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Effects of Longitudinal Body Mass index Variability on Microvasculature over 5 years in Middle-aged and Elderly Chinese

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Keywords: Body Mass Index, BMI variability, BMI trend, BMI fluctuation, microvasculature, retinal vascular caliber

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What is already known about this subject:

- The retinal vessel is a specific part of human's vascular system which provides a direct window to study early structural changes of the microvascular system.
- Some studies have investigated the cross-sectional association between BMI and microvasculature, as represented by retinal vascular caliber.

What this study adds:

- We explored the impacts of longitudinal BMI variability (BMI trend, BMI fluctuation) on microvasculature.
- Rising BMI trend was found significantly associated with narrower retinal arteriole and wider venule in the overall population, and significantly associated with narrower retinal arteriole even in non-obese individuals.
- BMI fluctuation was not statistically associated with retinal arteriolar or venular caliber.

Abstract

Objective: To explore the associations of 5-year trend and fluctuation in body mass index (BMI) with retinal vascular caliber in a middle-aged and elderly Chinese population.

Methods: Participants age ≥40 years were recruited in a prospective study. Baseline BMI data were collected in 2008 and the participants were re-examined annually until 2012. Retinal vascular caliber was measured from fundus photographs collected in 2012. BMI trend was calculated as the slope of BMI against the time of examinations. BMI fluctuation was defined as the root mean square error around the regression line of BMI over the time (BMI RMSE) and the coefficient of variation of BMI (BMI CV).

Results: Rising BMI trend was associated with narrower retinal arteriolar and wider venular calibers in the overall subjects, especially among persons with overweight and obesity (BMI≥ 25kg/m^2, *P*=0.004 and 0.033, respectively). Rising BMI trend was also found significantly associated with narrower retinal arteriole even in non-obese individuals with BMI <25kg/m^2 (*P*=0.017) when eliminating the effects of hypertension and diabetes. Neither BMI RMSE nor BMI CV was statistically associated with retinal vascular caliber (all *P*>0.05).

Conclusions: Annual rising trending BMI was associated with retinal microvascular alteration. The results suggest that weight gain probably increases the risk of cardiovascular diseases among middle-aged and elderly people.

Keywords: Body Mass Index, BMI variability, BMI trend, BMI fluctuation, microvasculature.

Introduction

Obesity is a well-known risk factor for cardiovascular damage and closely associated with cardiovascular morbidity and mortality in middle-aged and older people (1).Some studies have shown that high body mass index (BMI) can lead to structural damage in the microvascular system, potentially predisposing individuals to the development of clinical cardiovascular disease (CVD) in later life (2, 3).More recently, studies have also revealed that longitudinal variability in body weight/BMI (e.g. BMI change, BMI fluctuation) was also significantly associated with CVD morbidity and mortality (4, 5, 6, 7, 8, 9, 10, 11), which suggests detrimental impacts of the instable body weight/BMI on the vascular system.

The retinal vessel is a specific part of human's vascular system which provides a direct window to study early structural changes of the microvascular system (12). With the advancement of retinal imaging and computer-based analysis techniques, the non-invasive, quantitative measurement of retinal vascular caliber has been made feasible and valid nowadays (12, 13). Alterations in retinal vascular caliber have been recognized as surrogates for systemic microvascular damage and also, predictors for some major macrovascular events such as myocardial infarction and stroke (3, 12, 14, 15, 16).

Some studies have investigated the cross-sectional association between BMI and retinal vascular caliber (12, 15, 17). A few studies have examined the association of longitudinal changes on retinal vascular caliber with the incident obesity and significant weight/BMI gain (18, 19). However, to the best of our knowledge, the impact of longitudinal BMI variability (e.g. longitudinal trend and fluctuation) on microvasculature has not been investigated.

The purpose of the present study was to explore the associations of longitudinal BMI

variability and microvasculature, as represented by retinal vascular caliber, using 5-year annual data on BMI from a middle-aged and elderly Chinese cohort.

