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Total and Differential White Blood Cell Counts in Late-Life Predict Eight-Year Incident Stroke: The Honolulu Heart Program

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Abstract

Background/Objectives—Previous studies have found that higher white blood cell count is associated with incident stroke. However, there are inconsistent results in the elderly and only a few studies have included differential white blood cell counts or Asian populations. We studied the association between total and differential white blood cell counts and incident stroke in an older Asian population.

Design—Prospective population-based study with 8 years of follow-up.

Setting—The Honolulu Heart Program, Oahu, Hawaii.

Participants—Three thousand, three hundred and forty-two Japanese-American men (ages 71–93 years) who were free of stroke and had baseline WBC counts in 1991–93.

Measurements—Participants were divided into quartiles of total and differential WBC counts for analysis, and were followed for incident stroke (all strokes [ALL-CVA], thromboembolic [TE-

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CVA] and hemorrhagic [HEM-CVA]) for eight years using data from a comprehensive hospital surveillance system.

Results—Age-adjusted incident ALL-CVA rates increased significantly with total WBC quartiles (7.68, 9.04, 9.26, 14.10, per 1,000 person years follow-up, respectively, p=0.001).Hazard ratios for ALL-CVA for each quartile of total and differential WBC counts were obtained using Cox regression, with the lowest quartile as the reference group. After full adjustment including age, cardiovascular risk factors, fibrinogen, prevalent CHD, cancer or COPD, and aspirin/NSAID use, hazard ratios in the highest quartiles of total WBC and neutrophil counts were 1.62 (95%CI=1.04–2.52, p=0.033) and 2.19 (95%CI=1.41–3.39, p<0.001)respectively. These significant associations were also seen for TE-CVA, but not for HEM-CVA. No significant associations were found between lymphocyte or monocyte counts and incident stroke or subtypes.

Conclusion—In elderly Japanese-American men, higher total WBC and neutrophil counts were independent predictors of overall stroke, as well as thromboembolic stroke.

Keywords

White blood cell counts; differential WBC counts; incident stroke; Japanese-American men; longitudinal cohort study

INTRODUCTION

Stroke is a leading cause of mortality and serious long-term disability in the United States.[1] It is common in elderly populations, and the highest prevalence and annual rate of first-ever strokes are reported in those aged 85 years and older. Stroke imparts a tremendous burden to the elderly population, and they have a higher mortality and are less likely to be discharged to their original place of residence after stroke.[1]

Atherosclerosis is known to be the major cause of ischemic stroke, the most common subtype.[2] Many studies have revealed that atherosclerosis is an inflammatory disease and white blood cells(WBC) play an important role in the initiation, progression and rupture of atherosclerotic plaques.[3, 4]

Several prospective cohort studies have investigated the association between WBC counts and incident stroke,[5–13] but the results have been inconsistent. This inconsistency is especially prominent in the elderly population, which is under-represented in these cohort studies.[5, 6, 10, 11] There have also been inconsistent results reported among different ethnic groups and among men and women.[6] The NHANES I, conducted in 1971–1987, found a significant association between WBC and incident stroke only in White men and not at all in women or in Blacks. Despite this inconsistency, there have only been two previous cohort studies in Asian populations which were mostly middle-aged and also showed inconsistent results.[5, 9] Similarly, there are only a few studies investigating the association between differential WBC counts and incident stroke.[5, 9, 11] The purpose of this report is to determine the association between total and differential WBC counts and incident stroke in a large population of elderly Japanese-American men.

METHODS

Study Design and Population

The Honolulu Heart Program (HHP) is a prospective cohort study of stroke and coronary artery disease in 8,006 Japanese-American men living on the island of Oahu, Hawaii, which[14, 1514, 1514, 1514, 1514, 15] began in 1965.[14, 15] Participants were 45 to 68 years old at the time of study enrollment, and details of the cohort selection process have been previously published.[16] The study was approved by the Institutional Review Board of Kuakini Medical Center, and written informed consent was obtained from all participants at each examination.

