

Retinal Vessel Diameters and Obesity: A Population-Based Study in Older Persons

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Abstract

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Objective: Obesity is linked with large vessel atherosclerosis and diabetes. Its association with microvascular changes is less clear. We investigated the associations among retinal vessel diameters, vessel wall signs, and BMI in an older population.

Research Methods and Procedures: Retinal photographs were taken on 3654 persons aged 49+ years at baseline of the Blue Mountains Eye Study in Australia. Arteriolar and venular diameters were measured from digitized retinal photographs of the right eyes. BMI was calculated as weight (kilograms)/height (meters²). Incident obesity was defined in persons with BMI \leq 30 at baseline but $>$ 30 after 5 years. A significant weight gain was defined as an increase in BMI of 2+ SDs (4 or more units) over the 5-year period.

Results: At baseline, mean BMI was 26.1 (\pm 4.6) in this population. At 5-year examinations, 177 (10.0% of 1773 at risk) developed incident obesity, and 136 (6.4% of 2143 at risk) had significant weight gain. After adjusting for age, sex, smoking, triglyceride levels, and mean arterial blood pressure, persons with wider retinal venular diameters had a higher risk of incident obesity (odds ratio, 1.8; 95% confi-

dence interval, 1.0 to 3.1, comparing the highest with lowest venular diameter quintiles) and significant weight gain (odds ratio, 1.7; 95% confidence interval, 0.9 to 3.2). These associations were attenuated with further adjustment for baseline BMI. Arteriolar diameter was unrelated with baseline or change in BMI.

Discussion: Wider retinal venular diameter is associated with risk of obesity, independent of hypertension, diabetes, lipids, and cigarette smoking. These data may support a role for impaired microvascular function in the course of weight gain.

Key words: BMI, arteriole, venule, incidence, Blue Mountains Eye Study

Introduction

Obesity is an increasing epidemic not only in relatively wealthy, developed countries (1–8), but also in developing countries (9,10). Although a sedentary lifestyle and poor dietary habits play a predominant role in development of obesity, other predisposing factors have been hypothesized and investigated (11,12).

One potential risk factor that has not been well studied is microvascular disease. Microvascular processes have been suggested to contribute to the pathogenesis of type 2 diabetes and hypertension, and abnormalities of the microcirculation have been linked to insulin resistance and the metabolic syndrome, in which obesity is a key component (13–17). However, the mutual effect between obesity and small vessel (microvascular) structural and functional change is less well studied (18). In one recent clinical investigation of 28 subjects, de Jongh et al. (19) demonstrated that obese women tended to have more severe impairment of microvascular function than lean healthy women, supporting a possible role of microangiopathy in obesity pathogenesis. To our best knowledge, there are no prospective studies of microvascular disease markers and the risk of obesity in general populations.

The retinal vessels provide a direct, non-invasive window to study correlates and consequences of systemic microvas-

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cular disease in vivo. Recent studies have shown that changes in retinal vessel diameters predict a variety of cardiovascular outcomes. Narrowed arteriolar diameters have been linked with incident hypertension (20,21), coronary heart disease (in women) (22), and diabetes (23). Other studies have demonstrated that (larger) retinal venular diameter is associated with diabetes status (24,25), higher glycosylated hemoglobin levels (26), and, in people with diabetes, the incidence of gross proteinuria and nephropathy (27). In the current study, we examined associations between retinal vessel changes and both baseline BMI and the 5-year change in BMI, and the incidence of obesity in a general older population.

Research Methods and Procedures

The Blue Mountains Eye Study (BMES)¹ is a population-based cohort study of vision, common eye diseases, and other health outcomes in an urban population aged 49 years and older. Baseline participants ($n = 3654$, 1992 to 1994) represented 82.4% of eligible potential participants living in two postal code areas in the Blue Mountains region of Australia. Five years later, 2334 participants (75% of survivors in 1997 to 1999) from the original cohort were reexamined. This study was conducted according to the recommendations of the Declaration of Helsinki and was approved by the Western Sydney Area Human Ethics Committee. Written, informed consent was obtained from all participants.

