Associations between the Metabolic Syndrome and Retinal Microvascular Signs: The Atherosclerosis Risk in Communities Study

Tien Yin Wong,[1,2] Bruce B. Duncan,[3] Sherita Hill Golden,[4,5] Ronald Klein,[6] David J. Couper,[7] Barbara E. K. Klein,[6] Larry D. Hubbard,[6] A. Richey Sharrett,[5] and Maria I. Schmidt[3]

PURPOSE. To examine the cross-sectional relationship of the metabolic syndrome (hypertension, hyperglycemia, central obesity, and dyslipidemia) and retinal microvascular abnormalities in middle-aged men and women.

METHODS. A population-based, cross-sectional study involving 11,265 persons aged 49 to 73 years who had retinal photography from 1993 through 1995. Photographs were graded for presence of retinal microvascular signs (microaneurysms, retinal hemorrhages, arteriovenous nicking, and focal arteriolar narrowing) according to a standardized protocol. To quantify retinal vessel diameters, photographs were digitized and individual arteriolar and venular diameters were measured and summarized. The metabolic syndrome was defined according to the Third Report of the National Cholesterol Education Program Adult Treatment Panel.

RESULTS. After adjustment for age, gender, race, education, cigarette smoking and alcohol consumption, persons with the metabolic syndrome were more likely to have retinopathy (odds ratio [OR] 1.68, 95% confidence interval [CI], 1.45–1.96), arteriovenous nicking (OR 1.30, 95% CI, 1.16–1.45), focal arteriolar narrowing (OR 1.24, 95% CI, 1.10–1.38), generalized retinal arteriolar narrowing (OR 1.23, 95% CI, 1.12–1.35), and generalized retinal venular dilatation (OR 1.30, 95% CI, 1.18–1.48) than persons without the metabolic syndrome. Associations for arteriovenous nicking, focal arteriolar narrowing, generalized arteriolar narrowing, and venular dilatation were noted, even in people without diabetes or hypertension.

CONCLUSIONS. These data suggest that the metabolic syndrome is associated with microvascular changes in the retina. This finding reflects, in part, the associations of individual syndrome components with retinal microvascular abnormalities. (*Invest Ophthalmol Vis Sci.* 2004;45:2949–2954) DOI:10.1167/iovs.04-0069

The metabolic syndrome consists of a clustering of diseases, including central obesity, dyslipidemia, hyperglycemia, and high blood pressure. The syndrome is increasingly recognized as being a distinct entity affecting a large proportion of the U.S. adult population.[1,2] Persons with the metabolic syndrome are at known risk of development of large-vessel atherosclerotic diseases.[3,4] It is unclear, however, whether the metabolic syndrome is associated with microvascular disease.[5–7] Characteristics of large and small vessel disease, such as inflammation and endothelial dysfunction, have been reported to be associated with the metabolic syndrome in some, but not all, studies.[8–12]

The associations of diabetes and hypertension with retinopathy and other microvascular changes (e.g., retinal arteriolar narrowing and arteriovenous nicking) are well known.[13] Recent studies have shown that these retinal microvascular signs are also associated with systemic markers of inflammation and endothelial dysfunction,[14] and incidence of diabetes and hypertension.[15,16] However, the relationship of the metabolic syndrome and retinal microvascular signs has not been evaluated.

In the present study, we examined the cross-sectional association of the metabolic syndrome and retinal microvascular signs in a large population of middle-aged men and women.

METHODS

Study Population

The Atherosclerosis Risk In Communities (ARIC) study is a population-based cohort study that included 15,792 women and men 45 to 64 years of age at recruitment from 1987 through 1989.[17] Population samples were selected from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi (blacks only); suburbs of Minneapolis, Minnesota; and Washington County, Maryland.[17] Of those examined at baseline, 86.2% returned for the third examination 6 years from baseline (1993–1995).

