



# The Association of Rate of Weight Gain During Early Adulthood With the Prevalence of Subclinical Coronary Artery Disease in Recently Diagnosed Type 2 Diabetes: The MAXWEL-CAD Study

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## OBJECTIVE

To investigate the association of the rate of weight gain ( $\text{Rate}_{\text{max\_wt}}$ ) between the age of 20 years and the age of maximum lifetime weight gain with indicators of subclinical coronary artery disease (CAD) at the time of diagnosis of type 2 diabetes (T2D).

## RESEARCH DESIGN AND METHODS

We studied 1,724 consecutive Korean subjects aged  $\geq 30$  years with recently diagnosed (within 3 months) T2D and one or more cardiovascular risk factors to investigate the association of  $\text{Rate}_{\text{max\_wt}}$  with subclinical CAD. We used 64-slice cardiac computed tomography angiography to evaluate the degree of coronary artery stenosis, multivessel involvement, plaque characteristics, and coronary artery calcium score (CACS). Body weight at age 20 years ( $\text{Wt}_{20y}$ ) was obtained from participant records. Participants recalled their maximum weight ( $\text{Wt}_{\text{max}}$ ) before T2D diagnosis and age at maximum weight ( $\text{Age}_{\text{max\_wt}}$ ). The  $\text{Rate}_{\text{max\_wt}}$  was calculated as  $(\text{Wt}_{\text{max}} - \text{Wt}_{20y}) / (\text{Age}_{\text{max\_wt}} - 20 \text{ years})$ .

## RESULTS

The prevalence of coronary artery stenosis ( $\geq 50\%$ ), multivessel involvement (two or more vessels), plaque characteristics, and  $\text{CACS} \geq 100$  were 11.4%, 6.6%, 19.7%, and 12.8%, respectively. Mean  $\text{Wt}_{20y}$  and  $\text{Wt}_{\text{max}}$  were  $60.1 \pm 10.5$  and  $73.0 \pm 11.5$  kg, respectively. Mean  $\text{Age}_{\text{max\_wt}}$  was  $41.3 \pm 10.7$  years, and  $\text{Rate}_{\text{max\_wt}}$  was  $0.59 \pm 0.56$  kg/year. After adjusting for cardiovascular risk factors, including current BMI, the highest quarter of prior weight gain was significantly associated with coronary artery stenosis, multivessel involvement, and plaque characteristics, particularly mixed and noncalcified plaque.

## CONCLUSIONS

The findings suggest that a greater rate of prior weight gain may accelerate the development of subclinical vascular complications in patients with newly diagnosed T2D.

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Overweight and obesity are major risk factors for the development of type 2 diabetes (T2D) (1). Excess body fat increases insulin resistance, a condition characterized by increased insulin production and impaired glucose tolerance (2).

Even if it does not lead to obesity, weight gain by itself is associated with an increased risk of T2D and its complications (3,4). We recently showed a U-shaped association of BMI at T2D diagnosis but with higher cardiovascular disease and total mortality risks beyond a BMI of 30 kg/m<sup>2</sup> in white men and women living in Scotland (5). Although weight gain antedates the development of T2D by several years, quantitative investigation of the relationship between the amount and rate of weight gain and subclinical coronary artery disease (CAD) associated with T2D is lacking.

Weight gain may affect coronary vascular health by influencing various risk factors, such as insulin resistance, dyslipidemia, hypertension, the inflammatory process, and the prothrombotic state. Upper-airway tightness associated with weight gain can induce obstructive sleep apnea syndrome, leading to systemic insulin resistance (6).

Many studies have shown that overweight or obesity predisposes a person to heart diseases, such as heart failure and CAD (4,7). The pathophysiology of these entities and their link to obesity have been discussed previously (8).

Recent advances in computed tomography (CT) technology have allowed for a detailed evaluation of the coronary arteries, including the extent of stenosis and plaque composition (9,10). Noncalcified or mixed plaques are known to be more vulnerable to rupture than stabilized calcified plaques (11).

The current study examined the association between the rate of weight gain ( $\text{Rate}_{\text{max\_wt}}$ ) between the age of 20 years and the age at maximum lifetime weight with indicators of subclinical CAD at the time of T2D diagnosis. We hypothesized that rapid weight gain over and above the current BMI increases the risk of subclinical CAD in patients with newly diagnosed T2D.

## RESEARCH DESIGN AND METHODS

### Study Population

We established a cohort in 2006 to investigate the effect of maximum body weight in lifetime on the development

of T2D and its complications, the MAXWEL (12). We screened 5,321 individuals aged  $\geq 30$  years who visited the diabetes clinic for an initial evaluation at Seoul National University Bundang Hospital (SNUBH), Seongnam, Korea, from January 2007 to December 2009.

T2D was confirmed in 2,986 of these patients according to a glycosylated hemoglobin (A1C)  $\geq 6.5\%$  based on American Diabetes Association diagnostic criteria (13). Among this subset, we excluded 32 patients who had exertional chest pain with moderate to severe intensity that lasted 2–5 min over the sternum and that was relieved in 1–5 min by ceasing activities. Chest pain that radiated to either the shoulder or both arms was also included in this category. We also excluded patients with existing CAD or who received primary coronary intervention or coronary artery bypass graft according to their medical records or history taking if the medical record was not available. Finally, 2,044 participants without typical angina chest pain or existing CAD but with one or more risk factors were selected to enhance the power of the study. The risk factors were as follows: 1) BMI  $\geq 25$  kg/m<sup>2</sup> (overweight); 2) LDL cholesterol (LDL-C) level  $\geq 130$  mg/dL or taking statin medication; 3) triglyceride level  $\geq 150$  mg/dL, HDL cholesterol (HDL-C) level  $< 40$  mg/dL in men or  $< 50$  mg/dL in women, or taking lipid-lowering medications other than statins; 4) systolic blood pressure (SBP)/diastolic blood pressure (DBP)  $\geq 140/90$  mmHg or taking antihypertensive medication based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (14); 5) current smoker; and 6) a family history of CAD.

