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White blood cell count and cardiovascular biomarkers of atherosclerosis

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Abstract

Objective: To investigate the association with white blood cells (WBC) and atherosclerotic parameters including cardio-ankle vascular index (CAVI) and carotid intima–media thickness (CIMT) in the general population.

Methods: We investigated the relationship between WBC count and metabolic syndrome components, CAVI and CIMT in 3738 Japanese study participants.

Results: WBC count weakly correlated with CAVI in men ($\beta = 0.61$, $p = 0.043$), but not in women ($\beta = 0.35$, $p = 0.17$). On the other hand, WBC did not correlate with CIMT in either men or women ($p = 0.41$ and $p = 0.71$, respectively).

Conclusion: WBC count was associated with lipids, blood pressure and body mass index, although the correlations with CAVI and CIMT were weak or absent.

Keywords: *Cardio-ankle vascular index; carotid intima–media thickness; metabolic syndrome*

Introduction

White blood cells (WBC) comprise an inexpensive and reliable marker of inflammation that is universally applied in standard clinical practice. Recently atherosclerosis has been recognized as an active, inflammatory process (Ross 1999), and whether the elevation of WBC is merely a marker of inflammation, whether it directly enhances atherosclerosis and thrombosis, or both, has been discussed. It still remains unclear whether or not a relationship between WBC and subclinical atherosclerosis exists. Several studies have shown a positive and independent association between WBC and specific diseases including cancer (Grimm et al. 1985, Friedman & Fireman 1991), cardiovascular disease (CVD) (Grimm et al. 1985, Prentice et al. 1982), stroke (Prentice et al. 1982) and all-cause mortality (Grimm et al. 1985). Furthermore, Lao et al. (2008) recently identified a strong relationship between total WBC count and the constellation of metabolic syndrome components in an older Chinese population. Therefore, detecting a high WBC count or a change in the count might be important in predicting subsequent disease.

Recent advances in medical technology have allowed non-invasive assessment of early atherosclerosis (Vogel & Benitez 2000, Bots & Grobee 2002). High-resolution B-mode ultrasonography provides a non-invasive method of measuring arterial wall thickening, and indeed, this modality has shown that carotid intima–media thickness (CIMT) is a powerful predictor of CVD (Bots & Grobee

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2002), as it correlates with generalized atherosclerosis, myocardial infarction and stroke (Bots et al. 1997). Population studies have revealed that traditional cardiovascular risk factors such as age, smoking, low-density lipoprotein-cholesterol (LDL-C) and elevated blood pressure (BP) are closely associated with CIMT (Loimaala et al. 2006).

Pulse wave velocity (PWV) is a non-invasive clinical index of aortic stiffness (van Popele et al. 2001), and it can predict cardiovascular events as well as all-cause mortality in hypertensive patients and in the general population (Blacher et al. 1999, Shokawa et al. 2005). The novel cardio-ankle vascular index (CAVI), which reflects the stiffness of the aorta, femoral artery and tibial artery, involves the measurement of brachial-ankle PWV and BP (Yambe et al. 2004, Shirai et al. 2006). This index is essentially independent of changes in BP during the examination, but closely correlates with systolic BP. Kadota et al. (2008) suggested that CAVI, like PWV, can serve as a marker of the increase in central artery stiffness with age. Although Wakabayashi and Masuda (2006) revealed a correlation between WBC and CAVI in patients with type 2 diabetes mellitus (DM), this aspect has not been investigated in the general population.

In the present study, we investigated the association with WBC and atherosclerotic parameters including CAVI and CIMT in a relatively large general population.

Methods

The Special Committee of Nagasaki University provided ethical approval to proceed with this study (project registration number 0501120073), during a medical screening programme for the general population aged over 20 years, residing in Goto City (total population, 41 729 in 2008), Nagasaki Prefecture, Japan between 2005 and 2009. Data were collected by the staff of Nagasaki University, in cooperation with the staff of Goto City. We obtained written, informed consent from 4992 Japanese adults (1640 men and 3352 women) to participate in the study. However, 51 with severe hypertriglycaemia (>4.0 g l^{-1}) and 1203 in whom WBC, CAVI and CIMT were not measured were excluded from the study. Data from a total of 3738 participants (1165 men and 2573 women) were finally included for further analysis.