All data are based on the third examination, when retinal photography was first performed.[18] Of the 12,887 who returned for this examination, we excluded 271 with retinal vascular occlusions, 738 with ungradable photographs, 477 without fasting (>8 hours) glucose levels, and 56 with missing data on a component of the metabolic syndrome and, due to small numbers, 38 whose race was neither black nor white and 42 black residents in Minneapolis and Maryland, leaving 11,265 who provided data for the present study. Characteristics of participants with and without gradable retinal photographs have been reported.[18] Individuals with gradable photographs were younger and more likely to be white, but did not differ from participants with ungradable photographs on gender or smoking status.

TABLE 1. Prevalence of Retinal Microvascular Signs According to Metabolic Syndrome and Individual Components

Metabolic Syndrome and Components		Retinopathy		Arteriovenous Nicking		Focal Arteriolar Narrowing		Generalized Arteriolar Narrowing		Generalized Venular Dilatation	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Metabolic Syndrome	Present	4221	8.8	4144	16.4	4062	17.2	3907	27.5	1072	27.4
	Absent	7041	5.1	6929	12.8	6807	13.5	6552	23.6	1534	23.4
Syndrome Components											
Large waist	Present	6807	7.1	6694	15.3	6574	15.9	6317	25.9	6317	25.6
	Absent	4455	5.7	4379	12.4	4295	15.3	4142	23.7	4142	23.9
High triglyceride	Present	4123	7.3	4057	14.3	3971	15.1	3837	23.8	3837	27.4
	Absent	7139	6.1	7016	14.0	6898	14.8	6622	25.7	6622	23.5
Low HDL cholesterol	Present	3830	6.9	3768	15.5	3689	15.3	3573	26.8	3573	25.3
	Absent	7432	6.3	7305	13.4	7180	14.7	6886	24.2	6886	24.7
High blood pressure	Present	6032	8.1	5925	16.5	5793	19.9	5537	31.2	5537	25.2
	Absent	5230	4.7	5148	11.3	5076	9.2	4922	18.1	4922	24.6
High glucose	Present	2932	11.8	2861	15.8	2808	15.6	2701	25.5	2701	30.2
	Absent	8330	4.7	8212	13.5	8061	14.6	7758	24.9	7758	23.1

Institutional review boards at each study site and at the Fundus Photograph Reading Center at the University of Wisconsin, Madison, approved the study. Informed consent was obtained from all participants and the study was conducted in accordance with the Declaration of Helsinki.

Definition of the Metabolic Syndrome

Anthropometrics were taken with the subject wearing a scrub suit and no shoes.[19] Waist circumference was measured at the umbilicus (in centimeters). Participants were asked to fast for at least 8 hours before morning blood collection. Blood was drawn from the antecubital vein of seated participants and serum and plasma aliquots were frozen at −70°C and shipped to central laboratories for analysis.[20] Triglycerides, high-density lipoprotein (HDL) cholesterol, and glucose were assayed according to ARIC Study protocols.[19,20] Blood pressure was measured three times using a random-0 sphygmomanometer.[9,16]

We defined the metabolic syndrome according to criteria by the Third Report of the National Cholesterol Education Program Adult Treatment Panel (ATP III),[21] which include three or more of the following five components:

1. Waist circumference greater than 102 cm in men and 88 cm in women (defined as having a large waist in the present study)
2. Serum triglyceride level of at least 150 mg/dL (1.69 mM) (defined as having hypertriglyceridemia)
3. HDL-cholesterol level of less than 40 mg/dL (1.04 mM) in men and 50 mg/dL (1.29 mM) in women (defined as having low HDL-cholesterol)
4. Systolic blood pressure of at least 130 mm Hg or diastolic blood pressure of at least 85 mm Hg (defined as having high blood pressure)
5. Fasting (>8 hours in the ARIC study) glucose level of at least 110 mg/dL (6.1 mM; defined as having high glucose).

Individuals also met the criteria for high blood pressure and high fasting glucose if they reported taking medication for hypertension or diabetes, respectively, or if, in the case of diabetes, they reported a physician's diagnosis of the condition.

