Published in final edited form as:

Ophthalmology. 2011 April ; 118(4): 656–662. doi:10.1016/j.ophtha.2010.08.007.

Retinopathy Signs in People without Diabetes: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—To describe the prevalence of retinopathy and associations with cardiovascular risk factors in persons without diabetes in four racial/ethnic groups (white, black, Hispanic and Chinese).

Design—Population-based cross-sectional study.

Participants—6,176 subjects aged 45 to 84 years without diabetes, selected from six United States communities.

Methods—Fundus images were taken using 45° digital camera through dark adapted pupils and were graded for retinopathy as defined by the Early Treatment Diabetic Retinopathy Study severity scale: microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading and new vessels.

Main Outcome Measures—Retinopathy and the association with cardiovascular risk factors

Results—Prevalence rates of retinopathy in persons without diabetes were 12.5% overall, varying from 11.9% (white), 13.9% (black), 12.6% (Hispanic) to 17.2% (Chinese). Hypertension was strongly associated with retinopathy (odds ratio [OR] of 1.47, 95% confidence interval [CI] 1.23, 1.75). After adjusting for age, sex, race and other parameters, smoking (OR 1.50, 95% CI 1.09, 2.06) and increased internal carotid intima media thickness (OR 1.22, 95% CI 1.05, 1.41)

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A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>.

The authors have no conflicts of interest related to the article.

This article contains online-only material. The following should appear online only: Tables 1, 4 and 5

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were associated with retinopathy. A range of serum inflammatory factors were examined but none were found to be statistically significant.

Conclusions—Retinopathy in persons without diabetes is common, varies with race/ethnicity and associated with cardiovascular risk factors, including hypertension, smoking and carotid artery intima media thickness.

There is increasing evidence from population-based studies that isolated signs of retinopathy, such as microaneurysms and retinal hemorrhages, are common in people without diabetes.¹⁻¹⁰ Previous studies that utilized a clinical ophthalmological examination as the method of retinopathy detection in non-diabetic populations reported low prevalence rates of retinopathy lesions, ranging from 0.4% to 2.3%.¹¹⁻¹³ More recent population data using retinal photographs to document retinopathy have found the prevalence rates ranging from 4.8% to 9.8% (Figure 1),²⁻¹⁰ which is higher than it was previously considered.

Risk factors associated with retinopathy in non-diabetic persons remain uncertain. Numerous studies have confirmed a consistent and strong association between retinopathy and blood pressure.^{4-7,14,15} For example, the Atherosclerosis Risk In Communities Study (ARIC) found that for every 10-mmHg increase in mean arterial blood pressure the odds ratio for the presence of retinopathy was 1.25 (95% confidence interval, 1.15-1.37).⁹ Other associations, e.g., with increasing age^{4,10}; hyperglycemia^{6,10}; dyslipidemia^{8,16}, higher body-mass-index⁸ have been less consistently reported. Recent data from the Hoorn study have further demonstrated associations of systemic inflammatory markers with retinopathy in people without diabetes.¹⁷

The clinical significance of retinopathy is also unknown. In persons without diabetes, retinopathy has been cross-sectionally associated with carotid artery plaques^{7,16}, and increased intima-media thickness of the common and internal carotid arteries.⁷ Studies have further reported independent associations between retinopathy in non-diabetic persons and risk of stroke¹⁸, nephropathy¹⁹⁻²⁰, and congestive heart failure.²¹ It has been further suggested that retinopathy may be a pre-clinical marker of diabetes or hypertension.²² However, population-based data have not been consistent. Data from the Blue Mountains Eye Study showed no relationship between retinopathy and 5-year risk of diabetes²³ while in the ARIC study, retinopathy signs were not significantly associated with 3-year risk of diabetes except among individuals with a family history of diabetes.³ The Beaver Dam Eye Study found that retinopathy in non-diabetic individuals was associated with the 15-year incidence of hypertension and, in younger individuals less than 65 years of age, associated with incident diabetes.²⁴ These observations suggest that the risk factors and processes associated with retinopathy in persons without diabetes may carry prognostic information in terms of clinical significant outcomes, and thus warrant further study.

Finally, there are few data describing retinopathy in non-white populations.^{15,25} A higher prevalence of retinopathy signs has been reported among African American persons than among whites, a difference that is explained in large part by higher blood pressure among African-Americans.^{15,25} However, there are no prevalence data on non-diabetic retinopathy in Chinese or Hispanics.