Materials and Methods

Study population

The study populations were derived from an ongoing prospective study, the Lingtou Eye Cohort Study, which was mainly designed to investigate the cross-sectional and longitudinal associations of ocular abnormalities and systemic cardiovascular conditions. The participants were government employees who underwent life-long annual health examination at Guangzhou No.11 People's Hospital, Lingtou, Guangzhou, China. Inclusion criteria: ①age ≥ 40 years; ②with gradable retinal imaging; ③able to give their own informed consent. Exclusion criteria: ①with history of cardiovascular events, including myocardial infarction, heart attack and stroke; ②with autoimmune disease, malignant tumor, renal dysfunction and other severe health diseases that would preclude a long-term follow-up; ③with history of intraocular surgery or with any of the following eye diseases: ocular trauma, retinal artery occlusion, retinal vein occlusion and uveitis. Baseline physical and ocular examinations were conducted in 2008. The participants completed a physical examination, including height, weight, and blood pressure measurements. Fasting venous blood was drawn to determine fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-c) and high density lipoprotein cholesterol (HDL-c). A questionnaire was administrated by in-person interview to obtain health related risk factors and personal information, including detailed medical history and demographic socio-characteristics.

Follow-up examinations were performed annually. All the participants who had taken part in the baseline evaluation were invited to come back and attend. The procedures and protocols of the follow-up examinations were the same throughout the study. Up to 2012, a total of four follow-up examinations had been conducted.

The study was approved by the ethics committee of the Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Retinal photography and measurement of retinal vascular caliber

Retinal photographs centered at the optic disk of both eyes were collected in 2012, using a digital fundus camera (TRC-NW6S Topcon, Tokyo, Japan). Retinal vascular caliber was estimated with computer-assisted image analysis software (IVAN, University of Wisconsin, Madison).Three trained graders who were masked to the participants' personal information and BMI characteristics performed the analyses. Retinal vascular caliber in the right eye was measured from the retinal photo database. Left eye measurements were performed only when photographs of the right eye were ungradable. The graders measured all arterioles and venules crossing the circular zone 0.5 to 1.0 disc diameters from the margin of the optic disc. The outcomes were summarized as the average central retinal arteriolar and venular equivalents (CRAE and CRVE) using the Parr–Hubbard (20, 21, 22), representing the hypothesized average retinal arteriolar and venular caliber, respectively. Reliability was assessed by repeated measurements. The intra- and inter-grader intraclass correlation coefficients were 0.83 - 0.93 and 0.81 - 0.93, respectively.

BMI and its variability indices

Weight and height were measured to the nearest 0.1kg and 0.5cm, respectively, with light clothes and no shoes in the morning using the same ultrasonic height/weight/BMI scale (SK-CK+, Songka electronic technology, Shenzhen, China) throughout the study. This device was calibrated every day before use. BMI was calculated as the weight in kilograms divided by the squared height in meters (kg/m^2), representing the relative body weight. Only the participants with a BMI measurement at baseline (2008) and 2012 and a total of at least three BMI measurements during the 5-year follow-up period were included in the BMI variability analysis.

BMI variability was divided into two distinct components: trend over time and fluctuation over time. A simple linear regression model was used in which each individual's BMI values were regressed on the time of the survey. The slope coefficient of this model was used to represent an individual's overall longitudinal trend of BMI over time in terms of direction and magnitude (BMI trend), and mean of the individual's systematic weight increase (weight gain) or decrease (weight loss). The root mean square error around the slope (BMI RMSE) and the coefficient of variation of each participant's BMI values taken at each examination (BMI CV, defined as the standard deviation divided by the BMI mean) were used to represent the BMI fluctuation magnitude.

Definition of other characteristics

Sitting blood pressure was measured in the right arm using an oscillometric blood pressure

recorder (Omron HEM-906, OMRON Corporation, Kyoto, Japan). The device was calibrated every week before use. After the participant had sat at rest for 30 minutes, a single measure of blood pressure was taken using a cuff of appropriate size. Mean arterial pressure (MAP) was calculated as one-third of the systolic plus two-thirds of the diastolic blood pressure. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or as having a previous diagnosis of hypertension and using antihypertensive medication. Diabetes mellitus was defined as a fasting plasma glucose level ≥7.0 mmol/l, a self-reported history of diabetes, or use of diabetic medication.