At baseline (1992 to 1994), dilated, 30° stereoscopic retinal photographs of the macula, optic disc, and other retinal fields of both eyes were taken, using a fundus camera (model FF3; Carl Zeiss, Oberkochen, Germany). In 299 participants (8%), who had no retinal photographs taken, or had photographs but with a poor image that precluded measurement, or with retinal diseases that confounded measurement of retinal vessel width, were excluded. This study was based on retinal photographs of the right eyes of 3355 participants.

A computer-assisted grading method with high reproducibility was used to measure retinal vessel diameter. Details of this method have been described previously (28,29). In brief, digitized images were displayed and measured using customized RetinalAnalysis software (Department of Ophthalmology and Visual Science, University of Wisconsin-Madison, Madison, WI) coupled with Optimate (version 6.51) image library (run-time version of Optimas 6.51; Media Cybernetics, Silver Spring, MD). A digitized grid was placed over the image, and all vessels passing com-

pletely through zone B (0.5- to 1-disc diameter from the disc margin) were measured. The grader identified each vessel as a venule or arteriole, using the original photograph for reference.

The average retinal arteriolar or venular diameter was calculated using the Parr-Hubbard formula (30,31) and is presented as the central retinal arteriolar equivalent (CRAE) or central retinal venular equivalent (CRVE). Arteriole to venule ratio (AVR) was calculated from CRAE and CRVE. Intra- and inter-grader reliability of this method was high (28), with quadratic weighted κ values of 0.85 (CRAE) and 0.90 (CRVE) found for intergrader reliability and between 0.80 to 0.93 and 0.80 to 0.92 for intra-grader reliability of the two graders, respectively. Vessel diameters of right eyes were used for analysis. Generalized arteriolar narrowing was defined as arteriolar diameter falling in the lowest quintile of the population, whereas generalized venular dilation was defined as venular diameter falling in the highest quintile.

Focal arteriolar narrowing and arteriovenous (AV) nicking were also assessed from 35-mm slides of both eyes, using a light box and a stereoviewer with 5× magnification. Only arterioles located at least one-half-disc diameter away from the optic disc margin were assessed. A retinal specialist (P.M.) selected standard photographs for retinal microvascular signs from the standard photographic set developed for the Modified Airlie House Classification of Diabetic Retinopathy (32) and the training set developed for the Wisconsin Age-related Maculopathy Grading System (33). We graded focal arteriolar narrowing as absent/questionable (none/less severe than the standard photograph) or present (equal to or more severe than the standard). We defined AV nicking (nipping) as a decrease in venular width on both sides of the venule where crossed by an arteriole and was graded as absent/questionable, mild (less than the standard), or severe (equal to or greater than the standard). The intra-grader reliability for detecting focal arteriolar narrowing and AV nicking was high (κ statistic, 0.80 and 0.87, respectively). Retinal vascular signs included focal arteriolar narrowing, AV nicking, and presence of non-diabetic retinopathy lesions (microaneurysms or hemorrhages in persons without diabetes). We chose the worse eye affected to classify the extent of lesions for each person.

Participants had their blood pressure, weight, and height measured. Mean arterial blood pressure (MABP) was defined as $MABP = 0.33 \times \text{systolic blood pressure} + 0.67 \times \text{diastolic blood pressure}$. BMI was calculated as weight (kilograms)/height squared (meters squared). Overweight was defined as $BMI > 25$ but ≤ 30 , and obesity was defined as $BMI > 30$. Incident obesity was defined in subjects who had $BMI \leq 30$ at baseline but >30 at the 5-year examination. A significant weight gain was defined in subjects who had a change in BMI of 2 SDs or greater (4 or more units) between the baseline and 5-year examinations.

¹ Nonstandard abbreviations: BMES, Blue Mountains Eye Study; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, arteriole to venule ratio; AV, arteriovenous; MABP, mean arterial blood pressure; OR, odds ratio; CI, confidence interval; WHO, World Health Organization.

