Original Article

Influence of Leisure-Time Physical Activity on the Relationship between C-Reactive Protein and Hypertension in a Community-Based Elderly Population of Japan: The Tsurugaya Project

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There are several studies indicating an association between C-reactive protein (CRP) and blood pressure (BP) in the Japanese population, but the influence of physical activity has not been considered. Therefore, we designed a cross-sectional survey to determine whether leisure-time physical activity (LTPA) modifies the relation between CRP and hypertension among Japanese elderly. Our study population comprised 643 subjects aged 70 years and over in whom CRP, home BP, and self-reported LTPA were measured. LPTA was categorized into three levels of intensity—walking, brisk walking, and sports—and a questionnaire was used to estimate the level in each patient. Hypertension was defined as a home systolic BP of 135 mmHg or over and/or home diastolic BP of 85 mmHg or over or current use of antihypertensive agents. LTPA levels were associated with both CRP and hypertension. After adjustment for factors affecting CRP and hypertension, and additional adjustment for LTPA levels, the odds ratio (95% confidence interval) of hypertension by CRP was 2.21 (range: 1.33–3.72), 1.99 (1.17–3.42), and 2.38 (1.36–4.21) times higher in subjects in the second, third, and fourth quartiles of CRP, as compared to subjects in the first quartile, respectively. A multiple regression model showed a positive and significant relation between log-transformed CRP and systolic BP after adjustment for potential confounding factors when participants taking antihypertensive medication were excluded. This is the first study to clarify that the positive significant relation between CRP and hypertension was independent of LTPA levels among Japanese elderly. (*Hypertens Res* 2005; 28: 747–754)

***Key Words*: C-reactive protein, leisure-time physical activity, hypertension, Japanese, community-dwelling population**

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Introduction

C-reactive protein (CRP) is a classical acute-phase marker and a member of the pentraxin family of innate immune response proteins (*1*, *2*). The concentration of CRP in serum is generally less than 2 μg/ml but increases by as much as 1,000-fold in response to stimuli such as tissue injury or inflammation (*3*). Following removal of the inflammatory stimulus, CRP levels decline rapidly. These features have made CRP useful as a clinical marker of an inflammatory process. Over the last several years, increasing evidence has suggested that inflammation mechanisms are important in the pathophysiology of hypertension (*4*–*7*). Furthermore, several studies have shown that serum CRP levels are associated with the development of hypertension (*8*, *9*).

At the same time, numerous studies have indicated that physical activity (PA), including leisure-time physical activity (LTPA), is inversely related to the prevalence of hypertension (*10*, *11*) or serum concentration of CRP (*12*–*19*). A more recent study has also demonstrated that inflammatory markers including CRP were lower in older adults with higher levels of exercise and non-exercise PA (*12*). Considering these studies together, it is natural to assume that PA would be a potent modifier of the relationship between CRP and hypertension. But to our knowledge, there are only three reports that have investigated the relationship between CRP and hypertension adjusted for the effect of PA (*20*–*22*), and their results are inconsistent. Furthermore, although there have been several studies that indicated an association between serum CRP level and blood pressure (BP) in Japanese, the influence of PA on this relationship has not been considered (*23*–*27*). Therefore, we considered that it would be worthwhile to examine whether the relation between CRP and hypertension is dependent of LTPA, and designed the present cross-sectional analysis in Japanese community-dwelling elderly individuals for this purpose.

Methods

Study Participants

Our study population was comprised of subjects aged 70 years and older who were living in the Tsurugaya area of Sendai, one of the major cities in the Tohoku area of Japan. At the time of the study in 2002, there were 2,730 individuals aged 70 years and older living in Tsurugaya. We invited all of these individuals to participate in a comprehensive geriatric assessment, which included medical status, physical function, cognitive function and dental status, and 1,178 of them did so, giving their informed consent for analysis of the data. The protocol of this study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine.