Statistical Analysis

Univariate and multivariate linear regression analyses were used to explore the association between variability in BMI and retinal vascular caliber. In univariate analyses, variables with a *P* value of < 0.1 in association with retinal vascular caliber were considered as potential risk factors and included in multivariable analysis. The associations of longitudinal BMI trend and fluctuation with retinal vascular caliber were explored in three models. Model 1 was initially adjusted for age, gender and baseline BMI, and Model 2 additionally adjusted for TG, TC, FPG, MAP, cigarette smoking, alcohol drinking, physical activity, and diet. Fellow retinal vascular caliber (CRVE for CRAE and CRAE for CRVE) was also adjusted in Model 2 to control for influences from immeasurable variables like body size, genetic and magnification factors (23, 24). Since fasting plasma glucose trend (FPG trend) (25), systolic blood pressure trend (SBP trend), and diastolic blood pressure trend (DBP trend) (data not shown) were found significantly associated with retinal vascular caliber, we further adjusted these

variables in Model 3. Moreover, to compare the difference and similarity of the associations of BMI trend and fluctuation with retinal vascular caliber in BMI categories, the effects stratified below and above BMI 25kg/m^2 (a cutoff recommended by World Health Organization) at baseline were analyzed. Statistical analyses were performed using STATA (version12.0, Stata Corp., College Station, TX). All *P* values presented were two-sided, and *P*<0.05 was regarded as statistically significant. All data were displayed as mean ± SD, mean (95% confidence interval) or proportion, if not otherwise indicated.

Results

Among the 4063 eligible participants who had BMI measurements in 2008, 3494 with at least 3 measurements in the 5-year follow-up period (86.0%) were available for our analysis. One hundred and fourteen (2.8%) participants were excluded because of missing data on retinal vascular caliber and another 455 (11.2%) were excluded due to incomplete physical examinations. Compared to the 569 excluded subjects, those included in the analysis had higher MAP and lower fasting plasma glucose levels (both *P*<0.001) at baseline, while the other baseline characteristics were not significantly different (all *P*>0.05, data not shown).

The characteristics of the participants at baseline (2008) and endpoint (2012) are shown in Table 1. In the study population, 2091 (59.9%) were men, and 1403 (40.1%) were women, with an average age of 59.3 ±8.3 years at baseline. The BMI mean at baseline and in 2012 were 24.0 ± 3.0 kg/m^2 and 24.2± 3.1 kg/m^2, respectively. BMI at 2012 was significantly higher than at baseline (*P*<0.001). The percentage of participants with hypertension and diabetes mellitus increased from 46.5% to 55.3% and from 11.8% to 17.7%, respectively

(both *P*<0.001).

Characteristics of 5-year BMI profile in the current study are shown in Table 2. 2063 (59.0%) subjects had an annual rising trend (BMI trend >0 kg/m^2/y). Table 3 and table 4 present the associations of BMI trend and fluctuation with retinal arteriolar and venular caliber respectively. In the overall subjects, Rising BMI trend was found significantly associated with narrower retinal arteriole (β=-2.89, *P*=0.001) and wider venule (β=2.21, *P*=0.039), after adjusted for age, gender, TG, TC, FPG, MAP, baseline BMI, cigarette smoking, alcohol drinking, physical activity, diet, SBP trend, DBP trend, FPG trend and fellow retinal vascular caliber. The associations of rising BMI trend with narrower retinal arteriole and wider venule were abolished among the subjects with BMI <25kg/m^2, however the associations of rising BMI trend with narrower retinal arteriole and wider venule were still observed among those with BMI ≥25kg/m^2(β=-3.96 and 3.55, *P*=0.004 and 0.033, respectively). The measurements of BMI fluctuation (BMI RMSE, BMI CV) were not statistically associated with retinal arteriolar or venular caliber (all *P*>0.05).

With the consideration of possible effects of hypertension and/or diabetes on retinal vascular caliber, we further investigated the associations in persons without hypertension and/or diabetes throughout the follow-up period (table 5 and table 6).The association of rising BMI trend with narrower retinal arteriole was also found in the overall subjects (β=-4.07, *P*=0.003). Furthermore, the significant association was also observed in the subjects with BMI <25kg/m^2 (β=-4.08, *P*=0.017) and BMI ≥25kg/m^2 (β=-4.29, *P*=0.027). The association of BMI trend with retinal venular caliber was not found in the overall subjects without hypertension or diabetes and those with BMI<25kg/m^2. However, the significant

association of BMI trend and wider venule was still found in those subjects with BMI ≥25kg/m^2 (β=6.66, *P*=0.028).There was still no association between BMI fluctuation with retinal venular caliber (all *P*>0.05).

