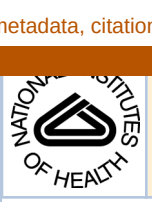

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Impact of long-term measures of glucose and blood pressure on the retinal microvasculature

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Abstract

Objective—Retinopathy and retinal microvascular abnormalities are common in adult populations, yet few long-term predictors have been identified. We therefore examined the association between systolic blood pressure (SBP) and fasting plasma glucose, assessed over 18 years, with retinopathy and retinal vascular caliber in 2,066 Carotid MRI participants, an Atherosclerosis Risk in Communities ancillary study.

Methods—Retinopathy and retinal vascular caliber were assessed by retinal photography. Confounder-adjusted weighted regression models were used to examine exposures defined as cumulative, long-term prospective, concurrent, and 18-year change.

Results—Long-term prospective (prevalence odds ratio (POR) per 10 mmHg: 1.14 (95% CI: 1.01, 1.30)) and cumulative (POR per 10 mmHg: 1.30 (95% CI: 1.09, 1.56) effects spanning approximately 18 years were found for SBP and retinopathy. The strongest long-term prospective association for plasma glucose and retinopathy was identified at the baseline visit (POR per 10 mg/dl: 1.26 (95% CI: 1.16, 1.38)); sustained glucose elevations over 18 years were also associated with prevalent retinopathy (POR per 10 mg/dl: 1.33 (95% CI: 1.24, 1.43)). Results were robust to the exclusion of participants with diabetes.

Conclusions—Modest and sustained long-term elevations in glucose and blood pressure are associated with retinopathy and retinal vascular caliber.

Keywords

epidemiology; microvascular disease; retinopathy; glucose; blood pressure

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INTRODUCTION

Retinopathy signs and other retinal microvascular abnormalities are common in adult populations with and without hypertension[1, 2] and have been associated with several cardiovascular diseases including stroke,[3] coronary heart disease,[4] and cognitive function.[5] Variations in retinal vascular caliber may be indicative of the presence of systemic vascular risk factors. For example, generalized arteriolar narrowing is one of the earliest retinal markers of hypertension.[6] Retinopathy, narrowed retinal arterioles and widened retinal venules are common in populations without type 2 diabetes.[7, 8] In fact, approximately 5–10% of non-diabetic persons may have retinopathy signs similar to diabetic persons with mild retinopathy.[9]

With the exception of blood pressure,[10, 11] few long-term predictors of retinopathy and retinal vascular caliber changes have been identified, although retinopathy and variations in retinal vascular caliber may reflect changes in the systemic microvasculature.[12, 13] Therefore, understanding the inter-relationships of major risk factors to the development of retinopathy and retinal vascular caliber changes may provide insights into the microvasculature involved in systemic vascular disease. In this report we examine the relationships between systolic blood pressure (SBP) and fasting glucose, two major vascular risk factors assessed over eighteen years, with retinal vascular caliber and the presence of retinopathy in 2,066 Carotid MRI participants, an Atherosclerosis Risk in Communities (ARIC) ancillary study.

MATERIALS AND METHODS

Study population

The ARIC study includes an ongoing biracial population-based cohort of 15,792 males and females, aged 45–64 years at baseline and sampled from four United States communities.[14] Standardized examinations and interviewer-administered questionnaires were conducted at baseline and at three triennial follow-up examinations. Participant follow-up through annual telephone interviews, review of hospitalization records and assessment of vital status is ongoing.

This study evaluated 2,066 ARIC participants who participated in the Carotid MRI ancillary study (CarMRI, 2004–2006) that measured novel correlates of carotid atherosclerosis and early pathologic arterial wall changes. CarMRI participants were selected from the population of ARIC study members alive in 2004 using a stratified sampling design to enrich for the presence of visible plaque. In total, 4,306 ARIC cohort members were invited to participate in the ARIC Carotid MRI study. Of those, 1,403 refused and 837 were ineligible for MRI examination. The Institutional Review Board at each participating institution approved the ARIC and Carotid MRI studies and all participants provided informed consent before each examination.

