Heritability of Retinal Vessel Diameters and Blood Pressure: A Twin Study

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Purpose. To assess the relative influence of genetic and environmental effects on retinal vessel diameters and blood pressure in healthy adults, as well as the possible genetic connection between these two characteristics.

Methods. In 55 monozygotic and 50 dizygotic same-sex healthy twin pairs, aged 20 to 46 years, interpolated diameter estimates for the central retinal artery (CRAE), the central retinal vein (CRVE), and the artery-to-vein diameter ratio (AVR) were assessed by analysis of digital gray-scale fundus photographs of right eyes.

Results. The heritability was 70% (95% CI: 54%–80%) for CRAE, 83% (95% CI: 73%–89%) for CRVE, and 61% (95% CI: 44%–73%) for mean arterial blood pressure (MABP). Retinal artery diameter decreased with increasing age and increasing arterial blood pressure. Mean vessel diameters in the population were 165.8 ± 14.9 μm for CRAE, 246.2 ± 17.7 μm for CRVE, and 0.67 ± 0.05 μm for AVR. No significant influence on artery or vein diameters was found for gender, smoking, body mass index (BMI), total cholesterol, fasting blood glucose, or 2-hour oral glucose tolerance test values.

Conclusions. In healthy young adults with normal blood pressure and blood glucose, variations in retinal blood vessel diameters and blood pressure were predominantly attributable to genetic effects. A genetic influence may have a role in individual susceptibility to hypertension and other vascular diseases. The results suggest that retinal vessel diameters and the possible associated variations in risk of vascular disease are primarily genetic characteristics. (*Invest Ophthalmol Vis Sci.* 2006;47:3539–3544) DOI:10.1167/iovs.05-1372

Having narrow arteries is strongly associated with past and present hypertension, independent of other risk factors.[1–6] Epidemiologic studies support that genetic predisposition plays a role in the development of hypertension, but the underlying mechanisms are largely unknown.[7–9] Recent studies have shown that structural abnormalities in small retinal arteries (general arterial narrowing and AV-nicking) often precede the development and progression of severe hypertension,[4,10,11] suggesting that these changes are an element in the pathogenesis of arterial hypertension rather than a consequence of it. Analysis of retinal vessel diameters in relatives has shown higher correlations than in the background population.[12] In the present study, we have assessed the relative influence of genetic and environmental effects on retinal vessel diameters and blood pressure in healthy young adult twins, as well as the influence of sex, age, blood pressure, body mass index, fasting blood glucose, glucose tolerance, and smoking.

Methods

Subjects and Protocol

This was a cross-sectional study of 59 monozygotic (MZ) and 55 dizygotic (DZ) same-sex twin pairs, aged 20 to 46 years. The participants were recruited from a population-based register comprising twins born in Denmark between 1870 and 1996 (The Danish Twin Registry, University of Southern Denmark, Odense, Denmark).[13] All subjects in self-assessed good health were invited to participate. To avoid ascertainment bias, no post hoc exclusion of subjects found to have hypertension or diabetes was permitted. Exclusion was made of all twin pairs where one or both twins were found to have unclear refractive media, manifest eye disease, or fundus photographs of unacceptable quality. Nine twin pairs were excluded because of missing or ungradeable fundus photographs. The remaining 55 MZ and 50 DZ twin pairs were included in the study.

Zygosity was determined by means of genetic markers using nine microsatellite and restriction fragment length polymorphism (RFLP) markers. The study was approved by the Medical Ethics Committee of Copenhagen County and followed the tenets of the Declaration of Helsinki, including informed consent.

All persons underwent an ophthalmic examination, including refraction, visual acuity determination, slit lamp biomicroscopy, and fundus photography after pupil dilation using phenylephrine hydrochloride 10% and tropicamide 1%. Blood pressure, body mass index (BMI; defined as weight in kilograms divided by height in square meters), fasting blood glucose, total cholesterol, family disposition for diabetes mellitus, and smoking history were obtained before an oral glucose tolerance test (OGTT) using 75 g glucose after a 12-hour overnight fast, assessing whole capillary blood glucose at 0, 30, and 120 minutes after ingestion.

