TABLE 1. Mean Values or Frequencies of Risk Factors by Status of Retinal Vein Occlusion

Variable	Non-RVO (n = 1736)	RVO (n = 38)	P
Age, y	62 ± 11	67 ± 7	0.002
Sex (men), %	38.5	50.0	0.15
Systolic blood pressure, mm Hg	133 ± 21	147 ± 18	<0.0001
Diastolic blood pressure, mm Hg	77 ± 11	81 ± 10	0.02
Hypertension, %	43.7	81.6	<0.0001
Total cholesterol, mmol/L	5.3 ± 0.9	5.4 ± 1.1	0.73
High-density lipoprotein cholesterol, mmol/L	1.5 ± 0.4	1.6 ± 0.4	0.16
Triglycerides, mmol/L	1.20 (0.59-2.98)	1.02 (0.51-2.19)	0.14
Body mass index, kg/m^2	23.1 ± 3.1	23.2 ± 3.5	0.77
Diabetes, %	12.6	10.5	0.70
White blood cells, $\times 10^3$/mm^3	5.8 ± 1.5	6.1 ± 1.6	0.15
Platelets, $\times 10^4$/mm^3	21.9 ± 5.2	19.8 ± 6.0	0.02
Hematocrit, %	40.1 ± 4.1	41.6 ± 3.6	0.03
ECG abnormalities, %	17.1	29.0	0.06
History of cardiovascular disease, %	2.7	5.3	0.42
Smoking habit (yes), %	17.5	18.4	0.88
Alcohol intake (yes), %	36.5	44.7	0.30
Regular exercise (yes), %	16.7	23.7	0.51

Data are expressed as the mean ± SD or percentages. Geometric mean value and 95% prediction interval of triglycerides are shown because of the skewed distribution. RVO, retinal vein occlusion.

retinal venules. The presence of any RVO was defined as the presence of branch or central RVO in either eye.

Data Collection

Information on smoking habits, alcohol intake, and regular exercise during leisure time was obtained by trained interviewers using a standard questionnaire. Smoking habits and alcohol intake were classified as either current use or not. Those subjects who engaged in sports or other forms of exertion three or more times per week during their leisure time were designated as the regular exercise group. The questionnaire also investigated history of cardiovascular disease, including stroke and coronary heart disease.

Blood pressure was measured three times in the sitting position after the subject had rested for at least 5 minutes. The average of the three measurements was used for the analysis. According to the 2007 European Society of Hypertension (ESH) and European Society of Cardiology (ESC) Practice Guidelines,[17] blood pressure levels were categorized as follows: optimal (systolic <120 mm Hg and diastolic <80 mm Hg), normal (120-129/80 to 84 mm Hg), high-normal (130-139/85 to 89 mm Hg), and hypertension (≥140/≥90 mm Hg or current use of antihypertensive medication).

Plasma glucose levels were determined by the glucose-oxidase method, and diabetes mellitus was defined by a 75-g oral glucose tolerance test or by fasting (≥7.0 mM) or postprandial (≥11.1 mM) blood glucose level, or by the use of hypoglycemic agents. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined enzymatically by using an autoanalyzer (TBA-80S; Toshiba Inc., Tokyo, Japan). White blood cell (WBC) and platelet counts and hematocrit levels were determined with a cell counter (STKS; Coulter Inc., Hialeah, FL). ECG abnormalities were defined as left ventricular hypertrophy (Minnesota code,[18] 3-1) or ST depression (4-1, 2, 3). Body height and weight were measured in light clothing without shoes, and the body mass index (in kilograms per square meter) was calculated.

Statistical Methods

We considered the following 18 possible risk factors for RVO: age, sex, systolic and diastolic blood pressures, hypertension, total cholesterol, HDL cholesterol, triglycerides, body mass index, diabetes mellitus, WBC count, platelet count, hematocrit, ECG abnormalities, history of cardiovascular disease, smoking habits, alcohol intake, and regular exercise. Mean values were compared by Student's t-test, and frequencies by the χ^2 test. We estimated the age- and sex-adjusted and multivariate-adjusted odds ratio (OR) and 95% confidence interval (CI) for each potential risk factor by using logistic regression analysis (SAS software; SAS Institute, Cary, NC[19]). A two-sided $P < 0.05$ was considered statistically significant.

Ethical Considerations

This study was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences and was per-

TABLE 2. Age-Specific Prevalence of RVO by Sex

Age Range, y	Men			Women			All Subjects			
	Subjects, n	Branch RVO, n (%)	Central RVO, n (%)	Subjects, n	Branch RVO, n (%)	Central RVO, n (%)	Subjects, n	Branch RVO, n (%)	Central RVO, n (%)	All RVO, n (%)
40-49	92	0 (0.0)	0 (0.0)	201	0 (0.0)	0 (0.0)	293	0 (0.0)	0 (0.0)	0 (0.0)
50-59	154	2 (1.3)	0 (0.0)	284	5 (1.8)	0 (0.0)	438	7 (1.6)	0 (0.0)	7 (1.6)
60-69	231	5 (2.2)	3 (1.3)	335	10 (3.0)	0 (0.0)	566	15 (2.7)	3 (0.5)	18 (3.2)
70-79	178	7 (3.9)	0 (0.0)	212	2 (0.9)	0 (0.0)	390	9 (2.3)	0 (0.0)	9 (2.3)
80+	33	2 (6.1)	0 (0.0)	55	2 (3.6)	0 (0.0)	88	4 (4.6)	0 (0.0)	4 (4.6)
Total	688	16 (2.3)	3 (0.4)	1087	19 (1.8)	0 (0.0)	1775	35 (2.0)	3 (0.2)	38 (2.1)
P_{trend}		0.01	0.87		0.15			0.005	0.66	0.005

RVO, retinal vein occlusion.