Patients with type 1 diabetes (measured by GAD antibody [ $n = 12$ ]) or diabetes with a secondary cause ( $n = 9$ ) were excluded. We also excluded patients with chronic diseases such as malignancy ( $n = 23$ ), gastrointestinal disorder ( $n = 16$ ), lung disease ( $n = 26$ ), and eating disorder and/or depression ( $n = 14$ ) or a history of taking medication for weight control for  $> 3$  months ( $n = 18$ ).

One hundred sixty-six subjects were excluded because they were unable to recall their maximum weight ( $\text{Wt}_{\text{max}}$ ) or age at maximum weight ( $\text{Age}_{\text{max\_wt}}$ ). Another 36 with a high serum creatinine

level ( $> 1.5$  mg/dL in men,  $> 1.4$  mg/dL in women) were excluded because of a contraindication to the radiocontrast dye. Finally, 1,724 participants gave written informed consent for CAD evaluation using cardiac CT angiography (CTA), which was performed within 3 months after T2D diagnosis. The protocol was reviewed and approved by the institutional review board of SNUBH (B-0909/083-008). This study was registered at ClinicalTrials.gov (NCT00816608).

### Assessment of Weight-Related Information

Body weight at age 20 years ( $\text{Wt}_{20y}$ ) was obtained in 54% of study participants from medical records, military service or college examination records, or personal records.  $\text{Wt}_{\text{max}}$  before T2D diagnosis and  $\text{Age}_{\text{max\_wt}}$  were self-reported. Weight from pregnancy and to 1 year after delivery was disregarded. In 31.0% of subjects ( $n = 535$ ) who were randomly selected from all participants, the recalled  $\text{Wt}_{20y}$  and  $\text{Wt}_{\text{max}}$  were validated by written documentation, including medical records, military service or college examination records, or personal recording. The absolute differences between the recalled  $\text{Wt}_{20y}$  and  $\text{Wt}_{\text{max}}$  and the written documentation were  $1.2 \pm 1.1$  and  $1.3 \pm 1.2$  kg, respectively. The actual differences between them were  $-0.2 \pm 1.7$  and  $-0.3 \pm 1.8$  kg, respectively. When agreement was defined as an absolute difference of  $\leq 0.5$  kg between the recalled  $\text{Wt}_{20y}$  and  $\text{Wt}_{\text{max}}$  and those obtained from written documentation, the agreement rates were high ( $r = 0.94$  and  $r = 0.92$ , respectively; both  $P < 0.001$ ) (Supplementary Fig. 1). We calculated the  $\text{Rate}_{\text{max\_wt}}$  by dividing the weight change (in kilograms) after age 20 years by the time difference in years between age 20 years and  $\text{Age}_{\text{max\_wt}}$ . The definitions of weight-related variables as well as the study design are shown in Fig. 1.

### Lifestyle Characteristics and Family History of CAD

Interviews for lifestyle characteristics were conducted by designated physicians using a standardized survey. Smoking status was divided into three categories: nonsmokers, ex-smokers, and current smokers. Alcohol intake was assessed by frequency and quantity of beer, spirits, sake, and wine intake

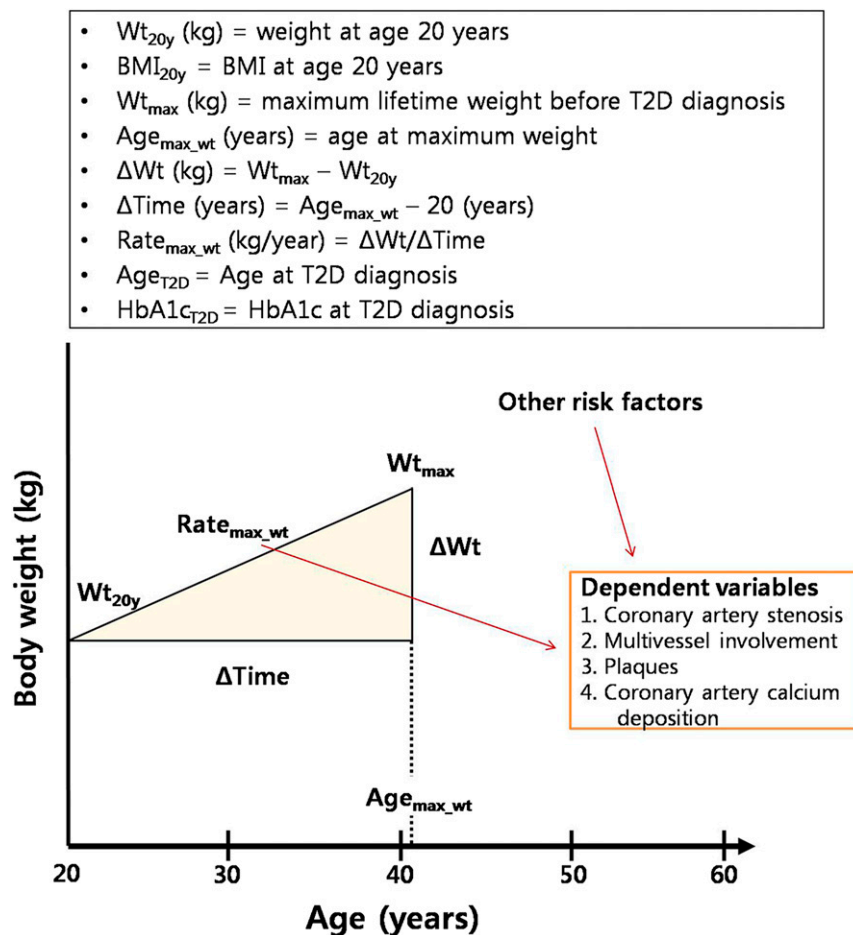


Figure 1—Definitions of weight-related variables and the study design.

during the past 12 months. Alcohol intake in grams of alcohol per week fell into two categories: light to moderate ( $\leq 199.9$  g/week) and heavy ( $\geq 200$  g/week). Physical activity fell into two categories: no or irregular (two or fewer times per week) and regular (three or more times per week), with each period defined as exercising for at least 30 min. Family history of CAD at age  $< 60$  years included first-degree relatives.