The mean arterial blood pressure (MABP) was calculated as 33% of the difference between the systolic and the diastolic blood pressure plus the diastolic blood pressure. Hypertension was defined as systolic blood pressure >140 or diastolic blood pressure >90, and/or current use of antihypertensive medication. Diabetes was defined according to the current World Health Organization (WHO) criteria (i.e., fasting whole capillary blood glucose concentration >6.1 mmol · L^{-1} or 2-hour OGTT whole capillary blood glucose concentration >11.1 mmol · L^{-1}. Impaired glucose tolerance was defined as fasting whole capillary blood glucose concentration <6.1 mmol · L^{-1} and 2-hour OGTT whole capillary blood glucose concentration ≥ 7.8 mmol · L^{-1}.[14] Smoking was categorized as being a current smoker or a current nonsmoker.

Digital gray-scale fundus photographs (50°, 1024 × 1024 pixels) centered on the macula and the optic disc were recorded in red-free illumi-

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Table 1. Clinical Characteristics and Retinal Vessel Calibers in Right Eyes of 105 Healthy Twin Pairs

	Monozygotic		Dizygotic		
	Male	Female	Male	Female	*P*‡
Subjects	52	58	42	58	
Smoker/non-smoker subjects	16/36	25/33	22/20	25/33	
Age* (ys)	36.1 (7.4)	34.3 (7.7)	35.9 (7.6)	35.1 (6.2)	0.55
Mean arterial blood pressure* (mm Hg)	86.3 (8.0)	82.9 (9.0)	88.1 (9.0)	84.4 (7.7)	0.02
BMI* (kg/m^2)	23.9 (2.6)	22.7 (2.5)	23.9 (3.0)	23.7 (3.7)	0.11
Total cholesterol*† (mmol/L)	5.4 (1.1)	5.0 (0.9)	5.8 (1.3)	5.4 (0.8)	0.003
Fasting blood glucose*† (mmol/L)	5.1 (0.5)	4.7 (0.4)	5.0 (0.4)	4.8 (0.4)	<0.0001
2-h OGTT*† (mmol/L)	6.0 (1.6)	6.2 (0.9)	5.7 (1.4)	6.5 (1.2)	<0.01
Artery diameter*§ (μm)	165.1 (15.2)	165.5 (16.6)	168.0 (12.4)	165.2 (14.7)	0.78
Vein diameter*§ (μm)	246.1 (19.7)	247.1 (19.4)	246.4 (15.6)	245.1 (15.7)	0.95
AVR*	0.67 (0.04)	0.67 (0.05)	0.68 (0.04)	0.67 (0.05)	0.61

* Data are the mean ± SD.

† Whole capillary blood.

‡ The variances are the same in the four groups, using the Bartlett test of variance homogeneity. One-way ANOVA testing the difference between mean values in all four groups.

§ Central retinal artery equivalent diameter and central retinal vein equivalent diameter.

nation (filter: Wratten 54; Eastman Kodak, Inc., Rochester, NY) using a retinal camera (TRC-50X; Topcon Corp., Tokyo, Japan). The study design and photography protocol has been described in previous publications on lens fluorescence and retinal nerve fiber layer thickness.[15,16]

Vessel calibers were assessed using a custom-developed semiautomated computer algorithm (Visiopharm A/S, Hørsholm, Denmark). A grid was placed on the 50° digital image, and only the diameters of retinal vessels crossing the circular zone from 0.5 to 1.0 disc diameters from the margin of the optic disc were analyzed. The grader chose the segment of each vessel within the circular zone that was deemed most suitable for measurement, based on image quality, contrast, straightness of the vessel, absence of branching and vessel crossings, and, if possible, measured the whole length of the vessel within the circular zone. When bifurcating or branching was found within the zone of interest, the trunk was preferred to the branches, unless the trunk was shorter than 80 μm. The program identified the six largest arteries and the six largest veins and calculated the central retinal artery equivalent (CRAE), the central retinal vein equivalent (CRVE), and the artery-to-vein ratio (AVR), according to the formulas described by Knudtson et al.[17] Equivalent diameters were found by pairing the largest- and the smallest-caliber vessels within a given class and proceeding to pair the resultant virtual vessels until only one remained, irrespective of the actual branching pattern on the optic disc. The formulas used for calculating trunk diameter from two branch diameters pairing were