For the purpose of subgroup analyses, diabetes was defined as fasting serum glucose levels of at least 126 mg/dL (7.0 mM), diabetic medication use or a physician's diagnosis of diabetes, and hypertension was defined as systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or use of antihypertensive medication during the previous 2 weeks.

Retinal Photography and Definitions

The retinal photography procedure and grading of retinal microvascular signs have been described in detail elsewhere.[14–16,18] Briefly, retinal photography of one randomly selected eye of each participant was taken at the third examination. If the eye selected randomly was considered too difficult or not possible to photograph with adequate quality (e.g., inability to dilate to at least 4 mm, inability to fixate adequately for proper photographic field definition, or opacities of the ocular media preventing a reasonably clear view of the retina), the fellow eye was photographed instead. After 5 minutes of dark adaptation, a 45° photograph was taken, centered on the region of the optic disc and the macula, with an autofocus camera.

Trained graders, masked to participant characteristics, examined the photographs for the presence of discrete retinal microvascular abnormalities, including retinopathy (e.g., microaneurysms, retinal hemorrhages and soft exudates), arteriovenous nicking, and focal arteriolar narrowing. The grading and definition of these lesions were based on a standard protocol described in other reports.[18] To quantify retinal arteriolar and venular diameters, the fundus photographs were digitized, and the diameters of all arterioles and venules coursing through a specified area surrounding the optic disc were measured by using a computer-assisted approach. Individual vessel diameters were combined into summary measures of arteriolar and venular diameters of the eye, based on previously published formulas.[18,22] Generalized arteriolar narrowing was defined as the lowest quintile (smallest 20%) of the population distribution of arteriolar diameters, and the higher four quintiles were defined as no arteriolar narrowing. Generalized venular dilatation was defined as the highest quintile (largest 20%) of the venular diameters, and the four lower quintiles were defined as no dilatation. Quality control procedures are described elsewhere.[18]

Statistical Analysis

The metabolic syndrome was categorized as present versus absent. Individual components of the syndrome were also analyzed separately. All retinal microvascular signs (retinopathy, arteriovenous nicking, focal arteriolar narrowing, generalized arteriolar narrowing, and generalized venular dilatation) were defined as binary variables.

Logistic regression was used to determine the odds ratios of various retinal microvascular signs, comparing the presence versus absence of the metabolic syndrome. All models were initially adjusted for age, gender, race, and field center. Because both the metabolic syndrome and retinal signs were associated with educational levels, cigarette smoking, and alcohol consumption status,[1,2,13] these were included in the final models as additional independent variables.

Finally, to examine the independent association between a specific metabolic syndrome component and retinal microvascular signs, logistic regression models of retinal microvascular signs were constructed with metabolic syndrome components entered simultaneously as in-

dependent variables, adjusting for age, gender, race, field center, education, cigarette smoking, and alcohol consumption.

RESULTS

In the study population, the mean age of participants was 59.8 ± 5.6 years, and 55.8% were female, 20.8% were African-American, 80.8% had completed high school, 58.7% had a history of cigarette smoking, and 75.6% a history of alcohol consumption.

Table 1 shows the prevalence of retinal microvascular signs among participants with and without the metabolic syndrome and its components. In general, the metabolic syndrome and specific syndrome components were associated with a higher prevalence of retinal microvascular signs.

Logistic regression models of retinal microvascular signs in association with the metabolic syndrome are shown in Table 2. After controlling for age, gender, race, field center, education, cigarette smoking, and alcohol consumption status, participants with the metabolic syndrome were more likely to have retinopathy, arteriovenous nicking, focal arteriolar narrowing, generalized retinal arteriolar narrowing, and venular dilatation than those without the syndrome. The pattern of association was not substantially different, excluding people with diabetes, hypertension, or both diabetes and hypertension, with the exception that the association with retinopathy was no longer significant in those without diabetes or hypertension.