**Anthropometric Parameters**

At the time of T2D diagnosis, height and body weight were measured with the participants barefooted and wearing light clothing to the nearest 0.1 cm or 0.1 kg, respectively. SBP and DBP were measured twice with a 5-min interval after the participant had been sitting for 10 min. The mean value for each blood pressure measurement was used.

**Biochemical Parameters**

Fasting glucose level and other biochemical parameters were measured

in a 12-h fasted state at the time of T2D diagnosis (Hitachi 747 chemistry analyzer; Hitachi, Tokyo, Japan). A1C level was measured in SNUBH, a National Glycohemoglobin Standardization Program Level II–certified laboratory.

**Cardiac CTA**

Cardiac CTA was performed at the time of T2D diagnosis with a 64-slice CT scanner (Brilliance 64; Philips Medical Systems, Best, the Netherlands) and standard scanning protocol (15). The median time difference between T2D diagnosis and cardiac CTA was 34 days (range, 0–92 days). All scans were analyzed independently in a blinded fashion by two experienced radiologists using a three-dimensional workstation (Brilliance; Philips Medical Systems). All coronary segments  $\geq 1.5$  mm in diameter were assessed. Image quality was evaluated on a per-segment basis, and noninterpretable segments were excluded from the analysis.

**Coronary Artery Stenosis**

Coronary artery stenosis was assessed by tracing semiautomatically the contrast-enhanced portion of the coronary lumen at the maximal stenotic site and comparing this with the proximal and distal reference sites (16). Narrowing of  $\geq 50\%$  of the lumen was defined as significant stenosis according to the modified classification by the American Heart Association (AHA) (17).

**Multivessel Involvement**

Multivessel disease was defined as the presence of stenosis of  $\geq 50\%$  in two or more coronary vessels.

**Atherosclerotic Coronary Segments (Any Plaque) and Plaque Characteristics**

The atherosclerotic coronary segment was identified for coronary artery segments with any plaque, which was defined as a structure of  $\geq 1$  mm<sup>2</sup> within and/or adjacent to the coronary vessel lumen that could be distinguished clearly from the lumen and surrounding epicardial

fat. Every single interpretable coronary artery segment was evaluated for the presence of plaque and its characteristics. Each plaque was categorized into one of three types: 1) calcified plaque containing calcified tissue occupying  $\geq 50\%$  of the plaque area (density  $> 130$  Hounsfield units on native scans); 2) mixed plaque containing calcified tissue occupying  $< 50\%$  of the plaque area; and 3) noncalcified plaque, which had no calcified tissue (16).

#### Calcium Score

The Agatston score was used as the coronary artery calcium score (CACS) (18). The CACS was categorized into two groups:  $< 100$  and  $\geq 100$ .

#### Statistical Analysis

All data are presented as the mean and SD or percentage and were analyzed with SPSS for Windows version 17.0 (IBM Corporation, Armonk, NY). The distributions of triglyceride level and  $\text{Rate}_{\text{max\_wt}}$  were skewed (Kolmogorov-Smirnov  $Z = 1.216$  and  $1.325$ , respectively; both  $P < 0.05$ ), and the values of triglyceride level and  $\text{Rate}_{\text{max\_wt}}$  were normalized by logarithmic transformation for all analyses. The Student  $t$  and  $\chi^2$  tests were used to compare variables. Coronary artery stenosis, multivessel involvement, atherosclerotic coronary segments (any plaque), plaque type, and CACS were compared according to quartiles of  $\text{Rate}_{\text{max\_wt}}$ .

To test independent associations of weight gain with various coronary lesions independent of  $\text{Wt}_{20y}$ , weight at T2D diagnosis, and other cardiovascular risk factors, we applied four separate multivariable logistic regression models to examine for associations with coronary artery stenosis ( $\geq 50\%$ ), multivessel involvement (two or more vessels), atherosclerotic coronary segments (any plaque), and high CACS ( $\geq 100$ ). Additional multivariable logistic regression models using weight change instead of the  $\text{Rate}_{\text{max\_wt}}$  were also conducted in association with these coronary artery lesions. Significance was defined as  $P < 0.05$  for all analyses.

## RESULTS

### Baseline Characteristics of the Participants

The baseline characteristics of the 1,724 participants are shown in Table 1. The percentage of men was 49.7%. The ranges of age and BMI at diagnosis of T2D were 30–68 years and 17.1–40.1  $\text{kg}/\text{m}^2$ , respectively, with participants

with more rapid weight gain being younger and heavier at diagnosis (Supplementary Fig. 2). Almost 20% had a family history of CAD. Among all participants, 50.8% were overweight as defined as  $\text{BMI} \geq 25 \text{ kg}/\text{m}^2$ ; 37.9% had an LDL-C level  $\geq 130 \text{ mg}/\text{dL}$  or were taking statin medication; 19.6% had a triglyceride level  $\geq 150 \text{ mg}/\text{dL}$ , HDL-C level  $< 40 \text{ mg}/\text{dL}$  in men, or  $< 50 \text{ mg}/\text{dL}$  in women or were taking lipid-lowering medication other than statins; and 24.5% had an SBP/DBP  $\geq 140/90 \text{ mmHg}$  or were taking antihypertensive medication at the time of T2D diagnosis.

### Weight-Related Variables

The weight change was  $\sim 12.9 \text{ kg}$ ; this value was calculated by subtracting the mean  $\text{Wt}_{20y}$  of 60.1 kg from the mean  $\text{Wt}_{\text{max}}$  of 73.0 kg (Table 1). The mean  $\text{Age}_{\text{max\_wt}}$  was 41.3 years, and the mean change in time was 21.3 years. From these two variables, the  $\text{Rate}_{\text{max\_wt}}$  was calculated as  $0.59 \pm 0.56 \text{ kg}/\text{year}$ . There was no significant difference in the amount and rate of weight gain between men and women.

