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Original Contribution

Differential Associations of Weight Dynamics With Coronary Artery Calcium Versus Common Carotid Artery Intima-Media Thickness

The CARDIA Study

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Change and fluctuation in body mass index (BMI; weight (kg)/height $(m)^2$) may be associated differently with coronary artery calcification (CAC) than with carotid artery intima-media thickness (IMT). The authors analyzed data on 2,243 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, initially aged 18–30 years, who were examined every 2–5 years over a 20-year period (1985–2006). BMI at year 0 was associated positively and linearly with CAC at year 20; however, the association of BMI with year 20 CAC became progressively U-shaped in subsequent examinations (years 10, 15, and 20). To understand the deepening U shape, the authors modeled year 20 BMI and its history using 3 indices: year 0 BMI, linear slope of BMI during 20 years, and BMI fluctuation during 20 years. In models including these 3 terms, year 0 BMI was associated positively with CAC, as was BMI fluctuation. However, adjusted odds ratios across quintiles of BMI slope (vs. the lowest quintile) were 0.7, 0.4, 0.5, and 0.4 ($P_{trend} < 0.01$), suggesting higher risk of CAC with weight loss, plateauing after moderate weight gain. In contrast, IMT was associated positively with BMI at all examinations and with 20-year BMI slope and was unassociated with BMI fluctuation. Surprisingly, CAC risk was higher with BMI loss and lower with BMI gain, whereas associations with IMT were as expected.

body mass index; body weight changes; carotid artery, common; coronary vessels; tunica intima; tunica media

Abbreviations: BMI, body mass index; CAC, coronary artery calcification; CARDIA, Coronary Artery Risk Development in Young Adults; IMT, intima-media thickness; SD, standard deviation.

Obesity has shown different associations with coronary artery calcification (CAC) than with carotid artery intima-media thickness (IMT), although both are commonly used subclinical markers of atherosclerosis. IMT has been consistently and strongly associated with various indices of obesity, including body mass index (BMI) and waist circumference (1–4). However, the adiposity measures have not been consistently related to CAC (5–12). Different adjustments for confounders have not explained this inconsistency.

Repeated measurement of weight over time allows us to study both the effects of baseline weight and the effects of changes in weight during the observation period. In the current worldwide obesity epidemic, weight change, including fluctuation, is a common phenomenon. Therefore, in addition to baseline body weight, change and fluctuation in body weight (or equally in BMI, if adjusted for height) may also be important in determining the risk of IMT or CAC. Also, the inconsistent associations of obesity with CAC and IMT may be explained by different associations of change and fluctuation in body weight with CAC or IMT.

We used data from a cohort followed longitudinally over 20 years (1985–2006), the Coronary Artery Risk Development in Young Adults (CARDIA) Study cohort, to examine the associations of weight change and weight fluctuation with CAC and carotid artery IMT at year 20. In a published

article on BMI and CAC in the CARDIA Study (8), only baseline BMI, not BMI at year 15, was positively and linearly associated with CAC at year 15. In the current study, we examined associations with both CAC and IMT by modeling year 20 BMI and its history using 3 indices: BMI at year 0, linear slope of BMI during 20 years, and BMI fluctuation around the linear slope during 20 years. Additionally, we examined associations between 3 indices of year 15 BMI and its history and the progression of CAC during 5 years from year 15 to year 20. This analytic approach has been used when repeated measurements of body weight during follow-up were available (13–15).

MATERIALS AND METHODS

Study population

In CARDIA, the evolution of cardiovascular disease risk was studied in participants who were initially aged 18–30 years (16). In brief, 5,115 African-American and white participants were recruited at baseline in 1985–1986 (year 0) in 4 US cities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California). Follow-up examinations were completed at years 2, 5, 7, 10, 15, and 20, with retention of 91%, 86%, 81%, 79%, 74%, and 72% of survivors, respectively. Institutional review board approval and informed consent were obtained at each site at every examination.