We excluded subjects whose high-sensitivity CRP had not been measured ($n=29$). Since we assessed hypertension using self-measured BP at home (home blood pressure [HBP]) data, subjects who did not measure HBP data more than 3 days during the 4-week study period were also excluded ($n=182$). This criterion was based on our previous observation that average BP values for the first 3 days did not differ significantly from those obtained during the entire study period (*28*, *29*). We also excluded those subjects whose serum CRP concentrations were higher than 10.0 mg/l ($n=24$), because those with acute inflammatory conditions were frequently found to have serum CRP levels ≥10.0 mg/l (*30*). Furthermore, we excluded subjects who did not complete the questionnaire items on LTPA ($n=109$). Finally, we excluded all potential subjects with notable comorbidity factors that might influence the frequency and degree of PA by a self-reported decline of physical function using the Medical Outcome Study (*31*) (physical functioning score ≤1; $n=77$) or arthritis ($n=114$). As a result of these exclusions, the final study population comprised 643 subjects (mean age, 75.5±4.4 years; men: 48.5%).

Measurements

Anthropometric measures (height, body weight) were recorded by a standardized protocol. HBP was measured with an HEM747IC device (Omron Life Science Co., Ltd., Tokyo, Japan), which uses the cuff-oscillometric method to generate a digital display of systolic and diastolic blood pressures (SBP and DBP). This device has been validated previously, and satisfies the criteria of the Association for the Advancement of Medical Instrumentation (*32*). We used the following procedure to ascertain the accuracy of the HBP measurement. First, physicians informed the population about HBP recording and taught them how to measure their own BP. The daily measurement was made within 1 h of awakening and before breakfast, with the subject seated and having rested for at least 2 min. In subjects receiving antihypertensive drugs, HBP was measured before taking the drugs. The HBP of an individual was defined as the mean of all measurements obtained for that person. The mean (±SD) number of HBP measurements was 15.9±10.5 (range, 3–49).

Blood samples were drawn from the antecubital vein of the seated subject with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing sodium fluoride for blood glucose, and no additives for lipids and CRP analyses.

Total cholesterol (T-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) levels and blood glucose levels were measured by enzymatic methods (T-C, Denka Seiken, Tokyo, Japan; TG, Kyowa Medex, Tokyo, Japan; HDL-C, Daiichi Pure Chemicals, Tokyo, Japan; blood glucose, Shino-Test, Tokyo, Japan). Serum uric acid levels were determined according to a uricase method (*33*) with the Olympus autoanalyzer AU-5000 (Olympus Corp., Tokyo, Japan).

Table 1. Definition of Physical Activity Level

	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6
N	147	131	148	71	80	66
Walking	None	Low	High	Any	Any	Any
Brisk walking	None	None	None	Low	High	Any
Sports	None	None	None	None	None	Low and High
Walking (*N*)						
None	147	0	0	25	49	30
Low	0	131	0	21	2	19
High	0	0	148	25	29	17
Brisk walking (*N*)						
None	147	131	148	0	0	41
Low	0	0	0	71	0	12
High	0	0	0	0	80	13
Sports (*N*)						
None	147	131	148	71	80	0
Low	0	0	0	0	0	58
High	0	0	0	0	0	8

High: at least 3–4 times per week for at least 30 min each time; Low: reporting some activity in the past year, but not enough to meet high levels; None: no leisure-time physical activity. *N*: number of subjects.

CRP levels were determined using an immunotechnique on a Behring BN II analyzer (Dade Behring, Tokyo, Japan). The BN II high-sensitivity assay utilizes a monoclonal antibody coated on polystyrene particles and fixed-time kinetic nephelometric measurements (*34*). The BN II nephelometer uses a 1:400 dilution to measure CRP concentrations between 3.5 and 210 mg/l. The assay has been approved by the US Food and Drug Administration for use in assessing the risk of cardiovascular and peripheral vascular disease.

Questionnaire of LTPA

LTPA was measured through a self-reported single-item question and corresponding response sets. The question asked whether the subject had performed any activities from the following categories in the previous 12 months: walking, brisk walking, or sports (*e.g.*, aerobics, tennis, swimming, jogging, *etc.*). If they had participated in a given activity, the frequency and duration spent in the activity were ascertained using the following categories: for frequency, 1) 1–2 times per month, 2) 1–2 times per week, 3) 3–4 times per week, or 4) almost every day; and for duration (per walk or workout), 1) 0–30 min, 2) 0.5–1 h, 3) 1–2 h, 4) 2–3 h, 5) 3–4 h, or 6) 4 h or more.

Statistical Analysis

Hypertension was defined as a home SBP of 135 mmHg or over and/or a home DBP of 85 mmHg or over or using antihypertensive agents (*35*, *36*). Based on the recently proposed cutoff point for CRP, we also categorized the study participants as having a low (less than 1.0 mg/l) or high level (at least 1.0 mg/l) of CRP (*37*, *38*). The high-sensitivity CRP value (ng/ml) was used for calculating the log-transformed CRP.

