household, transportation, leisure and recreation, and others).²⁹ The questionnaire evaluated regular exercise and sports participation during the 5 years preceding the interview.²⁹ Regular exercisers (at least once a week for 3 consecutive months) were asked to report details for up to three types of exercise/sports (i.e., type/intensity, duration [hours/week], and years of participation). Information on daily activities, including transportation-related activity, household activity, and others, was also collected. Transportation-related activity was assessed with four questions that asked about time spent (minutes/day) walking to and from work, walking for other reasons (e.g., household errands), cycling to and from work, and cycling for other reasons. Time spent in housework (hours/day; such as shopping, cooking, laundering, cleaning, and child care) and stairs climbed each day (flights/day) were also assessed. Physical activity energy expenditure was estimated using standard metabolic equivalent (MET) values.³⁰ The weighted average of energy expended in all activities reported over the 5 years preceding the interview (MET-hours/week/year) was used. A compendium of physical activity values in MET hours/week for each daily activity was used, including housework, 2.0 METs; walking, 3.3 METs; cycling, 4.0 METs; and per flight of stairs, 0.075 MET-hour.³¹ The MET intensity of physical activity was classified as light intensity (<3 METs), moderate intensity (3–6 METs), and vigorous intensity (>6 METs).³¹ Overall, METs were summed over METs from exercise and nonexercise physical activities. The latter were calculated as the sum of METs from walking and cycling for transportation, stair climbing, and household physical activity. Occupation-related physical activity was not considered (79% of participants were retired at study enrollment). Our validation study found that this questionnaire stratifies women by their activity levels in these subtypes reasonably well.²⁹ Spearman correlations for each activity type, compared with repeated 7-day recalls obtained over 12 months, were as follows: exercise ($r=0.62$), walking ($r=0.67$) and cycling ($r=0.66$) to and from work, walking ($r=0.33$) and cycling ($r=0.60$) for other reasons, stair climbing ($r=0.73$), and household activities ($r=0.46$).

Biomarker measurement

Cytokines and their receptors were assayed by using a Millipore MILLIPLEX[®] MAP High Sensitivity Human Cytokine multiplex kit for IL-1 β , IL-6, and tumor necrosis factor (TNF)- α and a Human Soluble Cytokine Receptor Panel multiplex kit for soluble IL-6 receptor (sIL-6R), soluble GP130 (sGP130, a regulator of IL-6/sIL-6R complex signaling), soluble TNF-R1 (sTNF-R1), and sTNF-R2 (Millipore Corporation, Billerica, MA, USA) at Vanderbilt Hormone Assay & Analytical Services Core. Plasma samples and standards were assayed in duplicate. High-sensitivity CRP was measured using ACE[®] High Sensitivity C-Reactive Protein Reagent (ACI-22) in the first batch and using the CRP (HS) Wide Range kit in the second batch. We adjusted for assay batch in all analyses. Intra-assay coefficients of variation for plasma inflammatory markers studied were <17.4%, and interassay

TABLE 1. ENERGY EXPENDITURE FROM PHYSICAL ACTIVITY BY SUBTYPES

Subtypes of physical activity	Contribution to overall physical activity energy expenditure (%) ^a
Nonexercise physical activity	93.8
Routine walking and biking for transportation	49.6
Household activity	38.2
Other nonexercise physical activity	6.0
Exercise physical activity	6.2

^aEstimated based on metabolic equivalent hours/week.

coefficients of variation were <21%.³² Urinary excretion of F₂-IsoPs and the major metabolite of F₂-IsoPs, 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostanes (F₂-IsoP-M), were measured by gas chromatography/negative ion chemical ionization mass spectrometry (GC/NICI MS) at Vanderbilt Eicosanoid Core Laboratory.³³ Both F₂-IsoPs and F₂-IsoP-M concentrations were expressed as nanograms per milligrams of creatinine. The precision of the assay was $\pm 6\%$ and accuracy was 96%.³³