TABLE 3. Age- and Sex-Adjusted and Multivariate-Adjusted OR of Relevant Factors of RVO

Association	Age- and Sex-Adjusted		Multivariate-Adjusted	
	OR	95% CI	OR	95% CI
Age, per 10 years			1.47*	1.04-2.08
Sex (men), %			0.93	0.42-2.07
Systolic blood pressure, per 10 mm Hg	1.23†	1.07-1.41		
Diastolic blood pressure, per 10 mm Hg	1.46*	1.09-1.97		
Hypertension	4.53†	1.94-10.6	4.25†	1.82-9.94
Total cholesterol, per 1 mmol/L	1.20	0.83-1.74		
High-density lipoprotein cholesterol, per 1 mmol/L	2.22	0.94-5.25		
Triglycerides, per 1 mmol/L	0.63	0.36-1.10		
Body mass index, per 1 kg/m^2	1.04	0.94-1.15		
Diabetes	0.65	0.23-1.87		
White blood cells, per $10^3/mm^3$	1.15	0.94-1.40		
Platelets, per $10^4/mm^3$	0.94	0.88-1.01		
Hematocrit, per 10 %	3.09*	1.13-8.46	1.10*	1.00-1.22
ECG abnormalities	1.57	0.76-3.26		
History of cardiovascular disease	0.91	0.21-3.91		
Smoking habit	0.95	0.39-2.34		
Alcohol intake	1.42	0.67-3.01		
Regular exercise	1.24	0.58-2.68		

RVO, retinal vein occlusion; OR, odds ratio; CI confidence interval.
* $P < 0.05$.
† $P < 0.01$.

formed in accordance with the Declaration of Helsinki. The study subjects provided written informed consent to participate in the study.

RESULTS

Table 1 shows the mean values or frequencies of potential risk factors according to the presence or absence of RVO. The geometric mean values and 95% prediction intervals of triglycerides are shown because of the skewed distribution. Subjects with RVO were older than those without RVO. Subjects with RVO had higher mean systolic and diastolic blood pressures and hematocrits, as well as a higher frequency of hypertension, whereas those without RVO had a lower mean platelet count.

The age-specific prevalences of RVO are shown by sex in Table 2. Of the 1775 subjects examined, 38 (2.1%) had RVO. Of the subjects with RVO, 35 (92.1%) had branch RVO. The prevalence of branch RVO was slightly but not significantly higher in the men than in the women (2.3% vs. 1.8%). Central RVO was observed only in the men (0.4%). The prevalence of all RVO significantly increased with advancing age in all the subjects ($P_{trend} = 0.005$), whereas the prevalence of branch RVO significantly increased with advancing age only in the men ($P_{trend} = 0.01$).

The results of age- and sex-adjusted and multivariate-adjusted logistic regression analyses of relevant factors for RVO are presented in Table 3. After adjusting for age and sex, we found that systolic and diastolic blood pressures, hypertension, and hematocrit were significantly associated with RVO. In multivariate analysis, age (per 10 years; OR, 1.47; 95% CI, 1.04-2.08), hypertension (OR, 4.25; 95% CI, 1.82- 9.94), and hematocrit (per 10%) (OR, 3.09; 95% CI, 1.10-1.22) remained independently significant relevant factors for RVO.

Table 4 demonstrates the age- and sex-adjusted OR of RVO according to blood pressure levels and quartiles of hematocrit. The age- and sex-adjusted OR of RVO significantly increased with elevated blood pressure levels ($P_{trend} < 0.001$). Compared with those with optimal or normal blood pressure, the OR of RVO was significantly higher, not only in the subjects with hypertension (age- and sex-adjusted OR, 11.9; 95% CI, 2.78-50.9), but also in the subjects with high-normal blood

TABLE 4. Age- and Sex-Adjusted OR of RVO According to Blood Pressure Levels and Quartiles of Hematocrit

Risk Factor Level	Subjects, *n*	Cases, *n*	Age- and Sex-Adjusted OR (95% CI)	P_{trend}
Blood pressure level				
Optimal	469	1	1.00 (reference)	<0.001
Normal	276	1		
High-normal	240	5	6.81 (1.30-35.6)*	
Hypertension	790	31	11.9 (2.78-50.9)†	
Hematocrit				
First quartile, <37.7	436	5	1.00 (reference)	0.004
Second quartile, 37.7-39.9	447	7	1.40 (0.44-4.46)	
Third quartile, 40.0-42.6	445	8	1.81 (0.58-5.70)	
Fourth quartile, ≥42.7	446	18	6.03 (1.85-19.7)*	

RVO, retinal vein occlusion; OR, odds ratio; CI, confidence interval.
* $P < 0.05$.
† $P < 0.01$.

TABLE 5. Age- and Sex-Adjusted OR of RVO According to the Presence or Absence of High Blood Pressure and High Hematocrit

	Subjects, *n*	Cases, *n*	Age- and Sex-Adjusted OR (95% CI)	*P*
Normal blood pressure + low hematocrit	595	1	1.00 (reference)	
Normal blood pressure + high hematocrit	150	1	4.81 (0.28–82.2)	0.28
High blood pressure + low hematocrit	742	20	11.9 (1.57–90.9)	0.02
High blood pressure + high hematocrit	288	16	36.0 (4.43–292)	<0.01

Normal blood pressure: optimal + normal; high blood pressure: high normal + hypertension; low hematocrit: first to third quartiles (<42.7%); high hematocrit: fourth quartiles (≥42.7%).

pressure (age- and sex-adjusted OR, 6.81; 95% CI, 1.30–35.6). The age- and sex-adjusted OR of RVO also significantly increased with rising hematocrit levels (P_{trend} = 0.003): the likelihood of RVO was significantly higher in the fourth quartile than in the first (age- and sex-adjusted OR, 6.03; 95% CI, 1.85–19.7).

Further, we examined both the combined and separate effects of high blood pressure and elevated hematocrit levels on RVO in the groups according to the presence or absence of high blood pressure (high normal blood pressure or hypertension) and high hematocrit level (fourth quartile, ≥42.7%). As shown in Table 5, compared with normotensive subjects without high hematocrit, the OR of RVO was significantly increased in subjects with high blood pressure alone (age- and sex-adjusted OR, 11.9; 95% CI, 1.57–90.9), whereas the OR of RVO was slightly but not significantly increased in subjects with high hematocrit alone (age- and sex-adjusted OR, 4.81; 95% CI, 0.28–82.2). Furthermore, the OR of RVO was markedly high in subjects having both high blood pressure and high hematocrit (age- and sex-adjusted OR, 36.0; 95% CI, 4.43–292). However, the interaction between high blood pressure and high hematocrit level was not significant (P = 0.35).

DISCUSSION

In a cross-sectional examination of a general Japanese population, we demonstrated that the prevalence of RVO was 2.1% and that age, high blood pressure, and elevation of hematocrit levels were independent relevant risk factors for RVO. In addition, the likelihood of RVO increased significantly in subjects having both high blood pressure and high hematocrit.