CAC was assessed at years 15 and 20 and IMT only at year 20; all of these measures were available for 2,288 participants. We replaced BMI with a missing value in females who were pregnant when examined, leading to 118 missing values in those specific examination years only. We then excluded 45 participants with missing data on BMI for that reason or any other reason at year 0, at year 20, or at 3 or more examinations among years 2, 5, 7, 10, and 15 (so that all participants had at least the initial measurement, the terminal measurement, and 5 total BMI measurements), leaving a final sample size of 2,243. Exclusion of all information from women who were ever pregnant during any examination did not change results.

Measurements

A common protocol and quality control procedures were used at all examinations. Participants were asked to fast for at least 12 hours and to avoid smoking and heavy physical activity for 2 hours before examination. Self-reported current smoking status was noted. Habitual physical activity was measured using the CARDIA Physical Activity History questionnaire (17). Body weight was measured in light clothing (to the nearest 0.2 pound (0.1 kg)), body height was measured without shoes (to the nearest 0.5 cm), and BMI was calculated as weight (kg) divided by height squared (m^2). Participants were twice asked about intentionality of weight loss or gain during follow-up (at year 7 for the period between years 5 and 7 and again at year 10 for the period between years 7 and 10). Concentrations of plasma total cholesterol, high density lipoprotein cholesterol, and triglycerides were determined enzymatically by Northwest Lipids Research Laboratory (Seattle, Washington) at all examinations. The level of low density lipoprotein cholesterol was derived by means of the Friedewald equation. Serum glucose concentration was measured at year 0, using the hexokinase ultraviolet method, by American Bio-Science Laboratories (Van Nuys, California) and at years 7, 10, and 15, using hexokinase coupled to glucose-6-phosphate dehydrogenase, by Linco Research, Inc. (St. Louis, Missouri).

Two computed tomography scans were obtained at each of year 15 and 20 using electron-beam computed tomography (Imatron C-150; GE Medical Systems, Milwaukee, Wisconsin (for the Chicago and Oakland centers)) or multidetector computed tomography scanners (GE Lightspeed, GE Medical Systems (for the Birmingham center) or Volume Zoom, Siemens, Erlangen, Germany (for the Minneapolis center)) (18). For each scan, 40 consecutive images from the root of the aorta to the apex of the heart were obtained. Participants remained supine between scans taken 1–2 minutes apart. Each scan was read centrally by a trained reader. The reader identified a region of interest for each potential focus of CAC, defined as 4 or more adjacent pixels (1.87 mm^2) with a computed tomography number greater than 130 Hounsfield units (field of view = 35 cm). Agatston scores were adjusted for between-center differences using a standard calcium phantom scanned underneath each participant, and scores were summed across the 4 major coronary arteries. Scans were adjudicated side-by-side within-year, if 1 scan was positive and the other was zero, or between years 15 and 20, if scans were widely discrepant or Agatston score decreased. In our data, there was greater noise in the computed tomography image in participants with higher BMIs, which led to falsely positive Agatston scores in the initial reading; these false-positive scores were reset to zero after rereading.

The thicknesses of the intima media layer of the common carotid artery at the carotid bulb and in the internal carotid artery were determined from images obtained by high-resolution B-mode ultrasonography at year 20 (Logiq 700 ultrasound machine; GE Medical Systems, Waukesha, Wisconsin). Calculation of IMT was performed at the CARDIA ultrasound reading center at Tufts-New England Medical Center (Boston, Massachusetts), using the maximum across the mean values in the near and far walls on the left and right sides, including plaque as part of the wall. Pearson correlation coefficients based on 58 replicate readings were 0.86 for the common carotid artery, 0.72 for the bulb, and 0.88 for the internal carotid artery.