Figure 1 shows that, after adjustment, the prevalence of each retinal microvascular sign was higher with the increasing number of syndrome components. For example, in the total population, the prevalence of retinopathy increased from 5.3% (no component) to 14.4% (five components) and in people without diabetes or hypertension, the prevalence increased from 4.6% (no component) to 10.4% (five components).

Finally, we examined the independent association between specific components of the metabolic syndrome and retinal microvascular signs (Table 3). Each model includes the five syndrome components, and age, gender, race, field center, education, smoking, and alcohol consumption as independent variables. There were independent association between high blood pressure and high glucose for retinopathy; between larger waist circumference, low HDL-cholesterol, and high blood pressure for arteriovenous nicking; between larger waist circumference and high blood pressure for focal arteriolar narrowing; between larger waist circumference, lower triglyceride, higher blood pressure, and lower glucose for generalized arteriolar narrowing; and between larger waist circumference, higher triglyceride, and higher glucose for generalized venular dilatation.

DISCUSSION

The National Cholesterol Education Program's ATP III report identified the metabolic syndrome as a specific entity deserving more clinical attention.[21] People with the syndrome have been shown to be at increased risk of developing cardiovascular disease, beyond the risk associated with individual components of the syndrome alone.[21] Our previous analyses focused on the association of hypertension, diabetes, and other cardiovascular risk factors with retinal microvascular signs.[14-16] The present study extended these investigations by addressing the relationship of the metabolic syndrome and retinal microvascular signs.

We showed that persons with the metabolic syndrome were significantly more likely to have retinopathy, arteriovenous nicking, focal arteriolar narrowing, smaller retinal arteriolar diameters, and larger retinal venular diameters, than

TABLE 2. Association of the Metabolic Syndrome and Retinal Microvascular Signs in the Total Population and in Participants without Diabetes and Hypertension

| Metabolic Syndrome | N | Retinopathy | | Arteriovenous Nicking | | Focal Arteriolar Narrowing | | Generalized Arteriolar Narrowing | | Generalized Venular Dilatation | |
		%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
All participants											
MS present	4223	8.8	1.68 (1.44, 1.96)	16.4	1.30 (1.16, 1.45)	17.2	1.24 (1.1, 1.38)	27.5	1.23 (1.12, 1.35)	27.4	1.30 (1.18, 1.48)
MS absent	7042	5.1	1.00	12.8	1.00	13.5	1.00	23.6	1.00	24.9	1.00
Participants without diabetes											
MS present	2928	5.6	1.22 (1.00, 1.49)	16.0	1.28 (1.13, 1.45)	17.8	1.31 (1.16, 1.48)	28.6	1.27 (1.15, 1.41)	25.6	1.24 (1.11, 1.38)
MS absent	6769	4.6	1.00	12.7	1.00	13.6	1.00	23.8	1.00	23.8	1.00
Participants without hypertension											
MS present	1599	6.3	1.46 (1.14, 1.86)	13.4	1.25 (1.05, 1.48)	12.9	1.26 (1.05, 1.51)	21.4	1.10 (0.96, 1.28)	27.9	1.34 (1.17, 1.54)
MS absent	5160	4.3	1.00	11.0	1.00	10.1	1.00	19.7	1.00	23.3	1.00
Participants without diabetes or hypertension											
MS present	1191	4.2	1.05 (0.76, 1.45)	13.1	1.23 (1.01, 1.49)	14.1	1.40 (1.16, 1.70)	23.0	1.19 (1.01, 1.39)	25.8	1.25 (1.07, 1.46)
MS absent	4963	4.0	1.00	10.9	1.00	10.1	1.00	20.0	1.00	23.3	1.00