Among the levels of exercise intensity, sports were considered the highest, followed in order by brisk walking and walking. Each of the three types was further classified into three subcategories according to the frequency and duration of the walks or workouts as follows (*11*, *39*): 1) High, at least 3–4 times per week for at least 30 min each time; 2) Low, some activity in the past year, but not enough to meet the criteria for the high group; and 3) None, no LTPA. Finally, we used these categories and subcategories to define the following six levels of LTPA (Table 1): 1) Level 1, no sports, no brisk walking, no walking; 2) Level 2, no sports, no brisk walking, low amount of walking; 3) Level 3, no sports, no brisk walking, high amount of walking; 4) Level 4, no sports, low amount of brisk walking, any amount of walking; 5) Level 5, no sports, high amount of brisk walking, any amount of walking; 6) Level 6, any amount of sports, any amount of brisk walking, any amount of walking. Since only 8 subjects reported participating in a high amount of sports activity, we combined high- and low-level sports activity into a single category. Table 1 also shows the number of participants according to the LTPA levels.

Diabetes was defined as a free blood glucose level of 200 mg/dl or over or current use of antidiabetic medication. Hypercholesterolemia was defined as a level of total cholesterol of 220 mg/dl or over, or current use of non-statin lipid-lowering agents. Gout was defined as a serum uric acid level of 7.0 mg/dl or over or current use of antihyperuricemic medication. Information on smoking status, drinking status and histories of prior cardiovascular diseases (CVD) were obtained from the questionnaire survey. Current drinkers

Table 2. Association between High Sensitive C-Reactive Protein Levels and Cardiovascular Disease Risk Factors

	C-reactive protein (mg/l)				*p* value
	0.05–0.27	0.28–0.54	0.55–1.16	1.17–9.96	
No. of participants	160	161	161	161	
Age (years)	75.2±4.4	75.6±4.1	75.8±4.8	75.2±4.5	0.51
Sex (male %)	41.9	49.1	51.6	51.6	0.26
BMI (kg/m^2)	22.0±3.1	23.5±2.9	24.3±3.0	25.0±3.3	<0.01
Hypertension (%)	54.4	75.2	75.8	79.5	<0.01
SBP (mmHg)	132.7±18.4	139.2±17.2	141.6±18.8	144.6±19.1	<0.01
DBP (mmHg)	74.7±9.0	76.3±10.0	77.9±9.4	79.1±9.8	<0.01
Hypercholesterolemia (%)	30.0	33.5	36.7	38.5	0.40
HDL-C (mg/dl)	60.8±14.5	55.9±13.5	53.8±13.3	52.2±14.3	<0.01
Diabetes (%)	3.1	8.7	11.8	13.7	<0.01
Gout (%)	10.0	16.8	17.4	25.5	<0.01
Smoker					
Current smoker (%)	11.3	14.3	12.4	18.0	0.32
Ex-smoker (%)	22.5	32.3	37.2	37.3	0.01
Non-smoker (%)	63.1	52.8	48.5	44.7	<0.01
Alcohol consumption (g)	11.8±29.3	12.7±32.7	13.5±28.7	11.9±24.2	0.95
Use of statin drugs (%)	13.8	16.8	21.1	17.4	0.38
Use of aspirin drugs (%)	5.0	10.6	10.6	13.7	0.07
History of CVD (%)	11.9	14.9	14.3	19.3	0.02

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; CVD, cardiovascular diseases. Variables are pressented as mean±SD. Hypertension: home SBP 135 mmHg or over and/or home DBP 85 mmHg or over or using antihypertensive agents.

Table 3. Correlation between Physical Activity and Blood Pressure or C-Reactive Protein