### Comparison of Cardiac CTA Findings According to the Quartiles of $\text{Rate}_{\text{max\_wt}}$

More participants in the higher quartiles of  $\text{Rate}_{\text{max\_wt}}$  had significant coronary artery stenosis, particularly in the left main or left anterior descending artery and left circumflex artery, and more frequent multivessel involvement and atherosclerotic coronary segments than those in the lower quartiles of  $\text{Rate}_{\text{max\_wt}}$  (Table 2). The log-transformed CACS did not differ among quartiles, but there was a trend for more participants in the higher quartiles of  $\text{Rate}_{\text{max\_wt}}$  to have a CACS  $\geq 100$  compared with those in the lower quartiles.

### Multivariable Logistic Regression Model of Variables Associated With CAD

In the multivariable linear regression for each phenotype of CAD (Table 3), high blood pressure or taking antihypertensive medication, more pack-years of smoking, family history of CAD, and high LDL-C level or taking statin medication were significantly associated with significant coronary artery stenosis, multivessel involvement, and atherosclerotic coronary segments. High blood pressure or taking antihypertensive

medication, more pack-years of smoking, family history of CAD, and high LDL-C level or taking statin medication were significantly associated with a high CACS. A higher  $\text{Rate}_{\text{max\_wt}}$  was significantly associated with significant coronary artery stenosis and atherosclerotic coronary segments. All variance-inflation factors among the independent variables were  $< 1.29$  in each regression model, suggesting that there was no significant collinearity among the covariates. Using weight change instead of the  $\text{Rate}_{\text{max\_wt}}$  produced a significant, but attenuated, association with coronary artery stenosis and mixed/noncalcified plaque but not with multivessel involvement, atherosclerotic coronary segments (any plaque), or the CACS (Supplementary Tables 1 and 2).

### Variables Associated With Plaque Types

The prevalence of mixed and noncalcified plaques was higher with higher  $\text{Rate}_{\text{max\_wt}}$ , whereas there was no relationship between the  $\text{Rate}_{\text{max\_wt}}$  and the presence of calcified plaques (Supplementary Fig. 3). We used a multivariable logistic regression model to investigate further the independent risk of the  $\text{Rate}_{\text{max\_wt}}$  on plaque type. After adjusting for the same variables used in the model for CAD, high SBP or taking antihypertensive medication, heavy smoking, family history of CAD, and high LDL-C level or taking statin medication were all significantly associated with any kind of plaque (Table 4). However, the highest  $\text{Rate}_{\text{max\_wt}}$  quartile was significantly associated with the presence of mixed and noncalcified plaques but not with calcified plaques.

## CONCLUSIONS

In this study of patients with newly diagnosed T2D and at least one risk factor for CAD, rapid weight gain from young adulthood was significantly associated with significant stenosis, multivessel involvement, and the presence of atheromatous plaques in the coronary arteries independent of current BMI. High blood pressure, heavy smoking history, and higher A1C and LDL-C levels were also independent predictors of the presence of CAD in these patients, lending external validity to the findings.

Few studies have investigated the relationship between weight gain during

**Table 1—Anthropometric and biochemical parameters at T2D diagnosis and weight-related variables in the total sample and according to quartile of the log-transformed Rate<sub>max\_wt</sub>**

	Total (n = 1,724)	Rate <sub>max_wt</sub> *				P value*
		Q1 (n = 430)	Q2 (n = 432)	Q3 (n = 430)	Q4 (n = 432)	
Rate <sub>max_wt</sub>	0.59 ± 0.56	0.15 ± 0.07	0.36 ± 0.05	0.58 ± 0.07	1.30 ± 0.70	<0.01
Range	0.01–4.08	0.01–0.27	0.28–0.46	0.47–0.72	0.73–4.08	
Age <sub>T2D</sub> (years)	49.9 ± 10.3	56.5 ± 8.7	52.3 ± 8.6	48.1 ± 9.0	42.8 ± 9.4	<0.01
Men (%)	49.7	46.3	48.4	53.5	50.7	0.18
Height (cm)	163.4 ± 8.9	163.0 ± 9.5	163.0 ± 8.6	163.6 ± 8.6	164.0 ± 8.8	0.23
Weight (kg)	68.1 ± 12.1	64.0 ± 10.3	67.1 ± 10.6	68.9 ± 11.4	72.4 ± 14.1	<0.01
BMI <sub>T2D</sub> (kg/m <sup>2</sup> )	25.4 ± 3.7	24.1 ± 3.0	25.2 ± 3.2	25.7 ± 3.5	26.8 ± 4.4	<0.01
SBP (mmHg)	129.9 ± 15.6	130.5 ± 15.8	130.6 ± 16.2	129.0 ± 15.3	129.6 ± 15.3	0.40
DBP (mmHg)	78.4 ± 10.7	77.4 ± 11.3	78.5 ± 10.5	77.9 ± 10.7	78.6 ± 10.5	0.22
Total cholesterol (mg/dL)	201.6 ± 39.6	200.4 ± 37.8	201.6 ± 39.4	201.0 ± 41.1	203.5 ± 40.0	0.69
Triglycerides (mg/dL)	158.5 ± 92.5	153.5 ± 87.2	152.0 ± 82.7	161.3 ± 96.2	163.3 ± 99.3	0.15
HDL-C (mg/dL)	51.0 ± 12.6	51.9 ± 12.9	51.0 ± 12.2	50.7 ± 12.8	50.4 ± 12.3	0.31
LDL-C (mg/dL)	107.6 ± 29.3	104.1 ± 27.4	108.7 ± 29.6	107.7 ± 28.9	109.9 ± 30.9	0.06
Fasting glucose (mg/dL)	154.2 ± 64.7	145.7 ± 56.8	145.8 ± 61.4	157.9 ± 67.1	167.3 ± 70.2	<0.01
Fasting insulin (mg/dL)	11.7 ± 7.1	11.0 ± 6.6	11.7 ± 7.0	12.0 ± 8.1	12.0 ± 6.5	0.23
A1C (%)	8.1 ± 1.5	7.7 ± 1.3	7.7 ± 1.2	8.2 ± 1.5	8.6 ± 1.8	<0.01
A1C (mmol/mol)	65 ± 16	61 ± 14	61 ± 13	66 ± 16	71 ± 20	<0.01
Creatinine (mg/dL)	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.2	0.86
Smoking (pack-years)	11.3 ± 17.3	10.9 ± 17.5	13.1 ± 19.4	12.5 ± 17.1	14.8 ± 15.9	0.12
Smoking status						0.34
Nonsmoker	58.2	61.9	59.2	56.0	59.6	
Ex-smoker	19.3	19.1	18.3	22.1	17.8	
Current smoker	22.5	19.0	22.5	21.9	22.6	
Alcohol consumption						0.52
Light–moderate	85.8	84.0	84.2	82.4	82.7	
Heavy	14.2	16.0	14.8	17.6	17.3	
Exercise habits						0.07
No or irregular	68.6	65.5	70.0	69.5	69.3	
Regular	31.4	34.5	30.0	30.5	30.7	
Family history of CAD	20.7	16.7	17.1	21.7	19.8	0.11
Weight-related variables						
Wt <sub>20y</sub> (kg)	60.1 ± 10.5	63.5 ± 10.4	60.1 ± 10.0	57.9 ± 10.4	59.2 ± 10.5	<0.01
BMI <sub>20y</sub> (kg/m <sup>2</sup> )	22.5 ± 3.1	23.8 ± 2.9	22.5 ± 2.9	21.5 ± 3.0	21.9 ± 2.9	<0.01
Age <sub>max_wt</sub> (years)	41.3 ± 10.7	48.7 ± 9.9	45.4 ± 9.0	40.2 ± 7.1	31.0 ± 6.9	<0.01
Wt <sub>max</sub> (kg)	73.0 ± 11.5	68.2 ± 9.8	71.0 ± 9.3	73.5 ± 10.9	79.4 ± 12.7	<0.01
BMI <sub>max</sub> (kg/m <sup>2</sup> )	27.3 ± 3.6	25.6 ± 2.8	26.7 ± 2.8	27.4 ± 3.3	29.5 ± 4.1	<0.01
ΔWt (Wt <sub>max</sub> – Wt <sub>20y</sub> )	12.9 ± 8.4	4.7 ± 3.4	10.9 ± 4.8	15.6 ± 6.1	20.3 ± 8.8	<0.01
ΔTime (Age <sub>max_wt</sub> – 20 years)	21.3 ± 10.7	28.3 ± 10.0	25.4 ± 9.0	20.2 ± 7.1	11.4 ± 7.6	<0.01