Statistical analysis

First, we calculated results based on cross-sectional analyses of CAC or IMT with BMI, all at year 20, and then calculated results for associations of year 20 CAC or IMT with BMI at year 0 and with BMI at year 10. Next, we studied 3 separate indices of year 20 BMI and its history: BMI at year 0, linear slope of BMI from year 0 to year 20, and BMI fluctuation around the BMI trend line during the 20-year period. Slope of and fluctuation in BMI from year 0 to year 20 were estimated using a simple linear regression

model, estimated separately for each of the 2,243 participants, in which the dependent variable was the participant's BMI and examination year was the independent variable. The slope coefficient of this model was used as an index representing the linear trend of a participant's BMI change in terms of direction and magnitude. The root-mean-square error for each subject (the residual variability around the overall time trend of BMI) was used to represent the magnitude of BMI fluctuation. Since height is essentially constant, negative BMI slope implies weight loss, positive BMI slope implies weight gain, and higher BMI fluctuation implies greater weight fluctuation. We sometimes refer to ''weight'' instead of BMI, recognizing that ''weight change'' is actually change in weight adjusted for height squared.

In this paper, we present results from analyses in which high CAC and high IMT were defined on the basis of Agatston score >20, the 90th percentile, and IMT >90th percentile value. In fact, when we used several cutoff points to represent high CAC (Agatston score >0, >10, >20, and >40) and high IMT (IMT >70th, >80th, and >90th percentile), the associations became progressively stronger the higher the cutoff point. Detailed results based on all definitions of CAC and IMT are presented in Web Tables 1–3, which are posted on the *Journal*'s Web site (http://aje.oxfordjournals.org/). Results based on continuous values of CAC and IMT were similar to those based on dichotomous values for these outcomes. Although there were 2 IMT outcomes, common carotid artery IMT and carotid bulb/internal carotid IMT, most significant associations were observed only with common carotid artery IMT. Therefore, we present results for common carotid artery IMT.

BMI at baseline, linear slope of BMI, and fluctuation in BMI were each divided into quintiles. We also present results obtained after further categorization of the lowest quintile of linear slope in BMI into weight loss and slight weight gain. In additional analyses, we excluded weight losers and studied only weight gainers. Adjustments were made for the year 20 covariates age, sex, race/ethnicity, study center, cigarette smoking, and physical activity. In additional models, we considered clinical cardiovascular disease risk factors as covariates, namely systolic blood pressure and levels of fasting glucose, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides at the year 20 examination, recognizing that these variables may be explanatory of findings related to BMI.

Because CAC was assessed at both year 15 and year 20 but IMT was assessed only at year 20, we could only examine progression for CAC. We examined increase in Agatston score >20 from year 15 to year 20 by conducting parallel analysis with the 3 components of BMI at year 15 included as independent variables and adjusting for year 15 covariates. We used SAS statistical software (version 9; SAS Institute Inc., Cary, North Carolina) for the analyses.

RESULTS

General characteristics

The 2,243 participants had a mean age of 45.3 years (standard deviation (SD), 3.5; range, 37–52) at year 20. Mean BMI increased monotonically across examinations from year 0 (24.2 (SD, 4.4)) to year 20 (29.0 (SD, 6.2)). The proportion of subjects with weight loss during 20 years was only 9.2% among all subjects (46.2% among subjects belonging to the lowest quintile of BMI slope). Table 1 shows several characteristics at year 20 according to the 3 different indices of year 20 BMI and its history: year 0 BMI, linear slope of BMI from year 0 to year 20, and BMI fluctuation during the 20-year period. Women and African Americans experienced both higher BMI gain and higher BMI fluctuation during the 20 years. Less weight gain and greater BMI fluctuation were associated with current smoking. On the other hand, more physically active persons had less weight gain and less BMI fluctuation.

Baseline BMI had a coefficient for correlation with year 20 BMI of 0.72. Slope of BMI was not associated with baseline BMI. BMI fluctuation was weakly and positively correlated with BMI slope ($r = 0.21$) but was more strongly associated with BMI at both baseline and year 20 ($r = 0.46$ for both). The correlation of IMT with Agatston score was 0.10.

Associations between BMI at various time points and CAC or IMT at year 20

Year 0 BMI was positively associated with CAC at year 20 (Table 2) ($P_{\text{trend}} < 0.01$). However, the association weakened progressively as the BMI measurement neared the time of CAC measurement, which we illustrate by showing the weaker association of year 10 BMI with CAC. The association became U-shaped at year 15 (data not shown) and deepened further with year 20 BMI ($P_{\text{quadratic}} = 0.02$). However, BMI at each measurement time was strongly associated with IMT at year 20 (Table 2).