The fourth HHP examination was performed from 1991 to 1993 and serves as baseline for this analysis. A total of 3,741 men ages 71 to 93 years participated in this examination, and were followed up for incident stroke through December 1999. Subjects with prevalent stroke at baseline (n=227) and those with missing WBC counts (n=172) were excluded from this analysis, leaving a final analytic sample of 3,342 for this report.

Data Collection

Predictor Variables - Total and Differential WBC Counts—Blood samples were sent to a local laboratory, Diagnostic Laboratory Services, Inc, to measure total and differential WBC counts. Whole blood specimens were obtained in EDTA vacutainer tubes. Complete blood cell (CBC) counts were measured within 6 hours after collection if stored at room temperature, or within 24 hours after collection if stored at 4 degrees Centigrade. Any specimens that were clotted or filled less than half of the tube were rejected. The total and differential WBC counts were assessed using the Technicon H-1 automated hematology analyzer (Technicon Instruments Corp, Terrytown, NY, USA).[17, 18] Compared to the gold standard, studies using this methodology have found that the coefficient of correlation for total WBC count, neutrophils, lymphocytes, monocytes, eosinophils, and basophils were 0.999, 9.994, 0.999, 0.946, 0.994, and 0.976, respectively.[19] The ratio of neutrophils, lymphocytes, monocytes, eosinophils, and basophils were provided as a result of differential WBC counts. Absolute counts for each differential count were calculated from the total WBC count and the ratio of each differential WBC count.

Outcome Variables - Incident Stroke and Sub-Types—There has been continuous, comprehensive surveillance for all mortality and selected morbidity including incident stroke since the beginning of the HHP study. All hospital discharges on the island of Oahu, death certificates and autopsy records were reviewed. For this report, stroke (ALL-CVA) was defined as acute onset of a neurological deficit for 2 weeks or until death confirmed by either blood in the cerebrospinal fluid or evidence on brain tomography or MRI. Possible strokes, defined as neurological deficits persisting for at least 24 hours but less than 2 weeks or unknown duration, were not included because of diagnostic uncertainty. Strokes were further classified as thromboembolic (TE-CVA), hemorrhagic (HEM-CVA), or unknown type based on clinical information and findings of imaging studies, surgery, or autopsy. A stroke was identified as TE-CVA when a focal neurologic deficit occurred usually without prolonged unconsciousness, nuchal rigidity, fever, pronounced leukocytosis, or blood in the

spinal fluid. Identification of HEM-CVA was made when a focal neurologic deficit was accompanied by loss of consciousness, headache, and blood present in the spinal fluid obtained by an atraumatic lumbar puncture or on the basis of computerized tomography or surgical findings. Subjects who had neurological deficit from other etiologies such as blood dyscrasias, neoplastic disease, head injury, surgical accident, meningoencephalitis, fat embolism, epilepsy or cardiac arrest were not included. Further details on the diagnosis of stroke have been reported in earlier publications.[20] All stroke diagnoses were reviewed and confirmed by a study neurologist and the Honolulu Heart Program Morbidity and Mortality Review Committee using the International Classification of Diseases, 8th Revision codes. Incident stroke data are available through December 1999, for a total 8 years of follow-up (mean=6.3 years, median=7.1 years, range=0.02–8.8 years).