$$\text{Artery (CRAE): } \hat{W}_A = 0.88\sqrt{(w_1^2 + w_2^2)}$$

and

$$\text{Vein (CRVE): } \hat{W}_V = 0.95\sqrt{(w_1^2 + w_2^2)},$$

where W represents the width of the trunk vessel, and w_1 and w_2 the width of each branch. The AVR was defined as CRAE/CRVE. Eyes were considered ungradeable if one of the six largest arteries or veins could not be measured or if the image was of poor quality (low contrast), as judged by the grader with reference to a standard image of least acceptable quality and contrast. Absolute distances were found assuming a uniform vertical optic nerve head diameter of 1800 μm.

Statistics

Retinal vessel calibers and clinical characteristics were normally distributed. Retinal vessel data were analyzed as continuous variables. Intragrader reproducibility was assessed using Pearson correlation and mean ± SD of the differences of two independent gradings of 59 fundus photographs. Differences, between the four groups, (MZ male, MZ female, DZ male, and DZ female pairs) in age, MABP, BMI, total cholesterol, fasting blood glucose, 2-hour OGTT, and retinal vessel parameters were compared by one-way ANOVA, assuming $P < 0.05$ to be indicative of statistical significance. The difference in variance in the four groups was tested with the Bartlett's test of variance homogeneity. Pearson correlations were estimated between retinal vessel calibers and relevant clinical characteristics for all the twins in the study.

Six twin pairs had a difference in refraction between twins A and B of more than 4 D and were tentatively excluded from the heritability analysis. Because this did not change the results, the full data without statistical correction for refraction have been reported throughout.

We compared vessel calibers and MABP between twin one and twin two for the four groups: MZ male, MZ female, DZ male, and DZ female pairs by means of intraclass (Pearson) correlations. Associations of covariates with vessel calibers and blood pressure as well as estimation of heritability by means of univariate structural equation modeling

Table 2. Correlations between Retinal Vessel Calibers and Clinical Characteristics in 105 Healthy Twin Pairs

Clinical Characteristics	CRAE*†	CRVE*†	MABP*
MABP	−0.42 ($P < 0.001$)	−0.20 ($P < 0.01$)	
Age	−0.27 ($P < 0.001$)	−0.21 ($P < 0.01$)	0.22 ($P < 0.01$)
BMI	−0.12 ($P < 0.1$)	−0.14 ($P < 0.05$)	0.40 ($P < 0.001$)
Total cholesterol	−0.23 ($P < 0.001$)	−0.15 ($P < 0.05$)	0.26 ($P < 0.001$)
Fasting blood glucose	0.04 ($P > 0.2$)	0.11 ($P < 0.2$)	0.15 ($P < 0.05$)
2-h OGTT	−0.07 ($P > 0.2$)	0.01 ($P > 0.2$)	0.04 ($P > 0.2$)

* Pearson correlation coefficient and probabilities of all the twins in the study ($n = 210$). Similar patterns of correlations are obtained if the analyses are limited to one of the twins (twin 1 or twin 2 chosen randomly) or only MZ or DZ twins.

