

Short stature is an inflammatory disadvantage among middle-aged Japanese men

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Abstract

Objectives A positive association between white blood cell count and carotid atherosclerosis has been reported. Our previous study also found an inverse association between height and carotid atherosclerosis in overweight but not non-overweight men. However, no studies have reported on the association between high white blood cell (WBC) count and height accounting for body mass index (BMI) status.

Methods We conducted a hospital-based general population cross-sectional study of 3016 Japanese men aged 30–59 years undergoing general health check-ups between April 2013 and March 2014. High WBC count was defined as the highest tertiles of WBC count among total subjects.

Results Independent of classical cardiovascular risk factors, height was found to be inversely associated with high WBC count, especially for subjects with a BMI ≥ 23 kg/m². The classical cardiovascular risk factors adjusted odds ratios (ORs) and 95 % confidence intervals (CIs) of high WBC count for an increment of one standard deviation (SD) in height (5.7 cm) were 0.91 (0.83–0.99) for total subjects, 1.00 (0.86–1.15) for subjects with a

BMI < 23 kg/m² and 0.86 (0.77–0.96) for subjects with a BMI ≥ 23 kg/m².

Conclusion Independent of classical cardiovascular risk factors, height was found to be inversely associated with high WBC count, especially for those with a BMI ≥ 23 kg/m². Compared to high stature, short stature appears to convey an inflammatory disadvantage among Japanese men, especially those with a BMI ≥ 23 kg/m².

Keywords Height · Inflammation · White blood cell · BMI

Introduction

Chronic low-grade inflammation is associated with the development of cardiovascular disease [1], and atherosclerosis is acknowledged to be an inflammatory condition [2]. In connection with this mechanism, previous studies have reported an association between white blood cell (WBC) count and carotid atherosclerosis [3, 4]. On the other hand, height is reported to be inversely associated with incidence of or mortality from cardiovascular disease [5–7]. Another study reported that carotid intima-media thickness is a well-known indicator of generalized atherosclerosis and is strongly associated with a risk of cardiovascular disease [8]. Furthermore, our previous study found that independent of known cardiovascular risk factors, height is inversely associated with carotid atherosclerosis in overweight but not in non-overweight men [9]. However, no studies have reported on the association between high WBC count and height accounting for body mass index (BMI) status. We, therefore, hypothesized that short stature correlates with high WBC count among Japanese men, especially in those with a higher BMI status, by indicating higher inflammatory activity.

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To investigate such associations, we conducted a hospital-based general population cross-sectional study of Japanese men who participated in a general medical check-up between April 2013 and March, 2014.

Materials and methods

Study populations

The survey population comprised 6645 men aged 30–59 referred for a general health check-up and recruited in-hospital (Inoue Hospital, Nagasaki, Japan) between April, 2013 and March, 2014.

Those from whom WBC data (1223) were not available were excluded. To avoid the influence of acute inflammatory disease, those with a WBC $\geq 10,000/\mu\text{L}$ (134 men) were also excluded. Additionally, those from whom BMI data (25 men), serum data (84 men), and interview data (2163 men) were not available were excluded, leaving 3016 men participating in this cross-sectional study. There were no differences in cardiovascular risk factors (blood pressure, BMI, and serum data) between participants for whom interview data were available and those for whom it was not.

Data collection and laboratory measurements

Participant height and weight in bare feet and light clothing were measured by an automatic height and body composition analyzer (DC-250, TANITA, Corporation, Tokyo, Japan), and body mass index (BMI) was calculated as $\text{weight (kg)}/[\text{height (m)}]^2$.

Trained interviewers obtained information on smoking status, drinking status, and medical history. Fasting blood samples were collected and stored in a siliconized tube. Serum triglycerides (TG), serum HDL-cholesterol (HDL), serum creatinine, and fasting blood sugar were measured using standard laboratory procedures, and serum LDL-cholesterol (LDL) was measured by direct methods. High WBC count was defined as the highest tertiles of WBC count among total subjects. Hypertension was diagnosed as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg and/or taking antihypertensive medication; and diabetes was diagnosed as a fasting blood sugar ≥ 126 mg/dL and/or taking glucose lowering medication. Dyslipidemia was defined as LDL ≥ 140 mg/dL and/or HDL < 40 mg/dL and/or TG ≥ 150 mg/dL and/or taking lipid lowering medication.