The height and weight of each participant were measured and body mass index (BMI; kg m^{-2}) was calculated as an index of obesity. Waist circumference (WC) was measured horizontally at the umbilicus with a tape measure after normal expiration. Systolic BP (SBP) and diastolic BP (DBP) were recorded at rest. Mean BP (MBP) was calculated as DBP + (SBP-DBP)/3.

Blood samples were collected from each participant after an overnight fast. Serum and plasma were separated and stored at -20°C and -80°C, respectively, until assay. Both WBC and red blood cells (RBC) were counted, and haemoglobin (HGB) and haematocrit (HCT) were measured using standard laboratory procedures. Serum concentrations of total cholesterol (TC), triglyceride (TG) and high-density lipoprotein-cholesterol (HDL-C) were also measured using standard laboratory procedures and LDL-C was calculated using the Friedewald equation (Friedewald et al. 1972). In addition, haemoglobin A_{1c} (HbA_{1c}), serum creatinine (CRE) and uremic acid (UA) were measured using standard laboratory procedures.

The physicians (Y.S., N.H., M.N. and N.T.) measured CIMT by ultrasonography of the right and left carotid arteries using a LOGIC Book XP with a 10-MHz linear array transducer (GE Medical Systems, Milwaukee, WI, USA). The far wall of the carotid artery was displayed on a longitudinal two-dimensional ultrasonographic image as two bright white lines separated by a hypoechoic space. The distance from the leading edge of the first (lumen-intima interface), to the leading edge of the second (media-adventitia interface) bright line was identified as the CIMT. Images obtained were stored on the hard disk of the ultrasound system, and were analysed using Intima Scope® software (MEDIA CROSS, Tokyo, Japan). Averages of the right and left CIMT were calculated and used in the analysis. Intra- (N.T., $n=32$) and interobserver (N.T. vs M.N., $n=41$) variations in CIMT were 0.91 ($p<0.01$) and 0.78 ($p<0.01$), respectively.

The CAVI in supine participants was recorded using a VaseraVS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan). The principles underlying CAVI have been described by Yambe et al. (2004). Electrocardiographic electrodes are placed on both wrists, a microphone for detecting heart sounds is placed on the sternum, and cuffs are wrapped around both arms and ankles to obtain automatic measurements. The data were then analysed using VSS-10 software (Fukuda Denshi), and calculated averaged values for the right and left CAVI further analysed.

Results are expressed as means ± SD or median (25th to 75th quartile). Differences in laboratory values between men and women were evaluated using a *t*-test and the Mann–Whitney *U*-test. Smoking status was analysed among three groups: current smoker, past smoker and never smoked. Differences in the smoking status and the ratio of current treatment for hypertension (HT), DM and dyslipidaemia (DL) were evaluated using the χ^2 test. WBC and other variables including laboratory values, CAVI and CIMT were evaluated using univariate linear regression analysis. Multivariate linear regression analysis was adjusted for age to evaluate WBC and other existing parameters. We evaluated associations between WBC and CAVI, CIMT using another multivariate linear regression analysis adjusted for age and

other confounding factors such as BMI, MBP, HbA_{1c} and HDL-C. To confirm whether relationships between WBC and CAVI, CIMT are independent of circulation dynamics, lipid metabolism and glucose metabolism, multivariate linear regression analysis was adjusted for age, BMI, MBP, HbA_{1c}, HDL-C and current treatment for HT and/or DM and/or DL. Because the distribution of TG was skewed, logarithmic transformation was performed for the univariate and multivariate linear regression analyses. Probability values below 0.05 were considered indicative of statistical significance. All data were statistically analysed using SPSS v17.0 software (SPSS Japan, Tokyo, Japan).