Statistical analysis

Participants with less than the detectable limits of biomarkers studied were excluded from the primary analysis (TNF- α , $n=4$; sTNF-R1, $n=5$; sTNF-R2, $n=1$; IL-1 β , $n=102$; IL-6, $n=71$; sGP130, $n=1$; sIL-6R, $n=3$; CRP, $n=90$; F₂-IsoPs, $n=0$; and F₂-IsoP-M, $n=0$), as were participants with outliers according to a box plot (sTNF-R1, $n=1$; sTNF-R2, $n=3$;

sGP130, $n=1$; sIL-6R, $n=6$; F₂-IsoPs, $n=2$; and F₂-IsoP-M, $n=2$). Log-transformation was conducted to normalize the distribution of the biomarkers studied. Geometric means of these markers according to quartiles of physical activity METs were obtained by using the general linear model after adjustment for potential confounding factors. Tests for linear trend were performed by entering categorical variables as continuous variables in the linear regression model. We also used a restricted cubic spline linear regression analysis³⁴ to evaluate the association of selected biomarkers with non-exercise physical activity on a continuous basis and to account for possible nonlinear effects. Knots were placed at the 5th, 50th, and 95th percentiles of the distribution of physical activity. We excluded participants whose nonexercise physical activity level was below the 0.5th or above the 99.5th percentile from the restricted cubic spline model to minimize the influence of outliers.

Potential confounders adjusted for in multivariable models included age, education, occupation, body mass index (BMI), cigarette smoking, alcohol consumption, regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID), regular use of vitamin supplements, dietary intakes of total energy and total fruits and vegetables, menopausal status, Charlson comorbidity score,^{35,36} diseases of the musculoskeletal system and connective tissue (International Statistical Classification of Diseases 9 codes: 710–739), and other infectious and inflammatory diseases. Supplementary Table S1 (Appendix 2) summarizes the health conditions and diseases included in each of these categories. Additionally, we adjusted for time interval between sample collection and last meal in a subgroup analysis of nonfasting samples. We also adjusted for use of antibiotics and vitamin supplements in the week before sample collection and assay batch.

TABLE 2. AGE-ADJUSTED CHARACTERISTICS OF STUDY PARTICIPANTS ACCORDING TO NONEXERCISE PHYSICAL ACTIVITY LEVEL^a

	Quartiles of nonexercise physical activity (MET-hours/week)				p for trend ^b
	≤ 70.7 ($n=249$)	70.8–94.5 ($n=253$)	94.6–122.5 ($n=251$)	> 122.5 ($n=252$)	
Age, ^c years	58.9 (8.5)	59.0 (8.3)	57.9 (8.9)	56.6 (9.3)	0.006
High school and above, %	42.4	29.7	30.8	27.1	0.002
Manual laborers, %	50.1	58.9	60.3	60.6	0.07
Ever cigarette smoking, %	4.3	3.7	3.6	3.0	0.89
Ever alcohol consumption, %	3.9	3.0	2.0	2.6	0.65
Postmenopausal, %	77.6	75.5	73.6	71.7	0.03
Aspirin and other nonsteroidal anti-inflammatory drug use, %	5.2	4.9	2.8	0.9	0.03
Multivitamin supplement use, %	25.3	18.5	18.5	12.0	0.004
History of infectious and inflammatory disease, %	63.5	62.7	62.0	51.9	0.02
History of disease of the musculoskeletal system and connective tissue, %	12.1	5.5	6.5	8.8	0.02
Charlson comorbidity score, mean (SE)	0.39 (0.04)	0.27 (0.04)	0.30 (0.04)	0.24 (0.04)	0.01
Body mass index, mean (SE), kg/m ²	24.8 (0.2)	24.5 (0.2)	24.7 (0.2)	24.7 (0.2)	0.82
Dietary intake, mean (SE)					
Total calories, kJ/d	7869.9 (124.2)	7891.1 (123.2)	8102.9 (123.2)	8165.0 (123.7)	0.05
Fruits, g/d	230.7 (10.2)	223.4 (10.1)	240.5 (10.2)	275.6 (10.2)	0.001
Vegetables, g/d	285.55 (10.9)	282.9 (10.8)	294.1 (10.8)	308.2 (10.9)	0.10

^aExcept for the mean age, data were standardized to the age distribution.