† Central retinal artery equivalent diameter and central retinal vein equivalent diameter.

was made using MX computer software.[18,19] Because of the limited number of twin pairs we only analyzed two or three covariates at a time. The classic twin model is based on the assumption that MZ twins have identical genotypes, for which reason all observed differences between the two twins in a pair are attributable to environmental factors. DZ twins, however, share on average 50% of their genes. The extent to which MZ twins are more alike than DZ twins is therefore assumed to reflect a genetic influence on the phenotype in question. Heritability is defined as the proportion of the total phenotypic variance that is attributable to genetic variance (heritability = genetic variance/total phenotypic variance)[20] and is calculated by means of structural equation modeling. Structural equation modeling quantifies sources of individual variation by decomposing the observed phenotypic variance into genetic and environmental variance. The genetic contribution can be further divided into an additive (A) genetic variance component (representing the influence of alleles at multiple loci acting in an additive manner) and a nonadditive (D) genetic variance component (representing intralocus interaction [dominance] and interlocus interaction [epistasis] of alleles). The environmental component can be subdivided into a common (C) environmental variance component (representing environmental factors affecting both twins in a pair, a source of similarity) and an unshared/random (E) environmental variance

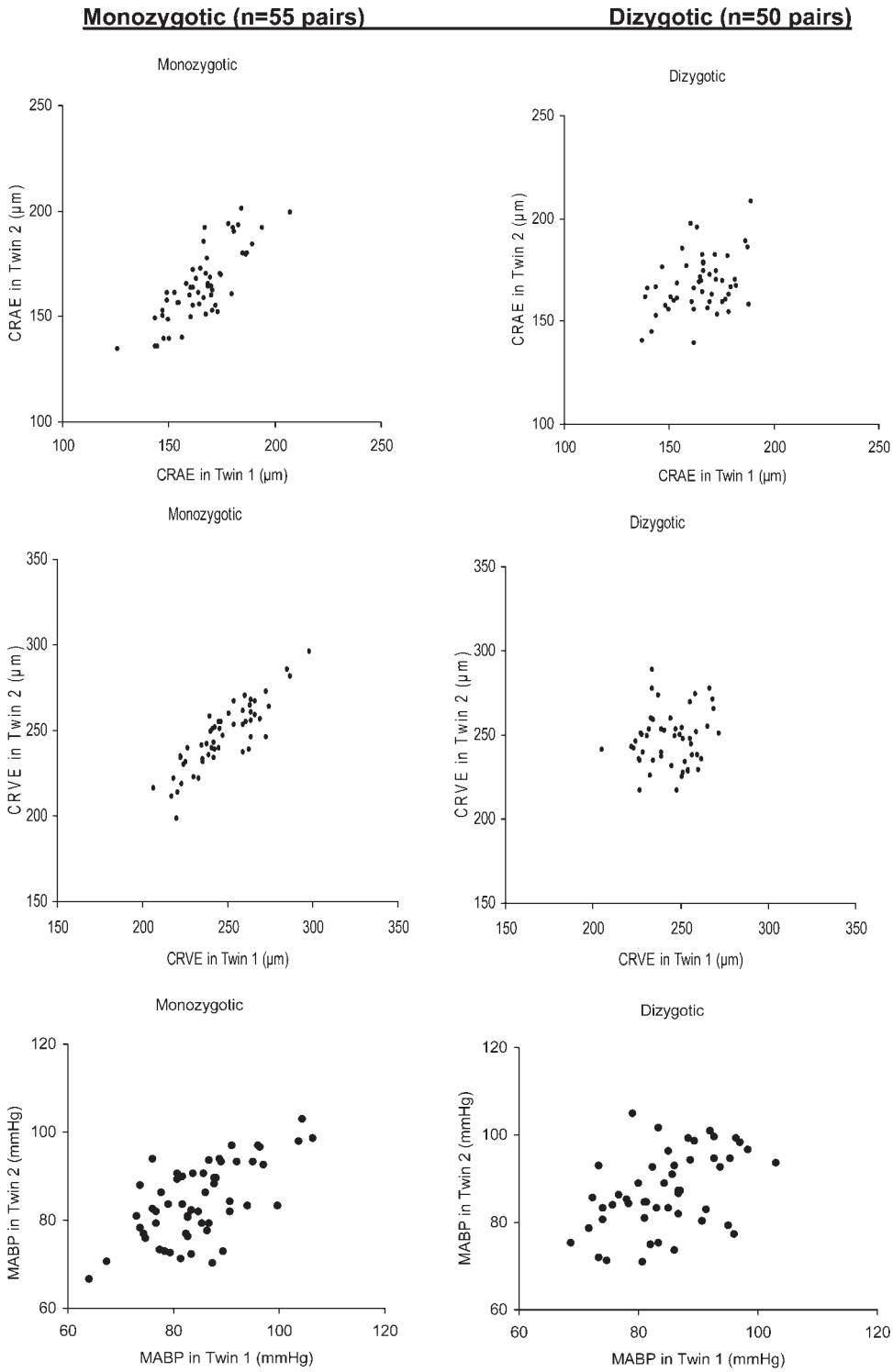

FIGURE 1. Scatterplot by zygosity for CRAE diameter and CRVE diameter in healthy twins. The intraclass correlation data are shown in Table 3.

TABLE 3. Intraclass Correlation Values by Gender and Zygosity for Vessel Diameters and Blood Pressure in 105 Healthy Twin Pairs

	Monozygotic		Dizygotic	
	Male	Female	Male	Female
Subjects	52	58	42	58
MABP*	0.59 (0.26, 0.79)	0.68 (0.41, 0.84)	0.47 (0.05, 0.75)	0.40 (0.04, 0.67)
CRAE diameter†	0.80 (0.60, 0.91)	0.80 (0.62, 0.90)	0.12 (−0.33, 0.53)	0.50 (0.16, 0.73)
CRVE diameter‡	0.87 (0.72, 0.94)	0.88 (0.75, 0.94)	−0.13 (−0.53, 0.32)	0.36 (−0.01, 0.64)

Pearson correlation coefficient (*r*) (95% CI) between twin 1 and twin 2. See Figure 1 for scatterplots of the intraclass correlations for MZ and DZ twins.