Associations of 3 indices of 20-year BMI and its history with CAC or IMT at year 20

To enhance understanding of the progressively deepening U-shaped association as the time of BMI measurement approached the time of CAC measurement, we included the 3 indices of year 20 BMI and its history simultaneously in the model. After we considered the effects of slope and fluctuation in BMI during 20 years, BMI at baseline was positively related to year 20 CAC (Table 3) ($P_{\text{trend}} = 0.03$); the pattern of association was similar to the one shown in Table 2 without adjustment for changes in BMI. However, the slope of BMI during 20 years (up to 4 units during 20 years) was inversely associated with CAC at year 20, independently of BMI at year 0 and fluctuation in BMI during 20 years (Table 3) ($P_{\text{trend}} < 0.01$). Participants in the lowest quintile of linear BMI slope showed the highest risk of CAC at year 20, and those who gained more weight during the 20-year period tended to have a lower risk of CAC ($P_{\text{trend}} < 0.01$). BMI fluctuation was significantly and positively associated with CAC at year 20 ($P_{\text{trend}} < 0.01$), particularly in the highest quintiles of fluctuation. All of these associations were similarly observed among never smokers (data not shown).

Table 1. Distribution of Traditional Cardiovascular Disease Risk Factors at Follow-up Year 20, According to 3 Indices of Year 20 Body Mass Index[a] and Its History, Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1985–2006

	Quintile 1 (n = 448)		Quintile 2 (n = 449)		Quintile 3 (n = 449)		Quintile 4 (n = 449)		Quintile 5 (n = 448)		P Value
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	
	BMI at Year 0										
	<20.7		**20.7–<22.5**		**22.5–<24.2**		**24.2–<26.9**		**≥26.9**		
Age, years	45.0 (3.6)		44.9 (3.4)		45.1 (3.5)		45.9 (3.5)		45.6 (3.6)		<0.01
Female sex, %		71.2		58.1		45.9		43.7		59.6	0.02
White race/ethnicity, %		63.6		66.1		61.7		60.1		41.1	<0.01
Current smoker, %		16.5		14.9		19.2		19.4		18.3	0.35
Physical activity score, exercise units[b]	332 (260)		388 (298)		363 (275)		332 (254)		273 (257)		<0.01
Systolic blood pressure, mm Hg	112.1 (13.9)		113.5 (14.4)		115.2 (13.3)		116.1 (12.7)		119.8 (15.9)		<0.01