Retinal Microvascular Measurements

We evaluated the association of SBP and plasma glucose with retinopathy and retinal arteriolar and venular caliber (summarized as the central retinal artery equivalent, CRAE and central retinal venular equivalent, CRVE, respectively) measured at the CarMRI visit. The retinal photographs used to measure these traits were obtained using previously described standardized protocols, as described earlier.[15]

Trained readers masked to participant information evaluated each photograph for retinopathy presence and severity using a modification of the Airlie House classification system. Early nonproliferative retinopathy was defined by level 20. Moderate to severe

nonproliferative retinopathy was defined as a severity score exceeding level 35.[15] Intra-and inter-grader kappa estimates for retinopathy lesions ranged from 0.61 to 1.00.[15] For this study, we defined any retinopathy as level 20 and above.

Retinal vascular caliber was measured using a computer-assisted technique. In short, retinal photographs were digitized and the diameters of individual arterioles surrounding the optic disc were measured.[15] To obtain CRAE and CRVE, measurements of individual arterioles and venules were combined using the Knudtson modification of the Parr-Hubbard formula. Intra- and inter-reader agreement estimates were 0.73 and 0.72 for CRAE and 0.86 and 0.76 for CRVE, respectively.[16]

Measurement of SBP, glucose and other risk factors

Resting SBP at each ARIC study visit was defined as the mean of two readings and measured using a random-zero sphygmomanometer. Fasting plasma glucose was measured using conventional techniques following at least eight hours fasting. Diabetes was defined as fasting glucose ≥ 126 mg/dl, non-fasting glucose ≥ 200 mg/dl, self-reported use of medications to lower blood sugar, or self-reported physician diagnosis of diabetes. Hypertension was defined as present if SBP ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or self-reported use of medications for high blood pressure. Education level, alcohol intake, and cigarette smoking were obtained by interviewer-administered questionnaires.

Statistical analysis

The outcome variables were retinopathy, CRAE and CRVE, which were measured at the CarMRI visit. Four types of exposure effects were evaluated using exposures (SBP and glucose) measured over 18 years (i.e. at ARIC visits 1–4 and at the CarMRI visit):

- "Cumulative", representing mean exposure effects over 18 years and estimated by the area under the curve (AUC, see below);
- "Long-term prospective", which examined SBP and glucose assessed 7–18 years before the retinal assessment
- "Concurrent", where SBP, glucose, and retinal outcomes were all measured at the CarMRI visit
- "Change over time", defined as the difference between SBP and plasma glucose measured at the CarMRI and baseline visits.

All statistical models included the following covariates measured at the baseline visit: age, sex, study center, cigarette smoking status (current; former; never), education level (< high school; some high school or vocational school; high school or vocational school; > high school or vocational school), and body mass index. Diabetes status was also included in SBP exposure models. All regression models were weighted by the inverse of the sampling fractions using methods for the analysis of complex sample survey design data. As a sensitivity analysis, associations between SBP and plasma glucose with retinopathy and retinal vessel caliber were performed after excluding participants with diabetes at any study visit.

Associations of SBP and plasma glucose and retinal characteristics were estimated using logistic (retinopathy) and linear (retinal caliber) regression models. Visit specific cross-sectional exposure effects for all visits except baseline were adjusted for exposures measured at earlier visits. The mean (i.e. cumulative) effect of each exposure across the entire follow-up time was estimated as the AUC using a random-effects model and adjusting for age, age^2, race, and sex.[17] The AUC were chosen over the arithmetic mean as the

cumulative effect measure because the method accommodates both missing data exposure measures and measures that were collected over non-uniform time intervals.

RESULTS

ARIC CarMRI participants contributed an average of 18 years of person-time from the baseline ARIC exam to the CarMRI visit and were on average 71 years of age at the CarMRI exam (Table 1). Approximately equal proportions of males and females were represented in the study population. At the baseline ARIC visit, fewer future CarMRI participants were classified as hypertensive (24.7%) or diabetic (5.9%) when compared to the total ARIC cohort (35.1% and 12.0%, respectively). By the CarMRI visit, the prevalence of hypertension and diabetes increased to 65.0% and 24.5%, respectively, which is consistent with an aging cohort. The prevalence of retinopathy increased monotonically with increasing SBP and fasting glucose category (Table 2). Increases in mean CRAE and CRVE were also observed for fasting glucose. An inverse association was estimated for CRAE and CRVE with SBP categories.

Effects of SBP

We identified several effects of SBP on retinopathy, which showed that both prior elevations in SBP as well as sustained SBP elevations over 18 years were associated with prevalent retinopathy (Figure 1, panel a). Specifically, long-term prospective effects of SBP (per 10 mmHg) on retinopathy after adjustment for earlier SBP measures were limited to the baseline ARIC examination. Cumulative effects of SBP over 18 years also were identified: every 10 mmHg increment in mean SBP increased the odds of retinopathy by 1.30 (95% confidence interval (CI): 1.09, 1.56). No association between SBP change and the odds of retinopathy (1.01 (95% CI: 0.91, 1.12)) was identified.

