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ORIGINAL ARTICLE

Effect of blood pressure on the retinal vasculature in a multi-ethnic Asian population

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Blood pressure has a significant effect on retinal arterioles. There are few data on whether this effect varies by race/ethnicity. We examined the relationship of blood pressure and retinal vascular caliber in a multi-ethnic Asian population. The study is population-based and cross sectional in design. A total of 3749 Chinese, Malay and Indian participants aged ⩾24 years residing in Singapore were included in the study. Retinal vascular caliber was measured using a computer program from digital retinal photographs. The associations of retinal vascular caliber with blood pressure and hypertension in each racial/ethnic group were analyzed. The main outcome measures are retinal arteriolar caliber and venular caliber. The results show that retinal arterioles were narrower in persons with uncontrolled/untreated hypertension (140.0 μm) as compared with persons with controlled hypertension (142.1 μm, $P=0.0001$) and those with no hypertension (146.0 μm, $P<0.0001$). On controlling for age, gender, body mass index, lipids and smoking, each 10 mm Hg increase in mean arterial blood pressure was associated with a 3.1 μm decrease in arteriolar caliber ($P<0.0001$), with a similar magnitude seen in all three racial/ethnic groups: 3.1 μm in Chinese, 2.8 μm in Malays and 3.2 μm in Indians ($P<0.0001$ for all). Each 10 mm Hg increase in mean arterial blood pressure was associated with a 1.8 μm increase in venular caliber ($P<0.0001$); furthermore, the magnitude of this effect was similar across the three racial/ethnic groups. The effect of blood pressure on the retinal vasculature was similar across three major racial/ethnic groups in Asia.
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INTRODUCTION

Hypertension affects multiple organs in the body, including the retinal vasculature. Retinal arteriolar narrowing is a marker of the early structural microvascular damage associated with chronic hypertension.[1–3] Recent population-based studies using computer-based methods to measure retinal vascular caliber from fundus photographs have now established the strong linear relationship between elevated blood pressure (BP) and the severity of retinal arteriolar narrowing.[4–6] Newer analyses suggest that elevated BP may also have a weaker effect on retinal venules.[7–9] Prospective studies have further shown that retinal arteriolar narrowing predicts the incidence of hypertension[10–12] and clinical cardiovascular events, such as stroke and coronary heart disease, independent of traditional risk factors.[13–15] As such, an assessment of retinal vascular caliber may provide insights into early microvascular effects before the onset of clinical hypertension, and may help in the development of new treatment strategies targeted at microcirculation.[16]

However, whether the effects of BP on the retinal microvasculature are similar across different racial/ethnic groups remains unclear. There are well-recognized racial/ethnic differences in the association between BP and other markers of end-organ damage, including subclinical and clinical coronary artery disease,[17] left ventricular hypertrophy,[18] kidney disease[19] and cerebrovascular disease.[20] Previous studies on the relationship of BP on the retinal vasculature have been conducted in predominantly Caucasian populations,[7,9,21,22] with few studies in Asians,[23,24] and even fewer directly comparing racial/ethnic differences.[22]

The purpose of this study is to examine the relationship between BP and retinal vascular caliber in a multi-ethnic Asian population of Chinese, Malays and Indians in Singapore. These three racial/ethnic groups in Asia represent more than two-third of the world's population.

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METHODS

Study population

This study used data from the Singapore Prospective Study Program and Singapore Cardiovascular Cohort Study 2, which included participants from one of four previous cross-sectional studies: Thyroid and Heart Study 1982–1984,[25] National Health Survey 1992,[26] National University of Singapore Heart Study 1993–1995[27] or National Health Survey 1998.[28] All studies involved a random sample of individuals from the Singapore population, aged 24–95 years, with disproportionate sampling stratified by ethnicity to increase the number of minority ethnic groups (Malays and Indians). The Ministry of Health, Singapore, selected the study population.

Figure 1 shows a flow diagram of subjects that were considered for inclusion in the study. From 2003 to 2007, all 10 747 participants were invited to participate in this study by linking their unique national identification numbers with national registries; 85 individuals had errors in their identification (national registration identity card) number (preventing linkage to national registries), 555 had died before contact was made, 37 died before attending the clinic, and 6 had left the country. Participants were contacted first through mail, then by phone and if there was no response or no available phone number, interviewers visited the home; three different home visits were made before participants were deemed non-contactable (2292 individuals). Another 30 contacted participants refused to participate, leaving 7742 who were interviewed at their homes. The interviewer-administered questionnaire included data on demographic and lifestyle (alcohol intake, smoking) factors as well as medical history.