^bLinear regression models were used for continuous variables and Cochran-Mantel-Haenszel chi-square tests for categorical variables. MET, metabolic equivalent.

TABLE 3. MULTIVARIABLE-ADJUSTED CONCENTRATIONS OF INFLAMMATORY AND OXIDATIVE STRESS MARKERS IN WOMEN
ACCORDING TO QUANTILES OF NONEXERCISE PHYSICAL ACTIVITY^a

Markers	By quartiles of nonexercise physical activity, MET-hours/week ^b				By quartiles of walking and biking for transportation, MET-hours/week ^b				By quartiles of household physical activity, MET-hours/week ^b			
	n	Geometric mean (SE)	Difference, % ^c	p for trend	n	Geometric mean (SE)	Difference, % ^c	p for trend	n	Geometric mean (SE)	Difference, % ^c	p for trend
TNF- α , pg/mL	Q1	247	6.41 (1.05)	Reference	247	6.73 (1.05)	Reference	0.005	150	6.56 (1.06)	Reference	0.03
	Q2	252	6.02 (1.05)	-6.08	129	5.51 (1.07)	-18.13*		310	6.06 (1.04)	-7.62	
	Q3	249	5.89 (1.05)	-8.11	296	5.89 (1.04)	-12.48*		245	5.72 (1.05)	-12.80	
	Q4	249	5.39 (1.05)	-15.91**	325	5.54 (1.04)	-17.68**		292	5.63 (1.04)	-14.18*	
sTNF-R1, pg/mL	Q1	232	1097 (1.03)	Reference	235	1116 (1.03)	Reference	0.60	138	1102 (1.04)	Reference	0.72
	Q2	240	1137 (1.03)	3.59	122	1136 (1.04)	1.79		292	1145 (1.02)	3.96	
	Q3	239	1124 (1.03)	2.47	281	1095 (1.03)	-1.88		237	1128 (1.03)	2.41	
	Q4	239	1133 (1.03)	3.26	312	1149 (1.02)	2.90		283	1106 (1.03)	0.38	
sTNF-R2, pg/mL	Q1	232	4145 (1.02)	Reference	235	4230 (1.02)	Reference	0.25	138	4306 (1.03)	Reference	0.46
	Q2	240	4362 (1.02)	5.25	122	4278 (1.03)	1.15		294	4320 (1.02)	0.32	
	Q3	239	4380 (1.02)	5.68	281	4288 (1.02)	1.37		236	4368 (1.02)	1.42	
	Q4	241	4306 (1.02)	3.88	314	4368 (1.02)	3.28		284	4216 (1.02)	-2.10	
IL-1 β , pg/mL	Q1	226	1.45 (1.08)	Reference	228	1.42 (1.08)	Reference	0.048	136	1.48 (1.10)	Reference	0.08
	Q2	228	1.23 (1.08)	-15.17	112	1.21 (1.11)	-14.79		285	1.25 (1.07)	-15.54	
	Q3	224	1.22 (1.08)	-15.86	267	1.26 (1.07)	-11.27		223	1.23 (1.08)	-16.89	
	Q4	221	1.13 (1.08)	-22.07*	292	1.14 (1.07)	-19.72*		255	1.16 (1.07)	-21.62*	
IL-6, pg/mL	Q1	235	4.40 (1.08)	Reference	233	4.26 (1.08)	Reference	0.02	142	4.51 (1.10)	Reference	0.07
	Q2	235	3.72 (1.08)	-15.45	116	3.49 (1.11)	-18.08		300	3.64 (1.07)	-19.29	
	Q3	225	3.79 (1.08)	-13.86	276	4.01 (1.07)	-5.87		216	3.82 (1.08)	-15.30	
	Q4	235	3.16 (1.08)	-28.18**	305	3.27 (1.07)	-23.24**		272	3.44 (1.07)	-23.73*	
sGP130, pg/mL	Q1	228	174,622 (1.02)	Reference	231	178,000 (1.02)	Reference	0.33	136	173,277 (1.03)	Reference	0.20
	Q2	239	177,997 (1.02)	1.93	121	175,506 (1.03)	-1.40		293	177,645 (1.02)	2.52	
	Q3	239	181,030 (1.02)	3.67	281	178,166 (1.02)	0.09		233	183,521 (1.02)	5.91	
	Q4	238	182,459 (1.02)	4.49	311	182,049 (1.02)	2.27		282	179,697 (1.02)	3.70	