The prevalence of RVO has also been estimated in several other population-based studies (Table 6). The disease prevalence was reported to be 1.6% in the Blue Mountains Eye Study in Australia[16] and 1.1% in the Multiethnic Study of Atherosclerosis in the United States.[7] A study on a Chinese population, the Beijing Eye Study, reported an RVO prevalence of 1.2%,[12] and a study of a Malay population, the Singapore Malay Eye Study, reported a prevalence of 0.7%.[9] The prevalence of RVO in the present study (2.1%) seemed to be somewhat higher than those in the previous studies. Although the variation in disease prevalence among these studies could be due to differences in the characteristics of subjects and in the methodologies, our findings of a higher prevalence suggest that RVO is more common among the Japanese population than among other Asian or Western populations, since the same grading protocols and RVO definitions were used in most of those studies.[7,9,12,16] Indeed, some studies have shown racial differences in the prevalence of RVO.[9,10] The reason for such differences remains uncertain, although genetic or environmental factors could contribute to the discrepancy.

In the present study, we found that the prevalence of RVO increased significantly with advancing age. The etiology and pathogenesis of RVO are largely unknown. The consistent association with increasing age found in this study is in accordance with the findings in many others,[6,7,9] confirming the age-related nature of the disease.

Our data indicated a clear association between hypertension and RVO, which is consistent with clinical knowledge and the findings of other population-based studies.[6–8,10–12] Our results also showed that not only hypertension but also high-normal blood pressure was significantly associated with RVO. The Framingham Heart Study indicated that the risk of cardiovascular disease is significantly increased in patients with high-normal blood pressure and higher blood pressure levels.[20] Based on these findings, it may be reasonable to suppose that high-normal blood pressure promotes systemic arteriosclerosis, including retinal vascular changes, and thereby causes RVO. Therefore, subjects with high-normal blood pressure should be considered at high risk for RVO. Strict control of elevated blood pressure may be important in preventing the disease.

We found that a higher hematocrit level was associated with RVO, independent of age, sex, and hypertension. A previous case-control study also indicated that hematocrit was significantly higher in a branch RVO group than in the control subjects.[21] Moreover, another study reported a significantly higher prevalence of elevated hematocrit in subjects with central RVO than in control subjects.[22] RVO is caused by thrombosis of the vein, but the role played by various hematologic abnormalities in its etiology and pathogenesis remains unclear and controversial. It is known that elevated hematocrit increases blood viscosity.[22] Therefore, increased hematocrit may augment the risk of RVO through the increase in blood viscosity.

The present study showed an extremely increased likelihood of RVO in subjects who had both hypertension and a higher hematocrit level. Although the mechanism underly-

TABLE 6. Prevalence of RVO in the Hisyama Study and Other Population-Based Studies

Study	Country	Subjects, *n*	Age	*n* (Prevalence %)
Blue Mountains Eye Study[16]	Australia	3654	49	59 (1.6)
Multiethnic Study of Atherosclerosis[7]	United States	6147	45	65 (1.1)
Beijing Eye Study[12]	China	4439	40	58 (1.3)
Singapore Malay Eye Study[9]	Singapore	3280	40	22 (0.7)
Hisayama Study[15]	Japan	1775	40	38 (2.1)

ing this phenomenon is not clearly understood, a possible explanation is that hypertension is a strong risk factor for systemic arteriosclerosis, including retinal arteriosclerosis,[5,8] and sclerotic arteriolar walls in the retina may compress the underlying veins at arteriovenous crossings, leading to reduced blood flow, which in turn could facilitate the development of a thrombus and downstream venous occlusion. It is therefore speculated that increased hematocrit levels markedly enhance the likelihood of RVO by hyperviscosity in people whose retinal vessel walls have already been damaged by hypertension.

This study has several limitations. First, we ascertained RVO cases by using one photographic field per eye, whereas in most previous population-based studies, two to six photographic fields were taken per eye. This difference could have resulted in underestimation of the prevalence of RVO if peripheral lesions were overlooked. Second, the number of our RVO cases is relatively small, and therefore the CIs around the prevalence and ORs are very wide. It might be misleading to compare the prevalence in this study with that in other population-based studies, and there is a possibility that the ORs are inflated due to the small samples. The estimates of our study should be interpreted with caution. Third, because of the cross-sectional design of this study, it is still unclear how risk factors are related to the onset of RVO. Further prospective investigation would help to clarify this issue.

In conclusion, the results of this study suggest that RVO is more common among the Japanese than among other Asians or Caucasians and that older age, higher hematocrit, and not only hypertension but also high-normal blood pressure are risk factors for RVO in the Japanese. In addition, among subjects who have both high blood pressure and higher hematocrit, the likelihood of RVO was substantially increased. Therefore, patients having both high blood pressure and higher hematocrit should be considered a population at high risk for RVO and continued preventive efforts should be made in these patients to reduce the burden of the disease.

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Nine-Year Incidence and Risk Factors for Age-Related Macular Degeneration in a Defined Japanese Population

The Hisayama Study

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Purpose: To estimate the 9-year incidence and risk factors for age-related macular degeneration (AMD) in a general Japanese population.

Design: Population-based, cohort study.

Participants: In 1998, a total of 1775 Hisayama residents aged ≥40 years underwent a baseline eye examination. Of those, 1401 subjects (78.9%) took part in the follow-up eye examination in 2007 and were enrolled in the present study.

Methods: At both time points, the characteristics of AMD were determined by grading color fundus photographs using the Wisconsin Age-Related Maculopathy Grading System.

Main Outcome Measures: Incident early and late AMD.

Results: The age-standardized, 9-year cumulative incidence of early AMD was 10.0%, and that of late AMD was 1.4%. Men were found to have a significantly higher incidence of late AMD than women (age-adjusted odds ratio [OR], 2.97; 95% confidence interval [CI], 1.25–7.09). The incidence of both early and late AMD increased significantly with age. Multiple logistic regression analysis showed that older age (per 1 year; OR, 1.10; 95% CI, 1.05–1.16), smoking habits (OR, 3.98; 95% CI, 1.07–14.7), and higher circulating white blood cell (WBC) count (per 1000 cells/mm^3) (OR, 1.38; 95% CI, 1.07–1.79) were significantly associated with the development of late AMD.