All 7742 participants were then invited for a clinical examination that included systemic and ocular examination, retinal photography and laboratory investigations, of which 5157 attended. Logistic constraints, due to availability of one retinal camera, resulted in only 1 in 2 Chinese participants (the group with the largest sample size) who were asked to undergo retinal photography between 19 March 2005 and 20 February 2006. Consequently, 1020 (of 5517) Chinese participants did not undergo retinal photography. Out of the remaining 4137 participants, retinal photographs were obtained for virtually all those who underwent the procedure (4098 or 99.1% of 4137). Participants with

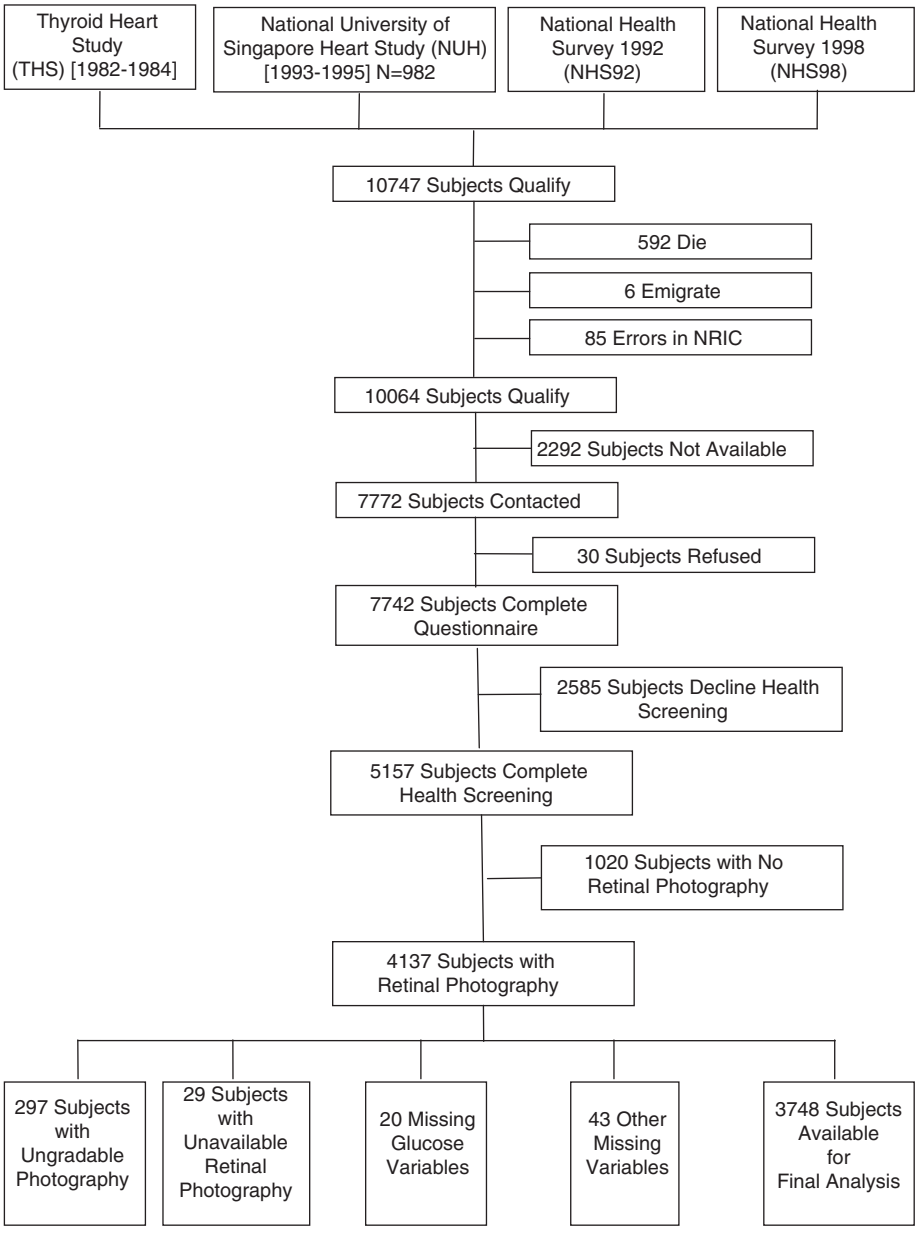

Figure 1 Flow diagram of subjects that were considered for inclusion in the study.

ungradable retinal photographs (n=297), missing information on BP or other relevant variables (n=52) were then excluded, leaving 3749 for the final analysis (48.4% of 7742 eligible participants). Excluded participants were found to be older and had higher high-density lipoprotein cholesterol, systolic BP and lower low-density lipoprotein cholesterol (all significant at $P<0.05$) than included participants. The Code of Ethics of the World Medical Association (the Declaration of Helsinki Principles, 1964 and Declaration of Tokyo, 1975, as revised in 1983) was followed, and institutional review board approval was granted at each study site. All participants provided written informed consent.