The purpose of this article is to describe retinopathy in persons without diabetes in a large multi-ethnic population, to compare the frequency of these signs by racial/ ethnic groups (whites, blacks, Hispanics and Chinese), and assess risk factors, including novel risk factors (markers of inflammation, coagulation and fibrinolysis), and to determine relationship with subclinical cardiovascular disease (e.g., coronary calcium scores)

Methods

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of men and women 45 to 84 years of age initially free of clinical evidence of cardiovascular disease and living in six United States communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan, New York; and St Paul, Minnesota). The study objective of MESA was to identify risk factors for subclinical and clinical cardiovascular disease. Methods of the study have been reported in detail elsewhere.²⁶ In brief, 6814 subjects participated in the baseline examination (July 2000 to August 2002) and were recruited from the 6 field centers above. Each site planned to examine about 1100 eligible participants, equally divided between men and women, according to site-specified race/ethnicity proportions. Each field site recruited from locally available sources, which included lists of residents, lists of dwellings, and telephone exchanges. In the last few months of the recruitment period, supplemental sources (i.e., lists of Medicare beneficiaries from the Centers for Medicare and Medicaid Services and referrals by participants) were used to ensure adequate numbers of minorities and elderly subjects. Participation rates among those screened were approximately 70% for whites, 61% for blacks, 59% for Hispanics, and 48% for Chinese.

Of these, 6176 (90.6%) returned for the second examination and had retinal photographs taken (August 2002 to January 2004). Of those with gradable retinal photographs, 5173 participants without diabetes (defined as fasting glucose <7.0 mmol/L or ≤ 125 mg/dl or not using insulin or oral hypoglycemic medications) and free from any retinal vein occlusion were included in the current study.

Tenets of the Declaration of Helsinki were followed, and institutional review board approval was granted at each study site. Written informed consent was obtained from each participant.

Retinal Photography and Assessment

At the second examination, fundus photography was completed following a standardized protocol.²⁷⁻³⁰ A 45-degree non-mydiatic digital camera (Canon, Lake Success, New York, USA) was utilized with participants seated in a dark room. Two photographic fields were taken of each eye; the first centered on the optic disc (field 1), and the second centered on the fovea (field 2). Standard software was used for image acquisition and archiving (Eye QSL; Digital Healthcare Inc, Cambridge, England). Images were then sent from the field centers to the University of Wisconsin, Madison, for assessment of retinopathy and other retinal diseases. Photographs were evaluated in semiquantitative fashion by a grader with a custom written Microsoft Access database, EyeQ Lite (an image-processing database for storage, retrieval, and manipulation of digital images), and a dual-monitor computer display.

Overall, there were ten graders plus RK (author) involved in the grading process. In summary, the grading system involved four levels of grading, including preliminary grading, detail grading, edit grading and finally adjudication by RK. All graders were blinded to ethnicity and did not have access to medical records. Medical records were only accessed by RK if adjudication was required. The inter- and intra-grader agreement was very good. When looking at retinopathy severity as 4 levels the Kappa ranged from 0.7 to 1.0 for all graders.

Retinopathy was considered to be present if any characteristic lesion as defined by the Early Treatment Diabetic Retinopathy Study³¹ severity scale was present: microaneurysms (MAs), hemorrhages, cotton wool spots (CWSs), intraretinal microvascular abnormalities (IRMAs),

hard exudates (HEs), venous beading, and new vessels. For each eye, a retinopathy severity score was assigned as follows according to a scale modified from the Arlie House Classification system.³²

Assessment and Definitions of Risk Factors

All participants underwent standardized interviews, clinical examinations, imaging and laboratory investigations for the assessment of systemic risk factors and features of subclinical cardiovascular disease (CVD), as detailed elsewhere.^{26-29,33} Standardized questionnaires were used to obtain information about medical history, education level, marital status, health insurance status, occupation, annual house-hold income, cigarette smoking and alcohol consumption and antihypertensive and antidiabetic medications. Smoking was defined as current, former or never. Data obtained from the baseline examination included:

- Traditional risk factors and general assessment: Hypertension, blood pressure, fasting blood glucose, lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride), body mass index, cigarette smoking, alcohol consumption, creatinine, urinary albumin:creatinine ratio
- Markers of subclinical CVD: Agatston calcium score, internal and common carotid intima media thickness (internal and common carotid IMT), and ankle brachial index
- Cardiac parameters: Left ventricular (LV) mass-volume ratio, LV mass function, LV mass index and aortic distensibility. LV parameters were obtained by MRI
- Markers of inflammation/ endothelial dysfunction: plasma fibrinogen, plasmin-antiplasmin complex (PAP), interleukin-6, D-Dimer, C-reactive protein, factor VIII, total homocysteine
- Sociodemographic data

Resting blood pressure was measured three times with participants in the seated position (Dinamap model Pro 100 automated oscillometric sphygmomanometer; Critikon, Tampa, Florida, USA). The average of the last two measurements was used in analysis.

Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive medications.³⁵ Height and weight were measured with participants wearing only light clothing without shoes. Body mass index (BMI) was classified as normal or overweight (grade 1, 2 or 3) according to the World Health Organization definitions. Fasting blood samples were drawn and analyzed for blood parameters using standardized protocols^{33,36}. Normal fasting blood glucose was defined as fasting glucose ≤ 5.5 mmol/L (99 mg/dL) and impaired fasting blood glucose was defined as fasting glucose 5.6-6.9 mmol/L (100-125 mg/dL). A comprehensive questionnaire was administered to attain information about education level, medical and ocular history, cigarette smoking, alcohol consumption, and medication use.

Blood samples were assayed for putative biochemical risk factors, including total and high-density lipoprotein (HDL) plasma cholesterol, plasma triglycerides, and serum glucose levels measured after a 12-hour fast. Analyses were performed at a central site at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, Minnesota, USA). Low-density lipoprotein (LDL) cholesterol was calculated with the Friedewald equation.

Statistical Analysis

Independent sample *t*-tests or Mann-Whitney U test depending on the distribution of data, were used to compare the characteristics of individuals with and without retinopathy in the population with normal and impaired fasting glucose. Analysis of Variance (ANOVA) or Kruskal Wallis tests was used to compare the characteristics of four different races. Chi-square test was used to compare the categorical characteristics.

We constructed logistic regression models to determine the odds ratio (OR) and 95% confidence intervals (CI) for the primary outcome variable (non-diabetic retinopathy) in association with putative risk factors (e.g., presence versus absence of hypertension, or per standard deviation (SD) change of blood pressure). This was initially performed for the total cohort with normal and impaired fasting glucose (n=5173) and then for the four racial/ethnic groups separately. In Model 1 adjustments were made for age, sex, race and center (and age, sex and center for race/ethnicity-specific models). Further adjustment for Model 2 included mean arterial blood pressure (except for mean arterial or pulse pressure), serum glucose (except for glucose or glycaemic status), total cholesterol, triglycerides, BMI, smoking and CRP.

In supplementary analysis, we examined the associations in subgroup analyses stratified by hypertension status. Interaction terms for sex and smoking status were also tested. All analyses were performed in SPSS version 12.0.1 (SPSS Inc, Chicago, III).

Results

Participant characteristics comparing four ethnic groups, including White, Black, Hispanic and Chinese are shown in Table 1 (available at <http://aaajournal.org>). Hypertension was found in 57.7% of Black participants compared to 40.9% White persons, 40.4% Hispanics and 36.3% Chinese. Blacks had the highest proportion of smokers and impaired fasting glucose and the highest mean BMI, systolic and diastolic blood pressure, pulse pressure and LV end-diastolic index. Whites had the highest proportion of alcohol intake.

Participant characteristics comparing risk factors in those with and without retinopathy in non-diabetic person are listed in Table 2. There were significant differences between participants with and without retinopathy; participants with retinopathy were much more likely to have hypertension or higher blood pressure ($p<0.001$), impaired fasting glucose ($p=0.02$), lower HDL cholesterol levels ($p=0.03$) and a higher total Agatston calcium score ($p=0.006$). Overall 645 from a total of 5173 participants without diabetes were found to have retinopathy (12.5% 95% CI 11.6, 13.4). The majority had lower level retinopathy according to the Arlie House Classification with only 35 persons having $\geq$ level 20 cut off.

The relationship of sex, and race/ethnicity to retinopathy is presented in Figure 2. The prevalence of retinopathy is highest in Chinese (17.2% 95% CI 14.2, 20.3) overall and by sex. Other ethnic groups revealed comparable rates of retinopathy. The prevalence of retinopathy in white persons was 11.9% (95% CI 11.6, 13.4) and in Black and Hispanic participants it was 13.9% (95% CI 12.1, 15.8) and 12.6% (95% CI 10.6, 14.6) respectively. Rates among males were higher than among females, except for Blacks where the reverse was observed.

Table 3 shows the associations of risk factors with retinopathy in persons without diabetes. Model 1 shows results adjusted for age, sex, race and center and compares characteristics. However, in model 2 after additional adjustments were made for mean arterial blood pressure, cholesterol, triglycerides, BMI, smoking and CRP, the relations were attenuated. Presence of hypertension remained strongly associated with retinopathy in both models,

with an odds ratio of 1.47 (1.23, 1.75) for model 1. Age was not found to be associated with retinopathy in either model. Systolic, diastolic, and mean arterial blood pressure and pulse pressure were strongly associated with retinopathy in both models. Common carotid IMT was no longer statistically significant in model 2. Several inflammatory risk factors, such as interleukin-6, interleukin-2, tumor necrosis factor and other markers of subclinical CVD such as total Agatston calcium score were not associated with retinopathy.