Statistical analyses

To evaluate the influence of age on height and WBC count, simple correlation coefficients were calculated.

Differences in age-adjusted mean values or prevalence of potential confounding factors by height and WBC count tertiles were calculated and tested by analysis of covariance. A trend test was performed with a regression model for mean values, and a logistic regression model was used for proportion. Logistic regression models were used to calculate odds ratios (ORs) and 95 % confidence intervals (CIs) to determine the influence of high WBC count on hypertension and diabetes. Logistic regression models were also used to determine the association between high WBC count and height.

In addition, subjects were stratified by BMI status, since in our previous study height was inversely associated with carotid atherosclerosis in overweight but not in non-overweight men [9]. Since the World Health Organization (WHO) identified BMI ≥ 23 kg/m² as an indicator for enhanced risk of disease in Asian populations [10], 23 kg/m² was set as the BMI cutoff point.

Adjustments for confounding factors were made in two ways. First, we adjusted only for age. Second, we included the other possible confounding factors, that is, BMI (kg/m²), smoking status (never smoker, former smoker, current smoker), alcohol consumption (non-drinker, sometimes drinker, daily drinker), serum triglycerides (mg/dL), serum HDL-cholesterol (mg/dL), LDL-cholesterol (mg/dL), and serum creatinine (mg/dL), (glucose lowering medication (yes, no), lipid lowering medication (yes, no), and serum glucose (mg/dL) for calculating the odds of hypertension; systolic blood pressure (mmHg), anti-hypertension medication (yes, no), and lipid lowering medication (yes, no) for calculating the odds of diabetes; and systolic blood pressure (mmHg), anti-hypertension medication (yes, no), glucose lowering medication (yes, no), lipid lowering medication (yes, no), and serum glucose (mg/dL) for calculating the odds of a high WBC count).

All statistical analyses were performed with the SAS system for Windows (version 9.3; SAS Inc., Cary, NC, USA). All *p* values for statistical tests were two-tailed, with values of < 0.05 regarded as being statistically significant.

Ethical considerations

This study was approved by the Ethics Committee for Human Use of Nagasaki University (Project registration number 15033078). Written consent forms were available in Japanese to ensure comprehensive understanding of the study objectives, and informed consent was provided by the participants.

Results

Of the 3016 men, 1198 men and 1818 men were defined as having a BMI < 23 kg/m² and a BMI ≥ 23 kg/m², respectively. Among the study population, age showed a

slight but significant inverse correlation with height, while no significant correlation was observed for WBC count, with the simple correlation coefficients between age and height, and age and WBC count of $r = -0.19$ ($p < 0.001$) and $r = -0.02$ ($p < 0.221$), respectively.

Age-adjusted characteristics of the study population according to height are shown in Table 1. White blood cell count was significantly inversely correlated with height whereas current drinker, and serum creatinine were significantly positively correlated with height.

Age-adjusted characteristics of the study population according to WBC counts are shown in Table 2. WBC count was significantly positively correlated with systolic blood pressure, diastolic blood pressure, BMI, current smoker status, hypertension, diabetes, dyslipidemia, triglycerides, LDL-cholesterol, and blood sugar, and significantly inversely correlated with current drinker status and HDL-cholesterol.

To evaluate the influence of high WBC count on cardiovascular risk, we also calculated the ORs and 95 % CIs of high WBC count for hypertension and diabetes. Compared to non-high WBC count, high WBC count was associated with a significantly higher risk of hypertension and diabetes (Table 3).

Table 4 shows the ORs and 95 % CIs for high WBC count according to height, demonstrating a significant inverse association between these two factors in total subjects. When the associations were stratified by BMI status, the significant

inverse association between height and high WBC count was limited to subjects with a BMI ≥ 23 kg/m².

Discussion

The major finding of the present study is that, independent of classical cardiovascular risk factors, height is inversely associated with high WBC count, especially for those with a BMI ≥ 23 kg/m².