Data are mean ± SD or %. Age<sub>T2D</sub>, age at T2D diagnosis; BMI<sub>20y</sub>, BMI at age 20 years; BMI<sub>max</sub>, maximum BMI; Q, quartile. \*Log-transformed values were used.

early childhood or adolescence and cardiovascular risk factors in later life (19,20). The Bogalusa Heart Study confirmed that obesity directly effects coronary atherogenesis in youth (21) and that this process is accelerated in the presence of combined metabolic abnormalities (22). In population-based long-term follow-up studies in subjects of mainly white European extraction, being overweight in childhood was associated with an increased risk of CAD (23,24). Excess weight gain was associated with more extensive atherosclerosis, insulin

resistance, dyslipidemia, and high blood pressure in the DCCT-EDIC (Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications) follow-up study (25). A study of Japanese people reported that rapid weight gain during early childhood was associated with a poor lipid profile and high blood pressure in adolescence (26). In a previous study of 115,818 American women, weight gain after 18 years of age was a strong predictor of CAD risk among those within a normal BMI range (27). In the ARIC (Atherosclerosis Risk in

Communities) study, weight gain since age 25 years was associated with elevated risk of CAD and stroke after controlling for baseline BMI and other covariates (28). These studies focused mainly on obesity or the amount of weight gain during a certain period rather than on weight dynamics. In the current study, the rate of or actual weight gain showed an association with cardiac CTA findings. However, the Rate<sub>max\_wt</sub> was associated with more types of subclinical atherosclerosis, and the degree of its association seemed to be higher than actual weight gain

**Table 2—Comparison of cardiac CTA findings according to the quartiles of the log-transformed Rate<sub>max\_wt</sub>**

	Rate <sub>max_wt</sub>				P value*
	Q1 (n = 430)	Q2 (n = 432)	Q3 (n = 430)	Q4 (n = 432)	
Log (Rate <sub>max_wt</sub> + 1)	0.15 ± 0.07	0.36 ± 0.05	0.58 ± 0.07	1.30 ± 0.70	0.001
Coronary artery stenosis					
Significant (≥50%)	41 (9.5)	42 (9.7)	51 (11.9)	62 (14.4)	0.015
By location of involved artery					
Left main/LAD	18 (4.2)	22 (5.1)	27 (6.3)	35 (8.1)	<0.01
Left circumflex	11 (2.6)	13 (3.0)	18 (4.2)	21 (4.9)	<0.01
Right coronary	11 (2.6)	7 (1.6)	9 (2.1)	9 (2.1)	0.321
Multivessel involvement†					
Two or more vessels	20 (4.7)	22 (5.1)	28 (6.5)	44 (10.2)	<0.01
Plaques					
Atherosclerotic coronary segments (any plaque)	64 (14.9)	80 (18.5)	91 (21.2)	105 (24.3)	<0.01
CACS					
Log-CACS	1.17 ± 2.03	1.18 ± 2.00	1.18 ± 2.15	1.21 ± 2.14	0.875
CACS >100	48 (11.2)	50 (11.6)	59 (13.7)	64 (14.8)	0.069

Data are mean ± SD or n (%). LAD, left anterior descending; Log-CACS, log-transformed CACS; Q, quartile. \*One-way ANOVA or linear-by-linear association test. †Any vessel stenosed by ≥50% was counted.

(Supplementary Table 1 and 2). These findings suggest that the Rate<sub>max\_wt</sub> may be more important in the development of atherosclerosis than actual weight gain, a testable hypothesis that future studies can address. Thus, we believe that the current study is possibly the first to show the influence of rapid weight gain

on the risk of subclinical CAD at the time of T2D diagnosis, although conceptually, more rapid weight gain is broadly linked to earlier development of obesity.