Long-term and concurrent associations between SBP and retinal arteriolar caliber (CRAE) were noted (Figure 1, panel b). For example, every 10 mmHg increase in mean SBP over 18 years was associated with a −1.9 (95% CI: −2.7, −1.1) decrement in CRAE. SBP measured at the baseline ARIC visit was inversely associated with CRAE: every 10 mmHg increase SBP (1987–1989) was associated with a −0.84 μm (95% CI: −1.4, −0.25) decrement in CRAE. Similar decrements in CRAE were apparent when examining SBP measured at the same time retinal arteriolar caliber was assessed (concurrent effect size = 1.5 μm (95% CI: −2.1, −0.94)). Unlike retinal arteriolar caliber, no associations between SBP and retinal venous caliber (CRVE) were estimated, with the exception of a concurrent positive effect of SBP on CRVE (Figure 1, panel c).

Effects of plasma glucose levels

All four visit-specific cross-sections predating the CarMRI visit demonstrated long-term prospective associations between plasma glucose and retinopathy (Figure 2). The strongest association was estimated for the baseline visit (POR = 1.26 (95% CI: 1.16, 1.38). An evaluation of cumulative plasma glucose effects also indicated that sustained high plasma glucose levels were associated with retinopathy (POR = 1.33 (95% CI: 1.24, 1.43)), although the association between change in glucose and retinopathy was null (POR = 0.94 (95% CI: 0.86, 2.29)). No associations between fasting plasma glucose and retinal arteriolar or venular caliber were noted (Figure 2).

As a sensitivity analysis, we examined associations between SBP and glucose with microvascular characteristics after excluding participants classified as having diabetes at any of the ARIC exams (Table 3). Associations for SBP and glucose estimated among participants classified as pre-diabetic were also examined (results not shown). Results

among participants without diabetes or among pre-diabetics were consistent with those in the total population, although somewhat less precise. Conclusions also were robust to substituting estimates of mean arterial pressure or diastolic blood pressure for SBP and the analysis of treatment-corrected SBP (results not shown).[18]

DISCUSSION

Results from this longitudinal cohort study suggest that blood pressure and fasting plasma glucose, two major and modifiable vascular risk factors, have long-term effects on retinopathy and retinal vascular caliber. Although previous studies have identified prospective associations between blood pressure and generalized arteriolar narrowing,[10, 11] few have described associations between these two key cardiovascular risk factors and retinal microvascular characteristics spanning almost two decades.

Associations between elevated blood pressure and retinal microvascular abnormalities have been documented since the late 1800s.[19] Although improved blood pressure control has greatly reduced the prevalence of the severe retinal microvascular abnormalities, retinal microvascular signs remain common in populations with and without a documented clinical diagnosis of hypertension.[2, 9] Here, we identified long-term prospective and cumulative effects of elevated blood pressure on retinal arteriolar caliber as well as retinopathy, suggesting that these microvascular characteristics may be long-term markers of changes in the retinal microvasculature resulting from chronically elevated blood pressure.[20] Although pharmacologic interventions to decrease short-term elevations in blood pressure have been associated with reductions in arteriolar narrowing,[21] hemodynamic microvascular changes induced by chronically elevated blood pressure may not be reversible upon the onset of vascular remodeling.[22] These results are consistent with reports by Beaver Dam Eye Study investigators who found the 15-year cumulative incidence of retinopathy to be elevated in non-diabetic participants with increased SBP[23] and by the Multi-Ethnic Study of Atherosclerosis investigators who demonstrated an association between aortic distensibility and retinal arteriolar narrowing.[24] Chronically elevated blood pressure in the non-hypertensive range also has been associated with accelerated vascular damage in adults[25] and increased carotid intima media thickness in children.[26] Reports documenting an association between retinopathy and several cardiovascular endpoints, particularly incident stroke,[3, 11, 14] further justify additional studies evaluating whether retinopathy represents a marker of the effects of long-term elevated blood pressure on the microvasculature of other organ systems.