	Physical activity						*p* for trend
	Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	
Walking	None	Low	High	Any	Any	Any	
Brisk walking	None	None	None	Low	High	Any	
Sports	None	None	None	None	None	Low and High	
N (total: 643)	147	131	148	71	80	66	
Hypertension (%)	75.5	77.9	74.3	69.0	57.5	60.6	<0.01
SBP (mmHg)	142.6±1.5	142.1±1.6	139.3±1.5	136.6±2.2	137.0±2.1	134.4±2.3	0.13
DBP (mmHg)	78.1±0.8	77.9±0.8	76.4±0.8	76.9±1.1	75.7±1.1	75.8±1.2	0.12
log-hsCRP (ng/ml)	6.5±0.1	6.5±0.1	6.3±0.1	6.3±0.1	6.2±0.1	6.2±0.1	0.14
High-CRP (%)	36.1	30.5	27.0	28.2	22.5	21.2	<0.01
Odds ratio (95% CI)							
Hypertension*	1.00	1.09 (0.61–1.96)	0.97 (0.56–1.67)	0.89 (0.47–1.73)	0.53 (0.29–0.97)	0.62 (0.33–1.19)	0.02
High-CRP*	1.00	0.70 (0.41–1.20)	0.64 (0.38–1.08)	0.70 (0.36–1.34)	0.57 (0.29–1.10)	0.49 (0.24–0.98)	0.04

N: number of subjects. SBP, systolic blood pressure; DBP, diastolic blood pressure; log-hsCRP, log-transformed high sensitivity C-reactive protein (CRP); CI, confidence interval. Variables are pressented as mean±SD. High-CRP: CRP≥1.0 mg/l. *Adjusted for age, sex, body mass index, and smoking status. High: at least 3–4 times per week for at least 30 min each time; Low: reporting some activity in the past year, but not enough to meet high levels; None: no leisure-time physical activity.

were further asked about drinking frequency, beverage types usually consumed, and amount consumed on a single occasion. From these responses, we calculated the average daily alcohol consumption in g. We also treated statin agents as independent confounding factors because they have been reported to lower CRP levels (*40*, *41*). The drug information was confirmed by a well-trained pharmacist.

The clinical and biochemical data of the subjects are presented as the means±SD, or as the median and interquartile range for variables with a skewed distribution or percentages.

Table 4. Adjusted Relationships of High Sensitive C-Reactive Protein Levels (Quartile) to Hypertension

	Level of C-reactive protein (mg/l)				*p* for trend
	0.05–0.27	0.28–0.54	0.55–1.16	1.17–9.96	
All					
N (total: 643)	160	161	161	161	—
N of hypertensives	87	121	122	128	—
Odds ratio (95% CI)					
Age- and sex-adjusted	1.00	2.57 (1.60–4.18)	2.67 (1.66–4.35)	3.41 (2.08–5.67)	<0.01
Multiple adjusted*	1.00	2.26 (1.36–3.78)	2.05 (1.21–3.50)	2.45 (1.41–4.31)	0.03
Multiple* and PA levels adjusted	1.00	2.21 (1.33–3.72)	1.99 (1.17–3.42)	2.38 (1.36–4.21)	0.04
	Level of C-reactive protein (mg/l)				*p* for trend
	0.05–0.29	0.30–0.57	0.58–1.34	1.35–9.96	
Participants without brisk walking or sports activity					
N (total: 426)	106	107	106	107	—
N of hypertensives	64	86	84	89	—
Odds ratio (95% CI)					
Age- and sex-adjusted	1.00	2.81 (1.52–5.32)	2.60 (1.42–4.89)	3.38 (1.80–6.55)	<0.01
Multiple adjusted*	1.00	2.46 (1.28–4.86)	1.98 (1.00–3.96)	2.48 (1.21–5.19)	0.11
	Level of C-reactive protein (mg/l)				*p* for trend
	0.05–0.23	0.24–0.51	0.52–0.93	0.94–9.25	
Participants with sports or brisk walking activity					
N (total: 217)	53	55	54	55	—
N of hypertensives	25	31	38	41	—
Odds ratio (95% CI)					
Age- and sex-adjusted	1.00	1.52 (0.71–3.33)	2.85 (1.28–6.51)	3.52 (1.56–8.27)	<0.01
Multiple adjusted*	1.00	1.30 (0.57–2.98)	2.00 (0.81–5.00)	2.67 (1.06–6.94)	0.04

N: number of subjects. PA, physical activity; CI, confidence interval. *Adjusted for age, sex, body mass index, hypercholesterolemia, high-density lipoprotein-cholesterol, gout, history of cardiovascular diseases, diabetes, smoking, alcohol consumption, use of aspirin,

