Age-related Change in Relationship between White Blood Cell Count and Some Features of the Metabolic Syndrome

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Abstract: To examine age-related change in the strength of the association of white blood cell count (WBC) with features of the metabolic syndrome (MS), body mass index, blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, fasting plasma glucose, and uric acid were assessed as the components of the MS in 5,218 Japanese male office workers aged 23–59 yr. The subjects were stratified by age into three groups of 23–39, 40–49, and 50–59 yr. WBC count showed a positive crude correlation with the components of the MS, except for HDL cholesterol (negative), in all three age groups. With an increase in age, an association between WBC count and each component of the MS declined, and an interaction with age weakened. After controlling for potential confounders, the largest differences of WBC count for each categorized feature of the MS were found among those aged 23–39 yr. Stratified analyses by smoking status and age showed that in both non-smokers and current smokers the adjusted WBC count increased as the number of features of the MS increased in all three age groups. In each category of the number of clustered features of the MS, differences of WBC count compared with the presence of no features of the MS were the largest in those aged 23–39 yr in both non-smokers and current smokers. The adjusted odds ratios of ≥ 3 features of the MS also increased with an increase in WBC count in all three age groups in both non-smokers and current smokers. The adjusted odds ratios of ≥ 3 features of the MS across quartiles of WBC count (lowest to highest) were the largest in the youngest age group. Our results indicate that a variety of features of the MS are associated with WBC count and that these tendencies are more pronounced in younger individuals in both non-smokers and current smokers.

Key words: White blood cell count, Metabolic syndrome, Risk factors, Clustering, Age, Cross-sectional study, Japanese men

Introduction

It has been repeatedly shown that white blood cells (WBCs) can participate in the pathogenesis of coronary heart disease (CHD) by an ability of the endothelium resulting in the lost of the vascular, antithrombotic and antiatherogenic properties of the vascular endothelium^{1–4}. In addition, stimulated

WBCs alter rheological properties with an increased tendency to adhere to vascular endothelium, and may result in capillary leukocytosis and subsequent increased vascular resistance^{5–7}. Recently, considerable interest has been focused on the relationship between inflammation and the metabolic syndrome (MS), which is characterized by insulin resistance accompanied by a cluster of risk factors for CHD (i.e. obesity, glucose metabolism disturbances, abnormal lipids, and high blood pressure)^{8,9}. Because WBC counts

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are positively associated with both insulin resistance and hyperinsulinemia^{10, 11}), an increase in the WBC count could be the expression of an insulin-resistant state or involvement of the MS. Although it is still being debated whether the relation between WBC count and CHD is independent of or mediated by the presence of concomitant risk factors for CHD, recent studies have documented the WBC count as an independent risk factor for CHD even when potential confounders are taken into account^{12, 13}.

As for the effect of age in the association with CHD risk factors, it has been demonstrated that the relative risk for cardiovascular disease associated with CHD risk factors such as obesity, hypertension, and dyslipidemia declines with age^{14–18}. Since atherosclerotic lesions appear at an early age^{19, 20}, detection and control of CHD risk factors are important to prevent the development of CHD in individuals, even while young. Several studies^{10, 21–25} have shown that clustered features of the MS is associated with the appearance of an increment in the number of WBC count. However, it has not been clarified whether the associations between WBC count and features of the MS changes with age. The aim of the present study was to examine whether there are any differences in the strength of the association of WBC count with some features of the MS by age in a large population-based sample.

Materials and Methods

A survey to evaluate the association between WBC count and different components of the MS was conducted in May 1996 at one of the biggest building contractors in Japan. The Industrial Safety and Health Law in Japan requires the employer to conduct annual health examinations of all employees, and employees are required by law to participate. A signed self-administered questionnaire is a part of this examination, and the employee data, which are anonymous, are available for research with the approval of the employer. All Japanese male office workers aged 23–59 yr in May 1996 were invited to take a survey ($n=5,280$), and the participation rate was 99.6% ($n=5,275$). Of the 5,275 participants, 57 men who had a past history of either CHD or stroke were excluded. The remaining 5,218 men constituted the study population, and no one answered yes to a question about illness with fever on the day of the examination.