Assessment of hypertension

Systolic and diastolic BP (SBP and DBP) were evaluated using a digital automatic BP monitor (Dinamap model Pro100V2; Criticon, Norderstedt, Germany). BP assessments were carried out by two operators who were trained in the standardized technique.[29] The BP was measured twice, at an interval of 5 min, with participants seated for five minutes with legs uncrossed. A proper sized cuff was used on the participant's right arm at the heart level, unless contraindicated. The second reading was taken after a lapse of 1–2 min. A third measurement was taken if the BP differed by more than 10 mm Hg in systolic and 5 mm Hg in diastolic readings. The mean between the two closest readings were then taken as the BP of that participant. In the case in which Dinamap was unable to detect a reading, a manual reading of BP was taken. The use of antihypertensive medication was obtained from the questionnaire. Names and doses of the participant's regular antihypertensive medications were recorded. Medications were categorized as β-blocker, angiotensin-converting enzyme inhibitor, calcium channel blocker, angiotensin receptor antagonist, diuretic, α-adrenergic blocker, vasodilator or centrally acting drug. Mean arterial BP (MABP) was calculated as 2/3 of the DBP plus 1/3 of the SBP value.

Hypertension was defined as a condition with SBP$\geqslant$140 mm Hg, DBP$\geqslant$90 mm Hg, or a physician diagnosis of hypertension. Hypertension was further classified into controlled hypertension in participants using antihypertensive medication, with SBP $<$140 mm Hg and DBP $<$90 mm Hg; or uncontrolled hypertension in participants with SBP$\geqslant$140 mm Hg or DBP$\geqslant$90 mm Hg, regardless of antihypertensive medication use.

Retinal photography and measurement of retinal vascular caliber

Digital fundus photographs were taken using a 45° digital retinal camera (Canon CR-DGi with a 10D SLR back, Canon, Tokyo, Japan) after pupil dilatation with 1% tropicamide and 2.5% phenylephrine. Two retinal images of each eye were obtained, one centered at the optic disc and another centered at the fovea, identical to the Early Treatment for Diabetic Retinopathy Study standard fields 1 and 2.[30]

Retinal vascular caliber was measured at the Retinal Vascular Imaging Centre, University of Melbourne using a computer-assisted software (IVAN, University of Wisconsin, Madison, WI, USA) according to the standardized protocol used in other population-based studies.[22,23,31] A trained grader, masked to participant characteristics, carried out the vessel measurements on the optic disc-centered image of the right eye for most participants, and of the left eye in those without gradable right eye images. All arterioles and venules crossing through a specified zone 0.5–1 disc diameter away from the optic disc margin were measured and summarized as the central retinal artery equivalent (CRAE) or central retinal vein equivalent (CRVE), respectively using a modification of the Parr-Hubbard formula[32] as described by Knudtson *et al*.[33] The retinal arterio–venous ratio (AVR) was calculated as the ratio of CRAE to CRVE.[32] A retinal photograph having less than six acceptable measurements of either vessel type was considered ungradable. Two hundred randomly selected retinal photographs were re-graded by the same assessor to assess reproducibility, with intra-grader reliability intraclass correlation coefficients of 0.99 (95% confidence interval (95% CI): 0.98–0.99) for CRAE and 0.94 (95% CI: 0.92–0.96) for CRVE.

Assessment of covariates

Age was defined as the age at the time of health screening, when BP and retinal images were captured. Height was quantified in centimeters, using a wall-mounted measuring tape; weight was assessed in kilograms, using a digital scale and body mass index (BMI) was calculated as 'body weight divided by the square of body height (kg m^{-2}).' Venous blood samples were analyzed on the same day at the National University Hospital Reference Laboratory for biochemical testing of serum total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides and fasting glucose. Diabetes mellitus was identified from fasting plasma glucose level of $\geqslant$7 mmol l^{-1}, self-reported use of diabetic medication or physician-diagnosed diabetes. Current smokers were defined as those who were currently smoking every day or every few days.

Statistical analysis

Statistical analyses were carried out using SAS version 9.1. software (SAS Institute, Cary, NC, USA). Characteristics of the participants were compared within ethnic groups by analysis of variance or χ^2 tests, whichever being appropriate. Retinal arteriolar (CRAE) and venular (CRVE) caliber and AVR