Table 1. Prevalence and incidence of obesity in the Blue Mountains Eye Study population (49 to 97 years old)

Age group (years)	Prevalence (%)		5-Year incidence (%)
	Overweight* (<i>n</i> = 3545)	Obesity† (women and men)	Obesity† (no. at risk 1773)
49 to 59	41.7	19.1	12.9
60 to 69	41.9	18.5	10.2
70 to 79	35.5	16.2	6.9
80+	29.6	8.5	4.6
All ages	39.0	17.2	10.0
	(<i>n</i> = 2000)	Women	(No. at risk 987)
49 to 59	36.0	20.7	13.4
60 to 69	36.5	22.2	11.6
70 to 79	31.0	18.7	6.3
80+	27.5	8.3	5.7
All ages	34.0	19.5	10.5
	(<i>n</i> = 1545)	Men	(No. at risk 786)
49 to 59	49.1	16.9	12.2
60 to 69	48.4	14.1	8.6
70 to 79	41.7	12.9	7.8
80+	32.6	8.9	2.9
All ages	45.5	14.1	9.3

* Defined as BMI > 25 but ≤30.

† Defined as BMI > 30.

Statistical analysis was conducted using SAS software (SAS Institute, Cary, NC). General linear models were used to examine the cross-sectional association between retinal vessel diameters and BMI categories while adjusting for age, sex, smoking, blood glucose, and MABP. Logistic regression models were used to assess cross-sectional associations between BMI (in quintiles) and generalized arteriolar narrowing or generalized venular dilation after dichotomizing and adjusting for the same covariables as in the general linear models. Associations between retinal vascular signs and obesity were assessed after additional adjustment for triglyceride and high-density lipoprotein-cholesterol levels.

Potential risk factors for incident obesity were screened using age-sex-adjusted logistic regression models. Diabetes or blood glucose, history of regular exercise, serum total cholesterol and high-density lipoprotein-cholesterol levels, serum fibrinogen, and while blood cell count were not found to be associated with incident obesity in the study population after adjusting for age and sex, but baseline triglyceride level was significantly associated with incident obesity. Longitudinal association among baseline retinal vessel diameters, retinal vascular signs, and incident obesity (or a

significant weight gain) was assessed using logistic regression models, after adjusting for age, sex, smoking, MABP, and triglyceride levels.

Associations with retinopathy lesions were assessed in persons without diabetes. Means and SDs, odds ratios (ORs), and 95% confidence intervals (CIs) are presented.

Results

Prevalence and 5-Year Incidence of Obesity in the Study Population

The prevalence of overweight and obesity at baseline (1992 to 1994) was 39.0% and 17.2%, respectively. Overweight was more prevalent in men (45.5%) than women (34.0%), but obesity was more prevalent in women (19.5%) than men (14.1%) (Table 1).

After excluding participants who were obese at baseline, 1773 of the 2334 participants who returned at the 5-year examinations were considered at risk of developing obesity. Of these, 177 (10.0%) developed obesity over a 5-year period, including 104 (10.5%) women and 73 (9.3%) men (Table 1).

Table 2. Cross-sectional association between BMI and generalized retinal arteriolar narrowing, retinal venular dilation in the Blue Mountains Eye Study population, including subgroups without hypertension or diabetes

BMI quintiles	Mean BMI (SD)	Whole population		Without hypertension		Without diabetes	
		N	Adjusted ORs*	N	Adjusted ORs*	N	Adjusted ORs*
CRVE							
Lowest	20.61 (1.60)	639	1.0	447	1.0	670	1.0
Second	23.62 (0.62)	660	1.3 (0.9 to 1.8)	403	1.4 (0.9 to 2.1)	681	1.3 (0.9 to 1.8)
Third	25.62 (0.57)	667	1.4 (1.0 to 2.0)	385	1.6 (1.1 to 2.4)	650	1.3 (1.0 to 1.8)
Fourth	27.86 (0.74)	668	1.6 (1.1 to 2.1)	368	1.9 (1.2 to 2.8)	656	1.5 (1.1 to 2.1)
Highest	33.01 (3.71)	672	1.7 (1.3 to 2.4)	307	2.2 (1.5 to 3.3)	612	1.6 (1.2 to 2.3)
<i>p</i> for trend			0.0004		<0.0001		0.0033
CRAE							
Lowest	20.61 (1.60)	639	1.0	447	1.0	670	1.0
Second	23.62 (0.62)	660	0.9 (0.7 to 1.3)	403	0.8 (0.5 to 1.2)	681	1.0 (0.7 to 1.3)
Third	25.62 (0.57)	667	0.9 (0.7 to 1.2)	385	0.7 (0.4 to 1.0)	650	0.9 (0.6 to 1.2)
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Highest	33.01 (3.71)	672	0.9 (0.7 to 1.2)	307	0.7 (0.4 to 1.1)	612	0.9 (0.7 to 1.3)
<i>p</i> for trend			0.32		0.14		0.52
AVR							
Lowest	20.61 (1.60)	639	1.0	447	1.0	670	1.0
Second	23.62 (0.62)	660	1.0 (0.7 to 1.3)	403	0.9 (0.6 to 1.3)	681	1.0 (0.7 to 1.3)
Third	25.62 (0.57)	667	0.9 (0.6 to 1.2)	385	0.8 (0.5 to 1.2)	650	0.8 (0.6 to 1.1)
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Highest	33.01 (3.71)	672	1.3 (1.0 to 1.8)	307	1.4 (0.9 to 2.1)	612	1.4 (1.0 to 1.9)
<i>p</i> for trend			0.015		0.045		0.021