The survey included medical history, a questionnaire on alcohol intake and smoking, physical examination, anthropometric measurements, blood pressure measurement, and collection of blood samples for laboratory

analysis. The participants were asked to fast for at least 8 h and to avoid heavy physical activity for more than 2 h before the examinations. Medical history and use of prescription drugs were assessed by the examining physicians. Data on alcohol intake and smoking habits were obtained by interview. The questions about alcohol intake included items about the frequency of alcohol consumption per week, the type of alcoholic beverage, and the usual amount consumed daily in units of “go” (a traditional Japanese unit of measurement, by volume, corresponding to 23 g of ethanol). Weekly alcohol intake was calculated and then converted to daily alcohol consumption by using standard Japanese tables. The questionnaire also asked about smoking habits (never, past, or current smoker); past or current smokers were asked about the number of cigarettes smoked per day and the duration of smoking in years. In this study, past and never smokers were combined, and the current amount of cigarettes smoked was used in the analysis. Body mass index (BMI, kg/m^2) was used as a measure of overall obesity. Blood pressures were measured by trained observers using standard mercury sphygmomanometers on the right arm of seated participants who had rested for 5 min. After the measurement of the blood pressure and while the participant was fasting, blood samples were drawn from an antecubital vein. WBC counts were determined by using a Sysmex E-4000 autoanalyzer (Toa Medical Electronics Co, Ltd., Tokyo, Japan). Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and uric acid and fasting plasma glucose were measured with Olympus AU-5200 equipment (Olympus Japan Co, Ltd., Tokyo, Japan) at FALCO Biosystems Tokyo Ltd. (Tokyo, Japan).

Characteristics of the MS were defined as follows^{26–29}: obesity, $\text{BMI} \geq 25 \text{ kg/m}^2$; hypertension, systolic blood pressure (SBP) $\geq 140 \text{ mmHg}$ and/or diastolic blood pressure (DBP) $\geq 90 \text{ mmHg}$ and/or medication for hypertension; hypercholesterolemia, total cholesterol level $\geq 5.69 \text{ mmol/l}$ and/or medication for dyslipidemia; low HDL cholesterol, HDL cholesterol level $< 1.03 \text{ mmol/l}$; hypertriglyceridemia, triglyceride level $\geq 1.69 \text{ mmol/l}$ and/or medication for dyslipidemia; high fasting plasma glucose, fasting plasma glucose level $\geq 6.1 \text{ mmol/l}$ and/or medication for diabetes; and hyperuricemia, uric acid level $\geq 446 \text{ } \mu\text{mol/l}$ and/or medication for hyperuricemia.

Statistical Analysis

One-way analysis of variance and the chi-square test were used to analyze the statistical differences among

Table 1. Characteristics of 5,218 Japanese male office workers who participated in the study, according to age*

Characteristic	Age (yr)				P value
	23–39 (n=1,865)	40–49 (n=1,894)	50–59 (n=1,459)	Total (n=5,218)	
White blood cell count (10^9 cells/l)	6.24 $\pm$ 1.63	6.77 $\pm$ 1.89	6.67 $\pm$ 1.76	6.55 $\pm$ 1.78	<0.001
Body mass index (kg/m^2)	23.0 $\pm$ 2.8	23.7 $\pm$ 2.8	23.6 $\pm$ 2.7	23.4 $\pm$ 2.8	<0.001
Alcohol consumption (g/day of ethanol)	16.1 $\pm$ 16.1	25.1 $\pm$ 20.3	25.4 $\pm$ 20.7	22.0 $\pm$ 19.5	<0.001
Current drinkers (%)	81.7	85.3	83.3	83.5	0.010
Cigarette smoking (cigarettes/day)	10.0 $\pm$ 13.2	15.1 $\pm$ 16.5	14.1 $\pm$ 15.9	13.0 $\pm$ 15.4	<0.001
Ex-smokers (%)	11.3	18.8	23.3	17.4	<0.001
Current smokers (%)	43.6	52.4	51.1	48.9	<0.001
Systolic blood pressure (mmHg)	121.6 $\pm$ 12.6	128.6 $\pm$ 14.6	132.0 $\pm$ 15.5	127.1 $\pm$ 14.8	<0.001
Diastolic blood pressure (mmHg)	71.4 $\pm$ 10.7	79.8 $\pm$ 11.4	81.4 $\pm$ 11.1	77.3 $\pm$ 11.9	<0.001
Total cholesterol (mmol/l)	4.67 $\pm$ 0.79	5.14 $\pm$ 0.83	5.16 $\pm$ 0.79	4.98 $\pm$ 0.84	<0.001
High-density lipoprotein cholesterol (mmol/l)	1.44 $\pm$ 0.32	1.43 $\pm$ 0.34	1.45 $\pm$ 0.37	1.44 $\pm$ 0.34	0.285
Triglyceride (mmol/l)	1.02 $\pm$ 0.88	1.37 $\pm$ 1.04	1.35 $\pm$ 0.96	1.24 $\pm$ 0.98	<0.001
Fasting plasma glucose (mmol/l)	4.72 $\pm$ 0.43	5.08 $\pm$ 1.00	5.24 $\pm$ 1.03	5.00 $\pm$ 0.88	<0.001
Uric acid ($\mu\text{mol}/\text{l}$)	341.6 $\pm$ 69.4	346.0 $\pm$ 74.2	341.2 $\pm$ 75.5	343.1 $\pm$ 72.9	0.090
Medical treatment (%)					
Hypertension	0.4	5.5	11.4	5.3	<0.001
Lipidemia	0.3	2.4	3.2	1.9	<0.001
Diabetes	0.2	1.8	4.1	1.9	<0.001
Hyperuricemia	0.3	1.1	3.3	1.4	<0.001
Others	2.0	4.5	4.6	3.6	<0.001