Table 1 Characteristics of study participants based on race/ethnicity

Characteristics	*Whole population* (n=*3749*)	*Chinese* (n=*2215*)	*Malay* (n=*807*)	*Indian* (n=*727*)	P-*value*[a]
Gender, male (%)	48.2	47.6	49.3	48.7	0.7
Hypertension (%)	39.3	36.6	45.9	40.6	<0.0001
Diabetes (%)	11.4	7.1	14.0	21.7	<0.0001
Current smoking (%)	12.0	10.3	17.0	11.7	<0.0001
Alcohol consumption (%)	33.7	44.6	6.4	30.8	<0.0001
Age, mean ± s.d. (years)	49.2 (11.3)	48.7 (11.7)	48.9 (11.0)	50.7 (10.3)	0.0002
Systolic blood pressure, mean ± s.d. (mm Hg)	131.6 (20.2)	129.5 (19.8)	136.3 (20.2)	132.6 (20.4)	<0.0001
Diastolic blood pressure, mean ± s.d. (mm Hg)	77.8 (10.7)	77.0 (10.7)	79.5 (10.6)	78.6 (10.6)	<0.0001
Serum glucose, mean ± s.d. (mmol l^{-1})	5.2 (1.6)	5.0 (1.2)	5.3 (1.8)	5.7 (2.2)	<0.0001
Body mass index, mean ± s.d. (kg m^{-2})	24.3 (5.2)	22.9 (3.6)	26.3 (4.8)	26.2 (7.6)	<0.0001
Total cholesterol, mean ± s.d. (mmol l^{-1})	5.2 (1.0)	5.2 (0.9)	5.5 (1.0)	5.2 (0.9)	<0.0001
HDL cholesterol, mean ± s.d. (mmol l^{-1})	1.4 (0.4)	1.5 (0.4)	1.4 (0.3)	1.2 (0.3)	<0.0001
LDL cholesterol, mean ± s.d. (mmol l^{-1})	3.2 (0.9)	3.1 (0.9)	3.4 (1.0)	3.3 (0.8)	<0.0001
Triglycerides, mean ± s.d., mmol l^{-1}	1.4 (0.9)	1.3 (0.9)	1.5 (1.2)	1.4 (0.7)	<0.0001
CRAE, mean ± s.d. (μm)	143.8 (14.3)	143.4 (14.3)	145.4 (13.8)	143.0 (14.5)	0.0008
CRVE, mean ± s.d. (μm)	220.8 (20.7)	219.5 (20.3)	226.9 (20.7)	218.0 (20.6)	<0.0001
AVR, mean ± s.d.	0.65 (0.1)	0.66 (0.1)	0.64 (0.1)	0.66 (0.1)	<0.0001

Abbreviations: AVR, arterio–venous ratio; CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]The *P*-value represents difference in characteristics by ethnicity based on the analysis of variance or χ^2 test as appropriate.

were analyzed as continuous variables. We used analysis of covariance to estimate mean retinal vascular calibers in association with normal BP, controlled hypertension and uncontrolled hypertension. We carried out these analyses initially for the total population and then separately for the three ethnic groups (Malays, Chinese and Indians) in three multivariable models: model 1: adjustment for age, gender and ethnicity; model 2: adjustment for variables in model 1 plus diabetes status, BMI, total cholesterol, triglycerides and current smoking (ethnicity was not included for ethnicity-specific models); model 3: adjustment for variables in model 2 plus CRVE in models for CRAE (and vice versa), which accounts for potential confounding from fellow vascular caliber.[34] Test of trend was determined by treating categorical risk factors (for example, categories of BP) as continuous ordinal variables in the multiple linear regression models. Using multiple linear regression models, we also estimated the mean difference in CRAE, CRVE and AVR with MABP as continuous variables in the same three models. To further account for the effect of antihypertensive medication, we repeated the analysis in model 3, with additional adjustment for antihypertensive medication use. Statistical interaction by age, gender, ethnicity and antihypertensive medication intake in the association between CRAE and MABP was tested by including cross-product interaction terms. In a supplementary analysis, we examined the association between CRAE and MABP stratified by age groups (younger (<40 years) and older ($\geqslant 40$ years)).

RESULTS

The study population consisted of 2215 Chinese (59.1%), 807 Malays (21.5%) and 727 Indian (19.4%) participants. The prevalence of hypertension in the total population was 39.3% and this was highest among the Malays (45.9%). Among those with known history of hypertension (n=759), 83.5% were on antihypertensive medication. Out of these, 30% of the participants on antihypertensive medication had their BP controlled.

Selected characteristics of the study population stratified by ethnicity are shown in Table 1. Malays were more likely to be smokers, had higher SBP and DBP, BMI, total cholesterol, low-density lipoprotein cholesterol, triglycerides, mean CRAE and mean CRVE compared with Chinese and Indians. Chinese were more likely to be alcohol drinkers and Indians were more likely to be older, had higher serum glucose and low high-density lipoprotein cholesterol level than did Malays and Chinese.

Table 2 shows the relationship of selected risk factors with retinal vascular caliber. After adjusting for age and gender, CRAE was associated with age, gender, smoking, alcohol consumption and BMI, whereas CRVE was associated with age, FPG, smoking, alcohol consumption, BMI and lipid profile.

Table 3 shows estimated mean CRAE, CRVE and AVR by hypertension status across ethnicity. CRAE was narrowest in participants with uncontrolled/untreated hypertension as compared with controlled hypertension and no hypertension. In model 3 after controlling for relevant risk factors and CRVE, CRAE was found to be 140.0 μm in persons with uncontrolled/untreated hypertension, 142.1 μm in persons with controlled hypertension and 146.0 μm those with no hypertension (P-value for trend <0.0001). After adjusting for potential confounders in model 3, CRVE was significantly wider in participants with uncontrolled/untreated hypertension compared with participants with normal BP (222.8 *vs.* 219.5 μm, respectively; $P<0.0001$) in the total population.