(continued)

TABLE 3. (CONTINUED)

Markers	By quartiles of nonexercise physical activity, MET-hours/week ^a				By quartiles of walking and biking for transportation, MET-hours/week ^b				By quartiles of household physical activity, MET-hours/week ^b			
	n	Geometric mean (SE)	Difference, % ^c	p for trend	n	Geometric mean (SE)	Difference, % ^c	p for trend	n	Geometric mean (SE)	Difference, % ^c	p for trend
sIL-6R, pg/mL	Q1 231 Q2 239 Q3 238 Q4 239	22,501 (1.03) 21,129 (1.03) 21,201 (1.03) 21,718 (1.03)	Reference -6.10 -5.78 -3.48	0.49	234 122 279 312	22,904 (1.03) 21,293 (1.05) 20,310 (1.03) 22,037 (1.03)	Reference -7.03 -11.33** -3.78	0.27	138 293 234 282	21,882 (1.04) 21,893 (1.03) 21,706 (1.03) 21,156 (1.03)	Reference 0.05 -0.80 -3.31	0.41
CRP, mg/L	Q1 182 Q2 201 Q3 201 Q4 206	1.14 (1.08) 1.22 (1.08) 1.33 (1.08) 1.09 (1.08)	Reference 7.02 16.67 -4.39	0.84	183 93 246 268	1.20 (1.08) 1.32 (1.12) 1.23 (1.07) 1.11 (1.07)	Reference 10.00 2.50 -7.50	0.38	109 241 200 240	1.19 (1.11) 1.11 (1.07) 1.30 (1.08) 1.19 (1.07)	Reference -6.72 9.24 0.00	0.55
F ₂ -IsoPs, ng/mg Cr	Q1 223 Q2 225 Q3 230 Q4 225	1.55 (1.03) 1.42 (1.03) 1.61 (1.03) 1.62 (1.03)	Reference -8.39 3.87 4.52	0.09	216 119 271 297	1.62 (1.04) 1.42 (1.05) 1.53 (1.03) 1.57 (1.03)	Reference -12.35** -5.56 -3.09	0.77	136 278 225 264	1.60 (1.04) 1.45 (1.03) 1.50 (1.03) 1.67 (1.03)	Reference -9.38 -6.25 4.37	0.06
F ₂ -IsoP-M, ng/mg Cr	Q1 211 Q2 217 Q3 227 Q4 220	0.60 (1.03) 0.56 (1.03) 0.59 (1.03) 0.59 (1.03)	Reference -6.67 -1.67 -1.67	0.99	209 111 264 291	0.60 (1.03) 0.58 (1.05) 0.59 (1.03) 0.57 (1.03)	Reference -3.33 -1.67 -5.00	0.37	129 267 219 261	0.58 (1.04) 0.57 (1.03) 0.57 (1.03) 0.60 (1.03)	Reference -1.72 -1.72 3.45	0.35

^aAdjusted for age, education, occupation, cigarette smoking, alcohol consumption, body mass index, menopausal status, vitamin supplement use, aspirin and other nonsteroidal anti-inflammatory drug use, total intake of fruits and vegetables, total energy intake, diseases of the musculoskeletal system and connective tissue, other infectious/inflammation-related diseases, Charlson comorbidity score, use of antibiotics or vitamin supplements in the week before sample collection, and assay batch using general linear models.