MS, metabolic syndrome.
* Adjusted for age, gender, race, field center, education, cigarette smoking, and alcohol consumption status.
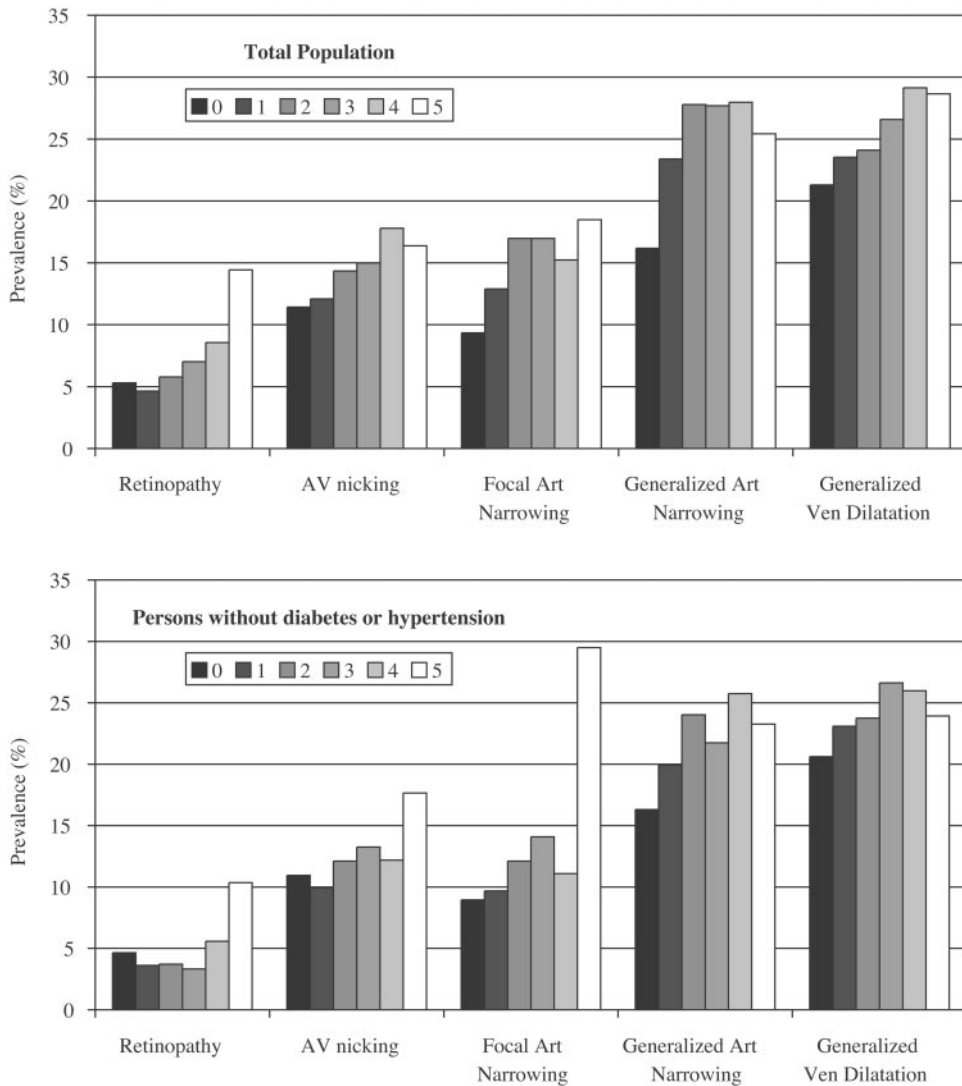
FIGURE 1. Prevalence of retinal microvascular signs according to number of metabolic syndrome components (0–5), adjusted for age, gender, race, center, education, smoking, and alcohol consumption. Total population (*top*) and participants without diabetes or hypertension (*bottom*).

people without the syndrome, independent of age, gender, race, education, cigarette smoking, and alcohol consumption. With the exception of retinopathy, most associations were significant even in people without diabetes or hypertension, suggesting that factors other than hyperglycemia and high blood pressure (i.e., dyslipidemia, obesity, and inflammation) may explain the occurrence of these retinal lesions. The association of the metabolic syndrome with retinal microvascular

abnormalities may in part reflect the impact of these individual syndrome components on the presence of these retinal lesions.