* r_{mz} = 0.64 (CI_{95} 0.45, 0.77) and r_{dz} = 0.45 (CI_{95} 0.20, 0.65).

† r_{mz} = 0.80 (CI_{95} 0.68, 0.88) and r_{dz} = 0.37 (CI_{95} 0.11, 0.59).

‡ r_{mz} = 0.87 (CI_{95} 0.79, 0.92) and r_{dz} = 0.14 (CI_{95} −0.14, 0.40).

component (representing environmental factors not shared by twins, a source of dissimilarity, including random factors and measurement errors).[21] We fitted the ADE and ACE models and the submodels AE, CE, and E to the data. The criterion for best-fitting model was based on Akaike's information criterion (AIC). The model with the lowest AIC reflects the best balance between goodness-of-fit and parsimony.[19]

RESULTS

In the study population of 210 healthy subjects aged 20 to 46 years, mean CRAE was 165.8 ± 14.9 μm (range, 125.9–208.0), mean CRVE was 246.2 ± 17.7 μm (range, 198.4–298.3 μm), and mean AVR was 0.67 ± 0.05 μm (range, 0.56–0.79). All vessel parameters and clinical characteristics demonstrated a normal distribution. MZ male and female twin pairs and DZ male and twin pairs were of comparable age, MABP, BMI, and retinal vessel calibers (Table 1). There was no difference in variance in MABP and vessel calibers in the four groups, using the Bartlett's test of variance (Table 1). A tendency was noted for smokers to have wider retinal arteries (167.8 vs. 164.4 μm; $P = 0.10$) and wider retinal veins (248.6 vs. 244.4 μm, $P = 0.08$, *t*-test) than nonsmokers. Blood pressure increased with age by 2.4 mm Hg per decade ($P = 0.005$). There was a significant correlation between CRAE and MABP, age, and total cholesterol; between CRVE and MABP, age, BMI, and total cholesterol; and between MABP and age, BMI, total cholesterol, and fasting blood glucose (Table 2). None of the participants had arterial hypertension. Sixteen patients were found to have impaired glucose tolerance, and five patients were found to have diabetes mellitus,[14] each of them fulfilling only one criterion for diabetes and none of them having had symptoms of diabetes before the study. All subjects were included in the analysis. Intragrader reproducibility, defined as the mean ± SD of the difference between two independent gradings from 59 eyes, was 0.32 ± 1.89 μm for CRAE and −0.02 ± 1.71 μm for CRVE, the Pearson correlation being 0.991 for CRAE and 0.995 for CRVE.