SD, standard deviation; OR, odds ratio; CRVE, central retinal venular equivalent; CRAE, central retinal arteriolar equivalent; AVR, arteriole to venule ratio.

* Adjusted for age, sex, smoking, blood glucose, and MABP.

Cross-Sectional Association

Among the 3355 baseline participants with all relevant data available, 1895 were women, and 1460 were men. The average age of this largely white study sample was 66.2 (± 9.8) years, and mean BMI was 26.1 (± 4.6). After excluding six subjects with missing data on blood pressure, 1512 of 3349 (45%) had hypertension and 216 of 3349 (6.4%) had diabetes. For men and women, mean CRAE was 191.2 (± 21.3) and 194.6 (± 20.4) μm , respectively, and mean CRVE was 225.5 (± 20.6) and 224.6 (± 20.8) μm , respectively.

After adjustment for age, gender, smoking, fasting glucose level, and MABP, baseline BMI was not associated with arteriolar diameter ($p = 0.20$) (Table 2; Figure 1) but was positively associated with wider venular diameter (β coefficient = 0.44, $p < 0.0001$) (Figure 2). Table 2 shows that after adjustment for age, gender, smoking, fasting glucose level, and MABP, persons in the highest quintile of BMI were more likely than those in the lowest quintile to

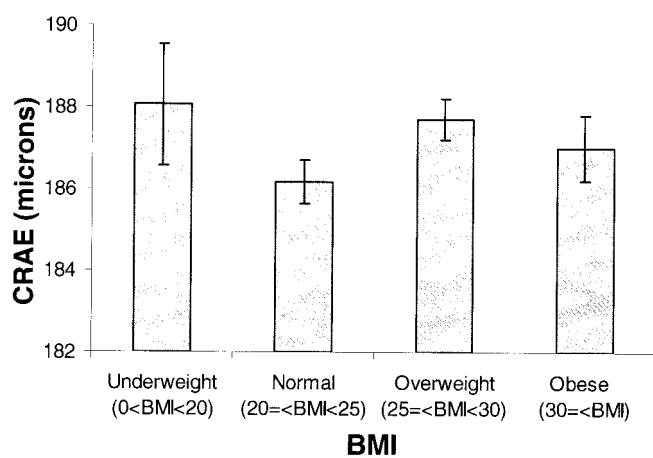


Figure 1: Adjusted mean CRAE by World Health Organization (WHO)-defined categories of BMI in the BMES population (adjusted for age, gender, smoking, fasting glucose level, and MABP).

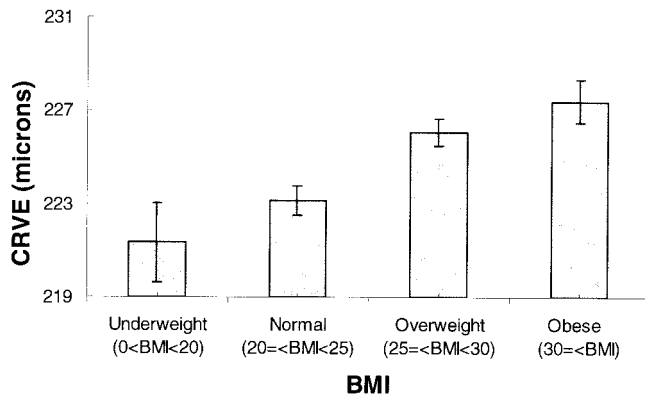


Figure 2: Adjusted mean CRVE by WHO-defined categories of BMI in the BMES population (adjusted for age, gender, smoking, fasting glucose level, and MABP).

