

Retinal Arteriolar Tortuosity and Cardiovascular Risk Factors in a Multi-Ethnic Population Study of 10-Year-Old Children; the Child Heart and Health Study in England (CHASE)

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Objective—To examine the association between cardiovascular risk factors and retinal arteriolar tortuosity in a multi-ethnic child population.

Methods and Results—Cross sectional study of 986 UK primary school children of South Asian, black African Caribbean, and white European origin aged 10 to 11 years. Anthropometric measurements and retinal imaging were carried out and a fasting blood sample collected. Digital images of retinal arterioles were analyzed using a validated semiautomated measure of tortuosity. Associations between tortuosity and cardiometabolic risk factors were analyzed using multi-level linear regression, adjusted for gender, age, ethnicity, arteriole branch status, month, and school. Levels of arteriolar tortuosity were similar in boys and girls and in different ethnic groups. Retinal arteriolar tortuosity was positively associated with levels of triglyceride, total and LDL cholesterol, and systolic and diastolic blood pressure. One standard deviation increases in these risk factors were associated with 3.7% (95% CI: 1.2%, 6.4%), 3.3% (0.9%, 5.8%), 3.1% (0.6%, 5.6%), 2.0% (−0.3%, 4.2%), and 2.3% (0.1%, 4.6%) increases in tortuosity, respectively. Adiposity, insulin resistance, and blood glucose showed no associations with tortuosity.

Conclusion—Established cardiovascular risk factors, strongly linked to coronary heart disease in adulthood, may influence retinal arteriolar tortuosity at the end of the first decade of life. (*Arterioscler Thromb Vasc Biol.* 2011;31:1933-1938.)

Key Words: epidemiology ■ risk factors ■ cardiovascular risk factors ■ childhood ■ retinal arteriolar tortuosity

Abnormalities of the retinal microcirculation in adult life, including microaneurysms, arteriolar-venular nicking, and arteriolar narrowing, are prospectively and independently related to cardiovascular disease, including both coronary heart disease (CHD) and stroke.^{1–3} Increased tortuosity of retinal arterioles (assessed subjectively) has been related to risk factors for coronary disease, particularly hypertension, both in adults and children.^{4,5} Arteriolar narrowing has been related to CHD in later life.^{6,7} Changes in the retinal microcirculation have also been observed with risk factors for cardiovascular disease; narrower arterioles have been associated with increased blood pressure⁸ and with body mass index.⁹

Recent studies have suggested that differences in retinal arteriolar morphology associated with cardiovascular risk may emerge early in life. Studies in children have shown strong

associations between blood pressure,¹⁰ body mass index,¹¹ and retinal arteriolar caliber, which mirror associations previously reported in adults.^{8,9} As well as measurement of vessel width, tortuosity is another morphological characteristic of the retinal vascular network, relying on the detection of vessel axes as opposed to the exact location of vessel edges.¹² Earlier studies of retinal arteriolar tortuosity in adults have suggested that it may be a marker for subsequent CHD risk. However, no studies to date have, to our knowledge, examined retinal arteriolar tortuosity in children and its association with established cardiovascular risk factors. We set out to use a validated objective measure to assess tortuosity in retinal arterioles (as a novel index of arteriolar function)¹³ in a multi-ethnic population of almost one thousand 10- to 11-year-old children and examine its associations with established cardiometabolic risk markers.

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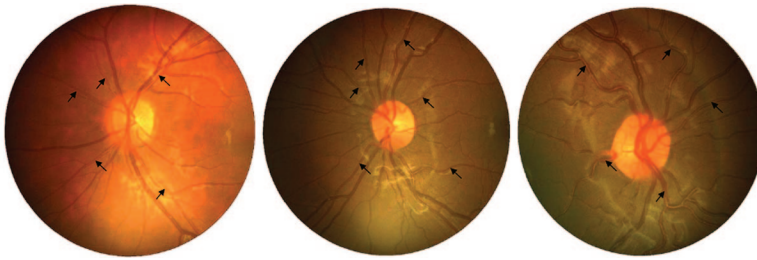


Figure 1. Images of children with low (1st percentile, 3.7×10^{-3} , white European), median (7.0×10^{-3} , black African Caribbean), and high (99th percentile, 16.5×10^{-3} , black African Caribbean) levels of tortuosity index (averaged over all arterioles in the image). Major arterioles are labeled with black arrows.