Conclusions: Our findings suggest that the 9-year incidences of late AMD are lower among the Japanese than among white people in Western countries, and it is higher than among black people. Smoking habits and higher circulating WBC count are significant risk factors for the development of late AMD in the Japanese.

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Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment and blindness in elderly populations in developed countries.[1] Despite the magnitude of this problem, the pathogenesis of AMD remains poorly understood. It is thus very important to determine the precise incidence of AMD and to identify its risk factors to develop preventive measures of the disease. To date, several population-based studies[2–7] including ours[8] have provided valuable information on incidence and risk factors for AMD. The risk factors examined include iris color,[2] hypertension,[3] atherosclerosis,[4] smoking habits,[5,8] higher total/high-density lipoprotein ratio,[6] and higher white blood cell (WBC) count.[7] However, information on the long-term risk of AMD is scarce[9–11] and nonexistent in Asians including Japanese.

The aim of this article was to examine the 9-year incidence of early and late AMD and its risk factors in a prospective study of a general Japanese population.

Materials and Methods

Study Population

The Hisayama Study is an ongoing, long-term, cohort study on cardiovascular disease and its risk factors in the town of Hisayama adjoining Fukuoka City, a metropolitan area in southern Japan.[12] As a part of the study, a follow-up survey of eye diseases among residents of the town has been underway.[8,13] In 1998, a total of 1775 individuals (688 men and 1775 women) aged ≥40 years underwent a baseline eye examination. Of those, 1404 subjects (79.1%) took part in the follow-up eye examination in 2007. After excluding 3 subjects who had ungradable photographs of either eye, 1401 (78.9% of the original cohort) were enrolled in the present study.

Ophthalmic Examination and Definition of Age-related Maculopathy

The methods used for the baseline eye examination have been described in detail previously.[13] Briefly, each participant under-

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went ophthalmic examination after pupil dilatation with 1.0% tropicamide and 10% phenylephrine. Fundus photographs (45°) were taken using a Topcon TRC NW-5 fundus camera (Topcon Corporation, Tokyo, Japan), and the 35-mm color transparencies were made using Fujichrome slide film (Sensia II; Fujifilm, Tokyo, Japan). At the 9-year follow-up eye examination, fundus photographs (45°) were taken using a Topcon digital TRC NW-6SF fundus camera (Topcon Corporation). Photographs were taken of 1 field per eye.

Both examinations used a similar, masked photographic grading technique based on the International Age-related Maculopathy Epidemiological Study Group grading protocol and the grids of the Wisconsin Age-related Maculopathy Grading System.[14,15] The Wisconsin Age-related Maculopathy Grading System grid was adapted to the magnification of the camera. This protocol divides AMD into early and late stages. Early-stage AMD was defined by the presence of large drusen (soft distinct and soft indistinct) or retinal pigment epithelium pigmentary abnormalities (hyperpigmentation or hypopigmentation),[15] within the grid in the absence of late AMD in either eye. Late-stage AMD was defined as the presence of neovascular AMD or geographic atrophy. Neovascular AMD included serous or hemorrhagic detachment of the retinal pigment epithelium or sensory retina, and the presence of subretinal or subretinal pigment epithelium hemorrhages or subretinal fibrous scar tissue.[15] Geographic atrophy was characterized by sharply edged, roughly round, or oval areas of retinal pigment epithelium hypopigmentation, with clearly visible choroidal vessels.[15] The minimum area of geographic atrophy was a circle ≥175 μm in diameter. In our study, 2 experienced graders (MY, TI), masked to the subject information, assessed the AMD. Interobserver and intraobserver variability were analyzed. The level of agreement between the graders was 0.80 and 0.86 for most features. Finally, we determined the final diagnosis for disagreement cases after discussion.

Data Collection

Blood pressure was measured 3 times after the subject had rested for ≥5 minutes in the sitting position. The average of the 3 measurements was used for the analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medication. Blood samples were collected from an antecubital vein after an overnight fast of ≥12 hours. After taking the fasting blood specimen, a 75-g oral glucose tolerance test was performed with a 75-g glucose equivalent carbohydrate load (Trelan G; Shimizu Pharmaceutical Inc., Shimizu, Japan). Diabetes was defined as a fasting plasma glucose level ≥7.0 mmol/L, a 2-hour postloading glucose level ≥11.1 mmol/L, or a medical history of diabetes. Serum total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were determined enzymatically using an autoanalyzer (TBA-80S; Toshiba Inc., Tokyo, Japan), and dyslipidemia was defined as a total cholesterol level ≥5.7 mmol/L, high-density lipoprotein cholesterol <1.0 mmol/L, serum triglyceride level ≥1.7 mmol/L, or the current use of antihyperlipidemic medication. The WBC counts were determined using a Coulter counter (STKS; Beckman Coulter Inc., Fullerton, CA). Information on smoking habits and alcohol intake was obtained using a standard questionnaire by trained interviewers at the initial examination. Subjects were classified as either current or past habitual use or as nonuser. Body height and weight were measured in light clothing without shoes, and the body mass index (kg/m^2) was calculated.

Statistical Methods

We calculated the 9-year incidences of AMD. Age-adjusted cumulative incidences of AMD were calculated by means of the direct method using the World Health Organization standard population in 1998. Incident early AMD was defined by the appearance at follow-up of either soft drusen or retinal pigmentary abnormalities in either eye of persons in whom no early or late AMD was present at baseline. Incident late AMD was defined by the development at follow-up of neovascular AMD or geographic atrophy in either eye of persons in whom no late AMD was present at baseline. We examined the relationships between risk factors at baseline and the incidence of early and late AMD. We considered the following 9 possible risk factors for AMD: age, gender, hypertension, diabetes, dyslipidemia, smoking habits, alcohol intake, body mass index, and WBC count. Age, body mass index, and WBC count were treated as continuous variables and the others as categorical variables. Each categorical variable was coded as either 1 or 0 depending on the presence or absence of the factor, respectively. Mean values were compared by the Student t test, and frequencies by the chi-square test. We estimated the age-adjusted and multivariate odds ratio (OR) and 95% confidence interval (CI) of each potential risk factor by using a logistic regression analysis. The SAS software package (SAS Inc, Cary, NC) was used to perform the statistical analyses. A 2-sided P value of less than 0.05 was considered statistically significant.

Ethical Considerations

This study was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences, and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Results

Table 1 shows the mean values or frequencies of potential risk factors for AMD at baseline by gender. Men were older than women. The frequencies of early AMD, hypertension, diabetes, smoking habits, and alcohol intake, and mean WBC count were higher for men than for women, whereas women had the higher frequency of dyslipidemia. There was no difference in mean body mass index between the genders.