*: Unless otherwise indicated, values are expressed as mean $\pm$ standard deviation.

characteristics of participants according to age. Categories of age were defined by the following three groups: 23–39, 40–49, and 50–59 yr. Spearman's rank correlation analyses were performed between values for WBC count and components of the MS. The interaction between age and each component of the MS was also tested by introducing product terms to models with the original variables. Differences of WBC count were calculated across categorized features of the MS by means of a multiple linear regression model. Except for obesity, differences of WBC count were adjusted for age (yr), cigarette smoking (cigarettes/d), alcohol consumption (g/d of ethanol), medical treatment (no or yes), and the remaining components of the MS (BMI [kg/m^2], systolic BP [mmHg], total cholesterol [mmol/l], HDL cholesterol [mmol/l], triglycerides [mmol/l], fasting plasma glucose [mmol/l], and uric acid [$\mu\text{mol}/\text{l}$]). As for obesity, differences of WBC count were adjusted for age, cigarette smoking, alcohol consumption, and medical treatment, because the other components of the MS are outcomes of obesity rather than confounders. Subjects with a different number of components of the MS were grouped into five subgroups (graded from 0 through ≥ 4). Differences of WBC count compared with the presence of no features of the MS were calculated by creating four dummy variables and were

adjusted for age, smoking, alcohol consumption, and medical treatment by means of a multiple linear regression model. Logistic regression analyses were also used to evaluate the multivariate relations between WBC count and the risk of ≥ 3 features of the MS. WBC count was divided into quartiles (<53 , 53–62, 63–73, and ≥ 74 10^9 cells/l), and the linear trends in risks were evaluated by using the median value for each category of WBC count.

Data were analyzed by using the SPSS/PC statistical package (SPSS Inc., Chicago, Ill., USA). All reported P values are two-tailed; those less than 0.05 were considered statistically significant.

Results

Table 1 shows the characteristics of the study sample, stratified by age into three groups of 23–39, 40–49, and 50–59 yr. The mean WBC count, BMI, alcohol consumption, cigarette smoked per day, SBP, DBP, total cholesterol level, triglyceride level, and fasting plasma glucose level and the percentages of participants who were current drinkers and ex- and current smokers and were taking medication for hypertension, dyslipidemia, diabetes, hyperuricemia, and other diseases differed significantly by age. Individuals aged

Table 2. Spearman's rank correlations of white blood cell count with age and selected variables of the metabolic syndrome, according to age