Differences in variables among the CRP groups were examined by analysis of variance (ANOVA) for continuous variables, or by the χ^2 test for variables of proportion. Multiple logistic regression analysis and analysis of covariance (ANCOVA) were used to examine the relation of LTPA with hypertension, SBP, DBP, log-transformed CRP and high-CRP ($\geq$1.0 mg/l) after adjustment for age, gender, body mass index (BMI), and smoking status. *p* values for linear trends were calculated using the level of LTPA as a continuous variable. The odds ratio (OR) and 95% confidence interval (CI) of hypertension for increasing CRP levels with the lowest level as the reference was also calculated using multiple logistic regression analysis. When we calculated the OR, we used an age-sex adjusted model and a multivariate model adjusted for age, sex, BMI, hypercholesterolemia, HDL-C, gout, history of CVD, diabetes, smoking habits/history, alcohol consumption, use of aspirin, and use of statin drugs; the final multivariable model was further adjusted for LTPA levels. *p* values for linear trends were calculated using the median (mg/l) of CRP levels. Multiple linear regression analysis was used to establish the relationship between BP and CRP after adjustment for age, gender, BMI, hypercholesterolemia, HDL-C, gout, history of CVD, diabetes, smoking, alcohol consumption, and LTPA levels in the subjects who were not using antihypertensive agents, aspirin, and statin drugs. Values of $p<0.05$ were considered to indicate statistical significance. All statistical analyses were performed using the Statistical Analysis System (version 9.1 for Windows; SAS Institute Inc., Cary, USA).

Results

Association between High-Sensitivity CRP Levels and Cardiovascular Disease Risk Factors

Table 2 shows the association between high-sensitivity CRP levels (quartile) and CVD risk factors. Both SBP and DBP were significantly higher in the highest CRP quartiles. BMI was also significantly higher in the highest CRP quartile and the mean HDL-C was lower in the highest CRP quartile. Mean age and alcohol consumption did not significantly differ among the CRP groups. The proportion of subjects with hypertension, diabetes, gout, history of smoking (*i.e.*, ex-smokers), and subjects with a history of CVD was larger in the highest CRP quartile. The proportion of subjects with no history of smoking was significantly smaller in the lowest

Table 5. Results of Multivariate Modelling for log-Transformed C-Reactive Protein

	log-CRP (ng/ml) (n=318)	
	β coefficient (SEM)	p value
SBP	0.008 (0.003)	<0.01
Age	0.013 (0.014)	0.34
Sex	−0.086 (0.183)	0.64
BMI	0.090 (0.020)	<0.01
Hypercholesterolemia	0.275 (0.126)	0.03
HDL-C	−0.009 (0.005)	0.06
Gout	0.242 (0.170)	0.16
History of CVD	−0.114 (0.218)	0.60
Diabetes	0.241 (0.207)	0.25
Current smoker	0.492 (0.200)	0.01
Ex-smoker	0.291 (0.183)	0.11
Alcohol consumption	−0.003 (0.002)	0.20
PA Level 2	−0.038 (0.180)	0.83
PA Level 3	−0.237 (0.169)	0.16
PA Level 4	−0.287 (0.202)	0.16
PA Level 5	−0.096 (0.186)	0.61
PA Level 6	−0.073 (0.206)	0.72

log-CRP, log-transformed C-reactive protein; SBP, systolic blood pressure; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; CVD, cardiovascular diseases; PA, physical activity.

CRP quartile. The gender ratio, the number of current smokers, and the rates of hypercholesterolemia, statin user, and aspirin use did not differ significantly among the CRP groups.

Correlation between LTPA Levels and BP or CRP

Table 3 shows the relationship between LTPA levels and the prevalence of hypertension, SBP, DBP, log-transformed high sensitivity CRP, or high-CRP after adjustment for age, gender, BMI and smoking status. In the crude model, increasing PA levels showed a significant inverse relationship with both the prevalence of hypertension (p for trend <0.01) and high-CRP (p for trend <0.01). Even after the adjustment for sex, age, BMI and smoking status, the significant inverse relation between PA levels and hypertension or high-CRP was unchanged (p for trend =0.02 and 0.04, respectively).