The age-adjusted, 9-year, cumulative incidences of early and late AMD lesions are shown by gender in Table 2. After excluding

Table 1. Mean Values or Frequencies of Potential Risk Factors for Age-related Macular Degeneration (AMD) by Gender at Baseline: The Hisayama Study, 1998 Early AMD and late AMD are Prevalence

Variables	Men	Women
n	524	877
Age (y), means ± SD	61±10	59±10
Early AMD (%)	18.7	11.6
Late AMD (%)	1.3	0.3
Hypertension (%)	49.4	37.6
Diabetes (%)	16.6	6.6
Dyslipidemia (%)	46.4	54.1
Body mass index (kg/m^2)	23.4±2.9	23.1±3.4
Smoking habits (%)	74.8	7.1
Alcohol intake (%)	69.1	19.6
White blood cells (×10^3/mm^3)	6.2±1.6	5.4±1.3

Table 2. Age-Standardized 9-Year Cumulative Incidences of Early and Late Age-related Macular Degeneration (AMD) by Gender: The Hisayama Study, 1998–2007

	Men		Women		All Subjects	
	Population at Risk	*Age- standardized† Incidence, n (%)*	*Population at Risk*	*Age- standardized† Incidence, n (%)*	*Population at Risk*	*Age- standardized† Incidence, n (%)*
Early AMD	426	50 (9.0)	775	93 (10.4)	1201	143 (10.0)
Pigmentary abnormalities	426	17 (3.3)	775	9 (1.3)*	1201	26 (2.0)
Soft distinct and indistinct drusen	426	33 (5.7)	775	84 (8.8)*	1201	117 (8.0)
Late AMD	517	15 (2.6)	874	8 (0.8)*	1391	23 (1.4)
Geographic atrophy	517	1 (0.1)	874	0 (0.0)	1391	1 (0.04)
Neovascular AMD	517	14 (2.5)	874	8 (0.8)*	1391	22 (1.4)

*$P<0.05$, men vs women.
†The incidence was standardized for age with the World Health Organization standard population.

190 participants with early AMD and 10 participants with late AMD at the baseline eye examination, a total of 143 participants (10.0%) developed incident early AMD during the follow-up. The incidence of early AMD was slightly but not significantly higher in women than in men. In regard to subtype of early AMD, the incidence of retinal pigmentary abnormalities was significantly higher in men than in women, whereas the incidence of drusen was significantly higher among women. After excluding 10 participants with late AMD at the baseline eye examination, a total of 23 participants (1.4%) developed late AMD during the follow-up. The incidence of late AMD was significantly higher in men than in women (age-adjusted OR, 2.97; 95% CI, 1.25–7.09) owing mainly to the significantly higher incidence of neovascular AMD in men.

Figure 1 demonstrates the age-specific incidences of early and late AMD by gender. The incidences of early and late AMD significantly increased with advancing age in both genders. In each age group, the incidence of early AMD was consistently higher in women than in men, whereas the incidence of late AMD was higher in men in age groups of ≥50 years.

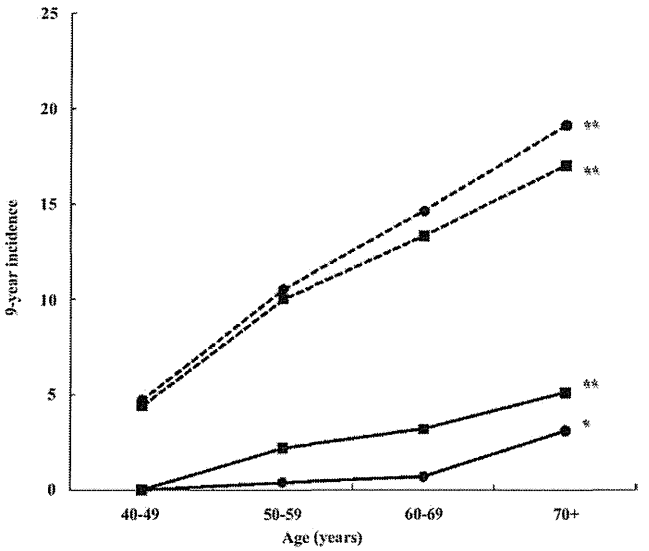

Figure 1. Age-specific 9-year incidences of early and late age-related macular degeneration by gender, the Hisayama Study. Broken line, early age-related macular degeneration; solid line, late age-related macular degeneration; black squares, men; black circles, women $**P<0.01$; $*P<0.05$ for trend.

Table 3 presents the age-adjusted, 9-year incidence of late AMD by presence or absence of early AMD at baseline. Progression to late AMD was approximately 4.4% among persons with early AMD and 0.7% among persons without early AMD. Progression to neovascular AMD was 1.8% among persons with pigmentary abnormalities and was 5.2% among persons with soft distinct and indistinct drusen. Overall, eyes with drusen at baseline were more likely to develop neovascular AMD.

The results of age- and multivariate-adjusted logistic regression analyses of risk factors for the development of early and late AMD are shown in Table 4. After adjusting for age, no associations were found between these risk factors and incident early AMD; however, male gender, smoking habits, and higher WBC count were significant risk factors for the development of late AMD. In multivariate analysis, older age, smoking habits, and higher WBC count were significantly associated with late AMD.

Discussion

To our knowledge, this is the first population-based cohort study to investigate the long-term incidence and risk factors for AMD in Japan. The findings showed that the overall, 9-year, cumulative incidence of early AMD was 10.0%, and that of late AMD was 1.4%. Both incidences increased with advancing age. Progression to late AMD was approximately 4.4% among persons with early AMD. On multivariate analysis, smoking and higher circulating WBC count were independently associated with the development of late AMD.