HDL cholesterol, mg/dL	60.5 (18.2)		57.9 (17.0)		53.3 (16.2)		51.2 (15.2)		50.4 (15.4)		<0.01
LDL cholesterol, mg/dL	108.9 (32.6)		108.9 (29.7)		111.6 (33.0)		113.0 (30.0)		110.3 (30.7)		0.20
Triglycerides, mg/dL	95.6 (76.0)		96.1 (58.5)		112.9 (83.8)		121.9 (88.8)		123.6 (90.3)		<0.01
Fasting glucose, mg/dL	92.7 (13.6)		92.8 (11.1)		96.1 (24.7)		98.4 (20.5)		107.1 (36.1)		<0.01
	Slope of BMI Change From Year 0 to Year 20, units/year										
	−1.12 to <0.08		**0.08–<0.17**		**0.17–<0.25**		**0.25–<0.40**		**0.40–1.16**		
Age, years	45.5 (3.2)		46.0 (3.2)		45.5 (3.4)		45.2 (3.7)		44.3 (3.9)		<0.01
Female sex, %		59.8		46.1		47.2		51.7		73.7	<0.01
White race/ethnicity, %		66.7		69.9		64.1		51.2		40.6	<0.01
Current smoker, %		24.3		19.4		16.9		15.1		12.5	<0.01
Physical activity score, exercise units	394 (276)		374 (264)		333 (277)		300 (250)		285 (278)		<0.01
Systolic blood pressure, mm Hg	113.1 (15.1)		113.6 (13.8)		115.4 (14.2)		117.8 (13.6)		116.9 (14.2)		<0.01
HDL cholesterol, mg/dL	63.5 (19.7)		56.9 (16.7)		51.8 (14.9)		50.9 (14.9)		50.2 (13.8)		<0.01
LDL cholesterol, mg/dL	98.3 (28.8)		111.6 (31.0)		115.3 (31.0)		114.5 (31.5)		112.93 (30.8)		<0.01
Triglycerides, mg/dL	87.5 (66.3)		100.1 (68.4)		114.5 (82.3)		123.9 (94.3)		124.0 (85.2)		<0.01
Fasting glucose, mg/dL	96.0 (33.2)		95.6 (21.2)		96.2 (19.1)		99.1 (19.3)		100.1 (21.9)		<0.01
	Fluctuation in BMI From Year 0 to Year 20										
	0.11–<0.63		**0.63–<0.91**		**0.91–<1.21**		**1.21–<1.79**		**1.79–9.07**		
Age, years	45.4 (3.3)		45.6 (3.5)		45.3 (3.5)		45.3 (3.5)		44.9 (3.8)		0.03
Female sex, %		44.9		48.6		53.9		58.1		73.0	<0.01
White race/ethnicity, %		70.3		63.0		62.4		50.6		46.4	<0.01
Current smoker, %		14.5		14.5		15.1		21.2		23.0	<0.01
Physical activity score, exercise units	410 (288)		345 (258)		339 (268)		311 (269)		281 (259)		<0.01
Systolic blood pressure, mm Hg	112.6 (12.0)		114.6 (14.2)		115.2 (13.9)		118.1 (15.7)		116.3 (14.9)		<0.01
HDL cholesterol, mg/dL	57.6 (18.4)		56.3 (17.5)		54.3 (16.3)		52.6 (15.2)		52.5 (16.1)		<0.01
LDL cholesterol, mg/dL	105.0 (30.5)		113.3 (31.8)		111.0 (23.9)		114.1 (33.2)		109.3 (30.9)		<0.01
Triglycerides, mg/dL	97.7 (74.6)		105.3 (66.1)		111.1 (77.8)		117.4 (97.6)		118.5 (84.8)		<0.01
Fasting glucose, mg/dL	93.2 (11.5)		95.8 (18.0)		96.3 (19.5)		99.5 (28.7)		102.1 (32.8)		<0.01