Like blood pressure, the association between diabetes and retinopathy has been extensively studied. Although earlier reports suggested that retinopathy signs were rare in populations with fasting glucose levels below 126 mg/dl,[27] recent studies have demonstrated that no clear and consistent glycemic threshold for retinopathy exists.[28] Instead, the relationship between plasma glucose and retinopathy is likely continuous and graded, supported by studies demonstrating that retinopathy and retinal vascular caliber changes occur in individuals without clinically manifest diabetes.[29, 30]

Here, we show that long-term prospective and cumulative measures of elevated fasting plasma glucose are associated with the odds of retinopathy over 18 years. This result is consistent with studies of diabetic retinopathy, which demonstrate that extended periods of elevated plasma glucose may induce irreversible changes in gene expression and cellular functions, which persist even after glucose levels have been reduced.[31] Cross-sectional studies have also demonstrated a relationship between elevated plasma glucose and whole-body atherosclerotic disease.[32]

Strengths of this study include the use of standardized methods to measure retinal microvascular signs and an extended follow-up time over which standardized exposure measurements were routinely available. Furthermore, the extended follow-up period facilitated the evaluation of different mechanisms through which SBP and plasma glucose could affect the retinal microvascular. We also evaluated interval scale measures of SBP and plasma glucose, which allowed us to detect associations that may not have been apparent if our analyses were limited to clinical categories.

However, several limitations warrant consideration in order to inform future efforts examining long-term predictors of microvascular characteristics. First, retinal photographs were only available on one eye per-participant and were obtained using technology which is no longer contemporary. While the actual grading methodology used in this study were identical to that applied currently to digital photographs, the older film-based methods of acquiring photographs yielded lower quality images which introduced additional measurement error in the grading process. Second, findings based on the retinal microvasculature are not necessarily directly generalizable to the coronary or systemic microvasculature. Nonetheless, the retina is one of the few windows allowing direct non-invasive visualization of the human microvasculature and reports documenting associations between microvascular characteristics and cardiovascular diseases including stroke,[3] coronary heart disease,[4] and cognitive function[5] support a common underlying pathophysiology. Third, although results were weighted to the ARIC cohort, they may not be generalizable to broader populations. For example, CarMRI participants were on average 71 years of age and were African American or Caucasian from four U.S. communities and were less likely to be diabetic or hypertensive at study baseline. Yet, very few studies have repeated and standardized exposure measures in a biracial population spanning almost two decades with which to assess the influence of SBP and plasma glucose. Fourth, we assessed glycemic control using fasting plasma glucose because hemoglobin A1c was not routinely measured by ARIC investigators. It is likely that HbA1c would have been a better marker of glycemic control overall. Finally, we evaluated an outcome measured 18 years after the ARIC baseline exam. It is unclear how selective survival may have affected the results, although demographics between the ARIC baseline and CarMRI visits are comparable and participant retention was high (>90%).

In conclusion, we report associations of SBP and fasting plasma glucose, two major modifiable vascular risk factors, on the retinal microvasculature, measured over an 18-year period. Our results, which were observed among participants without diabetes and below current SBP and glucose treatment thresholds, suggest that modest and sustained long-term elevations in these two major vascular risk factors are associated with markers of microvascular disease. Associations between these vascular risk factors and measures of atherosclerosis, observed in other studies as early as young adulthood,[26, 33] further underscore the need for population-wide approaches to reduce the burden of elevated blood pressure and glucose to prevent long-term deleterious effects on the vasculature.