have generalized retinal venular dilation (OR, 1.7; 95% CI, 1.3 to 2.4; p for trend < 0.0004). The retinal AVR was inversely associated with BMI (β coefficient = -0.00116, p < 0.0001) (Figure 3). The pattern of association between BMI and retinal vessel diameters was similar in persons without either hypertension or diabetes (Table 2).

Obesity was not associated with retinal vascular signs [focal arteriolar narrowing, OR, 1.1 (95% CI, 0.6 to 1.7); mild and moderate to severe levels of AV nicking, OR, 1.3 (95% CI, 1.1 to 1.7) and 1.0 (95% CI, 0.6 to 1.7); and retinopathy lesions, OR, 1.1 (95% CI, 0.8 to 1.5)]. Findings were similar in persons without either hypertension or diabetes (data not shown).

Longitudinal Association

After adjusting for age, sex, smoking, triglyceride level, and MABP, persons with the widest quintile of venular diameter at baseline were more likely than those with the

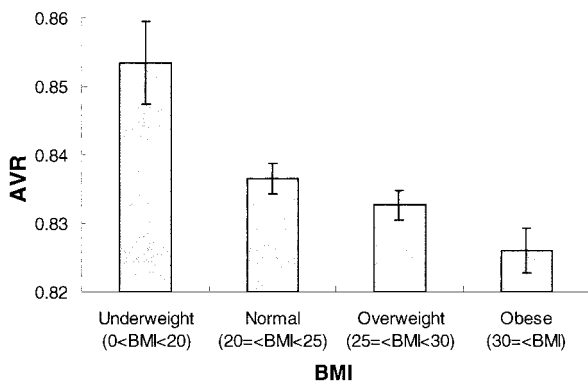


Figure 3: Adjusted mean AVR by WHO-defined categories of BMI in the BMES population (adjusted for age, gender, smoking, fasting glucose level, and MABP).

narrowest quintile to become obese at the 5-year follow-up (OR, 1.8; 95% CI, 1.0 to 3.1) (Table 3). The association between wider venular diameter and incident obesity was similar in persons without either diabetes (OR, 1.8; 95% CI, 1.0 to 3.2) or hypertension (OR, 1.7; 95% CI, 0.8 to 3.1). In a separate analysis that included further adjustment for baseline BMI in the multivariable models, these associations became weaker and non-significant (Table 3).

After excluding 191 participants with missing data, 2143 of the 2334 participants who returned at the 5-year examinations were included for the analysis of significant weight gain. Overall, 136 (6.4%) had a significant weight gain (BMI increases 4 or more units between the baseline and 5-year follow-up). After adjusting for age, sex, smoking, MABP, and triglyceride level, persons with the widest quintile of retinal venular diameter at baseline were more likely than those with the narrowest quintile to have a significant weight gain (OR, 1.7; 95% CI, 0.9 to 3.2).

In these analyses, baseline retinal arteriolar diameter was not associated with either incident obesity (Table 3) or significant weight gain (data not shown). The presence at baseline of retinal vascular signs was not associated with incident obesity (focal arteriolar narrowing, OR, 1.3; 95% CI, 0.6 to 3.0; mild or moderate to severe AV nicking, OR, 0.8; 95% CI, 0.6 to 1.2 and OR 1.1, 95% CI, 0.5 to 2.4; and retinopathy lesions, OR, 1.2; 95% CI, 0.7 to 2.0). Similar findings were found in persons without either hypertension or diabetes (data not shown).