Of note, Tirosh et al. (29) reported that the risk of CAD in midlife is associated with an elevated BMI in adolescence and young adulthood, whereas

the risk of T2D is associated mainly with increased BMI close to the time of diagnosis. Recently, Reis et al. (30) showed that longer periods of obesity over the level of current BMI were more strongly associated with coronary artery calcification. These findings, together with the current results in an

**Table 3—Multivariable logistic regression models for variables, including the Rate<sub>max\_wt</sub> associated with coronary artery lesions**

	Significant stenosis (≥50%)		Multivessel involvement (two or more vessels)		Atherosclerotic coronary segments (any plaque)		High CACS (≥100)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
	Age (years)	1.02†	1.01–1.04	1.01	1.00–1.03	1.01	0.99–1.02	1.01
Sex (male vs. female)	1.21	0.81–1.78	1.38	0.99–1.92	0.78	0.57–1.07	0.85	0.59–1.22
BMI <sub>20y</sub> (kg/m <sup>2</sup> )	1.03	0.97–1.09	1.03	0.98–1.08	1.01	0.97–1.06	1.03	0.98–1.09
BMI <sub>T2D</sub> (kg/m <sup>2</sup> )	1.03	0.98–1.07	1.01	0.97–1.05	0.98	0.95–1.02	1.00	0.95–1.04
SBP ≥140 mmHg or taking antihypertensive medication	1.49*	1.08–2.06	1.34*	1.02–1.76	1.61†	1.25–2.09	1.48*	1.09–1.99
Smoking (pack-years)	1.02†	1.01–1.03	1.01*	1.00–1.02	1.02†	1.01–1.02	1.01*	1.00–1.02
Alcohol intake (current vs. none)	0.74	0.46–1.20	0.67	0.44–1.02	0.85	0.58–1.25	1.15	0.75–1.76
Exercise (irregular or less vs. regular)	1.34	0.93–1.94	0.99	0.74–1.34	1.11	0.83–1.47	1.03	0.74–1.44
Family history of CAD (yes vs. no)	1.48*	1.02–2.15	1.44*	1.05–1.98	2.01†	1.50–2.69	1.52*	1.08–2.15
A1C (%)	1.22†	1.10–1.36	1.12*	1.02–1.23	1.13†	1.03–1.23	1.07	0.96–1.19
LDL-C ≥130 mg/dL or taking statins	2.07†	1.50–2.87	2.36†	1.79–3.10	2.05†	1.58–2.65	2.35†	1.74–3.19
Log-triglyceride (mg/dL)	1.01	0.72–1.42	1.15	0.87–1.53	0.83	0.64–1.09	0.88	0.65–1.21
HDL-C (mg/dL)	1.00	0.99–1.01	1.00	0.99–1.01	0.99	0.98–1.00	0.99	0.98–1.01
Log (Rate <sub>max_wt</sub> + 1)								
Q1 (lowest)	1	—	1	—	1	—	1	—
Q2	1.08	0.65–1.79	1.15	0.76–1.73	1.30	0.87–1.93	1.09	0.69–1.72
Q3	1.27	0.75–2.15	1.07	0.68–1.66	1.48	0.97–2.25	1.27	0.79–2.05
Q4 (highest)	1.74*	1.01–3.00	1.55	0.98–2.45	1.70*	1.09–2.65	1.33	0.80–2.22

Adjusted for age, sex, BMI<sub>20y</sub>, BMI<sub>T2D</sub>, SBP ≥140 mmHg or taking antihypertensive medication, smoking, alcohol intake, exercise habits, family history of CAD, A1C, LDL-C level ≥130 mg/dL or taking statin medication, log-transformed triglyceride, and HDL-C. BMI<sub>20y</sub>, BMI at age 20 years; BMI<sub>T2D</sub>, BMI at T2D diagnosis; OR, odds ratio; Q, quartile. \*P < 0.05. †P < 0.01.

**Table 4—Multivariable logistic regression models for variables, including Rate<sub>max\_wt</sub> associated with plaque type**

	Calcified plaque		Mixed plaque		Noncalcified plaque	
	OR	95% CI	OR	95% CI	OR	95% CI
Age (years)	1.01	0.99–1.03	1.00	0.98–1.02	1.01	0.99–1.03
Sex (male vs. female)	1.09	0.66–1.82	1.07	0.66–1.74	1.38	0.84–2.29
BMI <sub>20y</sub> (kg/m <sup>2</sup> )	1.02	0.95–1.10	1.00	0.93–1.07	1.06	0.99–1.14
BMI <sub>T2D</sub> (kg/m <sup>2</sup> )	0.97	0.91–1.03	1.03	0.97–1.09	0.98	0.93–1.05
SBP ≥140 mmHg or taking antihypertensive medication	1.49	0.98–2.29	1.79 <sup>†</sup>	1.21–2.66	1.64*	1.08–2.47
Smoking (pack-years)	1.01*	1.00–1.03	1.01*	1.00–1.02	1.01*	1.00–1.03
Alcohol intake (current vs. none)	0.85	0.45–1.62	1.32	0.79–2.23	0.80	0.42–1.51
Exercise (irregular or less vs. regular)	1.09	0.68–1.74	1.17	0.75–1.84	0.93	0.60–1.45
Family history of CAD (yes vs. no)*	1.78*	1.11–2.85	1.57*	1.02–2.41	2.32 <sup>†</sup>	1.50–3.60
A1C (%)	1.05	0.91–1.21	1.11	0.98–1.26	1.01	0.87–1.16
LDL-C level ≥130 mg/dL or taking statin medication	1.68*	1.09–2.58	1.83 <sup>†</sup>	1.23–2.71	1.52*	1.00–2.30
Log-triglyceride (mg/dL)	0.71	0.46–1.11	0.95	0.64–1.42	0.88	0.57–1.35
HDL-C (mg/dL)	1.00	0.98–1.02	0.98	0.97–1.00	1.00	0.99–1.02
Log (Rate <sub>max_wt</sub> + 1)						
Q1 (lowest)	1	—	1	—	1	—
Q2	1.27	0.67–2.42	1.81	0.92–3.59	1.44	0.74–2.81
Q3	1.17	0.58–2.34	2.01	0.99–4.06	2.03*	1.02–4.02
Q4 (highest)	1.66	0.81–3.37	2.11*	1.01–4.41	2.42*	1.19–4.94

BMI<sub>20y</sub>, BMI at age 20 years; BMI<sub>T2D</sub>, BMI at T2D diagnosis; OR, odds ratio; Q, quartile. \**P* < 0.05. <sup>†</sup>*P* < 0.01.