Abbreviations: BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; SD, standard deviation.

[a] Weight (kg)/height (m)^2.

[b] Physical activity score was derived from the CARDIA Physical Activity History questionnaire (17), a simplified version of the Minnesota Leisure Time Physical Activity Questionnaire. Physical activity is expressed in arbitrary exercise units. The theoretical range of the scores is 0 to 2,592; the actual maximum was 1,770.

Table 2. Adjusted[a] Odds Ratios for Risk of High Coronary Artery Calcification (>90th Percentile) and High Common Carotid Artery Intima-Media Thickness (>90th Percentile) at Follow-up Year 20, According to Category of Body Mass Index[b] at Years 0, 10, and 20, Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1985–2006

Outcome and BMI Measurement	BMI Category					P_{trend}	$P_{quadratic}$
	<22	22–<25	25–<30	30–<35	≥35		
Coronary artery calcification at year 20							
BMI at year 0							
No. of cases/no. of participants	45/762	66/748	83/530	19/144	10/59		
Unadjusted %	5.9	8.8	15.7	13.2	17.0		
Model 1 OR (95% CI)	Referent	1.1 (0.8, 1.7)	2.3 (1.5, 3.5)	2.3 (1.3, 4.2)	3.7 (1.6, 8.2)	<0.01	0.82
Model 2 OR (95% CI)	Referent	0.9 (0.6, 1.4)	1.7 (1.1, 2.5)	1.3 (0.7, 2.4)	2.1 (0.9, 5.0)	0.02	1.00
BMI at year 10							
No. of cases/no. of participants	40/493	36/536	86/726	42/301	19/187		
Unadjusted %	8.1	6.7	11.9	14.0	10.2		
Model 1 OR (95% CI)	Referent	0.5 (0.3, 0.8)	1.0 (0.6, 1.4)	1.4 (0.9, 2.3)	1.2 (0.7, 2.3)	0.02	0.16
Model 2 OR (95% CI)	Referent	0.4 (0.2, 0.7)	0.7 (0.4, 1.1)	0.8 (0.5, 1.4)	0.6 (0.3, 1.3)	0.81	0.18
BMI at year 20							
No. of cases/no. of participants	25/234	33/401	81/804	47/427	37/377		
Unadjusted %	10.7	8.2	10.1	11.0	9.8		
Model 1 OR (95% CI)	Referent	0.6 (0.3, 1.0)	0.6 (0.4, 1.0)	0.8 (0.5, 1.4)	0.9 (0.5, 1.7)	0.45	0.02
Model 2 OR (95% CI)	Referent	0.5 (0.3, 1.0)	0.5 (0.3, 0.9)	0.7 (0.4, 1.2)	0.8 (0.4, 1.4)	0.99	0.02
Intima-media thickness at year 20							
BMI at year 0							
No. of cases/no. of participants	29/762	71/748	84/530	31/144	10/59		
Unadjusted %	3.8	9.5	15.9	21.5	17.0		
Model 1 OR (95% CI)	Referent	2.2 (1.4, 3.4)	3.5 (2.2, 5.5)	5.3 (3.0, 9.5)	3.5 (1.5, 7.9)	<0.01	<0.01
Model 2 OR (95% CI)	Referent	2.0 (1.3, 3.2)	2.8 (1.8, 4.5)	3.8 (2.1, 7.0)	2.3 (0.9, 5.4)	<0.01	<0.01
BMI at year 10							
No. of cases/no. of participants	23/493	33/536	84/726	48/301	37/187		
Unadjusted %	4.7	6.2	11.6	16.0	19.8		
Model 1 OR (95% CI)	Referent	1.1 (0.6, 1.9)	1.8 (1.1, 3.0)	2.8 (1.6, 4.8)	4.1 (2.3, 7.4)	<0.01	0.54
Model 2 OR (95% CI)	Referent	0.9 (0.5, 1.6)	1.3 (0.8, 2.1)	1.6 (0.9, 2.9)	2.1 (1.1, 4.0)	<0.01	0.45
BMI at year 20							
No. of cases/no. of participants	6/234	20/401	67/804	65/427	67/377		
Unadjusted %	2.6	5.0	8.3	15.2	17.8		
Model 1 OR (95% CI)	Referent	1.6 (0.6, 4.2)	2.3 (1.0, 5.5)	4.5 (1.9, 10.9)	7.0 (2.9, 16.8)	<0.01	0.80
Model 2 OR (95% CI)	Referent	1.6 (0.6, 4.3)	1.9 (0.7, 4.8)	3.4 (1.3, 8.8)	4.8 (1.9, 12.4)	<0.01	0.71

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] Model 1 results were adjusted for age, sex, race/ethnicity, study center, cigarette smoking, and physical activity. Model 2 results were further adjusted for systolic blood pressure, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and fasting glucose. Each covariate was measured at the same examination as the corresponding BMI.

[b] Weight (kg)/height $(m)^2$.

IMT showed different patterns of association from those of CAC (Table 4). In models including the 3 indices of year 20 BMI and its history, BMI at baseline was strongly and positively related to IMT at year 20 ($P_{trend} < 0.01$). In addition, the slope of BMI during 20 years was positively associated with IMT at year 20 ($P_{trend} < 0.01$). BMI fluctuation during 20 years was not associated with IMT at year 20.