Variable	Age (yr)					
	23–39		40–49		50–59	
	<i>n</i> =1,865		<i>n</i> =1,894		<i>n</i> =1,459	
	<i>r</i>	P value	<i>r</i>	P value	<i>r</i>	P value
Age (yr)	0.101	<0.001	0.014	0.529	0.010	0.703
Body mass index (kg/m ²)	0.218	<0.001	0.122	<0.001	0.038	0.142
Systolic blood pressure (mmHg)	0.188	<0.001	0.092	<0.001	0.067	0.011
Diastolic blood pressure (mmHg)	0.131	<0.001	0.031	0.177	0.035	0.180
Total cholesterol (mmol/l)	0.120	<0.001	0.057	0.013	0.003	0.895
High-density lipoprotein cholesterol (mmol/l)	–0.209	<0.001	–0.183	<0.001	–0.174	<0.001
Triglyceride (mmol/l)	0.248	<0.001	0.202	<0.001	0.187	<0.001
Fasting plasma glucose (mmol/l)	0.119	<0.001	0.092	<0.001	0.101	<0.001
Uric acid (μmol/l)	0.099	<0.001	0.019	0.409	0.004	0.889
Interaction between age (years) and each of the selected variables*						
Body mass index (kg/m ²)	0.207	<0.001	0.122	<0.001	0.036	0.166
Systolic blood pressure (mmHg)	0.176	<0.001	0.086	<0.001	0.073	0.005
Diastolic blood pressure (mmHg)	0.143	<0.001	0.031	0.171	0.034	0.196
Total cholesterol (mmol/l)	0.142	<0.001	0.064	0.006	0.003	0.906
High-density lipoprotein cholesterol (mmol/l)	–0.187	<0.001	–0.176	<0.001	–0.168	<0.001
Triglyceride (mmol/l)	0.250	<0.001	0.201	<0.001	0.186	<0.001
Fasting plasma glucose (mmol/l)	0.136	<0.001	0.080	<0.001	0.091	<0.001
Uric acid (μmol/l)	0.135	<0.001	0.018	0.425	0.005	0.838

*: Interactions were tested by introducing product terms to models with original variables.

23–39 yr had the lower levels of WBC count, BMI, alcohol consumption, cigarettes smoked per day, total cholesterol, and triglyceride. The mean SBP, DBP and fasting plasma glucose level and the percentages of those who were taking medication for hypertension, dyslipidemia, diabetes, hyperuricemia, and other diseases increased with an increase in age. On the other hand, HDL cholesterol level and uric acid level did not differ significantly among three groups.

Table 2 shows Spearman's rank correlation coefficients of WBC count with age and selected variables of the MS according to age. There were statistically significant unadjusted correlations between WBC count and SBP, HDL cholesterol level (negative), triglyceride level, and fasting plasma glucose level in all three age groups. BMI and total cholesterol level were significantly associated with WBC count among those aged 23–39 and 40–49 yr. Age, DBP, and uric acid level were significantly associated with WBC count only among those aged 23–39 yr. The largest correlation coefficients between WBC count and each variable of the MS were observed among those aged 23–39 yr. As for the interaction between age and each component of the MS, the interactions with age weakened with an increase in age in all the components of the MS.

Table 3 shows the means and differences of WBC count

for cigarette smoking, alcohol intake, and medical treatment. In each age group of 23–39, 40–49, and 50–59 yr, the mean WBC count was significantly higher in current smokers than in never smokers, but did not differ significantly between ex-smokers and never smokers. As for alcohol intake, the mean WBC count was significantly lower in current drinkers than in non-drinkers in the age groups of 40–49 and 50–59 yr, but did not differ significantly in the age group of 23–39 yr. The mean WBC count was higher in those with medical treatment than in those without in each age group, and differed significantly in the age groups of 40–49 and 50–59 yr.

Table 4 shows the adjusted means and differences of WBC count for categorized components of the MS by age. After controlling for potential confounders for each component of the MS, the adjusted means of WBC count were significantly higher in subjects with obesity, hypertension, hypercholesterolemia, and hypertriglyceridemia among those aged 23–39 yr. For individuals aged 40–49 yr, the adjusted means of WBC count were significantly higher in those with obesity and hypertension. For individuals aged 50–59 yr, the adjusted means of WBC count were significantly higher in those with hypertension and high fasting plasma glucose level. The largest differences of WBC count for each categorized feature of the MS were observed among those

Table 3. Means and differences of white blood cell count (10^9 cells/l) for cigarette smoking, alcohol intake, and medical treatment, according to age