Covariates—To isolate the independent effect of total and differential WBC counts on stroke, statistical analysis included adjustments for possible confounders, including age and cardiovascular risk factors at baseline (HHP fourth examination, 1991–93). Body mass index (BMI) was defined as weight in kilograms divided by square of height in meters. Hypertension was defined as systolic blood pressure of 140 or greater, or diastolic blood pressure of 90 or greater, or use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose of 126 mg/dL or greater, or 2 hour post-load glucose of 200 mg/dL or greater, or use of insulin or oral hypoglycemic agents. Smoking was defined as current, past or never smoking by self-report. The physical activity index (PAI) quantified overall metabolic output during a typical 24-hour period by multiplying a weighting factor by the number of hours spent in 5 levels of activity (no activity=1.0, sedentary=1.1, slight=1.5, moderate=2.4, and heavy=5.0).[20] Serum total cholesterol, HDL cholesterol and fibrinogen levels were measured by standard procedures from blood collected after at least 12 hours of fasting. Alcohol intake was measured as ounces consumed per month by self-report at interview. We also included baseline prevalent chronic diseases as possible confounders, including coronary heart disease (CHD), cancer and chronic obstructive pulmonary disease (COPD). Prevalent CHD and cancer were identified by surveillance of hospital records using standardized criteria, and prevalent COPD was identified by self-reported history. Participants were asked to bring in all prescription and non-prescription medications to the examination, which were documented, including use of aspirin or non-steroidal anti-inflammatory drugs (NSAID). Further description of cardiovascular risk factors available in the HHP has been published previously.[14]

Statistical Analysis

The study population was divided into quartiles of total or differential WBC counts for analysis. Age-adjusted baseline risk factors were compared across quartiles using general linear models (GLM). Incident rates of ALL-CVA, TE-CVA, and HEM-CVA were calculated per 1,000 person-years of follow up by quartiles of total and differential WBC counts. Rates of disease free survival in each outcome were calculated using the Kaplan-Meier method and significant differences among quartile groups were analyzed by the log-rank test. The independent effect of total or differential WBC counts as predictors of incident stroke and sub-types was evaluated using Cox regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) for each outcome were measured in each quartile,

using the lowest quartile as reference. Test for trend across hazard ratios by quartiles was also assessed. In multivariate cox regression models, analyses were adjusted for covariates including age, BMI, hypertension, diabetes mellitus, current and past smoking, PAI, total cholesterol, HDL cholesterol, alcohol intake, fibrinogen level, use of aspirin or NSAIDs, and prevalent CHD, cancer and COPD. All analyses used the SAS software package (Version 9.2; SAS Institute, Cary, NC). For all statistical tests, 2 tailed probability values <0.05 were considered significant.

RESULTS

Baseline characteristics by quartiles of total WBC counts are shown in Table 1. Those in the higher quartiles were significantly more likely to have higher BMI, alcohol intake and fibrinogen levels, as well as higher rates of hypertension, diabetes mellitus, aspirin or NSAID use, cancer and COPD. They were also more likely to be current smokers. In contrast, they were significantly less likely to be never smokers, and were less physically active and had lower HDL cholesterol levels. Age, past smoking history, total cholesterol, prevalent CHD and cancer were not significantly associated with quartiles of total WBC counts.

During the 8 year follow-up period, 202 ALL-CVA, 137 TE-CVA and 51 HEM-CVA events were identified among the 3,342 participants free of stroke at baseline. Table 2 shows age-adjusted incidence rates of each type of stroke per 1,000 person-years of follow-up by quartiles of total WBC and neutrophil counts. The age-adjusted incidence rates of ALL-CVA and TE-CVA significantly increased with increasing quartile of total WBC and neutrophil counts. These two outcomes also had significant associations with quartiles of monocyte counts (p=0.023 for ALL-CVA and p=0.003 for TE-CVA, data not shown). The quartiles of lymphocytes counts did not have significant correlations with any type of stroke. There were no significant associations between incidence rates of HEM-CVA and quartiles of total or differential WBC counts. We also performed age-specific analyses of incidence rates, using two age groups at baseline: 71–79 years (n=2,384) and 80+ years (n=958) (Supplemental Table 2A). In the age-specific unadjusted analyses, there was still a significant increase in incidence of ALL-CVA and TE-CVA with increasing quartile of WBC and neutrophil counts in the age group 71–79 years (p for trend for both outcomes <0.001), but this association became non-significant in the age group 80+ years.