Associations between 3 indices of year 15 BMI and its history and progression of CAC

Table 5 presents associations of the progression of CAC from year 15 to year 20 with the 3 indices of year 15 BMI. In these progression analyses, the trends were similar to those in Table 3. The inverse association of the slope of BMI during 15 years and the positive association of the

Table 3. Adjusted[a] Odds Ratios for Risk of High Coronary Artery Calcification (>90th Percentile) at Follow-up Year 20, According to 3 Indices of Year 20 Body Mass Index[b] and Its History, Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1985–2006

	BMI at Year 0					P_{trend}
	Q1 (19.8)[c]	Q2 (21.6)	Q3 (23.4)	Q4 (25.3)	Q5 (29.7)	
No. of cases/no. of participants	28/448	25/449	46/449	59/449	65/448	
Unadjusted %	6.3	5.6	10.2	13.1	14.5	
Model 1 OR (95% CI)	Referent	0.8 (0.4, 1.4)	1.2 (0.7, 2.0)	1.3 (0.8, 2.2)	1.8 (1.1, 3.1)	<0.01
Model 2 OR (95% CI)	Referent	0.8 (0.4, 1.4)	1.1 (0.7, 1.9)	1.3 (0.8, 2.1)	1.6 (0.9, 2.8)	0.03
	Linear Slope of BMI From Year 0 to Year 20					
	Q1 (0.01)	Q2 (0.12)	Q3 (0.21)	Q4 (0.32)	Q5 (0.54)	
No. of cases/no. of participants	66/448	57/449	34/449	40/449	26/448	
Unadjusted %	14.7	12.7	7.6	8.9	5.8	
Model 1 OR (95% CI)	Referent	0.7 (0.4, 1.0)	0.4 (0.3, 0.6)	0.5 (0.3, 0.8)	0.4 (0.3, 0.7)	<0.01
Model 2 OR (95% CI)	Referent	0.7 (0.4, 1.0)	0.4 (0.2, 0.6)	0.5 (0.3, 0.8)	0.4 (0.2, 0.7)	<0.01
	Fluctuation in BMI During 20 Years					
	Q1 (0.49)	Q2 (0.77)	Q3 (1.05)	Q4 (1.46)	Q5 (2.34)	
No. of cases/no. of participants	36/448	42/449	39/449	61/449	45/448	
Unadjusted %	8.0	9.4	8.7	13.6	10.0	
Model 1 OR (95% CI)	Referent	1.2 (0.8, 2.0)	1.2 (0.7, 2.0)	2.1 (1.3, 3.4)	1.7 (1.0, 3.0)	<0.01
Model 2 OR (95% CI)	Referent	1.2 (0.7, 1.9)	1.1 (0.7, 1.9)	1.9 (1.2, 3.2)	1.7 (1.0, 3.0)	<0.01

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; Q, quintile.

[a] This table presents results from 2 separate models with different covariates. Each model included BMI at year 0, slope of BMI from year 0 to year 20, fluctuation in BMI from year 0 to year 20, and covariates measured at year 20. Covariates for model 1 were age, sex, race/ethnicity, study center, cigarette smoking, and physical activity. Covariates for model 2 were those for model 1 plus systolic blood pressure, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and fasting glucose.

[b] Weight (kg)/height $(m)^2$.

[c] Numbers in parentheses, median value.

fluctuation in BMI during 15 years were strengthened when we used stricter definitions of CAC progression (Web Table 4).

Sensitivity analyses

Within the lowest quintile of linear slope of BMI, prevalence and progression of CAC were greater for participants who lost weight than for those who gained a small amount of weight (data not shown). Analyses conducted only among subjects with weight gain (weight losers excluded) also showed similar inverse associations (data not shown). Additional adjustment for use of statins and bariatric surgery had little effect on adjusted estimates (data not shown). Generally, results based on waist circumference were similar to those based on BMI (Web Tables 5–8).

Approximately 40% of weight loss was stated to be intentional when participants were asked at years 7 and 10. Losing weight between years 5 and 7 was associated with a higher risk of CAC at year 20 irrespective of intentionality, but persons who lost weight intentionally between years 7 and 10 had an even higher risk of CAC at year 20 (23.1%) than those who lost weight unintentionally (15.5%).