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REFERENCES

1. Wong TY, Klein R, Amirul Islam FM, et al. Three-year incidence and cumulative prevalence of retinopathy: the atherosclerosis risk in communities study. American journal of ophthalmology. 2007; 143:970–976. [PubMed: 17399675]
2. Yu T, Mitchell P, Berry G, et al. Retinopathy in older persons without diabetes and its relationship to hypertension. Archives of ophthalmology. 1998; 116:83–89. [PubMed: 9445212]
3. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet. 2001; 358:1134–1140. [PubMed: 11597667]
4. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. JAMA : the journal of the American Medical Association. 2002; 287:1153–1159. [PubMed: 11879113]
5. Lesage SR, Mosley TH, Wong TY, et al. Retinal microvascular abnormalities and cognitive decline: the ARIC 14-year follow-up study. Neurology. 2009; 73:862–868. [PubMed: 19752453]
6. Scheie HG. Evaluation of ophthalmoscopic changes of hypertension and arteriolar sclerosis. A.M.A. archives of ophthalmology. 1953; 49:117–138. [PubMed: 13007237]
7. Cunha-Vaz J, Bernardes R. Nonproliferative retinopathy in diabetes type 2. Initial stages and characterization of phenotypes. Progress in retinal and eye research. 2005; 24:355–377. [PubMed: 15708833]
8. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. JAMA : the journal of the American Medical Association. 2002; 287:2528–2533. [PubMed: 12020333]
9. Klein R, Klein BE, Moss SE, et al. Hypertension and retinopathy, arteriolar narrowing, and arteriovenous nicking in a population. Archives of ophthalmology. 1994; 112:92–98. [PubMed: 8285901]
10. Sharrett AR, Hubbard LD, Cooper LS, et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. American journal of epidemiology. 1999; 150:263–270. [PubMed: 10430230]
11. Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. The British journal of ophthalmology. 2002; 86:1007–1013. [PubMed: 12185128]
12. Burchfiel CM, Tracy RE, Chyou PH, et al. Cardiovascular risk factors and hyalinization of renal arterioles at autopsy. The Honolulu Heart Program. Arteriosclerosis, thrombosis, and vascular biology. 1997; 17:760–768.
13. Mosseri M, Yarom R, Gotsman MS, et al. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. Circulation. 1986; 74:964–972. [PubMed: 3769180]
14. ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. American journal of epidemiology. 1989; 129:687–702. [PubMed: 2646917]
15. 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 Study. Ophthalmology. 1999; 106:2269–2280. [PubMed: 10599656]
16. Couper DJ, Klein R, Hubbard LD, et al. Reliability of retinal photography in the assessment of retinal microvascular characteristics: the Atherosclerosis Risk in Communities Study. American journal of ophthalmology. 2002; 133:78–88. [PubMed: 11755842]
17. Cook NR, Rosner BA, Chen W, et al. Using the area under the curve to reduce measurement error in predicting young adult blood pressure from childhood measures. Statistics in medicine. 2004; 23:3421–3435. [PubMed: 15505884]
18. Tobin MD, Sheehan NA, Scurrah KJ, et al. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. Statistics in medicine. 2005; 24:2911–2935. [PubMed: 16152135]
19. Gunn RM. On ophthalmoscopic evidence of general arterial disease. Trans Ophthalmol Soc UK. 1898; 18:356–381.

20. Wong TY, Mitchell P. Hypertensive retinopathy. The New England journal of medicine. 2004; 351:2310–2317. [PubMed: 15564546]
21. Hughes AD, Stanton AV, Jabbar AS, et al. Effect of antihypertensive treatment on retinal microvascular changes in hypertension. Journal of hypertension. 2008; 26:1703–1707. [PubMed: 18622251]
22. Sjolie AK, Klein R, Porta M, et al. Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebocontrolled trial. Lancet. 2008; 372:1385–1393. [PubMed: 18823658]
23. Klein R, Myers CE, Lee KE, et al. 15-year cumulative incidence and associated risk factors for retinopathy in nondiabetic persons. Archives of ophthalmology. 2010; 128:1568–1575. [PubMed: 21149781]
24. Cheung N, Sharrett AR, Klein R, et al. Aortic distensibility and retinal arteriolar narrowing: the multi-ethnic study of atherosclerosis. Hypertension. 2007; 50:617–622. [PubMed: 17698721]
25. Tomiyama H, Hashimoto H, Matsumoto C, et al. Effects of aging and persistent prehypertension on arterial stiffening. Atherosclerosis. 2011; 217:130–134. [PubMed: 21501841]
26. Toledo-Corral CM, Ventura EE, Hodis HN, et al. Persistence of the metabolic syndrome and its influence on carotid artery intima media thickness in overweight Latino children. Atherosclerosis. 2009; 206:594–598. [PubMed: 19446812]
27. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes care. 1997; 20:1183–1197. [PubMed: 9203460]
28. Wong TY, Liew G, Tapp RJ, et al. Relation between fasting glucose and retinopathy for diagnosis of diabetes: three population-based cross-sectional studies. Lancet. 2008; 371:736–743. [PubMed: 18313502]
29. Klein R, Klein BE, Moss SE. The relation of systemic hypertension to changes in the retinal vasculature: the Beaver Dam Eye Study. Transactions of the American Ophthalmological Society. 1997; 95:329–348. discussion 348-350. [PubMed: 9440178]
30. Wong TY, Klein R, Klein BE, et al. Retinal microvascular abnormalities and their relationship with hypertension, cardiovascular disease, and mortality. Survey of ophthalmology. 2001; 46:59–80. [PubMed: 11525792]
31. Roy S, Sala R, Cagliero E, et al. Overexpression of fibronectin induced by diabetes or high glucose: phenomenon with a memory. Proceedings of the National Academy of Sciences of the United States of America. 1990; 87:404–408. [PubMed: 2296596]
32. Pigna G, Napoli A, Zaccagna F, et al. The relationship between metabolic syndrome, its components, and the whole-body atherosclerotic disease burden as measured by computed tomography angiography. Atherosclerosis. 2011; 215:417–420. [PubMed: 21306711]
33. Paul TK, Chen W, Srinivasan SR, et al. Contrast of the impact of multiple cardiovascular risk factors on the femoral and carotid intima-media thickness in asymptomatic young adults: the Bogalusa Heart Study. Atherosclerosis. 2011; 216:359–364. [PubMed: 21376319]