Item	Age (years)											
	23–39				40–49				50–59			
	<i>n</i>	Mean	Difference (95% confidence interval)	P value	<i>n</i>	Mean	Difference (95% confidence interval)	P value	<i>n</i>	Mean	Difference (95% confidence interval)	P value
Cigarette smoking												
Never	842	5.79	–		545	5.95	–		373	5.86	–	
Past	210	5.87	0.08 (–0.15, 0.32)	0.495	357	6.00	0.04 (–0.19, 0.27)	0.721	340	6.03	0.17 (–0.07, 0.41)	0.158
Current	813	6.81	1.02 (0.87, 1.17)	<0.001	992	7.49	1.54 (1.36, 1.72)	<0.001	746	7.36	1.50 (1.30, 1.70)	<0.001
Current alcohol intake												
No	342	6.26	–		278	7.06	–		243	7.01	–	
Yes	1,523	6.24	–0.03 (–0.22, 0.16)	0.781	1,616	6.72	–0.34 (–0.58, –0.10)	0.005	1,216	6.60	–0.42 (–0.66, –0.18)	0.001
Medical treatment												
No	1,807	6.24	–		1,630	6.71	–		1,123	6.62	–	
Yes	58	6.36	0.12 (–0.28, 0.51)	0.562	264	7.08	0.37 (0.14, 0.59)	0.001	336	6.82	0.20 (0.01, 0.40)	0.039

Table 4. Adjusted means and differences of white blood cell count (10^9 cells/l) for categorized features of the metabolic syndrome, according to age

Item*	Age (yr)											
	23–39				40–49				50–59			
	<i>n</i>	Mean	Difference (95% confidence interval)	P value	<i>n</i>	Mean	Difference (95% confidence interval)	P value	<i>n</i>	Mean	Difference (95% confidence interval)	P value
Obesity [†]												
No	1,465	6.13	–		1,344	6.64	–		1,048	6.66	–	
Yes	400	6.65	0.51 (0.35, 0.68)	<0.001	550	7.07	0.42 (0.26, 0.59)	<0.001	411	6.69	0.03 (–0.15, 0.21)	0.720
Hypertension [‡]												
No	1,682	6.19	–		1,347	6.70	–		910	6.54	–	
Yes	183	6.71	0.52 (0.28, 0.75)	<0.001	547	6.93	0.24 (0.06, 0.41)	0.009	549	6.8	0.34 (0.16, 0.52)	<0.001
Hypercholesterolemia [‡]												
No	1,664	6.21	–		1,392	6.72	–		1,085	6.69	–	
Yes	201	6.54	0.33 (0.11, 0.56)	0.004	502	6.89	0.17 (–0.03, 0.37)	0.097	374	6.60	–0.09 (–0.28, 0.11)	0.378
Low high-density lipoprotein cholesterol level [‡]												
No	1,723	6.22	–		1,703	6.76	–		1,307	6.65	–	
Yes	142	6.48	0.25 (–0.02, 0.53)	0.066	191	6.80	0.04 (–0.24, 0.32)	0.762	152	6.83	0.19 (–0.11, 0.48)	0.211
Hypertriglyceridemia [‡]												
No	1,667	6.22	–		1,443	6.72	–		1,113	6.64	–	
Yes	198	6.47	0.25 (0.01, 0.49)	0.039	451	6.91	0.19 (–0.01, 0.39)	0.058	346	6.74	0.09 (–0.12, 0.31)	0.390
High fasting plasma glucose level [‡]												
No	1,847	6.24	–		1,777	6.76	–		1,306	6.63	–	
Yes	18	6.82	0.58 (–0.11, 1.28)	0.101	117	6.75	–0.02 (–0.34, 0.31)	0.928	153	6.94	0.31 (0.03, 0.58)	0.028
Hyperuricemia [‡]												
No	1,711	6.23	–		1,726	6.76	–		1,297	6.66	–	
Yes	154	6.34	0.10 (–0.15, 0.35)	0.419	168	6.80	0.04 (–0.24, 0.31)	0.790	162	6.72	0.06 (–0.20, 0.33)	0.644

*: Obesity, body mass index ≥ 25.0 kg/m²; hypertension, systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or medication for hypertension; hypercholesterolemia, total cholesterol level ≥ 5.69 mmol/l and/or medication for dyslipidemia; low high-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level < 1.03 mmol/l; hypertriglyceridemia, triglycerides ≥ 1.69 mmol/l and/or medication for dyslipidemia; high fasting plasma glucose level, fasting plasma glucose level ≥ 6.1 mmol/l and/or medication for diabetes; hyperuricemia, uric acid ≥ 446 μ mol/l and/or medication for hyperuricemia. [†]: Controls for age, cigarette smoking, alcohol intake, and medical treatment. [‡]: Controls for age, cigarette smoking, alcohol intake, medical treatment, and all other components of the metabolic syndrome.