Figure 2 shows the trend of narrowing of retinal arteriolar caliber with increasing MABP in all three ethnic groups, adjusting for covariates in model 3 (P-value for trend <0.0001).

Table 3 shows the mean change of CRAE, CRVE and AVR for each 10 mm Hg increase in MABP, controlling for covariates in three different models. In model 3, each 10 mm Hg increase in MABP was associated with a 3.1-μm ($P<0.0001$) decrease in CRAE and a 1.8-μm ($P<0.0001$) increase in CRVE in the total population. The magnitude of the change in CRAE/CRVE was similar in all three racial/ethnic groups. For example, each 10 mm Hg increase in MABP was associated with a 3.1-μm decrease in CRAE in Chinese, 2.8 μm in Malays and 3.2 μm in Indians ($P<0.0001$ for all). Table 4 shows the effect of changes in MABP on retinal vascular calibers, with regard to race/ethnicity. Results were largely similar in different racial/ethnic groups. The results were also similar in analysis repeated using SBP and DBP instead of MABP (data not shown).

The inverse association of MABP and CRAE remained even after further adjustment for antihypertensive medication (−1.9 μm; 95% CI: −2.7, −1.2, $P<0.0001$, data not shown). Moreover, this association was observed in all three ethnic groups consistently. There was no role for race/ethnicity, gender and antihypertensive medication in the association between CRAE and MABP. However, there was a significant interaction between age and MABP on CRAE (P-value for interaction=0.0004). When stratified by age group of <40 and $\geqslant 40$ years, each 10 mm Hg increase in MABP was associated with −3.3 μm change in the mean CRAE (95% CI: −3.7, −3.0; $P<0.0001$) in the younger age group (age <40 years) compared with −1.9 μm change of mean CRAE (95% CI: −2.7, −1.0; $P<0.0001$) in the older age group (age $\geqslant 40$ years) in model 3.

Table 2 Relationship of selected risk factors with retinal vascular caliber

		Retinal arteriolar caliber (CRAE)[a]		*Retinal venular caliber (CRVE)*[a]	
Risk factors	*Unit change*	*β (SE)*	*P-value*	*β (SE)*	*P-value*
Age	Per 10 years increase	−2.63 (0.20)	<0.0001	−4.0 (0.29)	<0.0001
Gender	Men *vs.* women	4.95 (0.45)	<0.0001	0.28 (0.66)	0.67
FPG	Per s.d. increase (1.6 mmol l^{-1})	0.12 (0.23)	0.61	1.37 (0.33)	<0.0001
Cigarette smoking	Current *vs.* never/past	3.74 (0.72)	<0.0001	9.25 (1.06)	<0.0001
Alcohol drinking	Current *vs.* never/past	−1.63 (0.56)	0.004	−3.50 (0.82)	<0.0001
BMI	Per s.d. increase (5.2 kg m^{-2})	−0.89 (0.23)	0.0001	1.17 (0.34)	0.0007
Total cholesterol	Per s.d. increase (0.95 mmol l^{-1})	−0.35 (0.23)	0.12	0.85 (0.33)	0.01
HDL cholesterol	Per s.d. increase (0.36 mmol l^{-1})	−0.27 (0.24)	0.27	−2.25 (0.36)	<0.0001
LDL cholesterol	Per s.d. increase (0.88 mmol l^{-1})	−0.16 (0.23)	0.49	1.18 (0.33)	0.0004
Triglycerides	Per s.d. increase (0.93 mmol l^{-1})	−0.27 (0.23)	0.24	1.10 (0.34)	0.001

Abbreviations: β, regression coefficient; BMI, body mass index, HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Model adjusted for age, gender and ethnicity.

Table 3 Relationship of retinal vascular caliber with hypertension status based on race/ethnicity