Discussion

To the best of our knowledge, this is the first study to report the effects of long-term BMI variability on microvasculature, as represented by retinal vascular caliber. In this sample of middle-aged and elderly Chinese, we found significant association between BMI trend and retinal arteriolar and venular alteration irrespective of the initial BMI. However, there was no significant association between the measurements of BMI fluctuation and alterations in retinal vascular caliber.

In the current study, we have observed BMI trend was associated with retinal arteriolar and venular alteration in the overall subjects, especially among persons with overweight and obesity (BMI≥25kg/m^2). It is noteworthy that rising BMI trend was found significantly associated with narrower retinal arteriole even in non-obese individuals (BMI <25kg/m^2) when eliminating the effects of hypertension and diabetes. The association was linear, such that annual BMI gain was association with an annual narrowing in retinal arteriolar caliber and widening in venular caliber. Alterations in retinal vascular caliber have been recognized as a surrogate for microvascular damage (3, 12). Narrower retinal arteriole and wider venule were significantly associated with CVD, and independently predicted CVD morbidity and mortality. Results from our study may therefore suggest that BMI gain over time may have a significant effect on microvasculature alteration, even in non-obese individuals, and thus

may increase the risk of CVD morbidity and mortality.

Fluctuation in body weight is a common phenomenon, which is defined as repeated weight gains and losses over time. Limited studies showed that large fluctuation in weight are associated with increased diseases and death, especially cardiovascular diseases (9, 10) which suggesting that BMI fluctuation might also have vascular effects. In our study, we first studied the association between BMI fluctuation and vasculature and found that there was no association between BMI fluctuation and retinal vascular caliber.

Mechanisms responsible for the association of rising BMI trend with narrower retinal arteriole and wider venule are unclear. We speculate that, first, increased body weight promotes low-grade inflammation and increases the levels of some vasoconstrictor molecules. Concomitant production of inflammatory and vasoconstrictor factors (TNFα, IL-6, angiotensin-II, endothelin-1, and other metabolites of arachidonic acid) would lead to retinal arteriolar narrowing (26, 27). On the other hand, some systemic inflammatory markers (white blood count, erythrocyte sedimentation rate, high-sensitivity C-reactive protein) and inflammation-related microvascular dysfunction may result in retinal venular widening (12, 15, 18). Second, insulin is a powerful vasodilator substance, which causes vascular dilation and exerts direct dose-dependent vasodilatory effects on the vasculature (28). The enlarged adipose tissue mass with excessive weight gain would lead to insulin resistance (29). The insulin-resistant state would impair the insulin-induced vasodilatory effects of microvessels. In addition, insulin resistance may predispose individuals to endothelial dysfunction and atherosclerosis (30), which possibly contributes to arteriolar alteration. Third, nitric oxide (NO) derived from vascular endothelium is a potent relaxing factor causing vascular

vasodilatation (31). The levels of NO and its reactions to vasodilator acetylcholine tend to decrease in those with excessive body weight. This might result in impaired vasodilatation of the vasculature and endothelium-dependent dysfunction (32), thereby potentially explaining the subsequent vascular vasoconstriction.

In addition, weight gain may increase the level of leptin, which is directly related to adipose tissue abundance (33). Leptin, a hormone mainly secreted by adipose tissue (34), has been shown to induce oxidative stress in endothelial cells (35), increase vascular cell calcification (36), and stimulate smooth muscle cell proliferation and migration (37); all of which can contribute to microvascular change. Moreover, leptin has two opposite effects on the regulation of vascular tone. It induces direct and indirect vasodilatation through endothelial mechanisms and the endothelial NO system respectively, which may cause widening in retinal venule (18, 38). On the other hand, leptin also induces indirect vasoconstriction through central stimulation of sympathetic nervous activity (38). In particular circumstances, the increase in contractile effect of the sympathetic nervous activity induced by leptin might overcome its opposite vasodilator effect in retinal arteriole. The imbalance of vasomotor tone may be responsible for retinal arteriolar vasoconstriction. Besides, people with excessive weight tend to have increased total blood volume, and capacitance venous vessels dilate to accommodate this increased volume, which could explain wider retinal venule (12). Finally, ion channels in smooth muscle regulate vascular tone. Changes in the activity of microvascular Ca^{2+} and k^{+} channels could elicit vasoconstriction (39), which may contribute to obesity-induced arteriolar narrowing.