The distribution of CRAE, CRVE, and MABP demonstrated higher correlation in MZ twins than in DZ twins (Fig. 1), as did the intraclass (Pearson) correlations (Table 3), similar patterns of intraclass correlations are obtained when analyzed according to gender (Table 3). The intraclass correlation being approximately two times higher for MZ twins than for DZ twins indicated that an AE model was likely the best fit by structural equation modeling for both arteries and veins, which was supported by low AIC values. This means that observed interindividual differences in vessel calibers were best explained by the effect of additive genetic factors (A) and unshared environmental factors (E). For CRAE, after correcting for MABP, age, and gender, additive genetic factors (i.e., heritability) explained 70% (95% CI: 54%–80%, Table 4) of the total phenotypic variance in retinal artery diameter, unshared environmental factors accounting for the remaining 30% (95% CI: 20%–46%). The results were independent of whether systolic or diastolic blood pressure or MABP was used. Correction for covariates while ignoring the effect of MABP resulted in increasing values of heritability after correction for smoking (76%; Table 5) and 2-hour OGTT (77%; Table 5). Age and MABP influenced the heritability results significantly and were both inversely correlated with artery diameter, MABP by −5.45 μm/10 mm Hg (95% CI: −7.60 to −3.29) and age by −4.36 μm/10 y (95% CI: −7.48 to −1.24). Gender, smoking, BMI,

TABLE 4. Model-Fitting Analyses of Retinal Vessel Diameters Corrected for MABP, Gender and Age in 55 Monozygotic and 50 Dizygotic Twin Pairs

	Genetic Components		Environmental Components		Goodness-of-Fit Tests			
Model	**A**	**D**	**C**	**E**	χ^2	*df*	*P*	**AIC**
Artery								
1. ADE	0.50 (0.00–0.80)	0.20 (0.00–0.79)		0.30 (0.20–0.45)				
2. AE	**0.70 (0.54–0.80)**			**0.30 (0.20–0.46)**	**0.139**	**1**	**0.710**	**−1.861**
3. E				1.00 (1.00–1.00)	42.664	2	0.000	38.664
4. ACE	0.70 (0.28–0.80)		0.00 (0.00–0.37)	0.30 (0.20–0.46)	0.139	0	incalculable	0.139
5. CE			0.53 (0.37–0.65)	0.47 (0.35–0.63)	9.751	1	0.002	7.751
Vein								
6. ADE	0.00 (0.00–0.83)	0.83 (0.00–0.88)		0.17 (0.12–0.26)				
7. AE	**0.83 (0.73–0.89)**			**0.17 (0.11–0.27)**	**3.804**	**1**	**0.051**	**1.804**
8. E				1.00 (1.00–1.00)	72.507	2	0.000	68.507
9. ACE	0.83 (0.63–0.89)		0.00 (0.00–0.18)	0.17 (0.11–0.27)	3.804	0	incalculable	3.804
10. CE			0.56 (0.42–0.68)	0.44 (0.32–0.58)	33.269	1	0.000	31.269

Boldface type indicates best fitting model. Data are the proportion of total variation attributable to model component (CI_{95} %). AIC, Akaike's information criterion.

TABLE 5. Model-Fitting Analyses of Central Retinal Artery Diameter Corrected for Covariates in 55 Monozygotic and 50 Dizygotic Twin Pairs