Figure 1 shows Kaplan Meier stroke-free survival curves, which demonstrate higher 8-year incidence of ALL-CVA among those in the highest quartiles of total WBC count and neutrophil count(p=0.003 and p<0.001 respectively).

Cox regression analyses calculated hazard ratios (HRs) for 8-year incident stroke and sub-types among quartiles of total WBC and neutrophil counts, using the lowest quartile as reference for both analyses (Table 3). In the age-adjusted model, those in the highest quartile of total WBC and neutrophil counts had significantly higher risk of incident ALL-CVA and TE-CVA. The highest quartile of monocyte count also had higher risk of incident ALL-CVA and TE-CVA (HR=1.54, 95% CI 1.03–2.28, p=0.034, and HR=1.91, 95% CI 1.17–3.12, p=0.010, respectively). After adjustment for all potential confounders, including age, BMI,

hypertension, diabetes, current and past smoking, physical activity index, total and HDL cholesterol, fibrinogen level, alcohol intake, use of aspirin or NSAID, and prevalent CHD, cancer and COPD, monocyte count quartiles were no longer a significant predictor of incident stroke or subtypes. However, in multivariate analyses, there remained a significant association between the highest quartile of total WBC and neutrophil counts and incident stroke. In the highest quartile of total WBC count (compared to the lowest), there was a 62% increase in incidence of ALL-CVA, and a 69% increase in incidence of TE-CVA. In the highest quartile of neutrophil count (compared to the lowest), there was more than double the risk of both ALL-CVA and TE-CVA. There were no statistically significant associations between HEM-CVA and quartiles of total or any differential WBC counts.

In order to avoid bias due to extreme values of WBC counts (defined as total WBC count < 2.5 or >15), we repeated the analyses after excluding these subjects (n=14). The results of the multivariate analyses did not change after this exclusion (data not shown).There have been previous reports of an association between stroke and myeloproliferative disorders such as polycythemia vera. We found 23 possible cases in our cohort (WBC > 15,000, hemoglobin > 18.5 or platelet estimate increased). We repeated the multivariate analyses after excluding these subjects (n=23). The results of the multivariate analyses did not change substantially after this exclusion (data not shown), except that the association between total WBC and TE-CVA became borderline significant (Q4 vs. Q1 p=0.08, test for trend p=0.054).

DISCUSSION

In this prospective population-based study, the highest quartiles of total WBC and neutrophil counts were independent predictors of overall and thromboembolic stroke over 8 years of follow-up among elderly Japanese-American men. These associations remained significant even after adjustment for multiple covariates including known risk factors and prevalent chronic diseases. Compared to the lowest quartile, the highest quartile of total WBC count had a 62% increased risk of overall stroke and 69% increased risk of thromboembolic stroke. The highest quartile of neutrophil count had more than twice the risk of overall and thromboembolic stroke. Monocyte and lymphocyte counts did not have significant independent associations with stroke or its sub-types, and no associations were seen between hemorrhagic stroke and total or any differential WBC counts.

While several previous prospective cohort studies have shown a significant association between WBC and incident stroke, results in elderly populations have been mixed. The NHANES I study was conducted from 1971 to 1987 in 5,867 White and Black men and women ages 45–74 years. After a mean of 12 years of follow-up, they found a significant association with incident stroke only in white women ages 45–64, but no significant association was found in women ages 65–74 years.[6] The Adult Health Study was conducted in 1958–1974 in 16,090 Japanese participants, and also found no significant association between WBC or differential counts and 16-year incident stroke in the elderly subgroup (age ≥ 65 years), even though they found a significant association in the entire cohort.[5] The Northern Manhattan Study included 3,103 participants with a mean age of 69 years who were followed for up to 10 years, and found a significant but weaker association in those

aged 70 years and over, compared to those less than 70.[10] Our study was unique in that all our subjects were over age 70 years at baseline, whereas the elderly were not as well represented in the studies listed above (for example, the Adult Health Study included only 8% of their population over 65 years of age). The only other study with a significant proportion of elderly subjects was the Women's Health Initiative, which followed 72,242 women of which 65.7% were age 60 years or older at baseline, and also found a significant association between WBC count and incident stroke.[12] In our study, there was a strong association between WBC quartiles and incident stroke and thromboembolic stroke in those aged 71–79 years, but this association became non-significant in those aged 80 years and over. This finding suggests that the pathophysiology underlying stroke may be more complicated in the oldest-old, which needs further study. Other factors, including frailty, may become more important in this oldest-old group.