Methods

Study Population

This investigation was carried within the Child Heart and Health Study in England (CHASE Study), a school-based survey of the cardiovascular health of British Primary School children living in 3 UK cities, London, Leicester and Birmingham. Full details of the study design have been reported elsewhere.¹⁴ Ethical approval was obtained from the relevant Multicenter Research Ethics Committee, and the study was carried out in accordance with the principles expressed in the Declaration of Helsinki. Informed written consent was obtained from each pupil's parent or guardian. The study was based in a sample of 200 Primary Schools, providing balanced numbers of children of South Asian origin (including Indian, Pakistani, and Bangladeshi origin), black African-Caribbean origin (including black African and black Caribbean) and white European origin. The present investigation was based in 46 schools in the final phase of the study, in which children attended for the main survey and returned for measurements of retinal arteriolar tortuosity on a separate occasion. Children were in Year 5 (aged 9 to 10 years) for the cardiovascular risk survey, and Year 6 (aged 10 to 11 years) for the ocular examination.

Cardiovascular Risk Factor Assessment

A single survey team including 3 trained research nurses and a support fieldworker carried out all survey measurements between June 2006 and February 2007. Survey methods have been described in detail elsewhere.¹⁴ Participating children provided a blood sample after an overnight fast and had measurements of height, weight, and waist circumference. Right-sided skinfold thicknesses were measured in 4 sites (biceps, triceps, subscapular, suprailiac); analyses are based on the sum of the 4 measurements. Leg-to-arm bioimpedance was measured using the Bodystat 1500 bioimpedance monitor (Bodystat Ltd, Isle of Man, UK); fat mass was derived using equations derived specifically for children using dual energy X-ray absorptiometry validation¹⁵ and presented as a fat mass index (fat mass/height³), which was independent of height. Seated blood pressure was measured twice in the right arm after 5 minutes rest using an Omron 907 blood pressure recorder, with an appropriately sized cuff; the average of the 2 measures was used. Pubertal status was measured in the girls using Tanner scales.¹⁶ Participating children provided questionnaire information on parental and grandparental country of birth and reported any current health problems. The parent or guardian was asked to provide information on the ethnicity of both parents and that of the child (coded using a classification similar to the 2001 UK Census), and on their occupation, coded using the National Statistics Socioeconomic Classification (NS-SEC). Ethnicity of the children was defined using the ethnicity of both parents or (if not available) the ethnicity of the child; in a small proportion of cases in which parental information was not available (1%), child information on the place of birth of parents and grandparents was used to define ethnic origin, described in more detail elsewhere.¹⁴ Children were defined as white European (including white British, white Irish, white European, or a combination of these), black African-Caribbean (black African, black Caribbean, black British, black other, or a combination of these), South Asian (Indian, Pakistani, Bangladeshi or a combination of these), or other Asian. The latter group included those with a specified Asian place of origin (mainly Afghanistan, China, and Turkey) other than South Asian, so that subjects of Indian, Pakistani, Bangladeshi, and Sri Lankan origin are excluded from other Asian. All laboratory analyses were carried out blind to participant ethnicity.