Covariates	A	E	AIC	*P*
Age and MABP	0.70 (0.56–0.80)	0.30 (0.20–0.44)	−1.946	0.816
Age, MABP, and gender	0.70 (0.54–0.80)	0.30 (0.20–0.46)	−2.000	0.994
MABP, smoking, and age	0.70 (0.56–0.80)	0.30 (0.20–0.44)	−2.000	0.995
MABP and gender	0.71 (0.56–0.81)	0.29 (0.19–0.44)	−1.967	0.856
MABP and smoking	0.72 (0.57–0.81)	0.28 (0.19–0.43)	−1.995	0.945
MABP, 2-h OGTT, and age	0.71 (0.56–0.80)	0.29 (0.20–0.44)	−2.000	0.994
Age and smoking	0.73 (0.60–0.82)	0.27 (0.18–0.40)	−2.000	
Age, smoking, and gender	0.73 (0.60–0.82)	0.27 (0.18–0.40)	−2.000	
Age and gender	0.74 (0.62–0.83)	0.26 (0.17–0.38)	−1.972	0.868
Age, gender, and cholesterol	0.74 (0.60–0.83)	0.26 (0.17–0.40)	−2.000	0.997
Age and 2-h OGTT	0.75 (0.62–0.83)	0.25 (0.17–0.38)	−1.993	0.934
Age, 2-h OGTT, gender	0.75 (0.62–0.83)	0.25 (0.17–0.38)	−2.000	0.998
Gender and smoking	0.76 (0.64–0.84)	0.24 (0.16–0.36)	−2.000	
Gender and 2-h OGTT	0.77 (0.65–0.84)	0.23 (0.16–0.35)	−2.000	

Data are the proportion of total variation attributable to model component (CI_{95} %). AIC Akaike's information criterion.

total cholesterol, fasting blood glucose, and 2-hour OGTT had no significant effect on artery diameters or heritability.

For CRVE, after correcting for MABP, age, and gender, additive genetic factors were found to account for 83% (95% CI: 73%–89%; Table 4) of the phenotypic variance in retinal vein diameter and unshared environmental factors for the remaining 17% (95% CI: 11%–27%). Vein diameters decreased with increasing age by −4.50 μm/10 years (95% CI: −8.45 to −0.56). Gender, MABP, diastolic blood pressure, systolic blood pressure, smoking, BMI, total cholesterol, fasting blood glucose, and 2-hour OGTT had no significant effect on vein diameters or heritability. For MABP, the heritability was 61%. After adjustment for CRAE, the heritability decreased to 54%, and, after adjustment for CRVE, the heritability decreased to 59% (Table 6).

DISCUSSION

In the study population of 210 healthy, normotensive, adult twins, retinal vessel diameters were found to be governed mainly by genetic factors, which accounted for 70% or more of the variance in artery diameters and 83% of the variance in vein diameters, the remainder being attributable to unshared environmental factors. The heritability of vessel diameters was not affected by gender, whereas correction for age and MABP was essential for the estimation of heritability. With adjustment for MABP, CRAE heritability decreased from 75% to 70% (Table 5), which may be because blood pressure shares a small proportion of heritability with retinal vessel calibers. In contrast smoking, BMI, total cholesterol, fasting blood glucose, 2-hour OGTT did not significantly influence artery and vein diameters in this study.

Mean arterial blood pressure was also found to be governed mainly by genetic factors, with a heritability of 61%, when controlling for gender and age. This result was in agreement with an earlier twin study finding 44% to 63% heritability of ambulatory systolic and diastolic blood pressure.[7]

We wanted to find out whether blood pressure and retinal vessels share genes, but we found only minor interaction between the two. The decrease in MABP heritability from 61% to 54% after adjustment for CRAE failed to reach statistical significance. The most likely interpretation is that both genetic and nongenetic variance contribute and the former more than the latter, because if their interaction was mainly in their correlation in nongenetic variances, the heritability of CRAE would not decrease by adjustment for MABP.

We found a nominal AVR heritability of 45%, but this percentage is likely to be lower than the true heritability, because of the combination of environmental influences of CRAE and CRVE, as CRAE (associated with blood pressure) and CRVE (associated with inflammatory markers and metabolic index) have quite different environmental associations.

The present study was designed to optimize fundus vessel imaging by applying direct digital imaging in red-free illumination rather than digitization of color diapositives. This procedure also allows immediate image quality control. The resolution of 1024 × 1024 pixels per 50° frame is lower than with the best currently available gray-scale sensors, but it is probably as good as that obtained with three-chip color sensors of higher nominal resolution.