	No Hypertension (n=2274)	*Hypertension, controlled (n=223)*	*Hypertension, uncontrolled/ untreated (n=1252)*	P-*value*[a]
Retinal arteriolar caliber (CRAE)				
Model 1[a]				
All individuals	146.2 (0.3)	142.5 (0.9)[b]	139.5 (0.4)[b]	<0.0001
Model 2[c]				
All individuals	146.2 (0.3)	142.4 (0.9)[b]	139.6 (0.4)[b]	<0.0001
Chinese	145.6 (0.4)	141.7 (1.2)[b]	139.3 (0.6)[b]	<0.0001
Malays	148.3 (0.7)	145.6 (2.0)	141.6 (0.8)[b]	<0.0001
Indians	146.0 (0.7)	141.9 (2.1)	138.1 (0.9)[b]	<0.0001
Model 3[d]				
All individuals	146.0 (0.3)	142.1 (0.8)[b]	140.0 (0.4)[b]	<0.0001
Chinese	145.3 (0.3)	141.5 (1.0)[b]	139.9 (0.5)[b]	<0.0001
Malays	147.8 (0.6)	143.7 (1.7)	142.5 (0.7)[b]	<0.0001
Indians	146.2 (0.6)	141.6 (1.9)	138.7 (0.9)[b]	<0.0001
Retinal venular caliber (CRVE)				
Model 1[a]				
All individuals	221.2 (0.4)	222.0 (1.4)	220.1 (0.6)	<0.0001
Model 2[c]				
All individuals	221.4 (0.4)	221.9 (1.4)	219.6 (0.6)	<0.0001
Chinese	220.3 (0.6)	220.1 (1.7)	217.9 (0.8)	<0.0001
Malays	228.2 (1.0)	232.6 (3.1)	224.3 (1.2)	<0.0001
Indians	218.3 (1.0)	215.8 (2.9)	217.7 (1.3)	<0.0001
Model 3[d]				
All individuals	219.5 (0.4)	222.9 (1.2)	222.8 (0.5)[b]	<0.0001
Chinese	218.6 (0.5)	221.4 (1.6)	221.1 (0.8)[b]	<0.0001
Malays	226.1 (1.0)	231.9 (2.8)	228.3 (1.2)	<0.0001
Indians	216.2 (0.9)	216.6 (2.6)	221.3 (1.2)[b]	<0.0001
Arterio–venous ratio (AVR)				
Model 1[a]				
All individuals	0.664(0.001)	0.646 (0.004)	0.638 (0.002)	<0.0001
Model 2[c]				
All individuals	0.663 (0.001)	0.646 (0.004)	0.639 (0.002)	<0.0001
Chinese	0.663 (0.002)	0.648 (0.005)	0.642 (0.003)	<0.0001
Malays	0.652 (0.003)	0.629 (0.009)	0.634 (0.003)	<0.0001
Indians	0.671 (0.003)	0.660 (0.009)	0.637 (0.004)	<0.0001

Data presented are analysis of covariance models showing mean ± s.e. of retinal arteriolar and venular caliber (in μm).
[a]Model 1: adjusted for age, gender and ethnicity.
[b]*P*-value based on analysis of covariance models, comparing hypertension controlled and hypertension uncontrolled with no hypertension.
[c]Model 2: adjusted for age, gender, ethnicity (except for ethnicity-specific models), diabetes status, body mass index, total cholesterol, triglycerides, current drinking and current smoking.
[d]Model 3: adjusted for variables in Model 2 and also for CRVE (in models of CRAE), and CRAE (in models of CRVE).

In comparison with non-hypertensive participants, mean CRAE for participants with controlled hypertension achieved by antihypertensive medication was smaller (146.0 ± 0.3 *vs.* 142.2 ± 0.8 μm, respectively; P=0.0001). In comparison, the mean CRVE of non-hypertensive individuals and those with hypertension controlled by antihypertensive medication was not significantly different (219.5 ± 0.4 *vs.* 222.7 ± 1.3 μm, respectively; P=0.08). There was no statistically significant difference in mean CRAE or CRVE based on the type of antihypertensives medication.

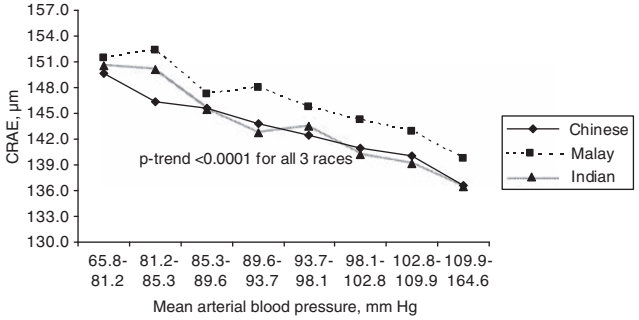

Figure 2 Estimated Retinal Arteriolar Caliber (CRAE), by mean arterial blood pressure and by race/ethnicity, adjusted for variables in Model 3 (age, gender, diabetes status, body mass index, total cholesterol, triglycerides, current smoking and central retinal vein equivalent).

Finally, Table 5 shows the relationship of retinal vascular caliber with blood pressure categories, as defined by the European Society of Hypertension and the European Society of Cardiology guidelines for the management of arterial hypertension. Following multivariable adjustment, CRAE narrowing was more marked in those with Grade 3 hypertension, compared with those with Grade 2 or Grade 1 hypertension (β:−10.8 ±0.9, −8.6 ± 0.7, −8.1 ± 0.6, for hypertension Grades 1, 2 and 3, respectively, $P<0.0001$). There was no clear pattern of CRVE widening and different Grades of hypertension (β: 4.8 ± 0.9, 3.9 ± 1.1, 4.8 ± 1.4, for hypertension Grades 1, 2 and 3, respectively, $P\leqslant 0.0004$).

DISCUSSION

In this study, we examined the relationship of BP and retinal vascular caliber in the three major racial/ethnic groups in Asia. Increasing levels of BP was strongly associated with the narrowing of retinal arterioles and slight widening of retinal venules, with the magnitude of associations similar across Chinese, Malays and Indians.