Discussion

In this older Australian population, we found a significant cross-sectional association between wider retinal venular diameter and higher BMI at baseline and a significant longitudinal association between wider retinal venular diameter at baseline and the 5-year incidence of obesity or significant weight gain, independent of age, gender, cigarette smoking, blood pressure, lipid, and glucose levels. Persons with BMI in the highest quintile of the population were 70% more likely to have dilated retinal venules. Non-obese persons with retinal venular diameter in the highest quintile at baseline were 80% more likely to have change in BMI consistent with obesity after 5 years, compared with those in the lowest quintile. Our findings could indicate that wider venular diameter is a marker of high BMI. Alternatively, it is possible that wider venular diameter is an intervening variable in the course of weight gain, indicated by the finding that higher baseline BMI is associated with both wider venular diameter and risk of obesity (1,2) and that the association between wider venular diameter and incident obesity was attenuated in multivariate analyses that also adjusted for baseline BMI (Table 2).

Previous studies of obesity have largely focused on the associations with large vessel disease. Less data are available regarding a possible association between small vessel

Table 3. Longitudinal association between small vessel diameters and incident obesity in the Blue Mountains Eye Study population

Quintiles of retinal vessel diameter	Mean (SD) microns	Affected (%)	Incident obesity ORs (95% confidence intervals)		
			Age-sex-adjusted	Multivariate adjusted*	Multivariate adjusted†
CRVE					
Narrowest	197.8 (9.4)	6.7	1.0	1.0	1.0
Second	215.1 (3.3)	9.9	1.4 (0.8 to 2.5)	1.3 (0.8 to 2.4)	1.1 (0.6 to 2.1)
Third	224.9 (2.7)	10.0	1.4 (0.8 to 2.4)	1.4 (0.8 to 2.4)	1.2 (0.6 to 2.3)
Fourth	235.2 (3.2)	10.8	1.5 (0.9 to 2.6)	1.3 (0.8 to 2.3)	1.1 (0.6 to 2.1)
Widest	253.5 (10.4)	13.9	2.0 (1.2 to 3.3)	1.8 (1.0 to 3.1)	1.4 (0.8 to 2.7)
<i>p</i> for trend		0.0048	0.012	0.052	0.26
BMI at baseline (per unit)					2.1 (1.9 to 2.4)
CRAE					
Widest	211.9 (8.9)	9.8	1.0	1.0	1.0
Fourth	196.8 (2.9)	7.8	0.8 (0.5 to 1.4)	0.8 (0.4 to 1.4)	0.8 (0.4 to 1.4)
Third	187.4 (2.7)	14.7	1.7 (1.1 to 2.7)	1.6 (1.0 to 2.6)	1.4 (0.8 to 2.4)
Second	178.0 (3.0)	9.8	1.1 (0.7 to 1.8)	1.1 (0.6 to 1.8)	1.3 (0.7 to 2.4)
Narrowest	162.4 (9.8)	9.0	1.0 (0.6 to 1.7)	0.9 (0.5 to 1.6)	0.9 (0.5 to 1.6)
<i>p</i> for trend		0.97	0.59	0.85	0.88
BMI at baseline (per unit)					2.1 (1.9 to 2.4)
AVR					
Highest	0.94 (0.04)	7.9	1.0	1.0	1.0
Fourth	0.87 (0.01)	10.5	1.4 (0.8 to 2.3)	1.4 (0.8 to 2.3)	1.4 (0.8 to 2.5)
Third	0.83 (0.01)	10.6	1.4 (0.8 to 2.4)	1.2 (0.7 to 2.0)	1.1 (0.6 to 2.0)
Second	0.80 (0.01)	7.7	1.0 (0.6 to 1.8)	0.9 (0.5 to 1.6)	0.9 (0.5 to 1.7)
Lowest	0.74 (0.03)	14.9	2.2 (1.3 to 3.6)	1.8 (1.1 to 3.0)	1.6 (0.9 to 2.9)
<i>p</i> for trend		0.03	0.0086	0.097	0.29
BMI at baseline (per unit)					2.1 (1.9 to 2.4)

OR, odds ratio; SD, standard deviation; CRVE, central retinal venular equivalent; CRAE, central retinal arteriolar equivalent; AVR, arteriole to venule ratio.

* Adjusted for age, sex, smoking, triglycerides, and mean arterial blood pressure.

† Further adjusted for baseline BMI.