Relationships between High-Sensitivity CRP Levels (Quartile) and Hypertension

Adjusted relationships between CRP levels (quartile) and the prevalence of hypertension are shown in Table 4. The age- and sex-adjusted OR of hypertension increased from the lowest (reference) to the highest CRP quartiles in all subjects. These results were somewhat attenuated when we adjusted for other potential confounders: the ORs for hypertension of the second, third, and fourth CRP quartiles were 2.26 (95% CI: 1.36–3.78, p<0.01), 2.05 (95% CI: 1.21–3.50, p<0.01), and 2.45 (95% CI: 1.41–4.31, p<0.01), compared with the first group as a reference, and the frequency of hypertension was significantly higher in the high CRP group. When we additionally adjusted for the LTPA levels, which are potential confounding factors, the significantly positive association was unchanged: the ORs for hypertension of the second, third, and fourth CRP quartiles were 2.21 (1.33–3.72), 1.99 (1.17–3.42), and 2.38 (1.36–4.21), respectively. We also analyzed the relation between the CRP quartiles adjusted for hypertension and the subgroups, *i.e.*, participants who participated in sports or brisk walking (LTPA levels 4–6) and those who did not (LTPA levels 1–3). The relations between CRP and hypertension were mostly identical among these subgroups (p for interaction =0.95).

Multiple Regression Model Analysis of the Relationship between log-Transformed CRP and BP

To confirm the relationship between CRP and SBP values, we performed a multiple regression analysis among subjects who did not use antihypertensive medication, aspirin, or statin drugs. The multiple regression model showed a positive and significant relationship between log-transformed CRP and SBP after adjustment for potential confounding factors, including LTPA levels (Table 5). The SBP distinctly showed a significant relationship with log-transformed CRP (p<0.01). BMI, hypercholesterolemia, and current smoking were also positively related to log-transformed CRP. There was no significant interaction between LTPA levels and SBP for log-transformed CRP values (p for interaction =0.63).

Discussion

Hypertension is one of the most important modifiable risk factors for CVD in Western and Asian populations (*42*, *43*). It is well known that lifestyle changes (*e.g.*, diet, weight loss, exercise and smoking cessation, *etc.*) can reduce cardiovascular risk; in particular, regular PA reduces coronary and cardiovascular morbidity and mortality, independently from the other risk factors (*44*, *45*). PA is one of the most important independent contributors to the prevalence of hypertension (*10*, *11*). In this cross-sectional survey of Japanese community-dwelling elderly individuals, we found LTPA levels in daily life were inversely correlated with both serum CRP and the prevalence of hypertension.

Since the LTPA level was inversely related with both CRP and the prevalence of hypertension, we tested our hypothesis that the relation between CRP and hypertension would be dependent of LTPA levels. However, the positive significant relation between CRP and hypertension remained even after adjustment for the LTPA levels. Furthermore, there was a strong relation between the CRP and SBP values that was independent of the LTPA level among participants not taking antihypertensive or statin drugs or aspirin. Thus, we were able

to conclude for the first time that the relation between CRP and hypertension was independent of LTPA levels in a Japanese elderly population.

Several prospective studies have employed the amount of subjects' PA as one of the confounding factors in their multivariate analysis of the causal relationship between serum CRP and the development of hypertension and/or metabolic syndrome (*20*–*22*). In two of these studies (*21*, *22*), the amount of exercise did not attenuate the relationship between CRP and BP. The third prospective cohort study (*20*) also considered the influence of PA on the relation between CRP and BP, but in contrast to the other two studies, the results indicated that CRP was not a significant predictor of the development of hypertension or other metabolic syndromes. Although the reason for these discrepancies remains unclear, our data are similar to the first two studies, which indicated that CRP may be related to hypertension independent of PA levels.

In this study, we used HBP measurement. HBP makes it possible to obtain multiple measurements over a long observation period under relatively controlled conditions (*46*, *47*). It has been reported that multiple measurements eliminate observer bias and regression dilution bias; therefore, HBP measurements are more reliable than conventional BP measurements taken in medical settings (office BP) (*46*–*48*). We also adjusted for a considerable number of confounding factors. In this way, we were able to confirm the positive and significant relation between log-transformed CRP and SBP in subjects who were not using antihypertensive agents.

This study had several limitations. First, most of the participants were sufficiently active to participate in the survey. Therefore, we lacked the participation of those who were physically dependent or disabled due to metabolic syndromes or hypertension, leading to underestimation of the relation between CRP and hypertension. Second, since this study was a cross-sectional study, we could not conclude that CRP causes hypertension or that hypertension leads to increased CRP among subjects aged 70 years and over. Third, we did not directly measure the exercise intensities of walking, brisk walking and sports. Still, one may easily discriminate one's own "brisk walking" from ordinary walking. We therefore believe that the categorization of relative walking intensity based on the subjects' own perceptions was reliable. It is well known that ratings of perceived exertion correspond well to exercise intensity as measured by oxygen uptake (*49*).