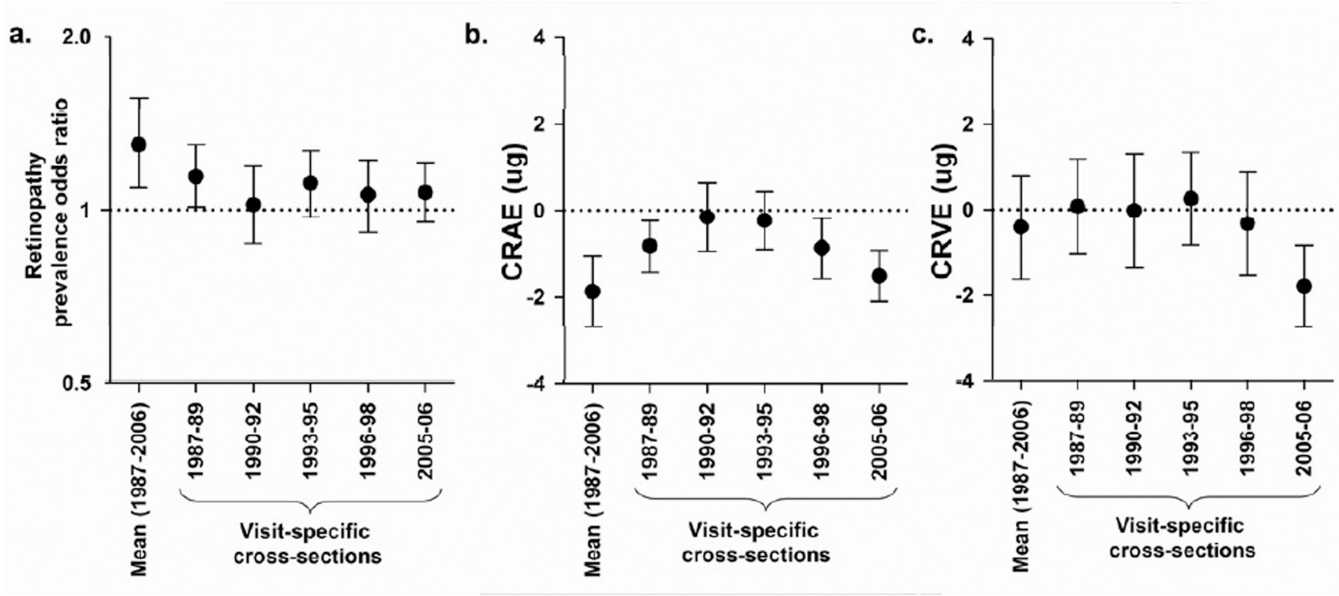

Figure 1.

Associations of systolic blood pressure (SBP) with retinopathy (panel a), central retinal artery equivalent (panel b), and central retinal venous equivalent (panel c) estimated in n=2,066 Atherosclerosis Risk in Communities (ARIC) Carotid MRI study participants, 1987–2006. Visit-specific cross-sections refer to SBP measured at ARIC Visits 1–4 and the CarMRI visit and are adjusted for earlier SBP measures. Estimates are presented per 10 mmHg SBP.