Previous cohort studies have also found differences in the association between WBC and incident stroke among different ethnic groups. In the NHANES I study, there was a significant association between WBC counts and incident stroke in white men which became non-significant after adjustment for smoking, but no association was found in Blacks.[6] To our knowledge, there have been only two prospective cohort studies in Asian populations. The Adult Health Study was conducted in a Japanese population and found a significant association between WBC and incident stroke, but this study was not able to make complete adjustments for smoking because of lack of data availability.[5] The other Asian cohort study, the Chin-Shan Community Cohort Study was conducted in 1990–2007 in 3,416 Taiwanese people (age range 35 to ≥ 75 years, majority <65 years) and found a significant association between WBC and 17-year incident stroke even after full adjustment for risk factors, which is consistent with our findings in a Japanese-American cohort.[9]

Another unique aspect of our study was that we included differential WBC counts in addition to the total WBC count. Like other studies using differential WBC counts (Japanese RERF Study, Taiwan Chin-Shan Community Cohort Study, and the Malmo Swedish cohort), we also found that neutrophil count was an independent predictor of overall stroke and thromboembolic stroke.[5, 9, 11] All three previous studies using differential WBC counts had a majority of young or middle-aged participants, in contrast with our study. Although it is known that monocytes are important in the development of atherosclerosis,[3] we did not find significant associations between monocyte count and incident overall or thromboembolic stroke after adjustment for risk factors. Our results are similar to those of other cohort studies using differential WBC counts as a predictor of stroke.[5, 11] One potential explanation is that monocytes are only important in the initiation of atherosclerosis, and neutrophils become more important in the stability of plaques and correlate with rupture of atherosclerotic plaques, and therefore with thromboembolic stroke.[4, 21]

In our study, there were no significant associations between incident hemorrhagic stroke and total or differential WBC counts, suggesting different mechanisms underlying the development of ischemic stroke and hemorrhagic stroke, with no role for inflammation in the pathogenesis of hemorrhagic stroke.

Our study found that higher WBC count was associated with higher BMI and other cardiovascular risk factors such as hypertension and diabetes mellitus. Several other studies have found a significant association between higher WBC count and obesity and metabolic syndrome components.[22–24] Pro-inflammatory cytokines such as Leptin, Tumor Necrosis Factor alpha and IL-6 have been considered to be potential causes of this association. These cytokines are produced from adipose tissue and have a positive myelopoietic effect, as well as inducing inflammatory reactions.

Recent studies have found that inflammation playsan important role in the development of atherosclerosis and stability of atherosclerotic plaques.[25] Pro-inflammatory cytokines activate cellular functions of WBC differential counts, especially monocytes and neutrophils. For example, cytokines stimulate the expression of WBC adhesion molecules on the endothelial surface, which promotes the binding of WBCs to their surface. With the effect of cytokines, these cells then enter the arterial intima, where the protein mediators of inflammation such as macrophage-colony stimulating factor or matrix metalloproteinase activate WBC cellular functions such as expression of scavenger receptors for lipoproteins and permit lipid accumulation.[3, 4, 25, 26] To detect the role of inflammation in atherogenesis, various inflammatory markers have been studied. Of these, WBC count is the most cost effective marker to detect inflammation, and is widely used worldwide as part of the complete blood cell count. The growing body of evidence that inflammation plays an important role in all stages of atherothrombosis[25] confirms the findings in this report.