Analyses of HbA1c, glucose, and blood lipids were carried out in the Department of Clinical Biochemistry, Newcastle Hospitals NHS Trust, which received blood samples within 48 hours of collection. Glucose was measured in plasma using the hexokinase method. HbA1c was measured in whole blood by ion exchange high performance liquid chromatography; HbA1c values were recalculated to adjust for abnormal hemoglobin variants or for increased amounts of normal variant fetal hemoglobin where present. Triglyceride and HDL cholesterol were measured in serum using an Olympus auto-analyzer. Serum, separated and frozen on dry ice after collection, were used for measurement of insulin (Department of Medicine, University of Newcastle, UK) using an ELISA method which does not cross-react with proinsulin¹⁷ and C-reactive protein, which was assayed by ultra-sensitive nephelometry (Dade Behring, Milton Keynes, UK). The homeostasis model assessment model equations were used to provide an estimate of insulin resistance.¹⁸

Ocular Examination

Ocular assessment included the measurement of vision, visual acuity, and open-field autorefractometry (SRW-5000, Shin-Nippon Commerce Inc, Tokyo, Japan) without cycloplegia and noncontact ocular biometry (Zeiss IOL Master, Carl Zeiss Meditec, UK).^{13,19} Fundus imaging included 2 digital images (30°, 1280×960 pixels) centered on the optic disc of each child's eye recorded in subdued lighting using the Nidek NM-200D handheld fundus camera (Nidek Co, Ltd, Hiroishi, Japan).¹³ Image processing was carried out using the Computer Assisted Image Analysis of the Retina (CAIAR) program.^{13,20,21} CAIAR identifies vessel segments (typically 10 to 16 per eye) and returns measures of tortuosity for each segment beyond a circle 120 pixels in diameter (equivalent to 1.8 mm in the objective plane of an emmetropic eye) centered on the optic disc (to exclude most overlapping vessels emerging from the disc) to a diameter of 400 pixels (equivalent to a measurement area of 100 mm²). A simple tortuosity measure based on the mean change in subdivided chord lengths was used.¹³ The units of tortuosity, which are dimensionless as they represent a ratio measure, have been validated against subjective measures of tortuosity in this age group and show good agreement.¹³ Images from children of different ethnic origin are shown in Figure 1 with low, medium, and high levels of tortuosity (1st, median, and 99th percentile of measure). Measures of vessel tortuosity were obtained for arterioles and different levels of bifurcation (primary, secondary, tertiary, 4 or more branches) assessed subjectively. Time taken to process 400 vessels is approximately 3 hours.¹³

Statistical Analysis

Statistical analyses were carried out using STATA/SE software (Stata/SE 10.1 for Windows, StataCorp LP, College Station, TX). The tortuosity index (the outcome/dependent variable) exhibited a positive skew and was log transformed to normalize the distribution before analysis. Histograms of the tortuosity index before and after transformation are shown in Figure 2. Other variables requiring log transformation included ponderal index, fat mass index, waist circumference, sum of skinfolds, insulin, triglyceride, and C-reactive protein. Gender and ethnic differences in these variables were examined as fixed effects using multi-level linear regression models with school as a random effect to allow for the clustering of children within school. Analyses of tortuosity index additionally included a random effect for child to allow for the correlation of multiple measures of tortuosity within the same child; this avoids loss of data by summarizing vessel measures within