Asian population, a group at greater cardiometabolic risk for a given BMI, indicate that the processes of atherosclerosis development depend not only on the level of obesity at the time of measurement but also on the rate of weight change in younger years and linked to this, the overall duration of obesity.

In this study, 1.2% (*n* = 21) of participants had a BMI <18.5 kg/m<sup>2</sup> at age 20. There was no significant alteration in the association of rapid weight gain with coronary artery stenosis after excluding these underweight participants.

A significant association was found in this study between the Rate<sub>max\_wt</sub> and the presence of mixed or noncalcified plaques. There is no clear explanation for this finding, but conceivably, a rapid increase in weight could be more damaging to the vascular system than a slow increase, given the shorter period of time available to adapt to weight increase (31). Rapid weight and adiposity gains lead to alterations in gene expression of growth factors and cytokines, such as transforming growth factor- $\beta$ , that are known to play important roles in vascular integrity (32) and plaque stability (33). Of course, it is possible that other, not easily measurable characteristics are also associated with rapid weight gain and plaque promotion. Regardless of the mechanism, the current

findings further strengthen the concept that CAD development depends more on the dynamics of weight change (i.e., its trajectory over life) than the current level of adiposity. This important point is not well appreciated but has clinical and public health ramifications.

A scientific statement from the AHA (34) and the expert consensus document from the American College of Cardiology and AHA (35) concluded that cardiac CTA may be helpful in screening for CADs in asymptomatic individuals at an intermediate risk for CAD. In the current study, we used cardiac CTA to screen for subclinical CAD in patients with newly diagnosed T2D who had at least one cardiovascular risk factor. Advanced CT techniques, such as 64-slice cardiac CTA, can measure the degree of stenosis with high diagnostic accuracy and can provide details about plaque composition, including whether the plaque is noncalcified or mixed and rupture prone (11). In studies that investigated the prognostic value of cardiac CTA, coronary artery stenosis and great plaque burden were stronger predictors of future cardiovascular events than were routine clinical predictors, exercise stress test results, or the CACS in patients without known CAD (36,37). Similarly, in studies of outpatients at low to intermediate risk, coronary artery stenosis severity, the presence of noncalcified

and/or mixed plaque, and multivessel involvement were superior to traditional risk factors, including the CACS, for predicting CAD (11,38).

The MAXWEL cohort has several strengths. First, weight information at age 20 years was obtained accurately from official written documents in 54% participants. Second, identification of T2D was based on laboratory results and not on self-report, and we carefully excluded patients with likely type 1 diabetes. Third, only patients with newly diagnosed T2D were included, which enabled us to assess their glycemic level and the status of diabetic macrovascular complications within 3 months after diagnosis. Finally, studies in people of Asian ethnicity that comprehensively assessed the coronary arteries with multislice CT are limited; hence, the present data are novel and important.

There are also some limitations of this study. First, identification of Wt<sub>max</sub> and Age<sub>max\_wt</sub> was based on the participants' self-report. Although there was high agreement rate between the recalled Wt<sub>max</sub> and the written documentation, Age<sub>max\_wt</sub> could possibly be prone to recall error, and thus, the rate of weight change is likewise potentially influenced. Second, we excluded participants who had lost weight between the age of 20 years and the time of T2D diagnosis (36 patients [2.1%]), but this

small number was unlikely to have biased the results. Third, other factors that can contribute to body weight, such as smoking habit, alcohol consumption, physical activity, and dietary pattern, in a time-dependent manner as well as consumption of diet pills and psychological stress were not considered. Fourth, we did not assess weight fluctuation, which may affect low-grade systemic inflammation (39) or metabolic abnormalities (40). However, other studies reported that weight fluctuation was not related to cardiovascular morbidity or mortality (41,42). Finally, a possibility of unknown duration of diabetes exists, which may have influenced the study results.

In conclusion, a greater Rate<sub>max\_wt</sub> from young adulthood was associated with early development of CAD, including the presence of noncalcified or mixed plaques in patients with newly diagnosed T2D independent of weight/BMI at the time of cardiovascular phenotyping. The current findings imply that the rate of evolution of atherosclerosis may be affected by weight gain from young adulthood, a modifiable and avoidable risk factor (43). It is true that small changes early on can be leveraged to great benefits later in life. Taken together with other emerging data, the results suggest that population-based approaches for weight control during adolescence, including behavioral factors, should be highlighted to reduce the risk of macrovascular complications in general and in people at elevated risk for diabetes.