Adjustment for refractive errors did not attenuate vessel diameter heritability in this study. Because refraction is highly heritable[22] and we are testing the difference between two twins in a pair with largely the same refraction, we may not have been able to assess the full influence of refraction. A previous study has shown, however, that correction for refraction is unimportant in fundus vessel diameter studies.[23]

The random acquisition of the fundus photographs in relation to the cardiac cycle in this study is likely to confer a higher level of random variation than what can be achieved with electrocardiograph-gated photography, but it is unlikely to offset the mean results. Fundus vessel pulsation is detectable mainly in the largest

TABLE 6. Model-Fitting Analyses of Blood Pressure Corrected for Retinal Vessel Diameters, Gender, and Age in 55 Monozygotic and 50 Dizygotic Twin Pairs

Phenotype	Covariates	A	E
MABP	Gender and age	0.61 (0.44–0.73)	0.39 (0.27–0.56)
MABP	Gender, age, and CRAE	0.54 (0.34–0.68)	0.46 (0.32–0.66)
MABP	Gender, age, and CRVE	0.59 (0.42–0.72)	0.41 (0.28–0.58)

Data are the proportion of total variation attributable to model component (CI_{95} %).

veins of the retina.[24] In relation to heritability, added random variation has the effect of decreasing the heritability.

The vessel diameters found in this study were comparable to those found in the Beaver Dam Eye Study,[12] supporting that twins do not differ in retinal vessel calibers from singletons, as is also true of blood pressure.[7] The familial correlation of retinal vessel calibers was found to be 0.2 to 0.27 in the Beaver Dam Eye Study population.[12] Genetic predisposition cannot be assessed in studies of familial correlations in natural families, because there is no way to distinguish between genetic and shared familial environmental influences on the trait. If there is no familial shared environment according to twin (and adoption) studies, then the familial correlation may be multiplied by two to get the heritability corresponding to that obtained in twin studies (i.e., 0.40–0.54), of which estimates the siblings usually has the higher one and the parent-offspring the lower one. Owing to the age differences and other environmental differences, non-twin siblings are usually somewhat more different from DZ twins. Thus, a heritability of 0.7 in our study implies a correlation of 0.35 between the DZ twin pairs, which is higher and not too far from that observed in most non-twin siblings, which in the Beaver Dam Eye Study population study was 0.20 to 0.23. The twin-based heritability can also be higher because of nonadditive genetic variance, which for the DZ twins would mean that the genetic part of their between-twin correlation is lower and the possible shared environmental contribution to the correlation is higher. This can also fit with family studies, where it seems likely that nontwin siblings share fewer environments than DZ twin pairs, and therefore would have a lower correlation than the DZ twin pairs. In addition, such nonadditive genetic variance can also explain the higher correlation between nontwin siblings than between parent-offspring, as can a sibling-specific shared environment. Additional advantages of twin studies include the ability to assess the relative influence of genetics and environment as well as lower susceptibility to cohort effects.

Narrow retinal arteries are independently associated with the presence of arterial hypertension and the risk of development of hypertension in humans.[4,10,11] Arteriolar narrowing has also been found to precede the development of hypertension in rats.[25] It may be reasonable to view retinal arterioles as effectors rather than sensors in relation to arterial hypertension in the future. The hypothetical inference may be that the antihypertensive medications that most effectively reduce the morbidity and mortality associated with arterial hypertension are the ones that most effectively eliminate retinal arteriolar contraction, independent of their effect on blood pressure. Arterioles also quite possibly act as sensors, as arterioles and blood pressure mutually affect each other in a vicious cycle in hypertensive subjects.

Our study population was a healthy, normotensive young adult twin population, and the findings can be applied only to normotensive subjects with a similar age range. In hypertensive populations, the mutual influence between blood pressure and retinal vessel calibers is likely to be different from that of normotensive subjects. In spite of this, our results may suggest that retinal vessel calibers and the associated variations in risk of systemic disease may be a primary genetic characteristic rather than a reflection of variations in blood pressure.

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