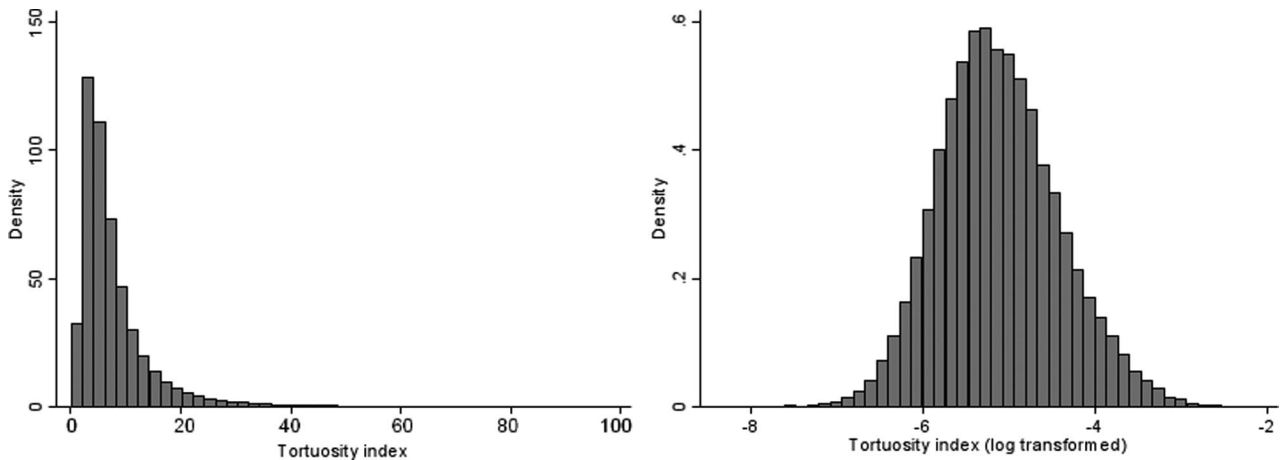


Figure 2. Histograms showing untransformed and log transformed tortuosity index (units of tortuosity are dimensionless but are multiplied by 10^3).

the same individual as a single mean. The xtmixed command in STATA was used, which allows a distinct variance for each random effect within a random-effects equation and assumes that all covariances are zero. The percentage difference in arteriolar tortuosity for an SD increase in cardiometabolic risk factor (log transformed where appropriate) was examined; cardiometabolic risk factors were chosen a priori. All analyses were adjusted for age group, gender, ethnicity, month, and arteriole branch status (all as fixed effects); adjustment for the latter was made as levels of tortuosity increased with branch status. Effect of additionally adjusting tortuosity differences for axial length or spherical equivalent refraction was examined. Tests for interaction were used to examine whether associations of arteriolar tortuosity to cardiometabolic risk differ by gender or ethnic group; interactions were not considered in the absence of main effects.

Results

Of 1642 children invited to participate in this phase of CHASE, 1176 (72%) took part (mean age 9.8 years, 48% male). Fundus imaging and refractive assessment were carried out in 986 children; blood sample data were available for 872 of these children. Participation rates were similar among children of white Europeans (77%), South Asians (77%), Asian others (76%), and lower among those of black African Caribbean origin (63%). Measures of tortuosity were obtained for a total of 16 670 retinal arterioles from 1963 eyes (8.5 arterioles per eye). The difference in the number of arterioles measured per eye between ethnic groups was not statistically significant (Likelihood Ratio Test, $P=0.2$): South Asians 9.2 arterioles per eye, Asian other 7.0, white Europeans 8.6, and black African Caribbeans 8.4 arterioles.

There was appreciable variation in tortuosity within this population (overall mean index: 6.8×10^{-3} , SD 2×10^{-3} ; Figure 2). Levels of arteriolar tortuosity by sex and ethnic group are summarized in Table 1. Arteriolar tortuosity did not differ appreciably between boys and girls. Compared to white Europeans, South Asian and black African Caribbean children had similar levels of tortuosity; Asian other and other miscellaneous ethnic groups had lower levels of tortuosity. Adjusted associations of age, body size, and cardiovascular risk factors with retinal tortuosity are shown in Table 2. Diastolic, and to a lesser extent systolic, blood pressure showed positive associations with arteriolar tortuosity, whereas levels of triglyceride and LDL cholesterol showed

stronger positive associations. The associations of retinal arteriolar tortuosity to blood pressure (systolic and diastolic) levels of triglycerides and LDL cholesterol (by quintiles) were generally graded (Figure 3). Adiposity markers (ponderal index, waist circumference, sum of skinfolds, fat mass index) and diabetic risk factors (HbA1c, glucose, insulin, insulin resistance) all showed weak positive associations with arteriolar tortuosity, but none of these were statistically significant. The effect of adjustment for axial length (as well as height) made little difference to the associations (Table 2); percentage differences were similar after adjustment for spherical equivalent refractions instead of axial length (data not presented). The mutual independence of these risk factor associations was examined. The positive associations between triglycerides, cholesterol, and arteriolar tortuosity were unaffected by adjustment for systolic blood pressure. Associations with blood pressure were marginally weakened (by approximately a quarter) after adjustment for LDL cholesterol (Table 2). The associations between cardiometabolic risk factors and retinal arteriolar tortuosity were generally similar for boys and girls and in different ethnic groups (all tests for interaction, $P>0.1$).