Inflammation is important in the initiation, progression, and clinical outcomes of atherosclerosis [11], which is strongly associated with cardiovascular disease [8].

Furthermore, C-reactive protein (CRP: a maker of inflammation) has been shown in multiple prospective studies to predict cardiovascular disease [12, 13] and higher WBC count, which has also been identified as a marker of systemic inflammatory activity known to be associated with hypertension [14], atherosclerosis [3, 4], and cardiovascular disease incidence and mortality [15, 16]. Insulin resistance also has been found to be enhanced by the link between measures against insulin resistance and WBC count, both in the general population [17] and in non-diabetic subjects [18]. In addition, our previous studies have reported a significant positive association between WBC and participants with diabetes of a type that constitutes a risk of atherosclerosis, but not for those with diabetes of a type that does not pose

Table 1 Age-adjusted characteristics of study population in relation to height

	Height tertiles			<i>p</i> for trend
	T1 (low)	T2	T3 (high)	
Median height (cm)	165.0	170.3	176.0	
No. of participants	996	1010	1010	
Age (years)	48.9 ± 7.0	47.1 ± 7.0	45.9 ± 6.6	
White blood cells (/μL)	5906	5755	5706	0.005
Systolic blood pressure (mmHg)	126	127	127	0.868
Diastolic blood pressure (mmHg)	80	81	81	0.278
Body mass index (kg/m ²)	24.1	24.2	24.0	0.496
Current drinker (%)	69.6	74.9	75.2	0.007
Current smoker (%)	38.3	37.9	38.9	0.897
Hypertension (%)	32.3	31.2	31.7	0.875
Diabetes (%)	6.6	7.7	7.7	0.554
Dislipidemia (%)	53.8	54.7	49.5	0.047
Serum HDL-cholesterol (HDL) (mg/dL)	58	59	58	0.323
Serum LDL-cholesterol (LDL) (mg/dL)	128	129	125	0.019
Serum triglycerides (TG) (mg/dL)	131	131	132	0.982
Blood sugar (mg/dL)	100	102	101	0.306
Serum creatinine (mg/dL)	0.85	0.90	0.90	0.001

Age: mean ± standard deviation

Height tertiles are: <167.9 cm for T1, 167.9–172.7 cm for T2, and >172.7 cm for T3

Table 2 Age-adjusted characteristics of study population in relation to white blood cell (WBC) count

	WBC tertiles			<i>p</i> for trend
	T1 (low)	T2	T3 (high)	
Median white blood cells (μL)	4400	5600	7200	
No. of participants	998	1007	1011	
Age (years)	47.4 \pm 7.2	47.6 \pm 6.9	47.0 \pm 6.9	
Systolic blood pressure (mmHg)	125	126	129	<0.001
Diastolic blood pressure (mmHg)	79	80	82	<0.001
Body mass index (kg/m^2)	23.3	24.0	25.0	<0.001
Current drinker (%)	78.7	73.0	68.1	<0.001
Current smoker (%)	21.5	36.6	56.9	<0.001
Hypertension (%)	28.0	30.1	37.0	<0.001
Diabetes (%)	4.7	6.9	10.5	<0.001
Dislipidemia (%)	28.0	30.1	37.0	<0.001
Serum HDL-cholesterol (HDL) (mg/dL)	62	58	54	<0.001
Serum LDL-cholesterol (LDL) (mg/dL)	123	129	131	<0.001
Serum triglycerides (TG) (mg/dL)	107	132	155	<0.001
Blood sugar (mg/dL)	99	101	103	<0.001
Serum creatinine (mg/dL)	0.89	0.89	0.87	0.428

Age: mean \pm standard deviation

WBC count tertiles are: <5100/ μL for T1, 5100–6200/ μL for T2, and >6200/ μL for T3

Table 3 Odds ratios (ORs) and 95 % confidence intervals (CIs) of high white blood cell count for hypertension and diabetes