As is mentioned above, a few studies suggested that BMI fluctuation might have

vascular effects. However, we didn't find the associations between BMI fluctuation and microvasculature in our study. One possible explanation for this disagreement on findings is that weight fluctuation in the current study had little vascular impact on the microcirculation compared with weight change. In the studied population, the amplitudes of fluctuation were comparatively mild, making it difficult to detect measurable changes in the retinal microvasculature. Another possible explanation is that weight fluctuation might essentially have no discernible microvascular effects. Further studies are required to clarify this issue.

The strengths of this study include its large sample collected using standardized methods throughout the study. In addition, the data used in our study were based on sequential annual physical examinations. Therefore, we could use real measurements for the weight and height instead of self-reported values to calculate BMI and its variability, which removes information bias and guarantees the authenticity and reliability of BMI and its variability indices. Potential limitations of our study include the make-up of the study sample, which mainly consisted of government employees. This could possibly have resulted in sampling bias. Therefore, caution is needed when generalizing the findings of this study. We also did not collect information on the reasons for BMI change because the final outcome variable of the study was relative body weight.

In summary, this study revealed that annual rising trend in BMI is significantly associated with narrower retinal arteriole and wider venule, while BMI fluctuation is not associated with retinal vascular caliber. Our results suggest that weight gain may result in microvascular alteration, even in non-obese individuals without hypertension and diabetes. This change on microvasculature perhaps suggests an increased risk of cardiovascular diseases among

middle-aged and elderly people.

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Table 1. Characteristics of the study population in 2008 and 2012

Characteristic	N=3494		*P*
	2008	2012	
Age (year)	59.3 ±8.3	63.3 ±8.3	<0.001
Men (n, %)	2091 (59.9%)	2091 (59.9%)	---
Hypertension (n, %)	1625(46.5%)	1933(55.3%)	<0.001
Diabetes mellitus (n, %)	412(11.8%)	617(17.7%)	<0.001
TG (mmol/L)	1.75±1.43	1.73±1.40	0.406
TC (mmol/L)	5.46±0.95	5.43±1.05	0.086
LDL-c (mmol/L)	3.79±0.88	3.30±0.92	<0.001
HDL-c (mmol/L)	1.48 ±0.01	1.55±0.01	<0.001
FPG (mmol/L)	5.59±1.31	5.77±1.41	<0.001
MAP (mmHg)	93.1 ± 12.1	90.4 ± 11.4	<0.001
BMI (kg/m^2)	24.0 ± 3.0	24.2 ± 3.1	<0.001
Education status			
<high school (n, %)	475(13.6%)	---	---
High school (n, %)	835(23.9%)	---	---
>high school (n, %)	2184(62.5%)	---	---

Data are presented as mean ± standard deviation or number (proportion), and compared using paired *t* test.

Table 2. Characteristics of 5-year BMI profile in studied population

BMI trend, kg/m^2/y	
Overall (n=3494)	
mean	0.06 ± 0.33
Rising trend	
Number (%)	2063(59.0%)
Median	0.22(0.10, 0.37)
Stable or descending trend	
Number (%)	1431(41.0%)
Median	-0.18(-0.33, -0.08)
BMI fluctuation	
BMI RMSE, kg/m^2	0.53 ± 0.33
BMI CV, %	3.00 ± 1.00

Data are presented as mean ± standard deviation, number (proportion), or median (25th to 75th percentile)

Table3. Associations of variability indices in BMI with retinal arteriolar caliber