Results

Table 1 shows the characteristics of the study participants. The men were significantly older than the women (average 66.0 ± 10.9 vs 64.0 ± 11.2 years, $p < 0.01$). Besides age, BMI, WC, MBP, WBC, RBC, HGB, HCT, CRE, UA, TC, TG, HDL-C, LDL-C, CAVI and CIMT, as well as the ratio of current smoker, past smoker and current treatment for DM and DL, differed significantly between men and women. The numbers of participants who were diagnosed with HT, DM and DL, but not under drug treatment, were 12, 24 and 31, respectively, out of all the participants.

Univariate linear regression analysis showed that WBC correlated in men and in women with age, BMI, WC, MBP, RBC, HGB, HCT, UA, TC, log TG, HDL-C, LDL-C and HbA_{1c}. In addition, smoking status in men, and CRE in women also correlated (Table 2). This analysis revealed that WBC did not correlate with CAVI and CIMT in either men or women.

Multivariate linear regression analysis adjusted for age revealed that WBC correlated with BMI, WC, smoking status, MBP, RBC, HGB, HCT, CRE, UA, TC, log TG, HDL-C, LDL-C, HbA_{1c}, CAVI and CIMT in men. In women, WBC correlated with the same parameters except for smoking status, CAVI and CIMT (Table 3).

Multivariate linear regression analysis adjusted for confounding factors including CAVI showed that WBC correlated with age ($\beta = -0.19$, $p < 0.001$), BMI ($\beta = 0.64$, $p < 0.001$), smoking status ($\beta = 5.1$, $p < 0.001$) and HDL-C ($\beta = -0.093$, $p = 0.002$) in men, and with age ($\beta = -0.18$, $p < 0.001$), BMI ($\beta = 0.33$, $p < 0.001$), MBP ($\beta = 0.049$, $p = 0.025$), HbA_{1c} ($\beta = 1.1$, $p = 0.017$) and HDL-C ($\beta = -0.075$, $p < 0.001$) in women (Table 4). The WBC count weakly correlated with CAVI in men ($\beta = 0.61$, $p = 0.043$) but not in

Table 1. Characteristics of the study participants.

	Men ($n = 1165$)	Women ($n = 2573$)	All ($n = 3738$)
Age (years)	66.0 ± 10.9	64.0 ± 11.2*	64.6 ± 11.2
BMI (kg m^{-2})	23.5 ± 3.2	22.9 ± 3.4*	23.1 ± 3.4
WC (cm)	85.0 ± 8.7	81.2 ± 9.9*	82.4 ± 9.7
MBP (mmHg)	103.0 ± 12.9	102.1 ± 13.1*	102.7 ± 13.1
WBC (10^9 cells l^{-1})	6.0 ± 1.5	5.7 ± 1.4*	5.8 ± 1.4
RBC (10^{10} cells l^{-1})	457.3 ± 43.9	424.8 ± 36.8*	434.9 ± 41.9
HGB (g l^{-1})	143.3 ± 12.9	128.6 ± 11.3*	133.0 ± 13.6
HCT (%)	43.9 ± 3.8	40.0 ± 3.3*	41.2 ± 3.9
CRE (mg l^{-1})	9.2 ± 2.6	7.1 ± 1.7*	7.8 ± 2.3
UA (g l^{-1})	61.5 ± 13.9	48.7 ± 12.2*	52.7 ± 14.1
TC (g l^{-1})	1.9 ± 0.3	2.1 ± 0.3*	2.1 ± 0.3
TG (g l^{-1})	1.1 (0.75–1.6)	1.0 (0.73–1.5)*	1.0 (0.74–1.5)
HDL-C (g l^{-1})	0.55 ± 0.15	0.62 ± 0.15*	0.59 ± 0.15
LDL-C (g l^{-1})	1.1 ± 0.3	1.3 ± 0.3*	1.2 ± 0.3
HbA_{1c} (%)	5.3 ± 0.6	5.2 ± 0.6	5.2 ± 0.6
CAVI	8.5 ± 1.6	8.1 ± 1.4*	8.2 ± 1.5
CIMT (mm)	0.73 (0.64–0.82)	0.69 (0.61–0.78)*	0.70 (0.62–0.80)
Current smoker, *n* (%)	264 (22.7)	86 (3.3)*	350 (9.4)
Past smoker, *n* (%)	445 (38.2)	48 (1.9)*	493 (13.2)
HT, *n* (%)	337 (29.0)	704 (27.4)	1041 (27.8)
DM, *n* (%)	69 (5.9)	88 (3.4)*	157 (4.2)
DL, *n* (%)	62 (5.3)	263 (10.2)*	325 (8.7)