Although this study was cross-sectional, the findings provide support to both experimental and clinical studies that have suggested that microvascular disease may be an integral component of the metabolic syndrome.[5–7] For example, experimental studies have shown that Zucker rats, which exhibit obesity, diabetes, and other elements of the metabolic syn-

TABLE 3. Association of Individual Metabolic Syndrome Components and Retinal Microvascular Signs

Metabolic Syndrome Components (Independent Variables)		Retinopathy OR (95% CI)*	Arteriovenous Nicking OR (95% CI)*	Focal Arteriolar Narrowing OR (95% CI)*	Generalized Arteriolar Narrowing OR (95% CI)*	Generalized Venular Dilatation OR (95% CI)*
Large waist	Present vs. absent	0.99 (0.77, 1.10)	1.28 (1.13, 1.44)	1.14 (1.00, 1.29)	1.16 (1.05, 1.29)	1.14 (1.03, 1.27)
High triglyceride	Present vs. absent	1.03 (0.87, 1.22)	0.90 (0.79, 1.01)	0.97 (0.86, 1.10)	0.83 (0.74, 0.92)	1.13 (1.02, 1.26)
Low HDL cholesterol	Present vs. absent	1.01 (0.85, 1.21)	1.17 (1.04, 1.33)	0.91 (0.81, 1.04)	1.05 (0.95, 1.17)	1.05 (0.94, 1.17)
High blood pressure	Present vs. absent	1.31 (1.10, 1.55)	1.37 (1.22, 1.54)	2.34 (2.07, 2.64)	2.11 (1.92, 2.33)	0.94 (0.85, 1.03)
High glucose	Present vs. absent	2.41 (2.05, 2.84)	0.99 (0.88, 1.13)	0.88 (0.77, 1.00)	0.89 (0.79, 0.99)	1.31 (1.18, 1.46)

* Each logistic regression model includes the retinal microvascular sign as the dependent variable and the five metabolic syndrome components (large waist, high triglyceride, low HDL cholesterol, high blood pressure, high glucose, as defined in Table 1), age, gender, race, field center, education, cigarette smoking, and alcohol consumption as independent variables.

drome, have narrowed skeletal muscle arterioles and impaired arteriolar reactivity to vasoactive stimuli.[23] Clinical studies have also documented alterations in the structure and function of the microcirculation in skin and skeletal muscles of persons with the metabolic syndrome,[5–7] or with specific components of the syndrome, including persons with type 2 diabetes,[24] abdominal obesity,[25] dyslipidemia, and hypertension.[7–9,26] Studies by Serne et al.[6,7] and others[5] show that patients with insulin resistance have reduced capillary density and impaired capillary recruitment and acetylcholine-mediated vasodilatation in their skin. Most of these studies, however, have been conducted on small numbers of highly selected individuals. The present study provides evidence linking the metabolic syndrome to retinal microvascular disease in a large general population. However, it is difficult to determine from cross-sectional findings whether microvascular processes (evident in the retina) are causally related to development of the metabolic syndrome, or whether the metabolic syndrome is associated with risk of retinal microvascular signs.

A more detailed examination of the association of the metabolic syndrome with specific retinal microvascular abnormality reveals additional information. Retinopathy, defined to include microaneurysms, retinal hemorrhages, and soft exudates, is a well-known complication of diabetes and hypertension and is pathologically associated with a breakdown of the blood–retinal barrier.[13] In our study, after adjustment for other syndrome components, higher blood pressure, and fasting glucose, but not larger waist circumference, higher triglyceride, and lower HDL-cholesterol were associated with retinopathy (Table 3). In addition, the association with retinopathy was no longer present in people without diabetes or hypertension (Table 2). These observations further support the concept that retinopathy is related to factors associated with hyperglycemia and elevated blood pressure.