We show that Asians with hypertension have narrower retinal arteriolar caliber than those without hypertension, and that among persons with hypertension, those with uncontrolled/untreated hypertension have greater degree of narrowing than those with controlled hypertension. This observation has been reported in predominantly white populations in both persons with newly diagnosed[6,22] and chronic[35] hypertension. The relationship of BP and retinal arteriolar caliber was monotonic and linear, and consistent with other population-based studies.[5,6,8,9] For example, in our study, comparison for older Malays (aged ⩾40 years) in the cohort showed that for each 10 mm Hg increase in MABP, retinal arterioles narrowed by 1.9 μm, a magnitude which is less than that observed in the Singapore Malay Eye Study (narrowed by 2.7 μm), the Funagata Eye Study (2.8 μm) and Beaver Dam Eye Study in white population (2.3 μm).[7,23,24]

We also found that persons with hypertension had wider retinal venules compared with participants with normal BP, independent of hypertension control and smoking status. Each 10 mm Hg increase in MABP was associated with a 1.8-μm increase in retinal venular caliber in the multivariable model. This finding has now been observed in two other studies, the Rotterdam and Blue Mountains Eye Study.[36,37] In addition, the Blue Mountains Eye Study also reported that persons

Table 4 Effect of changes in MABP on retinal vascular calibers based on race/ethnicity

	Retinal arteriolar caliber (CRAE)		*Retinal venular caliber (CRVE)*		*Arteriole to venule ratio (AVR)*	
MABP, 10 mm Hg	*Mean Change (95% CI), μm*[a]	P-*value*	*Mean change (95% CI), μm*[a]	P-*value*	*Mean change (95% CI)*[a]	P-*value*
Model 1[b]						
All individuals	−3.3 (−3.7, −2.9)	<0.0001	−0.5 (−1.1, −0.06)	0.08	−0.014 (−0.015, −0.011)	<0.0001
Model 2[c]						
All individuals	−3.4 (−3.8, −3.0)	<0.0001	−0.9 (−1.5, −0.3)	0.002	−0.013 (−0.014, −0.011)	<0.0001
Chinese	−3.5 (−4.0, −3.0)	<0.0001	−1.1 (−1.9, −0.3)	0.0005	−0.013 (−0.015, −0.010)	<0.0001
Malays	−3.5 (−4.3, −2.7)	<0.0001	−2.1 (−3.3, −0.8)	0.001	−0.010 (−0.014, −0.006)	<0.0001
Indians	−3.4 (−4.2, −2.6)	<0.0001	−0.5 (−1.7, 0.7)	0.4	−0.014 (−0.017, −0.010)	<0.0001
Model 3[d]						
All individuals	−3.1 (−3.4, −2.8)	<0.0001	1.8 (1.3, 2.3)	<0.0001	—	
Chinese	−3.1 (−3.6, −2.7)	<0.0001	1.7 (0.9, 2.4)	<0.0001	—	
Malays	−2.8 (−3.5, −2.1)	<0.0001	0.7 (−0.5, 1.8)	0.25	—	
Indians	−3.2 (−3.9, −2.5)	<0.0001	2.0 (0.9, 3.1)	0.0004	—	

Abbreviations: CI, class interval; MABP, mean arterial blood pressure.
[a]Regression coefficient of MABP in linear regression models for CRAE, CRVE and AVR.
[b]Model 1: Adjustment for age, gender and ethnicity.
[c]Model 2: Adjustment for age, gender, ethnicity, diabetes status, body mass index, total cholesterol, triglycerides, current drinking and current smoking, except in ethnicity-specific strata (no adjustment for ethnicity).
[d]Model 3: Adjustment for variables in Model 2 plus venular caliber (in models of arteriolar caliber) and arteriolar caliber (in models of venular caliber).

Table 5 Relationship of retinal vascular caliber with ESH/ESC blood pressure categories[a]

Unit change	*Model 1*[b]		*Model 2*[c]		*Model 3*[d]	
	β (s.e.)	P-*value*[e]	*β (s.e.)*	P-*value*[e]	*β (s.e.)*	P-*value*[e]
Retinal arteriolar caliber (CRAE)						
Normal BP	−4.1 (0.7)	<0.0001	−4.3 (0.7)	<0.0001	−3.6 (0.6)	<0.0001
High normal BP	−6.5 (0.7)	<0.0001	−6.7 (0.7)	<0.0001	−5.7 (0.6)	<0.0001
Grade 1 hypertension	−8.5 (0.7)	<0.0001	−8.8 (0.7)	<0.0001	−8.1 (0.6)	<0.0001
Grade 2 hypertension	−9.5 (0.8)	<0.0001	−10.1 (0.8)	<0.0001	−8.6 (0.7)	<0.0001
Grade 3 hypertension	−11.7 (1.0)	<0.0001	−12.6 (1.0)	<0.0001	−10.8 (0.9)	<0.0001
Isolated systolic hypertension	−1.8 (0.6)	0.003	−1.7 (0.6)	0.007	−1.2 (0.5)	0.02
Retinal venular caliber (CRVE)						
Normal BP	−0.9 (1.0)	0.35	−1.8 (1.0)	0.07	1.5 (0.9)	0.08
High normal BP	−1.8 (1.1)	0.10	−2.9 (1.1)	0.008	2.3 (1.0)	0.02
Grade 1 hypertension	−1.0 (1.0)	0.34	−2.1 (1.0)	0.04	4.8 (0.9)	<0.0001
Grade 2 hypertension	−2.2 (1.2)	0.07	−3.9 (1.3)	0.002	3.9 (1.1)	0.0004
Grade 3 hypertension	−2.7 (1.5)	0.08	−5.1 (1.6)	0.001	4.8 (1.4)	0.0004