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## References

1. Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med* 2001;161:1581–1586

2. Olefsky JM, Kolterman OG, Scarlett JA. Insulin action and resistance in obesity and noninsulin-dependent type II diabetes mellitus. *Am J Physiol* 1982;243:E15–E30

3. Hanson RL, Narayan KM, McCance DR, et al. Rate of weight gain, weight fluctuation, and incidence of NIDDM. *Diabetes* 1995;44:261–266

4. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med* 2002;162:1867–1872

5. Logue J, Walker JJ, Leese G, et al.; Scottish Diabetes Research Network Epidemiology Group. Association between BMI measured within a year after diagnosis of type 2 diabetes and mortality. *Diabetes Care* 2013;36:887–893

6. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 2002;165:670–676

7. Eckel RH, Barouch WW, Ershow AG. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on the pathophysiology of obesity-associated cardiovascular disease. *Circulation* 2002;105:2923–2928

8. Poirier P, Giles TD, Bray GA, et al.; American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006;113:898–918

9. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;359:2324–2336

10. Moon JS, Yoon JS, Won KC, Cho IH, Lee HW. Diagnostic accuracy of 64-slice MDCT coronary angiography for the assessment of coronary artery disease in Korean patients with type 2 diabetes. *Diabetes Metab J* 2013;37:54–62

11. Nance JW Jr, Schlett CL, Schoepf UJ, et al. Incremental prognostic value of different components of coronary atherosclerotic plaque at cardiac CT angiography beyond coronary calcification in patients with acute chest pain. *Radiology* 2012;264:679–690

12. Lim S, Kim KM, Kim MJ, et al. The association of maximum body weight on the development of type 2 diabetes and microvascular complications: MAXWEL study. *PLoS One* 2013;8:e80525

13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012;35(Suppl. 1):S64–S71

14. Chobanian AV, Bakris GL, Black HR, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–2572

15. Lim S, Choi SH, Choi EK, et al. Comprehensive evaluation of coronary arteries by multi-detector-row cardiac computed tomography according to the glucose level of asymptomatic individuals. *Atherosclerosis* 2009;205:156–162

16. Hausleiter J, Meyer T, Hadamitzky M, Kastrati A, Martinoff S, Schömig A. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. *J Am Coll Cardiol* 2006;48:312–318

17. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975;51(Suppl.):5–40

18. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–832

19. Calarge CA, Xie D, Fiedorowicz JG, Burns TL, Haynes WG. Rate of weight gain and cardiometabolic abnormalities in children and adolescents. *J Pediatr* 2012;161:1010–1015

20. Ekelund U, Ong KK, Linné Y, et al. Association of weight gain in infancy and early childhood with metabolic risk in young adults. *J Clin Endocrinol Metab* 2007;92:98–103

21. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med* 1998;338:1650–1656

22. Tzou WS, Douglas AS, Srinivasan SR, et al. Increased subclinical atherosclerosis in young adults with metabolic syndrome: the Bogalusa Heart Study. *J Am Coll Cardiol* 2005;46:457–463

23. Baker JL, Olsen LW, Sørensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med* 2007;357:2329–2337

24. DiPietro L, Mossberg HO, Stunkard AJ. A 40-year history of overweight children in Stockholm: life-time overweight, morbidity, and mortality. *Int J Obes Relat Metab Disord* 1994;18:585–590

25. Purnell JQ, Zinman B, Brunzell JD; DCCT/EDIC Research Group. The effect of excess weight gain with intensive diabetes mellitus treatment on cardiovascular disease risk factors and atherosclerosis in type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) study. *Circulation* 2013;127:180–187

26. Fujita Y, Kouda K, Nakamura H, Iki M. Association of rapid weight gain during early childhood with cardiovascular risk factors in Japanese adolescents. *J Epidemiol* 2013;23:103–108

27. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. *JAMA* 1995;273:461–465

28. Stevens J, Erber E, Truesdale KP, Wang CH, Cai J. Long- and short-term weight change and incident coronary heart disease and ischemic



- stroke: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2013;178:239–248
29. Tirosh A, Shai I, Afek A, et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. *N Engl J Med* 2011;364:1315–1325
30. Reis JP, Loria CM, Lewis CE, et al. Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age. *JAMA* 2013;310:280–288
31. Lingohr MK, Buettner R, Rhodes CJ. Pancreatic beta-cell growth and survival—a role in obesity-linked type 2 diabetes? *Trends Mol Med* 2002;8:375–384
32. Jakobsson L, van Meeteren LA. Transforming growth factor  $\beta$  family members in regulation of vascular function: in the light of vascular conditional knockouts. *Exp Cell Res* 2013;319:1264–1270
33. Tse K, Ley K. Transforming growth factor- $\beta$ : transforming plaque to stability. *Eur Heart J* 2013;34:3684–3686
34. Budoff MJ, Achenbach S, Blumenthal RS, et al.; American Heart Association Committee on Cardiovascular Imaging and Intervention; American Heart Association Council on Cardiovascular Radiology and Intervention; American Heart Association Committee on Cardiac Imaging, Council on Clinical Cardiology. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation* 2006;114:1761–1791
35. Greenland P, Bonow RO, Brundage BH, et al.; American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography); Society of Atherosclerosis Imaging and Prevention; Society of Cardiovascular Computed Tomography. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *Circulation* 2007;115:402–426
36. Dedic A, Genders TS, Ferket BS, et al. Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing. *Radiology* 2011;261:428–436
37. Chow BJ, Wells GA, Chen L, et al. Prognostic value of 64-slice cardiac computed tomography severity of coronary artery disease, coronary atherosclerosis, and left ventricular ejection fraction. *J Am Coll Cardiol* 2010;55:1017–1028
38. Hou ZH, Lu B, Gao Y, et al. Prognostic value of coronary CT angiography and calcium score for major adverse cardiac events in outpatients. *JACC Cardiovasc Imaging* 2012;5:990–999
39. Tamakoshi K, Yatsuya H, Kondo T, et al. Long-term body weight variability is associated with elevated C-reactive protein independent of current body mass index among Japanese men. *Int J Obes Relat Metab Disord* 2003;27:1059–1065
40. Zhang H, Tamakoshi K, Yatsuya H, et al. Long-term body weight fluctuation is associated with metabolic syndrome independent of current body mass index among Japanese men. *Circ J* 2005;69:13–18
41. Lee JS, Kawakubo K, Kobayashi Y, Mori K, Kasihara H, Tamura M. Effects of ten year body weight variability on cardiovascular risk factors in Japanese middle-aged men and women. *Int J Obes Relat Metab Disord* 2001;25:1063–1067
42. Dyer AR, Stamler J, Greenland P. Associations of weight change and weight variability with cardiovascular and all-cause mortality in the Chicago Western Electric Company Study. *Am J Epidemiol* 2000;152:324–333
43. Taylor J. The impact of childhood obesity on heart disease. *Eur Heart J* 2009;30:1817–1818