Table 5. Adjusted means and differences of white blood cell count (10^9 cells/l) for clustered features of the metabolic syndrome, according to smoking status and age

Smoiking status	Age (yr)											
	23–39				40–49				50–59			
	<i>n</i>	Mean	Difference (95% confidence interval)	P value	<i>n</i>	Mean	Difference (95% confidence interval)	P value	<i>n</i>	Mean	Difference (95% confidence interval)	P value
Non-smokers*												
0	643	5.57	–		275	5.71	–		180	5.67	–	
1	249	6.01	0.44 (0.25, 0.63)	0.002	279	5.83	0.12 (–0.11, 0.35)	0.324	224	5.87	0.20 (–0.04, 0.44)	0.105
2	111	6.32	0.75 (0.48, 1.01)	<0.001	194	6.18	0.47 (0.21, 0.73)	<0.001	151	6.08	0.40 (0.13, 0.68)	0.004
3	32	6.43	0.86 (0.40, 1.33)	<0.001	82	6.19	0.48 (0.13, 0.83)	0.007	97	6.14	0.47 (0.16, 0.78)	0.003
≥4	17	7.19	1.62 (0.98, 2.27)	<0.001	72	6.68	0.97 (0.60, 1.34)	<0.001	61	6.33	0.65 (0.29, 1.02)	0.001
P value for trend				<0.001				<0.001				<0.001
Current smokers [‡]												
0	432	6.51	–		342	7.21	–		205	7.35	–	
1	209	7.00	0.48 (0.20, 0.76)	0.001	270	7.45	0.24 (–0.07, 0.55)	0.127	240	7.18	–0.18 (–0.52, 0.17)	0.316
2	103	7.14	0.63 (0.26, 1.00)	0.001	198	7.51	0.30 (–0.04, 0.64)	0.084	147	7.50	0.15 (–0.25, 0.54)	0.460
3	46	7.50	0.98 (0.47, 1.50)	<0.001	108	7.89	0.68 (0.26, 1.11)	0.002	94	7.40	0.04 (–0.41, 0.50)	0.848
≥4	23	7.82	1.31 (0.60, 2.02)	<0.001	74	8.30	1.09 (0.60, 1.58)	<0.001	60	7.68	0.32 (–0.22, 0.86)	0.242
P value for trend				<0.001				<0.001				0.165

*: Controls for age, alcohol intake, and medical treatment. †: Additional control for cigarette smoking.

aged 23–39 yr.

Table 5 shows the adjusted means and differences of WBC count for clustered components of the MS by smoking status and age. Never smokers and ex-smokers were combined as non-smokers, because the mean WBC count did not differ significantly between never smokers and ex-smokers. For non-smokers aged 23–39 yr, the adjusted differences of WBC count in those with the presence of 1, 2, 3, and ≥4 features of the MS, compared with those without features of the MS, were 0.44, 0.75, 0.86, and 1.62 10^9 cells/l, respectively, with a statistically highly significant trend (P for trend <0.001). The respective differences of WBC count compared with non-smokers without features of the MS were 0.12, 0.47, 0.48, and 0.97 10^9 cells/l for those aged 40–49 yr and 0.20, 0.40, 0.47, and 0.65 10^9 cells/l for those aged 50–59 yr (P for trend <0.001 for both). For current smokers aged 23–39 yr, the adjusted differences of WBC count in those with the presence of 1, 2, 3, and ≥4 features of the MS, compared with those without features of the MS, were 0.48, 0.63, 0.98, and 1.31 10^9 cells/l, respectively (P for trend <0.001). The respective differences of WBC count compared with current smokers without features of the MS were 0.24, 0.30, 0.68, and 1.09 10^9 cells/l for those aged 40–49 yr and –0.18, 0.15, 0.04, and 0.32 10^9 cells/l for those aged 50–59 yr (P for trend <0.001 and =0.165, respectively). In each category of the number of clustered features of the MS, differences

of WBC count compared with the presence of no features of the MS were the largest in those aged 23–39 yr in both non-smokers and current smokers.