In contrast to retinopathy, the independent associations of the metabolic syndrome with other retinal microvascular signs are more difficult to understand, partly because less is known regarding the pathogenesis of these retinal characteristics. Generalized retinal arteriolar narrowing is believed to result from a combination of "active" vasomotor constriction and, with increasing age, more generalized arteriolosclerosis (e.g., intimal thickening, medial hyperplasia, hyalinization, and sclerosis).[13] Focal arteriolar narrowing may represent segmental areas of arteriolar constriction and sclerosis, whereas arteriovenous nicking may represent evidence of arteriolosclerotic processes at the crossing of arterioles and venules.[13] All three arteriolar abnormalities are strongly related to hypertension.[18,22] In the ARIC study, independent of blood pressure, generalized arteriolar narrowing was also related to systemic markers of inflammation, whereas arteriovenous nicking was related to markers of inflammation and endothelial dysfunction.[14] In people with diabetes, wider retinal venular diameters have been suggested to reflect hyperperfusion resulting from hyperglycemia and lactic acidosis from retinal hypoxia.[27,28] In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, retinal venular dilatation was associated with increased duration of diabetes, elevated glycosylated hemoglobin level and higher body mass index,[29] and predicted the incidence of gross proteinuria and renal dysfunction.[30] Taken together, these findings suggest that microvascular processes associated with inflammation, endothelial dysfunction, alterations in perfusion, and other processes may explain the occurrence of these retinal signs in persons with the metabolic syndrome.

In analyses of the associations with specific metabolic components, there were some unexpected findings (Table 3). For example, lower triglyceride and glucose levels were associated with generalized arteriolar narrowing, findings for which we have no explanation. A possible explanation is that, given the

common causality of syndrome elements, simultaneous modeling of all the elements as independent variables may have produced overadjustment.

The strengths of the present study include a large sample size with participants drawn from the general population rather than a clinic, the objective documentation of retinal microvascular signs, and the standardized identification of metabolic syndrome components. Study limitations should also be highlighted. First, these associations are cross-sectional, and prospective data are needed to evaluate the causal link between the metabolic syndrome and the risk of retinopathy and other microvascular changes. Second, our study used a 45° nonstereoscopic fundus photograph taken through nonpharmacologically dilated pupils to determine the presence of retinal microvascular signs. These signs are less likely to be detected than in grading of 30° stereoscopic fundus photographs taken through dilated pupils. In addition, because only one eye was photographed in the ARIC study, a proportion of people with retinal microvascular signs may be missed because of the possibility of the involved eye's not being photographed. However, we have no reasons to believe these would substantially bias the associations reported herein.

In conclusion, we documented cross-sectional associations of the metabolic syndrome with retinal microvascular signs. To a certain extent, these associations are manifestations of the individual effects of various components of the metabolic syndrome—in particular, hypertension and diabetes—on the presence of retinal microvascular abnormalities. Prospective studies will be useful in further determinig whether the metabolic syndrome is associated with an increased risk of retinopathy and other retinal microvascular abnormalities, beyond the effects of individual components.

References

1. Schmidt MI, Duncan BB, Watson RL, Sharrett AR, Brancati FL, Heiss G. A metabolic syndrome in whites and African-Americans: The Atherosclerosis Risk in Communities baseline study. *Diabetes Care*. 1996;19:414–418.

2. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356–359.

3. Moller DE, Flier JS. Insulin resistance: mechanisms, syndromes, and implications. *N Engl J Med*. 1991;325:938–948.

4. Golden SH, Folsom AR, Coresh J, Sharrett AR, Szklo M, Brancati F. Risk factor groupings related to insulin resistance and their synergistic effects on subclinical atherosclerosis: the Atherosclerosis Risk in Communities Study. *Diabetes*. 2002;51:3069–3076.

5. Irving RJ, Walker BR, Noon JP, Watt GC, Webb DJ, Shore AC. Microvascular correlates of blood pressure, plasma glucose, and insulin resistance in health. *Cardiovasc Res*. 2002;53:271–276.

6. Serne EH, Ijzerman RG, de Jongh RT, Stehouwer CD. Blood pressure and insulin resistance: role for microvascular function? *Cardiovasc Res*. 2002;55:418–419.