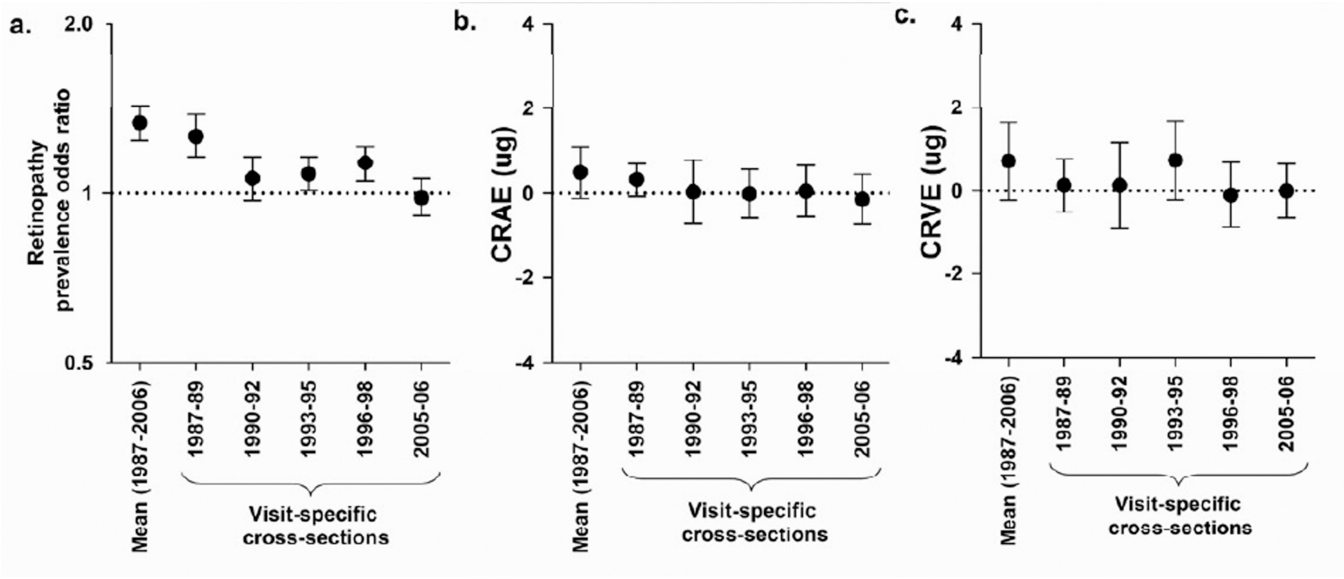

Figure 2.

Associations of fasting glucose with retinopathy (panel a), central retinal artery equivalent (panel b), and central retinal venous equivalent (panel c) estimated in n=2,066 Atherosclerosis Risk in Communities (ARIC) Carotid MRI study participants, 1987–2006. Visit-specific cross-sections refer to fasting glucose measured at ARIC Visits 1–4 and the CarMRI visit and are adjusted for earlier glucose measures.
Estimates are presented per 10 mg/dl fasting glucose.

TABLE 1

Characteristics of ARIC participants assessed at the baseline visit (1987–1989) and ARIC participants enrolled in the Carotid MRI ancillary study (2004–2006).

	ARIC baseline visit, 1987–1989*		Carotid MRI visit† (2004–2006)
Variable‡	**All ARIC participants (n = 15,744)**	**Carotid MRI† participants (n=2,066)**	**Carotid MRI† participants (n=2,066)**
Gender, male (%)	7,059 (44.8)	996 (43.2)	996 (43.2)
Race, African American (%)	4,266 (27.1)	515 (21.1)	515 (21.1)
Age (years)	54.2 (5.8)	52.7 (5.4)	70.3 (5.5)
Diabetes	1,867(12.0)	144 (5.9)	542 (24.5)
Hypertension	5,495(35.1)	595 (24.7)	1,424 (65.0)
BMI (kg/m^2)	27.7 (5.4)	27.1 (4.8)	29.0 (5.4)
Exposures			
Systolic blood pressure (mmHg)	121.3(19.0)	117.2(16.4)	125.9 (18.9)
Glucose (mg/dl)	109.0 (40.6)	101.9 (24.9)	108.9 (26.5)
Outcomes			
Central retinal artery equivalent (μm)	---	---	152.0 (16.4)
Central retinal venous equivalent (μm)	---	---	226.5 (26.9)
Retinopathy (%)	---	---	198 (9.1)

*All comparisons between Carotid MRI and non-Carotid MRI study participants at ARIC study baseline were significant at the $\alpha = 0.05$ level.

†Carotid MRI participants were selected from the population of ARIC study members alive in 2004 using a stratified sampling design.