A major strength of our study is the large prospective population-based design in a homogenous sample of Japanese-Americans, a previously under-studied group. Another major strength is that this is the first study done purely in an elderly population. The cohort has had excellent retention and follow-up rates. Surveillance for outcomes in the Honolulu Heart Program is almost complete due to low out-migration rates for this population. However, our study has several limitations. First, the study sample included only Japanese-American men, which may limit generalizability to other ethnic groups or women. However, this study does add meaningful information to the prior literature on this subject which included other ethnicities, women and younger age groups. Secondly, the measurement of total WBC and differential counts was performed only once in this study. Repeated measurement would provide more stable estimates of risk and would be less affected by measurement error, changes with follow-up or temporal changes due to acute illnesses. When we repeated the analyses after excluding extreme values of WBC counts (defined as total WBC count < 2.5 or >15), the results did not change. In addition, the Northern Manhattan Study investigated stability of WBC counts among individuals and found within-individual variability in WBC counts was only 1.1 × 10 cells/L among a subgroup of 114 event-free participants who had four or more WBC count measurements repeated annually.[10] Finally, we were able to control only for fibrinogen levels and did not have available information on other inflammatory biomarkers such as C-reactive protein.

In summary, we demonstrated that elderly Japanese-American men in the highest quartiles of total WBC and neutrophil counts had an independent increased risk of 8-year incidence of overall and thromboembolic stroke. This finding adds to the literature on this topic in people of different ethnicities, gender and age groups, suggesting that total WBC and neutrophil

counts can be utilized as prognostic markers for incident stroke in the elderly. To use these markers more effectively in the clinical setting, further studies are needed to establish cut-off values of WBC and neutrophil counts, and to assess the effectiveness of risk reduction in these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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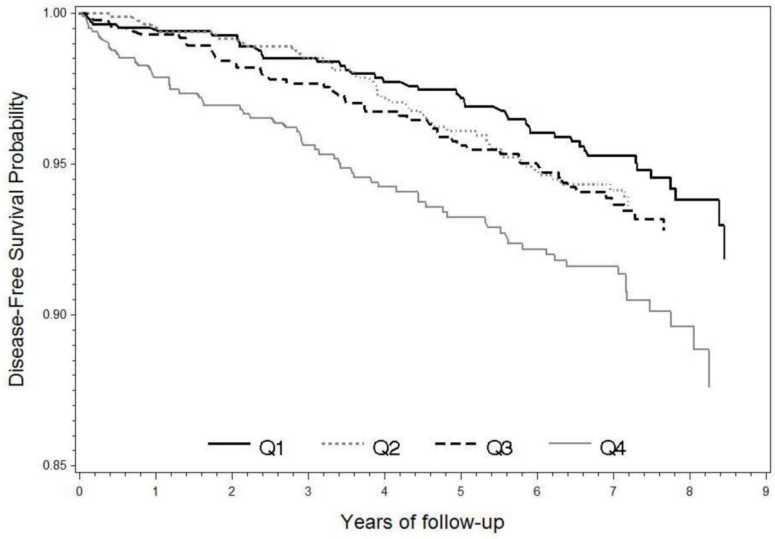
a.



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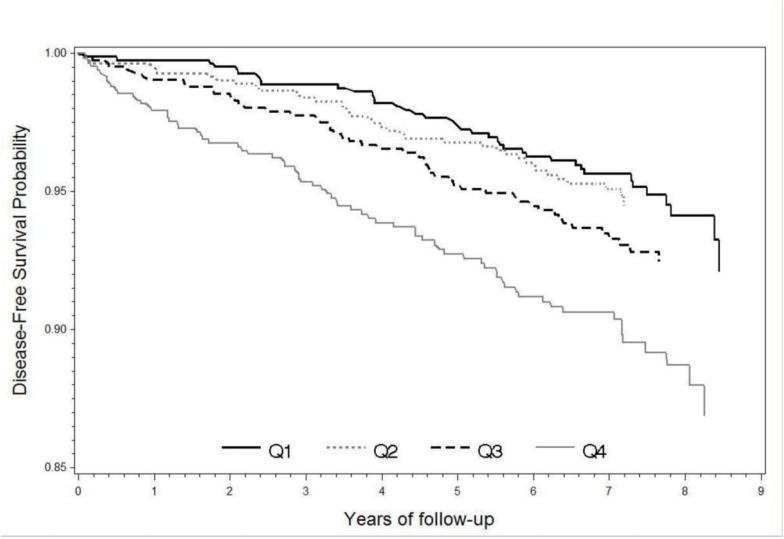