Table 1. Geometric Mean Retinal Arteriolar Tortuosity (95% CI) by Gender and Ethnic Group

	N	Geometric Mean Arteriolar Tortuosity (95% CI) $\times 10^{-3}$	P (Difference)†
Boys	462	6.7 (6.4, 7.0)	
Girls	524	6.6 (6.3, 6.9)	0.42
White European	222	6.9 (6.6, 7.3)	
Black African-Caribbean	243	6.8 (6.4, 7.2)	0.52
South Asian	276	6.7 (6.4, 7.1)	0.40
Asian other	65	5.8 (5.3, 6.4)	<0.001
Other	180	6.4 (6.1, 6.8)	0.03

All means are adjusted for age groups, gender (except by sex), ethnicity (except by ethnic group), month and branch status, and a random effect for child and school.

Log transformed tortuosity values have been exponentiated to give geometric means and 95% confidence limits. Note, units of tortuosity are dimensionless.

†P values for difference compare boys with girls, white Europeans with children of other ethnic group.

Table 2. Percentage Differences in Arteriolar Tortuosity for a one SD/Log SD Increase in a Range of Cardiometabolic Risk Factors

	Mean†	SD/GSD†	% Difference in Arteriolar Tortuosity (95% CI) p(Difference)						
			Adjustment 1		Adjustment 2		Adjustment 3		
Age (years)	9.8	0.4	−1.9	(−4.7, 0.8)	0.17	−2.0	(−4.7, 0.8)	0.16	
Height (cm)	139.2	7.0	0.2	(−2.1, 2.5)	0.88	0.5	(−1.8, 2.9)	0.67	
Ponderal index (kg/m ³)*	13.2	1.2	0.8	(−1.4, 3.0)	0.48	1.0	(−1.2, 3.2)	0.40	
Waist circumference (cm)*	63.7	1.1	0.2	(−2.0, 2.5)	0.84	0.5	(−1.7, 2.7)	0.68	
Sum of skinfolds (mm)*	42.6	1.6	1.4	(−0.9, 3.7)	0.24	1.5	(−0.7, 3.9)	0.18	
Fat mass index (kg/m ⁵)*	1.9	1.5	0.6	(−1.6, 2.9)	0.59	0.7	(−1.5, 3.0)	0.52	
Glucose (mmol/L)	4.5	0.3	0.9	(−1.6, 3.4)	0.48	0.9	(−1.6, 3.4)	0.48	
HbA1c (%)	5.3	0.3	0.7	(−1.6, 3.2)	0.55	0.7	(−1.7, 3.1)	0.56	
Insulin (mU/L)*	7.2	1.8	0.6	(−1.9, 3.2)	0.65	0.7	(−1.8, 3.3)	0.57	
Insulin resistance*	0.9	1.8	0.6	(−1.9, 3.2)	0.65	0.7	(−1.8, 3.3)	0.57	
Triglyceride (mmol/L)*	0.9	1.5	3.7	(1.2, 6.4)	0.004	3.7	(1.1, 6.3)	0.005	3.8 (1.0, 6.6) 0.01
Total cholesterol (mmol/L)	4.5	0.8	3.3	(0.9, 5.8)	0.01	3.3	(0.9, 5.7)	0.01	3.2 (0.8, 5.7) 0.01
LDL cholesterol (mmol/L)	2.7	0.7	3.1	(0.6, 5.6)	0.01	3.1	(0.6, 5.6)	0.01	2.9 (0.4, 5.5) 0.02
HDL cholesterol (mmol/L)	1.5	0.3	−0.2	(−2.5, 2.2)	0.89	−0.3	(−2.7, 2.1)	0.79	
Systolic BP (mm Hg)	104.4	10.7	1.9	(−0.3, 4.2)	0.09	2.0	(−0.3, 4.2)	0.09	1.5 (−1.0, 4.0) 0.24
Diastolic BP (mm Hg)	63.2	9.1	2.3	(0.1, 4.6)	0.04	2.3	(0.1, 4.6)	0.04	1.5 (−0.9, 3.9) 0.23
C reactive protein (mg/L)*	0.6	3.7	−0.2	(−2.5, 2.2)	0.86	−0.1	(−2.4, 2.2)	0.92	

Analyses of age and anthropometric measurements are based on 986 subjects; analyses of blood measurements are based on 872 subjects. GSD indicates geometric standard deviation.