Previously, several long-term, population-based studies estimated the incidence of AMD. It is reported that the 10-year cumulative incidence of early AMD was 12.1% in the Beaver Dam Eye Study in the United States[9] and 14.1% in the Blue Mountains Eye Study in Australia,[11] both of which focused on a white population. The Barbados Eye Study of the predominantly black population of African descent reported a 9-year incidence of early AMD of 12.6%.[16] Even when accounting for the 1-year shorter follow-up period, our 9-year incidence of early AMD seemed to be somewhat lower than that reported in the Beaver Dam Eye Study or the Blue Mountains Eye Study. The 9-year incidence of early AMD we found (10.0%) was also lower than that reported in the Barbados Eye Study performed in a black population. Early AMD is less com-

Table 3. Age-standardized 9-Year Incidences of Late Age-related Macular Degeneration (AMD) by Presence or Absence of Early AMD at Baseline: The Hisayama Study, 1998–2007

	Geographic Atrophy		Neovascular AMD		Any Late AMD	
	Population at Risk	*Age-standardize* Incidence, n (%)*	*Population at Risk*	*Age-standardized* Incidence, n (%)*	*Population at Risk*	*Age-standardized* Incidence, n (%)*
Early AMD (−)	1,191	0 (0.0)	1,191	12 (0.7)	1,191	12 (0.7)
Early AMD (+)	190	1 (0.3)	190	10 (3.9)	190	11 (4.4)
Pigmentary abnormalities	69	1 (1.7)	69	2 (1.8)	69	3 (2.2)
Soft distinct and indistinct drusen	121	0 (0.0)	121	8 (5.2)	121	8 (5.2)

*The incidence was standardized for age with the World Health Organization standard population.

mon among the Japanese population than among white people and black people in Western countries. This difference in the incidence of early AMD among these studies could be due to the differences in study participants' characteristics (e.g., age and proportion of gender among studies), to dietary factors, to genetic factors, or perhaps to the differences in methodology among these studies.

The incidence of late AMD we found (1.4%) was lower than that reported in studies performed in white populations (Beaver Dam Eye Study, 2.1%[9]; Blue Mountains Eye Study, 3.7 %[11]) but was higher than that found in the Barbados Eye Study (0.7%), which focused on a black population.[16] This suggests that late AMD is less common among the Japanese compared with white people, and it is more common among the Japanese compared with black people. Some studies have reported racial differences in the prevalence and incidence of AMD.[17,18] The reason for different incidences among different races is not clear. However, the lower risk of occurrence of late AMD in black population was previously postulated to reflect a protective effect of melanin.[19] Weiter et al[20] have also reported that increased ocular pigmentation (iris color and fundus pigmentation) tends to decrease the risk of developing AMD, whereas Friedman et al[17] speculated that white people are genetically predisposed to have more severe maculopathy. Racial difference in late AMD incidence among the cohort studies including ours could be due to the differences in ocular pigmentation, or perhaps to genetic factors.

In the current study, the 9-year incidence of neovascular AMD was 1.4%, and that of geographic atrophy was 0.04%; nearly all incident late AMD cases were neovascular AMD (n = 22), and there was only 1 case of incident geographic atrophy. In contrast, the Blue Mountains Eye Study has reported that the 10-year incidence of neovascular AMD was 2.2%, and that of geographic atrophy was 1.7%. The incidence of geographic atrophy we found was much lower than that reported in the Blue Mountains Eye Study. The lower prevalence rates of geographic atrophy were also observed in our previous study[8] and in another Japanese population survey.[21] The reason for this different incidence, especially of geographic atrophy between Japanese and white population, is not clear. It could be due to the differences in environmental exposure or genetic factors among races.

The current study found that the incidence of early and late AMD significantly increased with advancing age in both genders. The etiology and pathogenesis of AMD are largely unknown. The consistent association with increasing age found in this study corroborated findings from many

Table 4. Age- and Multivariate-Adjusted Odds Ratios of Risk Factors for the Development of Early and Late Age-related Macular Degeneration (AMD): The Hisayama Study, 1998–2007

	Early AMD		Late AMD			
	Age Adjusted		*Age Adjusted*		*Multivariate Adjusted*	
Risk factor	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Age (per 1 year)					1.10**	1.05–1.16
Gender (male)	0.92	0.63–1.33	2.97*	1.25–7.09	0.86	0.24–3.05
Hypertension	0.85	0.59–1.24	0.79	0.34–1.86		
Diabetes	0.70	0.37–1.31	0.68	0.16–2.95		
Dyslipidemia	0.92	0.65–1.31	1.32	0.56–3.08		
Body mass index (per 1 kg/m^2)	1.01	0.95–1.07	1.01	0.88–1.15		
Smoking habits	1.07	0.73–1.55	4.59**	1.86–11.3	3.98*	1.07–14.7
Alcohol intake	1.04	0.72–1.50	1.88	0.81–4.36		
White blood cells (per 10^3/mm^3)	1.03	0.91–1.16	1.52**	1.19–1.95	1.38*	1.07–1.79

CI, confidence interval; OR, odds ratio.
Multivariate adjustment was made for age, gender, smoking habit, and white blood cells.
*$P<0.05$; **$P<0.01$.

other studies,[9,11,16] confirming the age-related nature of the disease.

We found a significantly higher incidence of late AMD in men than in women. We have already reported that early and late AMD were more prevalent among men than women in a cross-sectional study of Hisayama residents.[13] A similar finding was also observed in another cross-sectional study in Japan.[21] In contrast, most studies conducted in Western, white populations have shown a higher prevalence of late AMD in women.[11,22] The reason for this difference is precisely unknown, but smoking habits, which are known to be a major risk factor for AMD,[7,22,23] are likely to contribute to a higher incidence of late AMD in Japanese men, because the proportion of habitual smoking is much higher for men than women in Japan.

The results of this study provide prospective evidence that cigarette smoking increases the risk of developing late AMD. Compared with those who never smoked, those who had smoked in the past or were currently smoking had approximately a 4.0 times higher risk of late AMD, after adjusting for other potential risk factors. These findings are consistent with other cross-sectional and cohort data, which showed that cigarette smoking was related to the development of late AMD.[7,22,23] Smoking habits remain highly prevalent among Japanese men (74.8% in our men), which translates to a 73.8% of population-attributable fraction for late AMD in our men that are attributable to their smoking behavior. Because smoking is a well-recognized, modifiable risk factor for AMD, smoking cessation is an important public health measure to reduce the burden of AMD, particularly among Japanese men.