Table 4 (available at <http://aaojournal.org>) presents the associations of risk factors for retinopathy, in persons without diabetes for each of the racial-ethnic groups separately. After adjusting for age, sex, enrolling center, mean arterial blood pressure, serum glucose, total cholesterol, triglycerides, BMI, smoking and CRP, the presence of hypertension was found to be strongly associated with retinopathy in Blacks (OR 1.78 95% CI 1.22, 2.60 $p=0.003$). Mean arterial blood pressure was associated with retinopathy in all racial/ethnic groups except the Chinese. Internal carotid IMT was associated with retinopathy in Whites and Hispanics. Several inflammatory factors were examined but none were found to be statistically significant.

Table 5 (available at <http://aaojournal.org>) presents the associations of risk factors with retinopathy in persons without diabetes and hypertension in models 1 and 2, and without impaired fasting glucose, diabetes and hypertension in model 3. After adjusting for age, sex, race and enrolling center, smoking, blood pressure parameters and internal carotid artery IMT were found associated with retinopathy (Models 2 and 3).

Discussion

The MESA has provided an opportunity to examine the frequency of retinopathy and its relationship to a range of cardiovascular risk factors as well as biomarkers of inflammation and endothelial cell dysfunction in a large, multiethnic cohort free of clinical cardiovascular disease at the baseline examination. This study has provided new data on the prevalence of non-diabetic retinopathy and the associated risk factors in four racial/ethnic groups. The overall prevalence of non-diabetic retinopathy in the MESA was approximately 12.5% with the highest frequency in the Chinese (17.2%), Figure 2. The prevalence of retinopathy in persons without diabetes among MESA participants is even higher than the prevalence found in other population-based studies including, BMES⁵, BDES,⁴ Hoorn,⁸ CHS,⁷ and Funagata¹⁰. These population-based data confirm that retinopathy is relatively frequent in adults without diabetes, with prevalence rates that vary amongst different ethnic/racial groups. The higher prevalence rate found in MESA compared to the other population-based studies can be partly explained by methodological differences as well as differences in population characteristics such as ethnicity.

Hypertension was strongly associated with retinopathy even after adjusting for age, sex, race and center. This strong association has been reported in other population-based studies.^{4-7,14,15} Additionally, in the MESA, the strongest association between hypertension and retinopathy was present in Blacks, with weaker non-statistically significant association in other racial/ethnic groups. Systolic and mean arterial blood pressure were associated with retinopathy even after excluding persons with hypertension (Table 5, available at <http://aaojournal.org>). This suggests that blood pressure at levels below commonly used criteria to define hypertension may have significant impact on the vasculature, as manifested by retinopathy signs.

It is possible that retinopathy signs are markers of early hypertensive damage, evident in associations seen with blood pressure even in those without hypertension. It is not known if these signs are markers of longer-term blood pressure damage although there are data that

suggests they are.²⁴ Recent longitudinal data describe most lesions as transient (around 65% of lesions at baseline disappeared) and found current smoking to be associated with an increased risk of persistent retinopathy lesions (Wang JJ et al. Long-Term Incidence of Isolated Retinopathy Lesions in Older Persons without Diabetes: the Blue Mountains Eye Study. Paper presented at: ARVO, May 3rd, 2010, Fort Lauderdale). The association with smoking was also found in our study and demonstrates its impact on the microcirculation.

Other factors, such as carotid artery IMT and smoking were also found to be associated with retinopathy in the MESA. Carotid artery disease (ocular ischemic syndrome) is well described as a causative factor in the development of more severe retinopathy.³⁷ Recent epidemiological data including our own demonstrate an association of retinopathy with carotid artery IMT.⁷ This association was also present after excluding persons with hypertension in our study. In addition, a positive association was demonstrated in our study between retinopathy and impaired fasting glucose and serum glucose but the association was attenuated after further adjustments in model 2. In contrast the Rotterdam⁶ and Funagata¹⁰ studies both found a positive association with serum glucose levels.

To our knowledge, the MESA provides the first data on associations with retinopathy in persons without diabetes for four racial/ethnic groups. In our Black population, blood pressure/hypertension was a significant risk factor. Interestingly, a large population-based study found the prevalence of hypertensive retinopathy was two times higher in African Americans compared to White persons, and the excess prevalence was explained by severity of blood pressure and hypertension, consistent with findings from the MESA cohort.¹⁵ There was a trend toward statistical significance with blood pressure/hypertension as a risk factor for retinopathy in our Chinese population, however, smaller numbers possibly explains the lack of statistical significance. Internal carotid IMT was a strong risk factor in our White and Hispanic populations and total Agatston calcium scores was an additional risk factor in the latter group. A report in a Japanese population did not report hypertension as a risk factor for retinopathy, but again, smaller numbers resulting in wide confidence intervals could provide an explanation.¹⁰

Strength of this study includes the high proportion of bilateral gradable digital fundus photographs from a large multi-ethnic population. Limitations to this study include its cross sectional nature, the variable participation rate amongst the ethnic groups,³³ the studies exploratory nature based on multiple comparisons and the possibility of selection bias. Hence, some of the significant associations identified should be viewed as preliminary and hypothesis generating. Also, the exclusion of persons with symptomatic disease at the baseline examination could have operated differentially across ethnic groups. In addition, we excluded from our analysis obvious cases of other retinal conditions such as branch retinal vein occlusions but some of the retinal lesions we classified as retinopathy might be related to conditions not specified in this study. However, these conditions would be rare. Relatively small sample size, especially within the specific racial/ethnic groups may have also limited our power to examine some associations.