^bQuartile cutoffs for nonexercise physical activity: 70.7, 94.5, and 122.5 MET-hours/week; quartile cutoffs for walking and biking for transportation: 31.4, 46.2, and 69.3 MET-hours/week; quartile cutoffs for household activity: 28.0, 42.0, and 56.0 MET-hours/week.

^cDifference (%) = (geometric mean of inflammatory marker in each quartile group of physical activity - geometric mean in the lowest quartile group)/geometric mean in the lowest quartile group.

* $p < 0.05$.

** $p < 0.01$.

Cr, creatinine; CRP, C-reactive protein; F₂-IsoPs, 15-F_{2t}-isoprostanes; F₂-IsoP-M, 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostanes; IL, interleukin; sGP130, soluble GP130; sIL-6R, soluble IL-6 receptor; sTNF-R1, soluble tumor necrosis factor receptor 1; sTNF-R2, soluble tumor necrosis factor receptor 2; TNF- α , tumor necrosis factor α .

In sensitivity analyses, participants with less than the detectable limits of markers were included to check whether nondetection differed by physical activity, and participants with CRP > 10 mg/L were excluded to reduce the influence of potential acute inflammation on our results. A subgroup analysis restricted to retired participants ($n=794$, 79%) was also conducted to evaluate potential influences of occupation-related physical activity on the results. Multicollinearity was not a concern, since the variance inflation factor for all variables studied were < 3. All statistical tests were two-sided and were performed using SAS statistical software, version 9.2 (SAS Institute, Cary, NC).

Results

In this study population, nonexercise physical activity accounted for 93.8% of overall physical activity METs (Table 1). Energy expenditure from routine walking and biking for transportation and household-related activity were the two major subtypes of nonexercise physical activity, accounting for 49.6% and 38.2% of overall physical activity METs, respectively.

Characteristics of study participants by quartile of nonexercise physical activity METs are presented in Table 2. Women with higher levels of nonexercise physical activity were more likely to be younger and have higher intakes of fruits and total energy. They were less likely to attain higher levels of education, take NSAIDs and vitamin supplements, or have a history of infectious or inflammatory disease. Other low-grade inflammation-related characteristics, such as BMI, cigarette smoking, or intake of vegetables, were not associated with levels of nonexercise physical activity.

After adjustment for age, assay batch, BMI, and other potential confounding factors, levels of nonexercise physical activity were inversely associated with circulating concentrations of IL-6 ($P_{\text{trend}}=0.004$), IL-1 β ($P_{\text{trend}}=0.03$), and TNF- α ($P_{\text{trend}}=0.01$) (Table 3). Multivariable-adjusted concentrations of these cytokines were 28.2% for IL-6, 22.1% for IL-1 β , and 15.9% for TNF- α lower in the highest quartile of nonexercise physical activity compared with the lowest quartile. Figure 1 visually depicts the shape of the correlation between nonexercise physical activity and selected inflammatory markers after adjusting for all potential confounding variables in a restricted cubic spline model. As shown in Fig. 1A and 1B, nonexercise physical activity was inversely and approximately linearly associated with concentrations of IL-6 and TNF- α . Similarly, IL-1 β concentrations were inversely associated with increasing nonexercise physical activity but leveled off at approximately 120 MET-hours/week (Fig. 1C). No significant associations between nonexercise physical activity and levels of soluble receptors of cytokines studied, CRP, or oxidative stress markers were found (Table 3).

Similar inverse associations with the inflammatory markers IL-6, IL-1 β , and TNF- α were found for two major components of nonexercise physical activity: walking and biking for transportation and household activity (Table 3). In a subgroup analysis of nonexercisers ($n=559$), household activity was also inversely associated with circulating levels of IL-6 ($P_{\text{trend}}=0.065$), IL-1 β (0.08), and TNF- α (0.03) (data not shown), essentially identical to the results observed in the entire study population (Table 3).