In conclusion, we have demonstrated that among elderly subjects 70 years and older the higher LTPA levels were associated with reductions of serum CRP levels and hypertension prevalence, but that the positive significant relation between CRP and hypertension was independent of LTPA levels.

References

1. Gewurz H, Zhang XH, Lint TF: Structure and function of the pentraxins. *Curr Opin Immunol* 1995; **7**: 54–64.
2. Volanakis JE: Human C-reactive protein: expression, structure, and function. *Mol Immunol* 2001; **38**: 189–197.
3. Claus DR, Osmand AP, Gewurz H: Radioimmunoassay of human C-reactive protein and levels in normal sera. *J Lab Clin Med* 1976; **87**: 120–128.
4. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW: C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999; **19**: 972–978.
5. Rodriguez-Iturbe B, Vaziri ND, Herrera-Acosta J, Johnson RJ: Oxidative stress, renal infiltration of immune cells, and salt-sensitive hypertension: all for one and one for all. *Am J Physiol Renal Physiol* 2004; **286**: F606–F616.
6. Brasier AR, Recinos A 3rd, Eledrisi MS: Vascular inflammation and the renin-angiotensin system. *Arterioscler Thromb Vasc Biol* 2002; **22**: 1257–1266.
7. Virdis A, Schiffrin EL: Vascular inflammation: a role in vascular disease in hypertension? *Curr Opin Nephrol Hypertens* 2003; **12**: 181–187.
8. Ridker PM, Wilson PW, Grundy SM: Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation* 2004; **109**: 2818–2825.
9. Das UN: Metabolic syndrome X: an inflammatory condition? *Curr Hypertens Rep* 2004; **6**: 66–73.
10. Chiriac S, Dima-Cozma C, Georgescu T, Turcanu D, Pandele GI: The beneficial effect of physical training in hypertension. *Rev Med Chir Soc Med Nat Iasi* 2002; **107**: 258–263.
11. Bassuk SS, Manson JE: Physical activity and the prevention of cardiovascular disease. *Curr Atheroscler Rep* 2003; **5**: 299–307.
12. Colbert LH, Visser M, Simonsick EM, *et al*: Physical activity, exercise, and inflammatory markers in older adults: findings from the health, aging and body composition study. *J Am Geriatr Soc* 2004; **52**: 1098–1104.
13. Wannamethee SG, Lowe GD, Whincup PH, Rumley A, Walker M, Lennon L: Physical activity and hemostatic and inflammatory variables in elderly men. *Circulation* 2002; **105**: 1785–1790.
14. Ford ES: Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. *Epidemiology* 2002; **13**: 561–568.
15. Abramson JL, Vaccarino V: Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Arch Intern Med* 2002; **162**: 1286–1292.
16. Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP: Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol* 2001; **153**: 242–250.
17. Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Rimm EB: Leisure-time physical activity and reduced plasma levels of obesity-related inflammatory markers. *Obes Res* 2003; **11**: 1055–1064.
18. Reuben DB, Judd-Hamilton L, Harris TB, Seeman TE: The associations between physical activity and inflammatory markers in high-functioning older persons: MacArthur Studies of Successful Aging. *J Am Geriatr Soc* 2003; **51**: 1125–1130.