This study may have important clinical and public health implications. The high prevalence of retinopathy in all ethnic groups, but especially the Chinese (17.2%) is concerning given previous findings associating retinopathy with risk of cerebrovascular disease and mortality.^{18,38} Further examination of the associated risk factors leading to such a high prevalence, particularly in Chinese is warranted. In addition, the higher prevalence of hypertension in our Black population is concerning.^{39,40} In conclusion, this study has provided data showing racial/ ethnic differences in the prevalence of retinopathy among persons without diabetes, and its relation to cardiovascular risk factors, such as hypertension, thickened carotid IMT, in nondiabetic persons. Awareness of the risk factors for non-diabetic retinopathy amongst

eye care practitioners and physicians is required, so that further ocular and systemic examinations and investigations may be appropriately directed.

Acknowledgments

Funding: This research was supported by contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute.” and “Additional support was provided by National Institutes of Health grants HL69979-03 (Klein R and Wong TY). The funding agencies had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript

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Figure 1. Prevalence of retinopathy in non-diabetic populations

AusDiab: Australian Diabetes, Obesity and Lifestyle Study (year began: 1999-2000, sample size 2,177) ⁽²⁾; ARIC: Atherosclerosis Risk in Communities study (year began: 1987-1990, sample size 10,954) ⁽⁹⁾; BDES: Beaver Dam Eye Study (year began: 1988-1990, sample size 4,926) ⁽⁴⁾; BMES: Blue Mountain Eye Study (year began: 1992-1994, sample size 3,654) ⁽⁵⁾; CHS: Cardiovascular Health Study (year began: 1989-1990, sample size 2,050) ⁽⁷⁾; Hoorn (year began: 1989-1992, sample size 626) ⁽⁸⁾; Rotterdam (year began: 1990-1993, sample size 6,191) ⁽⁶⁾; Funagata (year began: 2000-2002, sample size 1,481) ⁽¹⁰⁾

Figure 2. Prevalence of Retinopathy in Persons without Diabetes, by Sex and Racial/Ethnic group, in the Multi-Ethnic Study of Atherosclerosis

Table 1

Characteristics of the Ethnic groups in the Multi-Ethnic Study of Atherosclerosis.

Characteristics	White N=2209	Black N=1322	Hispanic N=1039	Chinese N=603	P*
Sex, Male	1045 (47.3)	584 (44.2)	498 (47.9)	297 (49.3)	0.12
Hypertension	903 (40.9)	763 (57.7)	420 (40.4)	219 (36.3)	<0.001
Smoking (current)	244 (11.1)	216 (16.4)	112 (10.8)	29 (4.8)	<0.001
Alcohol (current)	1508 (68.4)	612 (46.6)	458 (44.2)	197 (32.7)	<0.001
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age, years	63.8 (10.1)	63.0 (10.0)	62.0 (10.2)	62.7 (10.1)	<0.001
BMI, kg/m ²	27.5 (4.9)	29.7 (5.8)	29.0 (4.9)	23.9 (3.3)	<0.001
Systolic blood pressure, mmHg	120 (19)	129 (21)	124 (22)	119 (20)	<0.001
Diastolic blood pressure, mmHg	68.8 (9.6)	73.6 (10.1)	70.5 (10.1)	69.3 (9.9)	<0.001
Mean arterial blood pressure, mmHg	85.9 (11.3)	92.0 (12.1)	88.3 (12.5)	86.0 (12.1)	<0.001
Pulse pressure	51.3 (15.3)	55.3 (16.6)	53.6 (17.6)	50.1 (15.9)	<0.001
Glucose, mg/dL	95.7 (9.9)	96.9 (9.8)	97.8 (11.2)	97.8 (9.6)	<0.001
Common Carotid IMT (mm)	0.86 (0.20)	0.89 (0.19)	0.84 (0.18)	0.81 (0.16)	<0.001
LV end-diastolic mass index	75.3 (15.0)	80.7 (17.8)	79.6 (15.9)	73.5 (13.9)	<0.001
†Total Agatston Calcium score	4.5 (129)	0 (29)	0 (40)	0 (48)	<0.001
‡ Internal Carotid IMT (mm)	0.87 (0.61)	0.87 (0.56)	0.81 (0.45)	0.72 (0.27)	<0.001
‡ Hepatitis A antibodies	315 (349)	41 (326)	8.9 (10.3)	7.6 (6.5)	<0.001

* P-value based on chi-square (categorical), *t* test (quantitative and normal) or Kruskal Wallis test (quantitative and skewed), comparing characteristics of individuals with retinopathy and non-retinopathy of the population with normal and impaired fasting glucose. Results are shown as proportion, mean (SD) and ‡median (inter-quartile range).