We also evaluated the association between leisure time exercise and inflammatory markers. Exercise METs were

FIG. 1. Smoothed plot of logarithmically transformed concentrations of the proinflammatory cytokines **(A)** IL-6, **(B)** TNF- α , and **(C)** IL-1 β according to nonexercise physical activity levels. The value of the cytokines at the median level of the first quartile of nonexercise physical activity was treated as the reference. Changes in log-transformed concentrations of inflammatory cytokines according to nonexercise physical activity were estimated by using restricted cubic-spline linear regression models with knots placed at the 5th, 50th, and 95th percentiles of physical activity after adjustment for all potential confounding factors. Participants with nonexercise physical activity below the 0.5th or above the 99.5th percentile were not plotted. Point estimates are indicated by a solid line and 95% CIs by dashed lines. IL, interleukin; TNF, tumor necrosis factor α ; CI, confidence interval.

inversely associated with TNF- α levels ($P_{\text{trend}}=0.01$) but not with other inflammatory or oxidative stress markers studied (data not shown). The correlation between nonexercise and exercise physical activity METs was very weak (Spearman $r = -0.05$). When mutually adjusting for nonexercise and exercise physical activities, results for neither nonexercise nor exercise physical activity changed appreciably (data not shown).

In sensitivity analyses, inclusion of participants with undetectable measures (assigning one half the detectable limits to undetectable measures) or exclusion of participants with CRP > 10 mg/L ($n=29$, 2.89%) did not markedly change the results (data not shown). The subgroup analysis of nonfasting samples showed that additional adjustment for time interval between sample collection and last meal did not appreciably alter the results (data not shown). No evidence showed that the inverse association between nonexercise physical activity and inflammatory markers significantly differed by age, BMI, or health conditions (data not shown), or in a subgroup analysis restricted to participants who were retired at study enrollment (Supplementary Table S2 [Appendix 3]).

Discussion

In this study of 1005 middle-aged and elderly women, we found that daily, nonexercise physical activity was significantly and inversely related to circulating concentrations of the inflammatory cytokines TNF- α , IL-6, and IL-1 β . These associations were independent of a wide range of potential confounding variables, including socioeconomic status, lifestyle factors, BMI, medical conditions, and use of aspirin and other NSAIDs.

Overall physical activity energy expenditure was specifically measured by two categories of physical activity in this study: exercise and nonexercise physical activities. Nonexercise physical activity METs describe energy expenditure associated with routine everyday activity, such as sitting, standing, and walking, which is distinct from purposeful exercise (structured exercise). Levine *et al.*⁸ demonstrated a role for nonexercise physical activity in resistance to fat gain in humans. When obese individuals adopt nonexercise physical activity-enhanced behavior, they are likely to expend an additional 350 calories per day,⁹ which is approximately equivalent to the energy expended for a walk of 65–83 min at a speed of 3.5 miles/hr for people with a body weight of 120 to 180 lb.³⁷ It has been shown that some types of daily activity are associated with modulation of systemic inflammation.^{15,18,19} For example, Craft *et al.*¹⁸ reported that increases in walking and other daily life activity were associated with lower concentrations of IL-6 and CRP among patients with peripheral arterial disease. Another small study of 185 healthy, middle-aged adults revealed similar results that regular walking was associated with lower concentrations of both inflammatory and hemostatic markers, independent of vigorous physical activity.¹⁹ Interestingly, vigorous activity was found to be inversely associated with hemostatic markers, but not with inflammatory markers.¹⁹ Our results are in line with these previous reports,^{15,18,19} showing an inverse association of walking and biking for transportation with circulating concentrations of TNF- α , IL-1 β , and IL-6, even after accounting for BMI and other lifestyle and health conditions. We did not find an association between nonexercise physical activity and CRP levels in this study. CRP, a sensitive marker of low-

grade systemic inflammation, is produced in the liver at the stimulation of proinflammatory cytokines, including IL-6, IL-1 β , and TNF- α .^{38,39} Differences in modes of exercise and study populations may explain some of the discrepancies in these studies.