7. Serne EH, Stehouwer CD, ter Maaten JC, et al. Microvascular function relates to insulin sensitivity and blood pressure in normal subjects. *Circulation*. 1999;99:896–902.

8. Festa A, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation*. 2000;102:42–47.

9. Schmidt MI, Duncan BB, Sharrett AR, et al. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. *Lancet*. 1999;353: 1649–1652.

10. Duncan BB, Schmidt MI, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes.* 2003;52:1799–1805.

11. Balletshofer BM, Rittig K, Enderle Volk A, et al. Endothelial dysfunction is detectable in young normotensive first-degree relatives of subjects with type 2 diabetes in association with insulin resistance. *Circulation.* 2000;101:1780–1784.

12. Duncan BB, Schmidt MI, Chambless LE, Folsom AR, Carpenter M, Heiss G. Fibrinogen, other putative markers of inflammation, and weight gain in middle-aged adults–the ARIC study. *Obes Res.* 2000;8:279–286.

13. Wong TY, Klein R, Klein BEK, Tielsch JM, Hubbard LD, Nieto FJ. Retinal microvascular abnormalities and their relations with hypertension, cardiovascular diseases and mortality. *Surv Ophthalmol.* 2001;46:59–80.

14. Klein R, Sharrett AR, Klein BE, et al. Are retinal arteriolar abnormalities related to atherosclerosis? The Atherosclerosis Risk in Communities Study. *Arterioscler Thromb Vasc Biol.* 2000;20:1644–1650.

15. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of diabetes in middle-aged persons. *JAMA.* 2002;287:2528–2533.

16. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar diameters and risk of hypertension. *Ann Intern Med.* 2004;140:248–255.

17. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: Design and objectives. *Am J Epidemiol.* 1989;129:687–702.

18. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities (ARIC) Study. *Ophthalmology.* 1999;106:2269–2280.

19. NHLBI. Atherosclerosis Risk in Communities Study. *Operations Manual No. 2, Cohort Component Procedures.* Version 2.0. Chapel Hill, NC: ARIC Coordinating Center, School of Public Health, University of North Carolina; 1988.

20. Papp AC, Hatzakis H, Bracey A, Wu KK. ARIC hemostasis study. I: Development of blood collection and processing system suitable for multicenter hemostatic studies. *Thromb Haemost.* 1989;61:15–19.

21. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486–2497.

22. Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol.* 2002;86:1007–1013.

23. Frisbee JC. Remodeling of the skeletal muscle microcirculation increases resistance to perfusion in obese zucker rats. *Am J Physiol.* 2003;285:H104–H111.

24. Laakso M, Edelman SV, Brechtel G, Baron AD. Impaired insulin-mediated skeletal muscle blood flow in patients with NIDDM. *Diabetes.* 1992;41:1076–1083.

25. Laakso M, Edelman SV, Brechtel G, Baron AD. Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man: a novel mechanism for insulin resistance. *J Clin Invest.* 1990;85:1844–1852.

26. Caballero AE, Arora S, Saouaf R, et al. Microvascular and macrovascular reactivity is reduced in subjects at risk for type 2 diabetes. *Diabetes.* 1999;48:1856–1862.

27. Skovborg F, Nielsen AV, Lauritzen E, Hartkopp O. Diameters of the retinal vessels in diabetic and normal subjects. *Diabetes.* 1969;18:292–298.

28. Grunwald JE, DuPont J, Riva CE. Retinal haemodynamics in patients with early diabetes mellitus. *Br J Ophthalmol.* 1996;80:327–331.

29. Klein R, Klein BEK, Moss S, Wong TY, Hubbard LD, Cruickshanks KJ. Retinal vascular abnormalities in persons with Type 1 diabetes. The Wisconsin Epidemiological Study of Diabetic Retinopathy. *Ophthalmology.* 2003;110:2118–125.

30. Wong TY, Shankar A, Klein R, Klein BE. Retinal vessel diameters and the incidence of gross proteinuria and renal insufficiency in people with type 1 diabetes. *Diabetes.* 2004;53:179–184.