We found that a higher WBC count was associated with incident late AMD, independent of age, gender, and smoking status. A similar association was also observed in the Blue Mountains Eye Study.[7] Several recent experimental evidences suggest that the association between higher WBC count and late AMD is plausible, including the role of inflammatory mechanisms in subretinal neovascularization[24] and drusen development.[25] Chronic inflammatory cells, including macrophage leukocytes, have been observed in excised neovascular membranes from patients with late AMD.[26] Ultrastructural study on subretinal neovascularization associated with late AMD suggested that activated WBC are involved in the promotion of neovascular proliferation and exudation from new vessels.[24] These findings provide important evidence of an essential link between inflammation and late AMD development and suggest that local inflammatory processes that have long been known to be associated with subretinal neovascularization and drusen development may be reflected in the systemic inflammatory marker of higher WBC count.

This study has several limitations. First, losses to follow-up, an issue inherent to all long-term cohort studies, could have introduced selection bias, resulting in either an underestimation or overestimation of AMD incidence. Second, the early AMD definition used in this study is less strict and includes more early AMD cases than the definitions used by the Beaver Dam[11] and the Blue Mountains[13] Eye Studies: Drusen were defined as either indistinct or distinct drusen in our study, whereas they were defined as indistinct soft drusen in the abovementioned studies. If this study used the same early AMD definition used in other 2 studies, the early AMD incidence could have been lower than the currently reported 10%.

In conclusion, the results of this study suggest that early and late AMD is less common among the Japanese compared with white people in Western countries, although late AMD is more common among the Japanese compared with black people, and that older age, smoking habits and higher WBC count are relevant risk factors for late AMD in the Japanese. This finding provides important epidemiologic evidence of an essential link between inflammation and late AMD development, and also support the use of anti-inflammatory agents in the treatment of late AMD.

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Prevalence and systemic risk factors of retinal vein occlusion in a general Japanese population : the Hisayama Study

○ Miho Yasuda, Yutaka Kiyohara, Satoshi Arakawa, Yasuaki Hata, Mitsuo Iida, Tatsuro Ishibashi

Kyushu University, Japan

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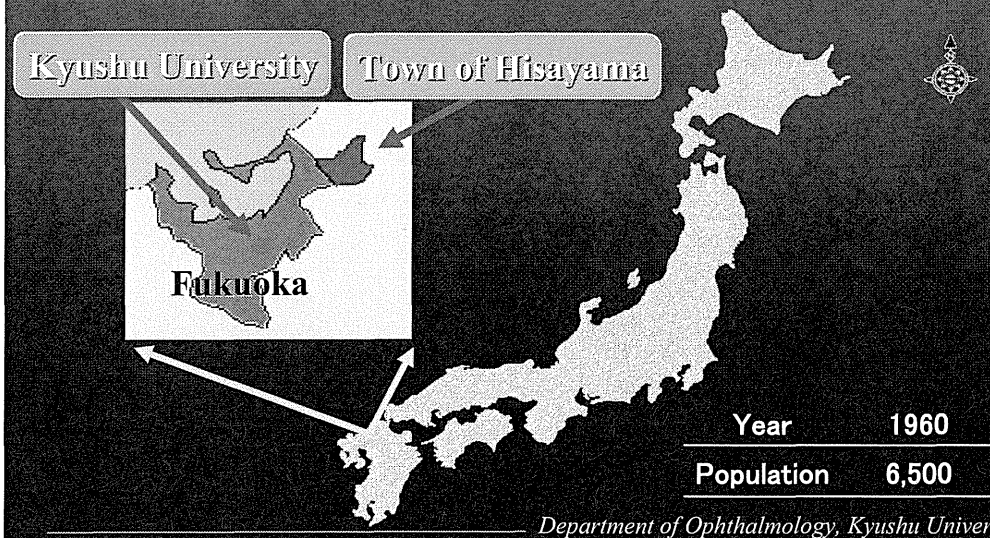
The Hisayama Study

The Hisayama Study is a long-term cohort study.
It has been conducted in the town of Hisayama since 1961.

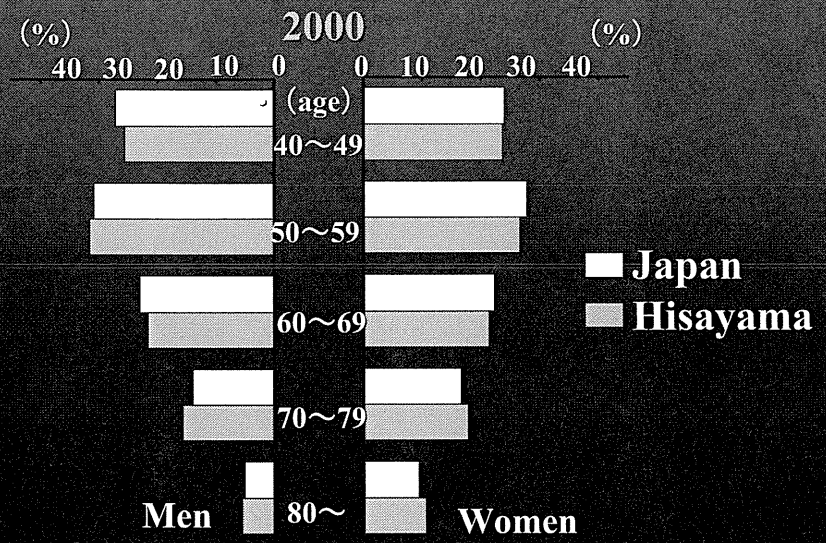


Year	1960	2007
Population	6,500	8,000

Department of Ophthalmology, Kyushu University

The Hisayama Study

The age distributions of Hisayama



Department of Ophthalmology, Kyushu University

Purpose

To examine the systemic risk factors for retinal vein occlusion (RVO) in a general Japanese population.

Department of Ophthalmology, Kyushu University

Study Population

The target population of this study was all the residents aged 40 years and older.

Year	Target population	Participants
1998 ---	4,187	1,775
		(participation rate 53%)

Department of Ophthalmology, Kyushu University

Methods : Definition of RVO

1. Fundus photographs were taken from both eyes of each participant after pupil dilation.
2. The presence of RVO was determined based on the grading of the color fundus photographs.

Central RVO

Branch RVO

The presence of any RVO was defined as the presence of central or branch RVO in either eye.

Department of Ophthalmology, Kyushu University

Methods : Statistical methods

1. We considered the following eighteen possible risk factors for RVO:

   age, sex, systolic and diastolic blood pressure, hypertension, total cholesterol, HDL cholesterol, triglycerides, BMI, diabetes mellitus, WBC, platelet, hematocrit, ECG abnormalities, history of cardiovascular disease, smoking habits, alcohol intake, and regular exercise

2. We examined the relationship between the risk factors and RVO.
   We also estimated the age- and sex- adjusted and multivariate odds ratio and 95% confidence interval of each risk factor using a logistic regression analysis.