*Log transformed variable.

†Arithmetic mean and SD or geometric mean and GSD for log transformed variables (95% central range is geometric mean \div GSD², is geometric mean \times GSD²).

All percentage differences in tortuosity are for a 1 SD increase in risk factor.

Adjustment 1: includes gender, age groups (except for age), ethnicity, observer (physical measurements only), month, retinal branch status, and a random effect for child within school.

Adjustment 2: includes all variables in adjustment 1 plus axial length.

Adjustment 3: includes all variables in adjustment 2, plus adjustment for height, sum of skinfolds, fasting insulin and (1) systolic blood pressure for triglyceride, LDL, and total cholesterol associations, (2) LDL cholesterol for BP associations.

Discussion

This study provides evidence that retinal arteriolar tortuosity shows appreciable variation between individuals in childhood and is positively associated with established cardiovascular

risk factors (including triglyceride, total and LDL cholesterol, systolic and diastolic blood pressure). These findings raise the possibility that early markers of cardiovascular disease, such as higher blood lipids (in particular triglyceride levels) and

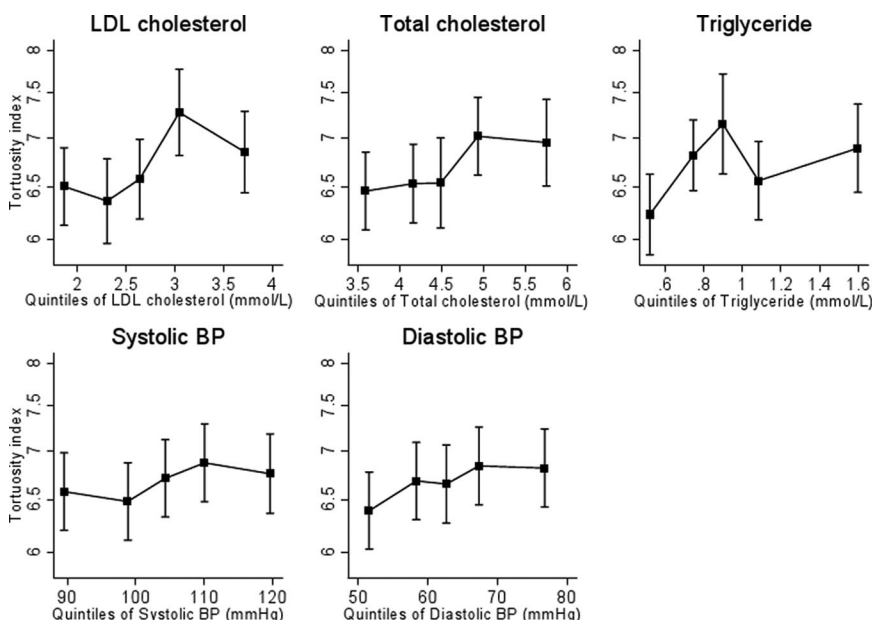


Figure 3. Level of tortuosity index (log scale) by quintiles of LDL and total cholesterol (mmol/L), triglyceride (mmol/L), and systolic and diastolic blood pressure (mm Hg).

blood pressure, influence retinal arteriolar tortuosity during the first decade of life.