Figure 1.

a. Kaplan-Meier stroke-free survival curves for ALL-CVA and WBC quartiles.

b. Kaplan-Meier stroke-free survival curves for ALL-CVA and Neutrophil quartiles.

Table 1

Baseline characteristics by quartiles of total white blood cell (WBC) count.

	Q1	Q2	Q3	Q4	p for trend
WBC quartile range	0.9–5.0	5.1 – 5.9	6.0 – 7.1	7.2 – 64.0	
N	836	838	858	810	
WBC count	4.35±0.60	5.50±0.25	6.50±0.34	8.64±2.84	
Age (years)	77.58±4.50	77.43±4.59	77.64±4.52	77.83±4.70	0.183
BMI (kg/m^2)[a]	22.85±2.92	23.47±2.88	23.92±3.05	23.72±3.29	<.001
Hypertension (%)[a]	68.4	73.3	74.8	78.6	<.001
Diabetes Mellitus (%)[a]	21.7	25.5	31.9	34.4	<.001
Current Smoker (%)[a]	2.6	4.7	6.4	15.5	<.001
Past Smoker (%)[a]	52.4	57.4	56.1	54.8	0.462
Never Smoker (%)[a]	45.0	38.0	37.5	29.8	<.001
Physical activity index[a]	31.31±4.60	31.29±4.88	30.94±4.49	30.48±4.34	<.001
Total Cholesterol (mg/dl)[a]	189.07±32.01	190.10±31.69	192.80±33.79	188.94±34.07	0.654
HDL Cholesterol (mg/dl)[a]	55.36±14.21	50.64±13.00	49.65±12.58	48.79±12.54	<.001
Alcohol(oz/month)[a]	16.64±31.38	18.05±36.38	18.22±42.50	20.93±45.89	0.040
Fibrinogen (mg/dl)[a]	288.13±52.91	296.24±52.66	306.75±58.00	334.34±76.73	<.001
ASA or NSAID use (%)[a]	25.8	29.6	28.0	31.5	0.027
Prevalent CHD (%)[a]	16.9	20.3	21.2	20.3	0.069
Prevalent Cancer (%)[a]	18.9	14.2	15.3	13.2	0.004
Prevalent COPD (%)[a]	1.8	2.0	2.0	5.8	<.001

Data are presented as percentage or mean ± standard deviation.

WBC indicates white blood cell; BMI, body mass index; HDL, high density lipoprotein; ASA, aspirin; NSAID, nonsteroidal anti-inflammatory drug; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease.

[a]adjusted for age at baseline

Table 2

Age-adjusted incidence rates of ALL-CVA, TE-CVA and HEM-CVA by total WBC and Neutrophil quartiles (per 1,000 person years follow-up).

		Q1	Q2	Q3	Q4	p for trend
Total WBC Count		836	838	858	810	
ALL-CVA	N	42	46	49	65	
	Rates	7.68	9.04	9.26	14.10	0.001
TE-CVA	N	27	28	35	47	
	Rates	4.92	5.58	6.68	10.18	0.001
HEM-CVA	N	14	13	11	13	
	Rates	2.52	2.36	1.97	2.74	0.895
Neutrophil Count		835	835	837	835	
ALL-CVA	N	39	39	51	73	
	Rates	7.27	7.53	9.74	15.32	<.001
TE-CVA	N	27	24	36	50	
	Rates	5.04	4.79	6.83	10.48	<.001
HEM-CVA	N	11	13	11	16	
	Rates	1.99	2.27	2.06	3.26	0.220

ALL-CVA indicates all stroke; TE-CVA, thromboembolic stroke; HEM-CVA, hemorrhagic stroke.