Values are means ± SD or median (25th to 75th percentile), unless otherwise indicated.
BMI, body mass index; WC, waist circumference; MBP, mean blood pressure; WBC, white blood cells; RBC, red blood cells; HGB, haemoglobin; HCT, haematocrit; CRE, creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C low-density lipoprotein cholesterol; HbA_{1c}, haemoglobin A_{1c}; CAVI, cardio-ankle vascular index; CIMT, carotid intima–media thickness; HT, under treatment for hypertension; DM, under treatment for diabetes mellitus; DL, under treatment for dyslipidaemia.
*$p < 0.01$ vs. men.

women ($\beta = 0.35$, $p = 0.17$). In the participants as a whole, WBC correlated with all confounding factors and also with CAVI ($\beta = 0.4$, $p = 0.028$). Furthermore, multivariate linear regression analysis adjusted for confounding factors including current treatment for HT and/or DM and/or DL showed that WBC did not correlate with CAVI in men, women or all participants ($p = 0.059$, $p = 0.27$ and $p = 0.063$, respectively; data not shown).

Multivariate linear regression analysis adjusted for confounding factors including CIMT showed that WBC correlated with age ($\beta = -0.17$, $p < 0.001$), BMI ($\beta = 0.62$, $p < 0.001$), smoking status ($\beta = 5.1$, $p < 0.001$), MBP ($\beta = 0.072$, $p = 0.036$), and HDL-C ($\beta = -0.094$, $p = 0.002$) in men, and with age ($\beta = -0.16$, $p < 0.001$), BMI ($\beta = 0.32$, $p < 0.001$), MBP ($\beta = 0.052$, $p = 0.019$), HbA_{1c} ($\beta = 1.2$, $p = 0.013$) and HDL-C ($\beta = -0.075$, $p < 0.001$) in women. WBC did not correlate with CIMT in either men or women ($p = 0.41$ and $p = 0.71$, respectively; Table 5). In the participants as a whole, WBC correlated with all confounding factors, although it did not correlate with CIMT ($\beta = 1.2$, $p = 0.51$).

Table 2. Univariate linear regression analysis of white blood cell count and other variables.

	Men		Women		All	
Variables	Correlation	*p*-Value	Correlation	*p*-Value	Correlation	*p*-Value
Age	0.15†	<0.001	-0.076†	<0.001	-0.092†	<0.001
BMI	0.18†	<0.001	0.11†	<0.001	0.14†	<0.001
WC	0.2†	<0.001	0.1†	<0.001	0.14†	<0.001
Smoking status	0.272†	<0.001	-0.016	0.41	0.2†	<0.001
MBP	0.1†	0.001	0.043*	0.031	0.069†	<0.001
RBC	0.19†	<0.001	0.16†	<0.001	0.19†	<0.001
HGB	0.21†	<0.001	0.13†	<0.001	0.18†	<0.001
HCT	0.21†	<0.001	0.15†	<0.001	0.19†	<0.001
CRE	0.034	0.25	0.078†	<0.001	0.092†	<0.001
UA	0.095†	0.001	0.13†	<0.001	0.14†	<0.001
TC	0.096†	0.003	0.053†	0.007	0.035*	0.046
logTG	0.26†	<0.001	0.2†	<0.001	0.22†	<0.001
HDL-C	-0.13†	<0.001	-0.094†	<0.001	-0.12†	<0.001
LDL-C	0.079†	0.007	0.053†	0.008	0.044†	0.007
HbA_{1c}	0.072*	0.014	0.053†	0.007	0.062†	<0.001
CAVI	0.001	0.98	-0.019	0.33	0.003	0.868
CIMT	-0.009	0.77	-0.018	0.37	-0.002	0.916

*$p < 0.05$; †$p < 0.01$.
Abbreviations are as shown in Table 1.