Department of Ophthalmology, Kyushu University

Results

Age- and sex-adjusted odds ratio of risk factors for RVO

Risk factor	Age- and sex-adjusted odds ratio	95% confidence interval
Systolic blood pressure	1.23**	1.07-1.41
Diastolic blood pressure	1.46*	1.09-1.97
Hypertension	4.53**	1.94-10.6
Total cholesterol	1.20	0.83-1.74
High-density lipoprotein cholesterol	2.22	0.94-5.25
Triglycerides	0.63	0.36-1.10
Body mass index	1.04	0.94-1.15
Diabetes	0.65	0.23-1.87
White blood cells	1.15	0.94-1.40
Platelets	0.94	0.88-1.01
Hematocrit	3.09*	1.13-8.46
ECG abnormalities	1.57	0.76-3.26
History of cardiovascular disease	0.91	0.21-3.91
Smoking habits	0.95	0.39-2.34
Alcohol intake	1.42	0.67-3.01
Regular exercise	1.24	0.58-2.68

**$p<0.01$, *$p<0.05$

Department of Ophthalmology, Kyushu University

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**$p<0.01$, *$p<0.05$

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Results

Age- and sex-adjusted odds ratio of risk factors for RVO

Risk factor	Age- and sex-adjusted odds ratio	95% confidence interval
Systolic blood pressure	1.23**	1.07-1.41
Diastolic blood pressure	1.46*	1.09-1.97
Hypertension	4.53**	1.94-10.6
Total cholesterol	1.20	0.83-1.74
High-density lipoprotein cholesterol	2.22	0.94-5.25
Triglycerides	0.63	0.36-1.10
Body mass index	1.04	0.94-1.15
Diabetes	0.65	0.23-1.87
White blood cells	1.15	0.94-1.40
Platelets	0.94	0.88-1.01
Hematocrit	3.09*	1.13-8.46
ECG abnormalities	1.57	0.76-3.26
History of cardiovascular disease	0.91	0.21-3.91
Smoking habits	0.95	0.39-2.34
Alcohol intake	1.42	0.67-3.01
Regular exercise	1.24	0.58-2.68

**$p<0.01$, *$p<0.05$

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Results

Multivariate-adjusted odds ratio of risk factors for RVO

Risk factor	Multivariate-adjusted odds ratio	95% confidence interval
Age	1.47*	1.04-2.08
Sex	0.93	0.42-2.07
Hypertension	4.25**	1.82-9.94
Hematocrit	1.10*	1.00-1.22

(Multivariate odds ratio is adjusted for age, sex, hypertension, and hematocrit.)

**$p<0.01$, *$p<0.05$

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Results

Multivariate-adjusted odds ratio of risk factors for RVO

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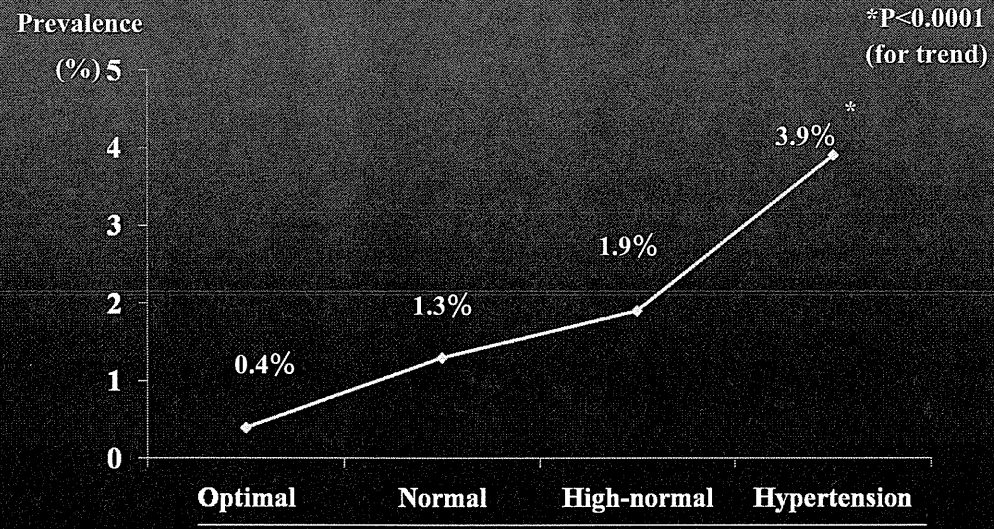
Results

The prevalence of RVO according to blood pressure levels



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Results

Age- and sex-adjusted odds ratios of RVO according to blood pressure levels

Risk factor level			Age- and sex-adjusted OR (95% CI)	*p* value for trend
Blood pressure level†	SBP	DBP		
Optimal	<120 and	<80	1.00 (reference)	<0.001
Normal	120-129 and/or	80-84		
High-normal	130-139 and/or	85-89	6.81 (1.30-35.6)*	
Hypertension	≥140 and/or	≥90	11.90 (2.78-50.9)**	

†2007 ESH-ESC practice guideline, ***p*<0.01, **p*<0.05

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Results

Age- and sex-adjusted odds ratios of RVO according to blood pressure levels

Risk factor level			Age- and sex-adjusted OR (95% CI)	*p* value for trend
Blood pressure level†	SBP	DBP		
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†2007 ESH-ESC practice guideline, **$p<0.01$, *$p<0.05$

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Results

Age- and sex-adjusted odds ratios of RVO according to quartiles of hematocrit

Risk factor level		Age- and sex-adjusted OR (95% CI)	*p* value for trend
Hematocrit			
First quartile	< 37.7	1.00 (reference)	0.004
Second quartile	37.7-39.9	1.40 (0.44-4.46)	
Third quartile	40.0-42.6	1.81 (0.58-5.70)	
Fourth quartile	≥ 42.7	6.03 (1.85-19.7)*	

**$p<0.01$, *$p<0.05$

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Results

Age- and sex-adjusted odds ratios of RVO according to quartiles of hematocrit

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**$p<0.01$, *$p<0.05$

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Summary

1. In the present study, we investigated the systemic risk factors for RVO in Japanese population.
2. The results showed that older age, higher hematocrit, and not only hypertension but also high-normal blood pressure were independent risk factors for RVO.

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