‡Presented as mean (SD) for interval scale variables and number (%) for ordinal variables. ARIC, Atherosclerosis Risk in Communities. BMI, body mass index. SD, stand deviation.

Table 2

The prevalence of retinopathy and estimated mean CRAE and CRVE by baseline systolic blood pressure and fasting plasma glucose categories among 2,066 participants from the ARIC Carotid MRI study.[*]

Variable	N.	Retinopathy (%)[†]	Mean CRAE (SD)[†]	Mean CRVE (SD)[†]
Systolic blood pressure (mmHg)[‡¥]				
<120	1,060	89 (7.7)	152.4(15.1)	226.6 (25.1)
120-<140	636	72 (9.1)	151.7(18.1)	226.7 (28.0)
140-<160	167	27(16.4)	149.9(19.1)	224.7 (34.8)
≥160	38	10 (30.2)	148.9 (17.3)	230.0 (41.8)
Fasting plasma glucose(mg/dl)[‡¥]				
≤80	16	0(0)	135.7 (22.6)	210.9 (27.9)
>80–100	962	70 (6.2)	151.6 (15.6)	225.9 (26.6)
>100–110	482	51 (7.5)	152.3 (16.1)	227.3 (25.5)
>110–125	175	36 (17.0)	152.5 (15.2)	227.0 (26.8)
>125	61	41 (40.1)	158.0 (24.9)	232.8 (36.9)

[*] Carotid MRI participants were selected from the population of ARIC study members alive in 2004 using a stratified sampling design.

[†] Measured at the Carotid MRI visit (2004–2006) and tabulated using sampling weights.

[‡] Measured at visit 1 (1987–1989).

P-value for trend < 0.001. ARIC, Atherosclerosis Risk in Communities study. CRAE, central retinal artery equivalent. CRVE, central retinal venous equivalent.

TABLE 3

Associations between systolic blood pressure and glucose with CRAE and retinopathy among participants without diabetes (n = 1,474), the ARIC Carotid MRI study (1987–2006).

	Glucose (per 10 mg/dl)			Systolic blood pressure (per 10 mmHg)		
Metric	**CRAE Effect size (95% CI)**	**CRVE Effect size (95% CI)**	**Retinopathy POR (95% CI)**	**CRAE Effect size (95% CI)**	**CRVE Effect size (95% CI)**	**Retinopathy POR (95% CI)**
Mean*	0.58 (−1.58, 2.74)	0.18 (−2.89, 3.25)	1.86 (1.06,3.26)	−3.21 (−5.30,−1.16)	−1.34 (−2.64, −0.03)	2.68 (1.36, 5.27)
Visit-specific cross-sections						
1987–89	4.05 (−0.37, 2.41)	0.23 (−2.50, 2.96)	1.56 (1.06,2.30)	−1.25 (−2.97, 0.47)	−0.51 (−1.71,0.70)	1.37 (0.82,2.29)
1990–92	0.01 (−1.34, 1.35)	−0.12 (−3.01, 2.76)	1.13(0.71, 1.79)	−1.83 (−3.76, 0.10)	−0.12 (−1.54, 1.30)	1.29 (0.77,2.15)
1993–95	−1.06 (−2.50, 3.76)	−1.77 (−4.02, 0.48)	1.20(0.81, 1.80)	−1.94 (−3.69,−0.18)	−0.46 (−1.78, 0.87)	1.78 (0.96,3.31)
1996–98	−1.13 (−2.77, 0.50)	−1.09 (−3.86, 1.68)	1.46(0.96,2.24)	0.13 (−1.69, 1.96)	−0.24 (−1.60, 1.13)	1.28 (0.60,2.71)
2004–06	1.02 (−0.63, 2.67)	1.55 (−0.30, 3.39)	1.00 (0.76, 1.31)	−1.49 (−3.02, 0.04)	−1.93 (−3.01,−0.85)	1.15 (0.70, 1.89)
Change	0.14 (−1.05, 1.34)	0.79 (−1.13, 2.71)	0.97(0.78, 1.27)	−1.17 (−2.54, 0.20)	−1.18 (−2.22,−0.14)	1.20 (0.79, 1.81)

*Assessed 1987–2006.

ARIC, Atherosclerosis Risk in Communities study. CI, confidence interval. CRAE, Central retinal artery equivalent. POR, prevalence odds ratio. CRVE, Central retinal venous equivalent. POR, prevalence odds ratio.