Abbreviations: BP, blood pressure; DBP, diastolic BP; SBP, systolic BP.
[a]BP classified according to the European Society of Hypertension and European Society of Cardiology (ESH/ESC) BP categories (optimal, SBP < 120 and DBP < 80 mm Hg; normal, SBP: 120–139 and/or DBP: 80–84 mm Hg; high normal, SBP: 130–139 and/or DBP: 85–89 mm Hg; grade 1 hypertension, SBP: 140–159 and/or DBP: 90–99 mm Hg; grade 2 hypertension, SBP: 160–179 and/or DBP: 100–109 mm Hg; grade 3 hypertension, SBP ⩾180 and/or DBP ⩾110 mm Hg; isolated systolic hypertension, SBP ⩾140 and DBP <90 mm Hg).
[b]Model 1: adjusted for age, gender, and ethnicity.
[c]Model 2: adjusted for age, gender, ethnicity (except for ethnicity-specific models), diabetes status, body mass index, total cholesterol, triglycerides, current drinking and current smoking.
[d]Model 3: adjusted for variables in Model 2 and also for CRVE (in models of CRAE), and CRAE (in models of CRVE).
[e]*P*-value, comparing specific group with optimal BP group.

with wider venular caliber had higher incidence of hypertension than those with narrower venules.[36]

Mechanisms underlying the association of BP and retinal arterioles have been previously hypothesized.[3,38,39] Arteriolar narrowing is thought to result from cumulative arteriolar changes associated with remodeling from chronic hypertension and arteriolosclerosis.[3,38] Our findings showed that retinal arteriolar narrowing remained evident even in individuals whose BP had been lowered by antihypertensive therapy, suggesting persistent arteriolar damage from chronic hypertension. It has also been suggested that the effect of BP on retinal arterioles is more marked in younger people, as the retinal vessels tend to be more compliant.[7,23] Conversely, the weaker association of BP and retinal vessels in older people may reflect age-related increases in rigidity and sclerosis of retinal arterioles, which reduces the impact that BP has on retinal arteriolar diameter compared with younger persons. Our findings support this idea by showing the relationship between MABP and retinal arteriolar narrowing being stronger in younger people than that found in older participants in all three ethnic groups.

In contrast, the pathophysiological mechanisms underlying the effect of BP and venular dilatation remain uncertain. Some studies have shown that wider retinal venules associated with increased BP may be a consequence of chronic retinal hypoperfusion,[40] cerebral hypoxia[41] or endothelial dysfunction[22] from damage to microcircula-

tion. Another potential mechanism is inflammation, which links hypertension and widening of venules,[8,22] although consistent relationships have not been found in all studies.[42]

The strength of our study includes a large population-based sample, a variety of potential confounders and standardized methods to measure BP and retinal vascular caliber. This study also includes limitations that should be noted. Its cross-sectional nature limits our ability to assess whether changes in the retinal vascular caliber are antecedent or consequential of elevated BP. Controlling for confounding effect using the contralateral vessel caliber may result in potential over-adjustment of the retinal vascular caliber.[34] There may also be unmeasured and unknown factors that could have influence on the variation of retinal vascular caliber, such as inflammatory markers for which we could not account. Furthermore, a large number of older participants were excluded from the study and this may result in potential selection bias in our study, for example, older people with narrower arteriolar caliber who were at risk for hypertension were more likely not to participate. Finally, misclassification of hypertension status may have occurred as classification of hypertension was based, in part, on two BP measurements during a single examination. However, such non-differential misclassification would only weaken the associations, suggesting that our observed associations should be even stronger if it was true.

In conclusion, we show the effect of BP on the retinal vasculature was similar amongst Chinese, Malays and Indians. These findings support the concept that precisely measured retinal vascular caliber from photographs may be a useful tool to study the microvascular changes of hypertension and are relevant in diverse racial/ethnic groups. Assessment of retinal vascular caliber may provide not only insights into early microvascular effects of BP, but may also help guide the development of new antihypertensive treatments.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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