	Model 1		Model 2		Model 3	
	β (95%CI)	*P*	β (95%CI)	*P*	β (95%CI)	*P*
All subject, n=3494						
BMI trend, kg/m^2/y	-2.79(-4.87,-0.72)	0.008	-2.49(-4.21,-0.77)	0.004	-2.89(-4.64,-1.14)	0.001
BMI RMSE, kg/m^2	-1.68(-3.81,0.45)	0.122	-0.93(-2.67,0.82)	0.297	-0.80(-2.56,0.96)	0.371
BMI CV, %	-0.61(-1.11,-0.11)	0.016	-0.40(-0.81,0.01)	0.054	-0.38(-0.79,0.03)	0.072
BMI<25kg/m^2, n=2241						
BMI trend, kg/m^2/y	-2.12(-4.85,0.60)	0.127	-1.82(-4.09,0.44)	0.115	-2.13(-4.45,0.18)	0.071
BMI RMSE, kg/m^2	-2.24(-5.06,0.57)	0.119	-1.13(-3.44,1.18)	0.338	-0.95(-3.29,1.39)	0.427
BMI CV, %	-0.84(-1.47,-0.21)	0.009	-0.45(-0.97,0.07)	0.089	-0.41(-0.94,0.11)	0.123
BMI≥25kg/m^2, n=1253						
BMI trend, kg/m^2/y	-3.68(-6.89,-0.46)	0.025	-3.33(-5.97,-0.68)	0.014	-3.96(-6.65,-1.27)	0.004
BMI RMSE, kg/m^2	-0.74(-4.01,2.53)	0.658	-0.55(-3.23,2.13)	0.686	-0.51(-3.19,2.17)	0.710
BMI CV, %	-0.16(-0.98,0.65)	0.699	-0.29(-0.95,0.38)	0.399	-0.26(-0.93,0.41)	0.440

Model 1: adjusted for age, gender and baseline BMI.

Model 2: adjusted for age, gender, baseline BMI, TG, TC, FPG, MAP, cigarette smoking, alcohol drinking, physical activity, diet factors, and fellow retinal vascular caliber.

Model 3: further adjusted for SBP trend, DBP trend, FPG trend on the basis of Model 2.

Table4. Associations of variability indices in BMI with retinal venular caliber

	Model 1		Model 2		Model 3	
	β (95%CI)	*P*	β (95%CI)	*P*	β (95%CI)	*P*
All subject, n=3494						
BMI trend, kg/m^2/y	0.68 (-1.80, 3.17)	0.590	1.98(-0.09,4.04)	0.061	2.21(0.11,4.31)	0.039
BMI RMSE, kg/m^2	-1.27 (-3.83,1.28)	0.328	-0.24(-2.34,1.86)	0.824	-0.29(-2.40,1.81)	0.785
BMI CV, %	-0.31 (-0.91,0.28)	0.304	0.07(-0.42,0.56)	0.780	0.05(-0.44,0.54)	0.838
BMI<25kg/m^2, n=2241						
BMI trend, kg/m^2/y	0.87(-2.36,4.11)	0.596	1.47(-1.23,4.16)	0.286	1.51(-1.24,4.26)	0.281
BMI RMSE, kg/m^2	-1.78(-5.13,1.56)	0.295	-0.32(-3.07,2.43)	0.820	-0.42(-3.20,2.36)	0.768
BMI CV, %	-0.55(-1.30,0.20)	0.149	-0.05(-0.67,0.56)	0.865	-0.08(-0.70,0.55)	0.810
BMI≥25kg/m^2, n=1253						
BMI trend, kg/m^2/y	0.68(-3.23,4.58)	0.734	2.83(-0.40,6.06)	0.086	3.55(0.28,6.82)	0.033
BMI RMSE, kg/m^2	-0.07(-4.04,3.90)	0.973	0.31(-2.96,3.57)	0.854	0.41(-2.83,3.66)	0.803
BMI CV, %	0.26(-0.73,1.25)	0.608	0.37(-0.44,1.19)	0.366	0.36(-0.45,1.17)	0.384

Model 1: adjusted for age, gender and baseline BMI.

Model 2: adjusted for age, gender, baseline BMI, TG, TC, FPG, MAP, cigarette smoking, alcohol drinking, physical activity, diet factors, and fellow retinal vascular caliber.

Model 3: further adjusted for SBP trend, DBP trend, FPG trend on the basis of Model 2.