	WBC category			<i>p</i> for trend
	Non-high WBC count		High WBC count	
	T1 (low)	T2	T3 (high)	
No. of participants	998	1007	1011	
Hypertension				
No. of hypertension (%)	280 (28.1)	308 (30.6)	369 (36.5)	
Age-adjusted ORs	1.00		1.48 (1.26–1.75)	<0.001
	1.00	1.13 (0.92–1.38)	1.58 (1.30–1.92)	<0.001
Multivariable ORs ^a	1.00		1.37 (1.13–1.65)	0.001
	1.00	1.09 (0.88–1.35)	1.44 (1.15–1.80)	0.002
Diabetes				
No. of diabetes (%)	47 (4.7)	71 (7.1)	104 (10.3)	
Age-adjusted ORs	1.00		1.96 (1.48–2.60)	<0.001
	1.00	1.55 (1.05–2.27)	2.49 (1.74–3.58)	<0.001
Multivariable ORs ^b	1.00		1.44 (1.05–1.96)	0.022
	1.00	1.32 (0.89–1.98)	1.70 (1.14–2.54)	0.008

Non-high WBC count and high WBC count are: <6200/ μL , and >6200/ μL

^a Adjusted further for age, body mass index, smoking status, alcohol consumption, glucose lowering medication use, lipid lowering medication use, serum triglycerides (TG), serum HDL-cholesterol (HDL), serum LDL-cholesterol (LDL), blood sugar, and serum creatinine

^b Adjusted further for age, systolic blood pressure, body mass index, smoking status, alcohol consumption, antihypertensive medication use, lipid lowering medication use, serum triglycerides (TG), serum HDL-cholesterol (HDL), serum LDL-cholesterol (LDL), and serum creatinine

such a risk [4, 19]. And in our present study, compared to participants with a non-high WBC count, high WBC count is a significant risk factor for hypertension and diabetes. Since hypertension and diabetes are well-

known cardiovascular risk factors, these results indicate that high WBC counts have an active inflammatory background component that underlies the risk of cardiovascular disease.

Table 4 Odds ratios (ORs) and 95 % confidence intervals (CIs) for high white blood cell (WBC) count in relation to height for total subjects, stratified by BMI status

	Height tertiles			<i>p</i> for trend	1 SD increment of height (5.7 cm)
	T1 (low)	T2	T3 (high)		
Total subjects					
No. of participants	996	1010	1010		
No. of cases (%)	358 (35.9)	333 (33.0)	320 (31.7)		
Age-adjusted ORs	1.00	0.86 (0.71–1.03)	0.80 (0.66–0.96)	0.019	0.93 (0.86–1.00)
Multivariable ORs	1.00	0.84 (0.69–1.03)	0.76 (0.67–0.94)	0.009	0.91 (0.83–0.99)
BMI < 23 kg/m²					
No. of participants	385	386	427		
No. of cases (%)	103 (26.8)	96 (24.9)	113 (26.5)		
Age-adjusted ORs	1.00	0.92 (0.66–1.27)	1.03 (0.73–1.38)	0.968	1.01 (0.89–1.16)
Multivariable ORs	1.00	0.95 (0.67–1.34)	0.98 (0.70–1.38)	0.932	1.00 (0.86–1.15)
BMI > 23 kg/m²					
No. of participants	611	624	583		
No. of cases (%)	255 (41.7)	237 (38.0)	207 (35.5)		
Age-adjusted ORs	1.00	0.82 (0.65–1.03)	0.72 (0.57–0.91)	0.006	0.89 (0.81–0.98)
Multivariable ORs	1.00	0.83 (0.64–1.06)	0.66 (0.51–0.85)	0.001	0.86 (0.77–0.96)

High white blood cell (WBC) count is defined as the highest tertile of WBC count for total subjects. Multivariable ORs: adjusted further for age, systolic blood pressure, body mass index, smoking status, alcohol consumption, anti-hypertensive medication use, glucose lowering medication use, lipid lowering medication use, serum triglycerides (TG), serum HDL-cholesterol (HDL), serum LDL-cholesterol (LDL), blood sugar, and serum creatinine

Height tertiles are: <167.9 cm for T1, 167.9–172.7 cm for T2, >172.7 cm for T3

In addition to the above, we also found a significant inverse association between height and high WBC count. Since height is reported to be inversely associated with carotid atherosclerosis [9] and incidence of or mortality from cardiovascular disease [5–7], height may be inversely associated with high WBC count by indicating the presence of inflammation.