Table 3. Multivariate linear regression analysis of white blood cell count adjusted for age.

	Men			Women			All		
Variables	β	95% CI	*p*-Value	β	95% CI	*p*-Value	β	95% CI	*p*-Value
BMI	0.77	0.49–1.0	<0.001	0.48	0.32–0.63	<0.001	0.6	0.47–0.73	<0.001
WC	0.33	0.23–0.43	<0.001	0.17	0.12–0.23	<0.001	0.24	0.19–0.28	<0.001
Smoking status	5.1	4.0–6.2	<0.001	0.0	-0.001–0.0	0.32	4.3	3.6–5.0	<0.001
MBP	0.12	0.057–0.19	<0.001	0.077	0.035–0.12	<0.001	0.1	0.067–0.14	<0.001
RBC	0.054	0.033–0.075	<0.001	0.055	0.041–0.07	<0.001	0.061	0.05–0.072	<0.001
HGB	2.1	1.4–2.8	<0.001	1.5	1.0–2.0	<0.001	1.8	1.5–2.2	<0.001
HCT	0.72	0.48–0.96	<0.001	0.59	0.43–0.75	<0.001	0.68	0.57–0.8	<0.001
CRE	4.0	0.59–7.4	0.022	7.1	4.0–10.2	<0.001	0.7	5.0–9.1	<0.001
UA	1.0	0.39–1.6	0.002	1.6	1.1–2.0	<0.001	1.6	1.3–1.9	<0.001
TC	0.031	0.003–0.059	0.032	0.023	0.007–0.38	0.004	0.013	-0.001–0.027	0.059
logTG	15.4	11.8–19.0	<0.001	13.2	10.9–15.6	<0.001	14.3	12.4–16.3	<0.001
HDL-C	-0.15	-0.21 to -0.087	<0.001	-0.099	-0.13 to -0.064	<0.001	-0.13	-0.16 to -0.1	<0.001
LDL-C	0.032	0.002–0.061	0.036	0.026	0.009–0.043	0.003	0.021	0.006–0.035	0.006
HbA_{1c}	2.2	0.82–3.6	0.002	1.7	0.77–2.6	<0.001	1.9	1.2–2.7	<0.001
CAVI	0.85	0.24–1.5	0.007	0.32	-0.13–0.78	0.17	0.68	0.32–1.0	<0.001
CIMT	6.8	0.58–12.9	0.032	2.7	-1.7–7.1	0.23	5.4	1.9–9.0	0.003

β, standardized regression coefficient; CI, confidence interval. Other abbreviations are as shown in Table 1.

Multivariate linear regression analysis adjusted for confounding factors including current treatment for HT and/or DM and/or DL also showed that WBC did not correlate with CIMT in men, women and all participants ($p = 0.46$, $p = 0.79$ and $p = 0.58$, respectively; data not shown).

Discussion

In this study, we showed that the WBC count correlated weakly with CAVI in men but not in women and that it did not correlate with CIMT in either sex after adjustment for confounding factors. To our knowledge, this is the first analysis of the relationship between WBC and atherosclerosis represented by CIMT and CAVI in a large community-based sample. We also showed that WBC was strongly correlated with metabolic syndrome markers such as BMI, WC, MBP, HbA_{1c}, TC, LDL-C and HDL-C, which is consistent with the findings of Lao et al. (2008). Their report also showed that the prevalence of metabolic syndrome significantly increased with higher WBC counts in both genders.

Our results showed a positive association between BMI and WBC, which is also consistent with previous findings (Saito et al. 2003). Obesity plays an important role in the pathogenesis of atherosclerosis through low-grade, chronic inflammation. Elevated free fatty acids associated with obesity, insulin resistance, DM and metabolic syndrome cause endothelial dysfunction by activating innate immune inflammatory pathways upstream of the nuclear transcription factor, nuclear factor-κB (Vincent et al. 2003), which promotes the synthesis and release of proinflammatory cytokines that enhance the attachment of monocytes and macrophages to the vessel walls (Koh et al. 2002). Damage to the vessel walls causes endothelium and smooth muscle cells to become transcriptionally active and synthesize proinflammatory proteins, including chemokines, cell adhesion molecules and cytokines.