Cardiovascular disease has long been viewed as a disease originating in middle age. However, there is now substantial evidence from pathological studies,^{22–24} epidemiological studies,^{25–31} and combined pathological-epidemiological studies^{32,33} that CHD risk originates earlier in life and that abnormalities in arterial structure and function are apparent before adult life. Abnormalities of retinal microvasculature, particularly affecting the arterioles, are known to be related to cardiovascular disease and CHD in adult life.^{1–3,34,35} However, less is known about changes in the morphology of retinal vessels among populations without overt cardiometabolic disease. Studies that do exist have focused on the measurement of vessel width, both in adults^{8,9} and children.^{10,11} Measures of width are more difficult in children with prominent vessel reflexes (especially on arterioles) and in different ethnic groups with varying levels of refractive error (with higher levels of myopia among Asians)^{19,36,37} and background levels of retinal pigmentation (with higher levels amongst black African-Caribbeans; see Figure 1). Measuring vessel tortuosity offers another morphological characteristic of the vascular network, which we found was less sensitive to these difficulties¹² and is effectively independent of vessel width. The findings from this study are consistent with earlier studies that have shown a positive association between retinal vessel tortuosity (assessed subjectively) and hypertension, both in child and adult populations,^{4,5,38} and among those with severe coronary disease.³⁹ However, not all studies have been consistent in their findings.^{40,41} This may reflect the unreliability of subjective assessment of tortuosity in many of these earlier studies. Objective measures of tortuosity will avoid measurement error inherent with subjective assessment (especially at lower levels of tortuosity).¹³

Strengths and Limitations

We have used a novel measure of tortuosity based on a subdivided chord length method (chosen a priori) that has been validated against subjective assessment in this age group, which shows good agreement and repeatability across a broad range of vessel tortuosity,¹³ from smoothly curved to highly tortuous retinal vessels in infants with retinopathy of prematurity.²⁰ Moreover, unlike dimensional measurements (such as width), we have also shown that the tortuosity measure is relatively unaffected by refractive error¹³ and is therefore likely to be particularly valid in this multi-ethnic population with large differences in ametropia and ocular biometry.¹⁹ Other strengths of this study include the appreciable sample size and multi-ethnic population, designed to detect modest differences in risk markers between major ethnic groups (white European, South Asian, black African Caribbean).¹⁴ Overall response rates were high with little difference between ethnic groups. The slightly lower response rate in black African-Caribbeans is unlikely to invalidate the results as there was no strong evidence of ethnic difference in the pattern of association between tortuosity and cardiovascular risk factors (except perhaps for blood cholesterol). Response rates for blood sampling were slightly lower (as expected), but this is unlikely to have affected the associations observed, especially as those with extremes in arteriolar tortuosity are unlikely to know and choose not to participate. The cross sectional nature of the present study means that it cannot be

assumed that cardiovascular risk factors caused increased retinal arteriolar tortuosity. Indeed, it is plausible that more tortuous microcirculation may lead to higher blood pressure.

Implications

We have observed appreciable variation in retinal arteriolar tortuosity and associations with established cardiovascular risk factors that were consistent in boys and girls and across ethnic groups. Our results suggest that unfavorable cardiovascular risk profiles in childhood may be having adverse effects on arteriolar structure and function in the first decade of life. The strength, consistency, and graded associations observed between several established cardiovascular risk factors and retinal arteriolar tortuosity suggest that the associations, very unlikely to have occurred by chance, may be causal. However, biological mechanisms for the findings remain uncertain, especially the strong positive association with triglycerides. The mechanisms by which blood lipids influence the wall of larger arteries are not likely to apply to arterioles; blood pressure could be having a mechanical influence on arteriolar structure and function.⁴² Further research in population-based studies is needed to clarify the associations between cardiovascular risk factors and retinal arteriolar tortuosity, and the relations between retinal arteriolar tortuosity and other markers of vascular structure and function. Prospective studies will also be useful in establishing the time sequence of these associations. In addition, more evidence on other potential determinants of retinal arteriolar tortuosity, including early life factors (such as birthweight or gestation),^{43,44} childhood lifestyle (including physical activity), and genetic predisposition⁴¹ may also be important in this context. We examined objective measures of physical activity in our study⁴⁵ but found no evidence of an association with arteriolar tortuosity (data not presented). The associations observed suggest that retinal arteriolar tortuosity may be influenced by cardiovascular risk factors in early life.

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Disclosures

None.

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