WBC quartiles: Q1=0.9–5.0; Q2=5.1–5.9; Q3=6.0–7.1; Q4=7.2–64.0.
Neutrophil quartiles: Q1=0.06–2.99; Q2=2.99–3.71; Q3=3.72–4.62; Q4=4.62–14.18.

Table 3

Hazard ratios for 8-year incidence of ALL-CVA, TE-CVA and HEM-CVA by total WBC and neutrophil count quartiles using Cox Regression (lowest quartile as reference).

		All Stroke (ALL-CVA)			**Thromboembolic Stroke (TE-CVA)**			**Hemorrhagic Stroke (HEM-CVA)**		
		HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**	**HR**	**95%CI**	**P value**
Total WBC Count Quartiles										
Age-adjusted	Q2 vs. Q1	1.14	0.75–1.74	0.529	1.09	0.64–1.84	0.760	0.93	0.44–1.98	0.855
	Q3 vs. Q1	1.22	0.81–1.84	0.351	1.35	0.82–2.23	0.241	0.81	0.37–1.79	0.603
	Q4 vs. Q1	1.89	1.28–2.79	**0.001**	2.11	1.31–3.39	**0.002**	1.11	0.52–2.37	0.779
	P for trend			**0.001**			**0.001**			0.895
Fully adjusted	Q2 vs. Q1	1.06	0.68–1.65	0.783	0.94	0.54–1.64	0.832	1.04	0.46–2.35	0.919
	Q3 vs. Q1	1.12	0.72–1.75	0.605	1.16	0.68–1.98	0.585	0.95	0.40–2.26	0.913
	Q4 vs. Q1	1.62	1.04–2.52	**0.033**	1.69	0.99–2.89	0.054	1.48	0.63–3.45	0.367
	P for trend			**0.035**			**0.037**			0.446
Neutrophil Count Quartiles										
Age-adjusted	Q2 vs. Q1	1.03	0.66–1.61	0.890	0.92	0.53–1.59	0.756	1.20	0.54–2.68	0.656
	Q3 vs. Q1	1.38	0.91–2.09	0.129	1.40	0.85–2.31	0.182	1.05	0.46–2.42	0.980
	Q4 vs. Q1	2.21	1.50–3.26	**<0.001**	2.16	1.35–3.45	**0.001**	1.71	0.79–3.69	0.171
	P for trend			**<0.001**			**<0.001**			0.220
Fully adjusted	Q2 vs. Q1	1.03	0.64–1.66	0.893	0.96	0.53–1.72	0.885	1.15	0.49–2.74	0.746
	Q3 vs. Q1	1.34	0.85–2.11	0.203	1.39	0.79–2.35	0.269	1.11	0.46–2.70	0.819
	Q4 vs. Q1	2.19	1.41–3.39	**<0.001**	2.13	1.25–3.63	**0.005**	2.19	0.95–5.06	0.067
	P for trend			**<0.001**			**0.002**			0.083

ALL-CVA indicates all stroke; TE-CVA, thromboembolic stroke; HEM-CVA, hemorrhagic stroke; WBC, white blood cell; HR, Hazard ratio; CI, confidence interval.

WBC quartiles: Q1=0.9–5.0; Q2=5.1–5.9; Q3=6.0–7.1; Q4=7.2–64.0.
Neutrophil quartiles: Q1=0.06–2.99; Q2=2.99–3.71; Q3=3.72–4.62; Q4=4.62–14.18.
Fully adjusted includes age, BMI, Hypertension, Diabetes Mellitus, Smoking status, Physical activity index, Total and HDL cholesterol, Alcohol intake, Fibrinogen level, Aspirin or NSAID use, and Prevalence of CHD, Cancer or COPD