Table 6 shows the distribution of number of features of the MS and adjusted odds ratios of ≥3 features of the MS across quartiles of WBC count by smoking status and age. For non-smokers, the percentage of those with the increased number of features of the MS increased with an increase in WBC count in each age group of 23–39, 40–49, and 50–59 yr (P for trend <0.001 for all). Among non-smokers aged 23–39 yr, the adjusted odds ratio of ≥3 features of the MS compared with WBC count of <53 10^9 cells/l was 1.36, 4.05, and 4.92 for WBC count of 53–62, 63–73, and ≥74 10^9 cells/l, respectively (P for trend <0.001). The respective adjusted odds ratios of ≥3 features of the MS compared with WBC count of <53 10^9 cells/l were 1.92, 2.16, and 3.34 for those aged 40–49 yr and 2.63, 3.05, and 2.54 for those aged 50–59 yr (P for trend <0.001 for both). For current smokers, the percentage of those with the increased number of features of the MS also increased with an increase in WBC count in each age group of 23–39, 40–49, and 50–59 yr (P for trend <0.001, <0.001, and =0.015, respectively). Among current smokers aged 23–39 yr, the adjusted odds ratio of ≥3 features of the MS compared with WBC count of <53 10^9 cells/l was 2.99, 7.62, and 8.94 for WBC count of 53–62, 63–73, and ≥74 10^9 cells/l, respectively (P for trend <0.001). The respective

Table 6. Distribution of number of features of the metabolic syndrome and adjusted odds ratios* of ≥ 3 features of the metabolic syndrome across quartiles of white blood cell count, according to smoking status and age

Smoking status	Age (yr)	Number of features	White blood cell count (10^9 cells/l)				P value for trend
			<53	53–62	63–73	≥ 74	
Non-smokers [†]	23–39	<i>n</i>	386	338	216	112	<0.001
		0	72.3%	61.5%	51.4%	40.2%	
		1	18.7%	26.0%	25.5%	30.4%	
		2	6.7%	9.2%	15.3%	18.8%	
		3	2.1%	2.7%	4.2%	5.4%	
		≥ 4	0.3%	0.6%	3.7%	5.4%	
		≥ 3	1.0 (–)	1.36 (0.54, 3.43)	4.05 (1.70, 9.67)	4.92 (1.92, 12.63)	
	40–49	<i>n</i>	296	272	208	126	<0.001
		0	40.5%	28.7%	22.6%	23.8%	
		1	32.8%	32.0%	29.8%	26.2%	
		2	16.9%	21.3%	27.4%	23.0%	
		3	5.7%	11.0%	11.1%	9.5%	
		≥ 4	4.1%	7.0%	9.1%	17.5%	
		≥ 3	1.0 (–)	1.92 (1.16, 3.18)	2.16 (1.27, 3.69)	3.34 (1.88, 5.93)	
	50–59	<i>n</i>	217	237	168	91	0.001
		0	33.2%	24.5%	22.6%	13.2%	
		1	35.9%	31.6%	25.0%	31.9%	
		2	19.8%	18.6%	22.6%	28.6%	
		3	8.8%	13.9%	17.9%	16.5%	
		≥ 4	2.3%	11.4%	11.9%	9.9%	
		≥ 3	1.0 (–)	2.63 (1.55, 4.46)	3.05 (1.75, 5.30)	2.54 (1.33, 4.87)	
Current smokers [‡]	23–39	<i>n</i>	141	205	217	250	<0.001
		0	68.8%	61.5%	49.3%	40.8%	
		1	19.9%	26.8%	25.8%	28.0%	
		2	9.9%	7.3%	13.8%	17.6%	
		3	1.4%	3.4%	7.8%	8.0%	
		≥ 4	0.0%	1.0%	3.2%	5.6%	
		≥ 3	1.0 (–)	2.99 (0.63, 14.19)	7.62 (1.75, 33.28)	8.94 (2.07, 38.67)	
	40–49	<i>n</i>	97	179	244	472	0.004
		0	42.3%	39.7%	38.9%	28.6%	
		1	26.8%	26.8%	25.8%	28.2%	
		2	20.6%	20.7%	18.4%	20.3%	
		3	7.2%	7.3%	10.7%	13.1%	
		≥ 4	3.1%	5.6%	6.1%	9.7%	
		≥ 3	1.0 (–)	1.23 (0.56, 2.74)	1.59 (0.75, 3.36)	2.15 (1.07, 4.35)	
	50–59	<i>n</i>	87	125	206	328	0.044
		0	34.5%	28.8%	24.8%	26.8%	
		1	24.1%	42.4%	36.4%	27.7%	
		2	24.1%	12.8%	19.9%	21.0%	
		3	11.5%	10.4%	12.6%	13.7%	
		≥ 4	5.7%	5.6%	6.3%	10.7%	
		≥ 3	1.0 (–)	0.93 (0.44, 1.97)	1.13 (0.57, 2.22)	1.57 (0.83, 2.98)	