Smoking is known as a risk factor for atherosclerosis. In our study, WBC was associated with smoking status in men but not in women. This is probably due to the small number of smokers among the women. Previous studies showed that there is a strong, positive relationship between the number of cigarettes smoked and WBC count (Hansen et al. 1990, Petitti & Kipp 1986).

Shankar et al. (2004) showed that the WBC count is associated with incidental hypertension in both sexes independently of smoking and most traditional cardiovascular risk factors in a predominantly Caucasian cohort. We found here that WBC also correlated with blood pressure in Japanese subjects. The concentration of the vasoconstrictor angiotensin II is often elevated in hypertensive patients. Angiotensin II can also contribute to atherogenesis by stimulating the growth of smooth muscle and its lipoxygenase activity, which can increase inflammation and LDL-C oxidation (Ross 1999).

The WBC count significantly correlates with HbA_{1c} in both DM and non-DM patients with known coronary

Table 4. Multivariate linear regression analysis of white blood cell count adjusted for confounding factors including CAVI.

	Men			Women			All		
Variables	β	95% CI	*p*-Value	β	95% CI	*p*-Value	β	95% CI	*p*-Value
Age	-0.19	-0.28 to -0.1	<0.001	-0.18	-0.23 to -0.12	<0.001	-0.18	-0.23 to -0.13	<0.001
BMI	0.64	0.35–0.93	<0.001	0.33	0.17–0.5	<0.001	0.42	0.27–0.56	<0.001
Smoking status	5.1	4.0–6.2	<0.001	-5.7	-0.001–0.001	0.88	3.9	3.2–4.6	<0.001
MBP	0.066	-0.002–0.13	0.055	0.049	0.006–0.092	0.025	0.059	0.023–0.096	0.001
HbA_{1c}	0.9	-0.45–2.3	0.19	1.1	0.2–2.1	0.017	1.2	0.4–1.9	0.003
HDL-C	-0.093	-0.15 to -0.034	0.002	-0.075	-0.11 to -0.04	<0.001	-0.077	-0.11 to -0.047	<0.001
CAVI	0.61	0.06–1.3	0.043	0.35	-0.14–0.78	0.17	0.4	0.044–0.76	0.028

β, Standardized regression coefficient; CI, confidence interval. Other abbreviations are as shown in Table 1.

Table 5. Multivariate linear regression analysis of white blood cell count adjusted for confounding factors including CIMT.

	Men			Women			All		
Variables	β	95% CI	*p*-Value	β	95% CI	*p*-Value	β	95% CI	*p*-Value
Age	-0.17	-0.25 to -0.078	<0.001	-0.16	-0.22 to -0.1	<0.001	-0.16	-0.21 to -0.12	<0.001
BMI	0.62	0.33–0.91	<0.001	0.32	0.15–0.49	<0.001	0.4	0.26–0.55	<0.001
Smoking status	5.1	4.0–6.2	<0.001	-6.9	-0.001–0.001	0.85	3.9	3.2–4.6	<0.001
MBP	0.072	0.005–0.14	0.036	0.052	0.008–0.095	0.019	0.063	0.027–0.099	0.001
HbA_{1c}	1.0	-0.35–2.4	0.15	1.2	0.25–2.1	0.013	1.2	0.46–2.0	0.002
HDL-C	-0.094	-0.15 to -0.034	0.002	-0.075	-0.11 to -0.04	<0.001	-0.078	-0.11 to -0.048	<0.001
CIMT	2.5	0.06–1.3	0.41	0.84	-0.14–0.78	0.71	1.2	0.044–0.76	0.51

β, Standardized regression coefficient; CI, confidence interval. Other abbreviations are as shown in Table 1.