Table abbreviations: BMI (body mass index), IMT (intima media thickness), LV (left ventricular), SD (standard deviation).

Table 2
Risk Factors for Retinopathy in Persons without Diabetes, the Multi-Ethnic Study of Atherosclerosis

	N	No Retinopathy n=4528	Retinopathy n=645	P
		%	%	
Sex, Male	5173	46.6	48.5	0.36
Alcohol consumption	5173	54.1	51.5	0.20
Current cigarette smoker	5173	11.5	12.8	0.35
Impaired fasting glucose (IFG)	5173	9.6	12.4	0.02
Hypertension	5173	43.4	52.4	<0.001
		Mean (SD)	Mean (SD)	
Age, years	5173	63.1 (10.2)	63.6 (9.9)	0.20
Body mass index (BMI), kg/m ²	5173	27.9 (5.2)	28.3 (5.4)	0.07
Waist hip ratio	5173	0.92 (0.08)	0.92 (0.08)	0.41
Systolic blood pressure, mmHg	5173	122 (20)	128 (22)	<0.001
Diastolic blood pressure, mmHg	5173	70.2 (9.9)	71.8 (10.7)	<0.001
Serum glucose, mg/dL	5168	96.5 (9.9)	97.9 (11.4)	0.001
HDL cholesterol, mg/dL	5169	53.0 (15.3)	51.6 (14.6)	0.03
‡Internal Carotid IMT (mm)	5051	0.83 (0.51)	0.87 (0.61)	0.09
Common Carotid IMT (mm)	5116	0.85 (0.19)	0.87 (0.20)	0.03
LV end-diastolic mass volume ratio	3915	1.14 (0.23)	1.17 (0.24)	0.01
LV end-diastolic mass index	3915	76.9 (15.9)	79.5 (16.1)	0.001
‡Total Agatston Calcium Score	5173	0.0 (62.1)	2.73 (90.4)	0.006
‡Tumor Necrosis Factor	774	1.25 (0.34)	1.31 (0.32)	0.05
‡Thrombin Activatable Fibrinolysis Inhibitor, µg/ml	774	4.36 (1.39)	4.63 (1.42)	0.03

* P-value based on chi-square (categorical), *t* test (quantitative and normal) or Mann-Whitney U test (quantitative and skewed), comparing characteristics of individuals with retinopathy and non-retinopathy of the population with normal and impaired fasting glucose. Results are shown as proportion, mean (SD) and †median (inter-quartile range).

Other characteristics tested but **not statistically significant** (p>0.05): Total cholesterol, triglycerides, plasma fibrinogen, plasmin-antiplasmin complex, interleukin-6, Factor VIII, ‡C-reactive protein (CRP), ‡D-Dimer, ‡Creatinine, ‡urinary albumin creatinine ratio, ‡total homocysteine, ‡ankle-brachial index, LV ejection fraction, ‡aortic distensibility, soluble intercellular adhesion molecule (sICAM), von Willebrand factor, E-selectin

Table abbreviations: HDL (high-density lipoprotein), IMT (intima media thickness), LV (left ventricular).

Table 3

Associations of Risk Factors with Retinopathy in Persons without Diabetes, the Multi-Ethnic Study of Atherosclerosis

Characteristics	Model 1*			Model 2†		
	OR (95% CI)	P		OR (95% CI)	P	
Impaired fasting glucose	1.31 (1.01, 1.69)	0.04		1.23 (0.95, 1.60)	0.12	
Hypertension, present vs. absent	1.47 (1.23, 1.75)	<0.001		1.40 (1.17, 1.69)	<0.001	
Age, per 10 years	1.06 (0.98, 1.15)	0.16		1.04 (0.96, 1.14)	0.34	
Systolic blood pressure, per SD (20.4 mmHg) increase	1.29 (1.18, 1.41)	<0.001		1.26 (1.15, 1.37)	<0.001	
Diastolic blood pressure, per SD (10.0 mmHg) increase	1.18 (1.08, 1.28)	<0.001		1.15 (1.05, 1.25)	0.002	
Mean arterial blood pressure, per SD (12.1 mmHg) increase	1.24 (1.14, 1.35)	<0.001		1.21 (1.11, 1.32)	<0.001	
Pulse pressure per SD (16.2 mmHg) increase	1.29 (1.18, 1.42)	<0.001		1.26 (1.14, 1.38)	<0.001	
Serum glucose, per SD (8.3 mg/dL) increase	1.12 (1.03, 1.21)	0.01		1.09 (1.00, 1.18)	0.06	
HDL cholesterol per SD (15.3 mg/dL) decrease	0.92 (0.84, 1.01)	0.07		0.91 (0.81, 1.01)	0.08	
Common Carotid IMT per SD (1.2 mm) increase	1.09 (0.99, 1.19)	0.07		1.04 (0.95, 1.15)	0.39	
LV end-diastolic mass volume ratio per SD (0.23 unit) increase	1.16 (1.04, 1.28)	0.01		1.04 (0.94, 1.16)	0.45	
LV end-diastolic mass index per SD (15.6 unit) increase	1.16 (1.04, 1.28)	0.006		1.08 (0.97, 1.21)	0.15	