(microvascular) changes and obesity. Our current study now provides prospective, population-based evidence linking diameter changes in the retinal venules to higher BMI and incident obesity. Our findings are consistent with and extend cross-sectional data from the Atherosclerosis Risk in Communities Study that showed wider retinal venular diameter was associated with increased waist diameter (OR, 1.14; 95% CI, 1.03, 1.27) and the metabolic syndrome (OR 1.30, 95% CI, 1.18 to 1.48) in middle-aged persons (34).

Retinal arterioles and venules, such as those measured in the current study, can be considered part of the microcirculation, which encompasses vessels 150 μ m in diameter or smaller in size (16,35). Our study was not designed to

provide an underlying explanation of why retinal venular diameter is associated with BMI. We suggest several possibilities. Firstly, there have been suggestions that microvascular processes may play a role in the pathogenesis of obesity as well as conditions closely associated with obesity, such as hypertension, diabetes, or the metabolic syndrome (36,37), possibly through hyperinsulinemia or inflammatory pathways (17,38–40). For example, a recent population-based study has shown that wider retinal venular diameter is associated with systemic markers of inflammation (white blood cell count, erythrocyte sedimentation rate) independent of blood pressure and other factors (41). Thus, we can postulate that our findings may partly reflect such

systemic processes in the development of obesity (17,38,42). Second, a loss of vascular autoregulation could provide a link between wider venular diameters and higher BMI (19,43,44). A recent clinical study in humans showed that obese women had impaired microvascular function (impaired skin capillary recruitment and acetylcholine-mediated vasodilation) compared with lean women (19). Animal studies show that Zucker rats that develop obesity and diabetes have altered skeletal microvascular circulation (45–47). Renal microvascular autoregulation, which shares similar features as the retinal circulation, has also been found to be impaired in obese Zucker rats (43,44). Third, leptin, a hormone related to fat metabolism and insulin resistance, has been shown to modulate endothelial nitric oxide synthesis and to cause vasodilatation in sympathectomized rats (48). This finding, in combination with possible impaired autoregulation of the retinal vasculature, could explain the altered venular diameter in association with obesity (49–51). Fourth, obese persons have been shown to have increased total blood volume, and because veins and venules are the principal capacitance vessels of the body, this could also explain the increased retinal venular diameter in obese individuals (52). Finally, we note that in multivariate-adjusted analyses that included baseline BMI, the longitudinal association between wider venular diameter and incident obesity was attenuated (OR reduced from 1.8 to 1.4) and became non-significant. Thus, it is also possible that the association between wider venular diameter and incident obesity is partly accounted for by the association between baseline BMI and incident obesity, and retinal venular diameter may be only a surrogate marker of BMI. Further research may provide greater insights and more specific explanations for our study findings.

It is unclear why BMI was not associated with arteriolar diameter. Our previous studies have shown that narrowed retinal arteriolar diameter at baseline predicted incident hypertension (20,21) and diabetes (23), two conditions closely related to obesity. Findings from our study provided no evidence in support of an association between arteriolar change and obesity. It is likely that retinal arteriolar and venular diameters reflect different systemic pathophysiological processes. Arteriolar changes, for example, seem to be strongly associated with elevated blood pressure (21,53,54). Wider retinal venular diameter has been suggested to reflect hyperperfusion resulting from hyperglycemia and lactic acidosis from retinal hypoxia, at least in people with diabetes (25).

Limitations of this study should be discussed. First, because there are distinct anatomical and physiological differences in capillaries between the retinal and the peripheral circulations (35), we cannot assume a complete correlation of change in microvascular caliber in the larger retinal vessels (arterioles and venules) with identical changes in the systemic peripheral vessels. Second, selection bias could

have occurred due to the proportion of our population who did not attend the 5-year follow-up examination. For example, if persons with narrower venular diameter and higher BMI had a higher risk of mortality, this could partially account for the findings of wider venular diameter and incident obesity. Third, although we assessed both cross-sectional and longitudinal associations between retinal vessel diameters and BMI or obesity, our findings cannot be inferred as indicating a causal relationship for either direction.

In conclusion, this study found that older persons with wider retinal venular diameter were more likely to have higher BMI and to develop temporal BMI changes consistent with obesity, independent of age, gender, cigarette smoking, blood pressure, lipids, and glucose levels. Our findings suggest that small vessel changes may be involved in the development of weight gain and obesity.

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