atherosclerosis, and this indicates an early association between glycaemia, inflammation and atherosclerosis before DM develops (Gustavsson & Agardh 2004). We also found a correlation between WBC and HbA_{1c}, which suggests that low-grade chronic inflammatory activity increases in hyperglycaemia. One possible explanation for this is that both a higher WBC count and insulin resistance reflect underlying activation of the immune system. DM is considered to be associated with activation of the innate immune system, and acute-phase reactants, such as C-reactive protein and sialic acid, are proposed predictors of the risk of developing type 2 DM (Crook 2004). A chronic inflammatory response involved in the atherosclerosis process might increase blood concentrations of acute-phase reactants including WBC. Cytokines such as interleukin-6, which is a potent WBC differentiation factor, are associated with insulin resistance (Fernandez-Real et al. 1997). Activation of the immune system caused by inflammation could increase WBC, and cytokine production might therefore decrease insulin sensitivity.

We found that TG and LDL-C were positively associated with WBC and that HDL-C was inversely associated. Wilson et al. (1983) identified a relationship between lipoprotein cholesterol levels and WBC in the Framingham heart study; an elevated WBC count was associated with decreased HDL-C and increased LDL-C in both smokers and non-smokers, suggesting that a higher WBC count is related to a more atherogenic lipid factor. A major cause of damage to the endothelium and underlying smooth muscle is LDL-C. Particles of LDL-C trapped in an artery undergo progressive oxidation and engulfment by macrophages through scavenger receptors on the surfaces of the endothelium and smooth muscle cells. Oxidized LDL-C is a feature of atherosclerotic lesions.

WBC play a crucial role in initiating and propagating the atherosclerotic process (Shankar et al. 2004). Stimulated WBC have an increased tendency to adhere to the vascular endothelium and easily penetrate the intima, causing capillary leukocytosis and increased vascular resistance. Additionally, WBC release various hydrolytic enzymes, cytokines and growth factors that can induce further vascular damage (Ross 1999). This cascade causes endothelial dysfunction and alters arterial elastic properties, leading to structural stiffness.

Lee et al. (2009) reported a positive association between WBC and brachial-ankle PWV that was independent of classical cardiovascular risk factors. On the other hand, we showed a weak correlation between WBC and CAVI in men ($\beta = 0.61$, $p = 0.043$), but not in women ($\beta = 0.35$, $p = 0.17$). This might be associated with the recognized sex difference in the mechanism and pathophysiology of atherosclerosis (Huang et al. 2001). Furthermore, we found that WBC did not correlate with CIMT in either men or women, which is inconsistent with previous studies (Loimaala et al. 2006, Magyar et al. 2003). Magyer et al. (2003) showed that the WBC count was significantly higher in patients with at least 30% internal carotid artery stenosis or occlusion than in controls, and that CIMT was increased in such patients compared with controls. In addition, WBC still correlated with CIMT after adjusting for lipid factors (Magyar et al. 2003). This contradiction might be due to the background of the study population and the method of statistical analyses. Further studies are needed to clarify the association between WBC and atherosclerosis represented by CAVI and CIMT.

Our study has some limitations. We included only one WBC measurement in the analysis, and whether an acute, brief inflammatory episode or chronic inflammation was responsible for the observed correlation could not be discriminated. We could not fully exclude individuals with relevant inflammation or infection, but although WBC varies from day to day (Pocock et al. 1989), a single measurement can nevertheless predict the risk of death and of specific diseases, including cancer and CVD (Hoffman et al. 2004, Madjid et al. 2004). Also, we did not estimate the data of other acute inflammatory markers such as CRP and fibrinogen, and did not analyse by comparing participants with or without current treatments due to the relatively small number of participants who are not under drug treatment. Furthermore, we only evaluated the whole WBC count and not the difference between the subtypes.

In conclusion, we showed that the WBC count is strongly associated with metabolic syndrome components such as lipids, BP and BMI, whereas correlations with CAVI and CIMT were weak or absent. Further evaluation is needed to clarify the value of the WBC count as a marker of atherosclerosis.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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