Each risk factor is in separate models, OR: Odds ratio (95% confidence intervals),

* Model 1: adjusted for age, sex, race and center (except for Age);

† Model 2: model 1 plus mean arteriolar blood pressure (except for mean arteriolar or pulse pressure), serum glucose (except for glucose or glycemic status), total cholesterol, triglycerides, Body mass index (BMI), smoking and C-reactive protein (CRP).

Risk factors examined but **not statistically significant** ($p > 0.05$) include BMI, interleukin 6, D-Dimer, soluble intercellular adhesion molecule (sICAM), Helicobacter pylori antibodies, Coronary artery calcium (CAC) score, Interleukin-2, Matrix Metalloproteinase 3, Matrix Metalloproteinase 9, Herpes simplex virus, Cytomegalovirus, Helicobacter pylori antibodies, Hepatitis A Virus antibodies, Plasminogen activator inhibitor (PAI-1), Soluble tissue factor (TF), Tissue factor pathway inhibitor (TFPI), Soluble Thrombomodulin, Remnant-like Particle Cholesterol, anti-human Heat Shock Protein-60, Cholesterol Ester Transfer Protein activity, Cholesterol Ester Transfer Protein Mass, Total Agatston Calcium Score per SD (11.4 unit) increase, tumour necrosis factor, Thrombin activatable fibrinolysis inhibitor (TAFI)

Table abbreviations: SD (standard deviation), HDL (high-density lipoprotein), IMT (intima media thickness), LV (left ventricular).

Table 4

Ethnic differences in associations of risk factors in persons without Diabetes, the Multi-Ethnic Study of Atherosclerosis.

Characteristics	White N=2209		Black N=1322		Hispanics N=1039		Chinese N=603	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Normal vs Impaired Fasting Glucose	1.39 (0.89, 2.15)	0.14	1.56 (0.98, 2.47)	0.06	1.00 (0.56, 1.80)	0.99	0.56 (0.23, 1.33)	0.19
Male	1.08 (0.80, 1.45)	0.62	0.82 (0.57, 1.17)	0.27	0.99 (0.66, 1.49)	0.98	1.16 (0.73, 1.84)	0.53
Smoking	1.47 (0.99, 2.19)	0.06	1.09 (0.69, 1.72)	0.70	1.34 (0.74, 2.46)	0.34	0.58 (0.17, 1.99)	0.39
Hypertension, present vs absent	1.30 (0.97, 1.73)	0.08	1.78 (1.22, 2.60)	0.003	1.23 (0.81, 1.88)	0.33	1.46 (0.89, 2.42)	0.14
Body mass index, kg/m ²	1.09 (0.93, 1.28)	0.30	1.01 (0.86, 1.19)	0.91	1.25 (1.01, 1.55)	0.04	0.93 (0.63, 1.37)	0.70
Hepatitis A Virus antibodies	0.89 (0.64, 1.24)	0.49	1.41 (0.86, 2.32)	0.17	2.49 (1.18, 5.28)	0.02	0.13 (0.0, 209.6)	0.59
Systolic blood pressure, per SD (20.4 mmHg) increase	1.28 (1.10, 1.51)	0.002	1.28 (1.08, 1.51)	<0.001	1.27 (1.05, 1.54)	0.02	1.24 (0.96, 1.60)	0.10
Diastolic blood pressure, per SD (10.0 mmHg) increase	1.04 (0.89, 1.21)	0.61	1.08 (0.91, 1.28)	0.36	1.41 (1.15, 1.73)	0.001	1.24 (0.97, 1.57)	0.08
Mean arterial blood pressure, per SD (12.1 mmHg) increase	1.16 (1.00, 1.35)	0.05	1.18 (1.01, 1.39)	0.04	1.34 (1.12, 1.62)	0.002	1.24 (0.98, 1.57)	0.07
Pulse pressure per SD (16.2 mmHg) increase	1.37 (1.16, 1.61)	<0.001	1.33 (1.12, 1.58)	0.001	1.17 (0.95, 1.43)	0.14	1.16 (0.87, 1.54)	0.31
Glucose, per SD (8.3 mg/dL) increase	1.15 (1.00, 1.32)	0.05	1.17 (0.98, 1.39)	0.08	0.93 (0.77, 1.13)	0.47	0.99 (0.77, 1.27)	0.92
Total Agatston Calcium Score per SD (11.4 unit) increase	1.02 (0.92, 1.14)	0.72	1.08 (0.92, 1.28)	0.34	1.18 (1.00, 1.39)	0.05	0.83 (0.47, 1.46)	0.51
Internal Carotid IMT per SD (0.56 mm) increase	1.17 (1.04, 1.33)	0.01	1.00 (0.84, 1.18)	0.95	1.27 (1.04, 1.54)	0.01	0.93 (0.65, 1.34)	0.71
LV end-diastolic mass index per SD (15.6 unit) increase	1.25 (1.04, 1.51)	0.02	1.00 (0.81, 1.21)	0.92	1.08 (0.84, 1.39)	0.54	0.92 (0.63, 1.33)	0.66