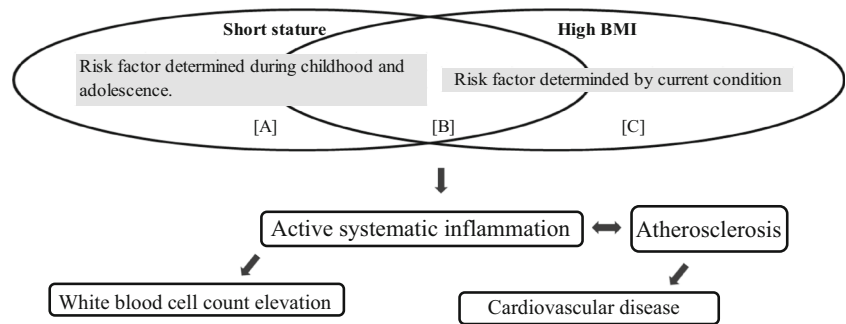
However, the reason why this association was restricted to those with a higher BMI warrants discussion. Height is regarded as a marker of childhood social and physical conditions [5–7, 9]. On the other hand, BMI is reported to be positively associated with increased risk of disease [10] and is largely influenced by current circumstances. Total cardiovascular risk factor is likely to comprise a combination of risk factors determined during both childhood and adolescence, as well as risk factors determined by current circumstances. For the analysis to determine the validity of our hypotheses, we divided the study population into three groups according to height and BMI status (Fig. 1). The first group [A], with a short stature but not high BMI, had characteristics that could elucidate the potential effect of childhood circumstances as a risk for atherosclerosis and cardiovascular disease. The second group [B], with a short stature and high BMI, which reflect both childhood circumstances and current conditions, features a higher risk of atherosclerosis and cardiovascular disease. The third group

[C], with a high BMI but not short stature, presented characteristics that could elucidate the potential effect of current conditions. Since high WBC count indicates high systematic inflammatory activity, both childhood circumstances and current conditions [B] may influence the presence of high WBC counts. Our previous study showing a significant inverse association between height and carotid atherosclerosis in overweight but not non-overweight men [9] might support these mechanisms.

An unfavorable lipid profile might also have an influence on the correlation between height and high WBC count. A primary association exists between genetically determined shorter height and increased risk of coronary artery disease—a link that is partly explained by the association between shorter height and an adverse lipid profile [20]. An unfavorable lipid profile is also reported to be associated with low-grade inflammation [21]. However, we found a significant correlation between height and high WBC count even after further adjustment for HDL-cholesterol, LDL-cholesterol, and triglycerides.

Possible limitations of this study warrant consideration. Because creatinine clearance data were not available and estimated glomerular filtration rate (GFR) is not effective for evaluating kidney function when comparing the association with various body heights [9, 22], we were not able to perform an analysis adjusted for precise renal function.

Fig. 1 Association between short stature and high BMI as systematic inflammation. [A] Area where potential effects of childhood circumstances can be elucidated. [B] Area where current condition includes risk of progression of atherosclerosis. [C] Area where potential effect of current condition can be elucidated



However, our study showed that the associations between height and high WBC count remained significant even after adjustment for serum creatinine. Additionally, since no data on high sensitive CRP were available, we were not able to evaluate the influence of inflammation from various perspectives. Finally, since this was a cross-sectional study, we were not able to establish any causal relationships.

In conclusion, we found that height was inversely associated with a risk of high WBC count among middle-aged Japanese men. This association was limited to those with a BMI ≥ 23 kg/m², which suggests that in addition to current conditions, childhood social and physical conditions may contribute to the progression of systematic inflammation in adulthood.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Human and animal rights and informed consents All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution research committee and with the 1964 Helsinki declaration and its later amendments for comparable ethical standards. The Ethics Committee for Human Use of Nagasaki University obtained ethical approval.

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