Table 5. Associations of variability indices in BMI with retinal arteriolar caliber in the subjects without hypertension or diabetes

	Model 1		Model 2		Model 3	
	β (95%CI)	*P*	β (95%CI)	*P*	β (95%CI)	*P*
All subject, n=1395						
BMI trend, kg/m^2/y	-4.25(-7.46,-1.04)	0.010	-3.70(-6.37,-1.03)	0.007	-4.07(-6.80,-1.34)	0.003
BMI RMSE, kg/m^2	1.17(-2.33,4.66)	0.513	0.88(-2.00,3.76)	0.550	0.94(-1.96,3.83)	0.526
BMI CV, %	-0.52 (-1.32, 0.28)	0.202	-0.40(-1.05,0.26)	0.235	-0.41(-1.07,0.25)	0.225
BMI<25kg/m^2, n=1081						
BMI trend, kg/m^2/y	-5.18(-9.06,-1.30)	0.009	-3.91(-7.17,-0.65)	0.019	-4.08(-7.44,-0.72)	0.017
BMI RMSE, kg/m^2	2.27(-1.90,6.44)	0.286	1.23(-2.22,4.68)	0.484	1.28(-2.20,4.76)	0.470
BMI CV, %	-0.46(-1.39,0.46)	0.324	-0.35(-1.12,0.41)	0.367	-0.36(-1.13,0.42)	0.368
BMI≥25kg/m^2, n=314						
BMI trend, kg/m^2/y	-4.74(-8.50,-0.98)	0.014	-4.22(-8.05,-0.39)	0.031	-4.29(-8.10,-0.49)	0.027
BMI RMSE, kg/m^2	-2.04(-8.27,4.20)	0.521	-0.88(-6.01,4.24)	0.733	-1.24(-6.34,3.86)	0.632
BMI CV, %	-0.69(-2.28,0.90)	0.392	-0.51(-1.82,0.79)	0.438	-0.56(-1.86,0.73)	0.394

Model 1: adjusted for age, gender and baseline BMI.

Model 2: adjusted for age, gender, baseline BMI, TG, TC, FPG, MAP, cigarette smoking, alcohol drinking, physical activity, diet factors, and fellow retinal vascular caliber.

Model 3: further adjusted for SBP trend, DBP trend, FPG trend on the basis of Model 2.

Table 6. Associations of variability indices in BMI with retinal venular caliber in the subjects without hypertension or diabetes

	Model 1		Model 2		Model 3	
	β (95%CI)	*P*	β (95%CI)	*P*	β (95%CI)	*P*
All subject, n=1395						
BMI trend, kg/m^2/y	0.41 (-3.46, 4.29)	0.834	2.40(-0.84,5.63)	0.147	2.66(-0.66,5.97)	0.116
BMI RMSE, kg/m^2	0.67 (-3.54, 4.88)	0.756	-0.17(-3.64,3.30)	0.925	-0.20(-3.70,3.31)	0.912
BMI CV, %	-0.07 (-1.03, 0.89)	0.887	0.20(-0.58,1.00)	0.607	0.23(-0.57,1.03)	0.571
BMI<25kg/m^2, n=1081						
BMI trend, kg/m^2/y	-0.80(-5.39,3.79)	0.732	1.45(-2.42,5.32)	0.463	1.52(-2.49,5.52)	0.458
BMI RMSE, kg/m^2	2.74(-2.18,7.66)	0.275	0.78(-3.30,4.86)	0.707	0.75(-3.38,4.88)	0.722
BMI CV, %	0.13(-0.96,1.22)	0.814	0.28(-0.63,1.18)	0.546	0.31(-0.61,1.23)	0.513
BMI≥25kg/m^2, n=314						
BMI trend, kg/m^2/y	4.37(-2.89,11.63)	0.237	5.33(0.65,11.31)	0.080	6.66(0.74,12.57)	0.028
BMI RMSE, kg/m^2	-4.52(-12.67,3.63)	0.276	-2.33(-9.03,4.37)	0.494	-2.01(-8.65,4.63)	0.551
BMI CV, %	-0.60(-2.68,1.48)	0.573	0.08(-1.79,1.63)	0.931	0.04(-1.65,1.73)	0.963

Model 1: adjusted for age, gender and baseline BMI.

Model 2: adjusted for age, gender, baseline BMI, TG, TC, FPG, MAP, cigarette smoking, alcohol drinking, physical activity, diet factors, and fellow retinal vascular caliber.

Model 3: further adjusted for SBP trend, DBP trend, FPG trend on the basis of Model 2.