Household activity was the second major contributor to overall physical activity energy expenditure in our study population, accounting for 38.2% of overall physical activity METs (Table 1). To the best of our knowledge, no study has directly examined the role of household activity in chronic inflammation and oxidative stress. We found, for the first time, that greater involvement in housework was related to lower concentrations of inflammatory markers. Women in the highest quartile (≥ 56 MET-hours/week, about 22 hr/week for household tasks with light effort³⁰) had TNF- α concentrations 14.2% lower, IL-1 β concentrations 21.6% lower, and IL-6 concentrations 23.7% lower than those in the lowest quartile (<28 MET-hours/week, about 11 hr/week for light household tasks³⁰). Moreover, these results were essentially identical to results in analyses restricted to women with no regular leisure time exercise, suggesting that adopting an active lifestyle by incorporating regular household physical activity may help to reduce chronic inflammation.

The association between leisure-time exercise and inflammation has been examined in several studies,^{15,16,18,19} with results generally pointing towards an inverse relationship, although not entirely consistent. In this study, a similar inverse association with exercise METs was found for TNF- α . However, this type of physical activity contributed to only a very small fraction (6.2%) of overall physical activity energy expenditure in this middle-aged and elderly population of Chinese women.

Results on the association between physical activity and oxidative stress markers have been mixed.^{22–24} For example, a randomized, controlled trial showed that aerobic exercise decreases urinary F₂-IsoP concentrations among 173 previously sedentary older women.²² However, no intervention effects on the oxidative stress marker were observed in an 8-week controlled aerobic exercise trial among adults with type 2 diabetes²³ or in a study of 5 weeks of resistance exercise in 69 adults.²⁴ We found no significant associations between F₂-IsoPs and physical activity, overall or by subtype of physical activity. Differences in study design, modes of exercise, intensity and duration of exercise, subject characteristics, or methods of lipid peroxidation measurement may explain some of the discrepancies in these studies. Clearly, this hypothesis needs to be further investigated.

It should be noted that this study has certain limitations. Because of its cross-sectional design, the study only allowed for an association analysis, and causal relationships cannot be inferred. As with all survey-based research design, measurement error in assessing physical activity is another concern, although the questionnaire has been previously evaluated to have reasonably good validity for the measurement of physical activity as compared with multiple 7-day physical activity recalls.²⁹ An objective measurement, such as accelerometry or doubly labeled water assessments,⁴⁰ should be considered in future research. Additionally, we could not completely rule out the possibility of residual confounding due to unmeasured or inadequately measured covariates, although many inflammation-related characteristics of participants were adjusted for in multivariable models. Moreover, because this

analysis was based on data from a case-control study of colorectal cancer nested in the SWHS, it is possible that the subjects included were not completely representative of the study population.

The effects of physical activity on inflammation are complex, varying according to the type of physical activity. Acute bouts of intensive exercise appear to induce a subclinical inflammatory response, manifested by transient increases in circulating proinflammatory cytokines and oxidative stress.^{38,39} Alterations in redox homeostasis induced by regular non-muscle-damaging exercise last only a few hours post exercise.⁴¹ In contrast, endurance-trained athletes and individuals exercising regularly exhibit decreased resting levels of proinflammatory cytokines compared with habitually sedentary individuals.^{42,43} In the SWHS, we found that middle-aged and elderly women significantly benefit from daily nonexercise physical activity.³¹ Women reporting no regular exercise but 10 or more MET-hours/day of nonexercise physical activity had 25%–50% lower mortality rates relative to inactive women (0–9.9 MET-hours/day).³¹ The present study's finding of an inverse association between nonexercise physical activity and circulating concentrations of inflammatory markers provides a possible biological mechanism for the health benefit of nonexercise physical activity.

In conclusion, higher levels of daily nonexercise physical activity are associated with lower concentrations of inflammatory markers among middle-aged and elderly women. A potential role of daily nonexercise physical activity in reducing inflammation warrants further investigations, which may have significant public health implications because this type of physical activity is the main contributor to total physical activity energy expenditure in middle-aged and elderly women.

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Author Disclosure Statement

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