19. Albert MA, Glynn RJ, Ridker PM: Effect of physical activity on serum C-reactive protein. *Am J Cardiol* 2004; **93**: 221–225.
20. Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean ME, Haffner SM: Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. *Diabetes Care* 2002; **25**: 2016–2021.
21. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM: C-reactive protein and the risk of developing hypertension. *JAMA* 2003; **290**: 2945–2951.
22. Niskanen L, Laaksonen DE, Nyyssonen K, *et al*: Inflammation, abdominal obesity, and smoking as predictors of hypertension. *Hypertension* 2004; **44**: 859–865.
23. Tomiyama H, Koji Y, Yambe M, *et al*: Elevated C-reactive protein augments increased arterial stiffness in subjects with the metabolic syndrome. *Hypertension* 2005; **45**: 997–1003.
24. Tsunoda K, Arita M, Yukawa M, *et al*: Retinopathy and hypertension affect serum high-sensitivity C-reactive protein levels in type 2 diabetic patients. *J Diabetes Complications* 2005; **19**: 123–127.
25. Saijo Y, Kiyota N, Kawasaki Y, *et al*: Relationship between C-reactive protein and visceral adipose tissue in healthy Japanese subjects. *Diabetes Obes Metab* 2004; **6**: 249–258.
26. Tamakoshi K, Yatsuya H, Kondo T, *et al*: The metabolic syndrome is associated with elevated circulating C-reactive protein in healthy reference range, a systemic low-grade inflammatory state. *Int J Obes Relat Metab Disord* 2003; **27**: 443–449.
27. Yamada S, Gotoh T, Nakashima Y, *et al*: Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population: Jichi Medical School Cohort Study. *Am J Epidemiol* 2001; **153**: 1183–1190.
28. Hozawa A, Ebihara S, Ohmori K, *et al*: Increased plasma 8-isoprostane levels in hypertensive subjects: the Tsurugaya Project. *Hypertens Res* 2004; **27**: 557–561.
29. Imai Y, Satoh H, Nagai K, *et al*: Characteristics of a community based distribution of home blood pressure in Ohasma, a northern part of Japan. *J Hypertens* 1993; **11**: 1441–1449.
30. Pepys MB, Hirschfield GM: C-reactive protein: a critical update. *J Clin Invest* 2003; **111**: 1805–1812.
31. Tarlov AR, Ware JE Jr, Greenfield S, Nelson EC, Perrin E, Zubkoff M: The Medical Outcomes Study. An application of methods for monitoring the results of medical care. *JAMA* 1989; **262**: 925–930.
32. Chonan K, Kikuya M, Araki T, *et al*: Device for the self-measurement of blood pressure that can monitor blood pressure during sleep. *Blood Press Monit* 2001; **6**: 203–205.
33. Kabasakalian P, Kalliney S, Westcott A: Determination of uric acid in serum, with use of uricase and a tribromophenol-aminoantipyrine chromogen. *Clin Chem* 1973; **19**: 522–524.
34. Ledue TB, Weiner DL, Sipe JD, Poulin SE, Collins MF, Rifai N: Analytical evaluation of particle-enhanced immunonephelometric assays for C-reactive protein, serum amyloid A and mannose-binding protein in human serum. *Ann Clin Biochem* 1998; **35**: 745–753.
35. Chobanian A, Bakris G, Black H, *et al*: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *JAMA* 2003; **289**: 2560–2571.
36. European Society of Hypertension–European Society of Cardiology Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology Guidelines for the manangement of arterial hypertension. *J Hypertens* 2003; **21**: 1011–1053.
37. Pearson TA, Mensah GA, Alexander RW, *et al*: Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; **107**: 499–511.
38. Hozawa A, Ohmori K, Kuriyama S, *et al*: C-reacitve protein related to the peripheral artery disease among Japanese elderly: the Tsurugaya Project. *Hypertens Res* 2004; **27**: 955–961.
39. Pate RR, Pratt M, Blair SN, *et al*: Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995; **273**: 402–407.
40. Albert MA, Danielson E, Rifai N, Ridker PM: Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001; **286**: 64–70.
41. Ridker PM, Rifai N, Lowenthal SP: Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation* 2001; **103**: 1191–1193.
42. Making a difference. The World Health Report 1999. *Health Millions* 1999; **25**: 3–5.
43. Roccella EJ, Bowler AE: Hypertension as a risk factor. *Cardiovasc Clin* 1990; **20**: 49–63.
44. Leon AS, Connett J, Jacobs DR Jr, Rauramaa R: Leisure-time physical activity levels and risk of coronary heart disease and death. The Multiple Risk Factor Intervention Trial. *JAMA* 1987; **258**: 2388–2395.
45. Gibbons LW, Clark SM: Exercise in the reduction of cardiovascular events. Lessons from epidemiologic trials. *Cardiol Clin* 2001; **19**: 347–355.
46. Bobrie G, Chatellier G, Genes N, *et al*: Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004; **291**: 1342–1349.
47. Ohkubo T, Imai Y, Tsuji I, *et al*: Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens* 1998; **16**: 971–975.
48. Tachibana R, Tabara Y, Kondo I, Miki T, Kohara K: Home blood pressure is a better predictor of carotid atherosclerosis than office blood pressure in community-dwelling subjects. *Hypertens Res* 2004; **27**: 633–639.
49. Noble BJ: Clinical applications of perceived exertion. *Med Sci Sports Exerc* 1982; **14**: 406–411.