*: Unless otherwise indicated, values are expressed as the relative risk (95% confidence interval). [†]: Controls for age, alcohol intake, and medical treatment. [‡]: Additional control for cigarette smoking.

adjusted odds ratios of ≥ 3 features of the MS compared with WBC count of $<53 \times 10^9$ cells/l were 1.23, 1.59, and 2.15 for those aged 40–49 yr and 0.93, 1.13, and 1.57 for those aged 50–59 yr (P for trend <0.001 and $=0.044$, respectively).

Discussion

In this study, WBC count was positively associated with the components of the MS, except for HDL cholesterol

(negative), in all three age groups of 23–39, 40–49, and 50–59 yr. With an increase in age, however, a crude correlation between WBC count and each component of the MS declined, and an interaction with age weakened. Adjusted differences in mean WBC count for each categorized feature of the MS were the largest in the youngest age group of 23–39 yr. Stratified analyses by smoking status and age showed that in both non-smokers and current smokers adjusted differences in mean WBC count for clustered features of the MS and adjusted odds ratios of ≥ 3 features of the MS across quartiles of WBC count were the largest in the youngest age group. Our results demonstrate that WBC count is strongly associated with a variety of features of the MS and that these tendencies are more pronounced in younger individuals in both non-smokers and current smokers.

However, the mechanism of how WBC count is associated with the features of the MS, a clinical condition that seems to be mediated by insulin resistance^{8, 9}, is still not clear. Because insulin reduces the interleukin (IL)-6 mediation of the acute-phase response³⁰, insulin resistance could lead to higher concentrations of inflammatory markers. IL-6 has been shown to be released by adipose tissue³¹. Other proinflammatory cytokines such as tumor necrosis factor- α produce insulin resistance by influencing the function of insulin receptor or impairing insulin action and inhibiting insulin secretion^{32, 33}. Because WBC counts are increased by cytokines, especially IL-6^{34, 35}, and are closely associated with both insulin resistance and hyperinsulinemia^{10, 11}, the relation of WBC count with the features of the MS could be due to the presence of a subclinical inflammatory reaction and could be the expression of an insulin-resistant state or involvement of the MS.

Several studies^{14–18} have examined the effect of age on the association with CHD risk factors and have documented that the relative risk for cardiovascular disease associated with these risk factors are small or negligible at higher ages. These data suggest that the impact of CHD risk factors on the risk for CHD may decrease with age. In view of the firm association of WBC count with the increased risk of CHD^{12, 13}, our results, which showed the weaker association between WBC count and the different features of MS among older individuals, may explain the previous observations of a decrease in the estimated relative risk of CHD associated with CHD risk factors among older cohorts^{14–18}. Consistent with previous studies^{36–38}, WBC count was positively associated with cigarette smoking and negatively with alcohol intake in this population. The associations of WBC count with cigarette smoking and alcohol intake were more pronounced in individuals aged 40–59 yr than in individuals

aged 23–39 yr. This tendency was also found for medical treatment. Thus, age-related change in the strength of the association of WBC count with some features of the MS may be in part mediated by the differences in the association of WBC count with cigarette smoking, alcohol intake, and medical treatment by age. However, the cross-sectional study design lacks information on the time sequence of events and, thus, does not permit identification of causal relationships. Further studies are needed to clarify whether WBC count, although within the normal range, contributes to the development of the MS and whether there are age differences in the strength of the association of WBC count with the features of the MS.

In conclusion, our data indicate that WBC count is strongly associated with a variety of disorders characterizing the MS and that these tendencies are more pronounced in younger individuals. In consideration of the strong association between WBC count and the different features of the MS, much remains to be learned about its value as a predictor rather than merely an indicator of current infection. The stronger association observed among younger individuals also indicates that multiple clinical laboratory tests, including serum total cholesterol, HDL cholesterol, triglycerides, fasting plasma glucose, and uric acid, may be needed in terms of CHD risk assessment for young individuals with an increased WBC count.

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