Each risk factor is in separate models, OR: Odds ratio (95% confidence intervals)

Model adjusted for age, sex, race and center (except for Age), mean arteriolar blood pressure (except for mean arteriolar or pulse pressure), serum glucose (except for glucose or glycemic status), total cholesterol, triglycerides, BMI (except BMI), smoking (except smoking) and CRP (Model 2 of Table 3).

Other characteristics tested but **not statistically significant** ($p > 0.05$): alcohol, D-dimer, soluble intercellular adhesion molecule (sICAM), helicobacter pylori antibodies, Thrombin activatable fibrinolysis inhibitor (TAFI), anti-human Heat Shock Protein-60, Age, per 10 years, HDL cholesterol per SD (15.3 mg/dL) decrease, Common Carotid IT per SD (1.2 mm) increase, LV end-diastolic mass volume ratio per SD (0.23 unit) increase, interleukin-6

Table abbreviations: SD (standard deviation), IMT (intima media thickness), LV (left ventricular).

Table 5

Associations of Risk Factors in Persons without diabetes and hypertension, the Multi-Ethnic Study of Atherosclerosis

Characteristics	Model 1*			Model 2†			Model 3§		
	OR (95% CI)	P		OR (95% CI)	P		OR (95% CI)	P	
Impaired fasting glucose	1.25(0.81, 1.91)	0.31							
Sex, Male vs Female	1.32 (1.04, 1.67)	0.02		1.14 (0.88, 1.48)	0.31		1.14 (0.87, 1.50)	0.34	
Smoking, current	1.50 (1.09, 2.06)	0.01		1.57 (1.14, 2.17)	0.006		1.56 (1.11, 2.18)	0.01	
Systolic blood pressure, per SD (20.4 mmHg) increase	1.24 (1.02, 1.50)	0.03		1.21 (0.99, 1.49)	0.07		1.22 (0.98, 1.51)	0.07	
Diastolic blood pressure, per SD (10.0 mmHg) increase	1.10 (0.94, 1.27)	0.23							
Mean arteriolar blood pressure, per SD (12.1 mmHg) increase	1.16 (0.98, 1.37)	0.08							
Pulse pressure per SD (16.2 mmHg) increase	1.25 (1.02, 1.52)	0.03		1.23 (1.00, 1.52)	0.05		1.22 (1.00, 1.52)	0.05	
Serum glucose, per SD (8.3 mg/dL) increase	1.09 (0.97, 1.23)	0.16							
Common Carotid IMT per SD (1.2 mm) increase	1.02 (0.88, 1.19)	0.78							
Internal Carotid IMT per SD (0.56 mm) increase	1.22 (1.05, 1.41)	0.008		1.20 (1.03, 1.40)	0.01		1.20 (1.02, 1.40)	0.01	

Each risk factor is in separate models, OR: Odds ratio (95% confidence intervals),

* Model 1: adjusted for age, sex (except for sex), race and center;

† Model 2: model 1 plus mean arteriolar blood pressure (except for mean arteriolar, systolic, diastolic or pulse pressure), serum glucose (except for glucose or glycemic status), total cholesterol, triglycerides, BMI, smoking and CRP.

§ Model 3: Model 3 and Model 2 are the same but Model 3 excludes participants with impaired fasting glucose, diabetes and hypertension.

Other characteristics tested but **not statistically significant** (p>0.05): alcohol, age per 10 years, HDL cholesterol per SD (15.3 mg/dL) decrease, LV end-diastolic mass volume ratio per SD (0.23 unit) increase, LV end-diastolic mass index per SD (15.6 unit) increase, Tumor Necrosis Factor, Thrombin activatable fibrinolysis inhibitor (TAFI), Total Agatston Calcium Score per SD (11.4 unit) increase

Table abbreviations: SD (standard deviation), IMT (intima media thickness).