DISCUSSION

The positive association of year 0 BMI with year 20 CAC progressively deepened in a U shape as the time of BMI measurement approached that of CAC, while IMT was consistently and positively associated with BMI irrespective of the time of BMI measurement. To enhance our understanding of this finding, we used identical analytic approaches to examine comprehensive associations of weight dynamics with CAC and IMT. Weight change and weight fluctuation showed different results depending on which subclinical marker of atherosclerosis was used as the outcome, including the unexpected findings that weight loss, modest weight gain, and greater weight fluctuation were associated with increased CAC at year 20 and CAC progression between years 15 and 20. Because BMI at year 20 can be thought of as the combination of BMI at year 0 with change in BMI over 20 years, this progression towards a nonlinear relation suggests the presence of countervailing pathways linking baseline BMI to higher prevalence and progression of CAC but increase in BMI to lower prevalence and progression of CAC. Although the positive association with baseline BMI may reflect the harmfulness of obesity itself, the inverse association with changes in BMI may reflect other aspects which are closely related to changes in amounts of

Table 4. Adjusted[a] Odds Ratios for Risk of High Common Carotid Artery Intima-Media Thickness (>90th Percentile) at Follow-up Year 20, According to 3 Indices of Body Mass Index[b] and Its History, Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1985–2006

	BMI at Year 0					P_{trend}
	Q1 (19.8)[c]	Q2 (21.6)	Q3 (23.4)	Q4 (25.3)	Q5 (29.7)	
No. of cases/no. of participants	15/448	21/449	41/449	61/449	87/448	
Unadjusted %	3.3	4.7	9.1	13.6	19.4	
Model 1 OR (95% CI)	Referent	1.3 (0.6, 2.5)	2.1 (1.1, 3.9)	2.8 (1.5, 5.1)	4.6 (2.5, 8.4)	<0.01
Model 2 OR (95% CI)	Referent	1.2 (0.6, 2.4)	2.0 (1.0, 3.7)	2.6 (1.4, 4.9)	3.6 (2.0, 6.8)	<0.01
	Linear Slope of BMI From Year 0 to Year 20					
	Q1 (0.01)	Q2 (0.12)	Q3 (0.21)	Q4 (0.32)	Q5 (0.54)	
No. of cases/no. of participants	35/448	27/449	48/449	58/449	57/448	
Unadjusted %	7.8	6.0	10.7	12.9	12.7	
Model 1 OR (95% CI)	Referent	0.7 (0.4, 1.2)	1.4 (0.9, 2.4)	1.7 (1.0, 2.7)	1.9 (1.1, 3.1)	<0.01
Model 2 OR (95% CI)	Referent	0.7 (0.4, 1.2)	1.4 (0.8, 2.3)	1.6 (0.9, 2.6)	1.8 (1.0, 3.0)	<0.01
	Fluctuation in BMI During 20 Years					
	Q1 (0.49)	Q2 (0.77)	Q3 (1.05)	Q4 (1.46)	Q5 (2.34)	
No. of cases/no. of participants	31/448	41/449	42/449	50/449	61/448	
Unadjusted %	6.9	9.1	9.4	11.1	13.6	
Model 1 OR (95% CI)	Referent	1.0 (0.6, 1.7)	1.0 (0.6, 1.7)	1.0 (0.6, 1.7)	1.3 (0.8, 2.2)	0.30
Model 2 OR (95% CI)	Referent	0.9 (0.5, 1.6)	1.0 (0.6, 1.6)	0.9 (0.5, 1.5)	1.2 (0.7, 2.1)	0.55

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; Q, quintile.

[a] This table presents results from 2 separate models with different covariates. Each model included BMI at year 0, slope of BMI from year 0 to year 20, fluctuation in BMI from year 0 to year 20, and covariates measured at year 20. Covariates for model 1 were age, sex, race/ethnicity, study center, cigarette smoking, and physical activity. Covariates for model 2 were those for model 1 plus systolic blood pressure, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and fasting glucose.

[b] Weight (kg)/height $(m)^2$.

[c] Numbers in parentheses, median value.

adipose tissue, as we discuss below. In contrast to CAC, linear change in BMI during 20 years showed positive associations with IMT. The association between baseline BMI and IMT was also stronger than that of CAC, while fluctuation in BMI was not associated with IMT.

The inverse association between linear weight change and CAC may be surprising, but it is not unprecedented. In several observational studies, investigators have reported that weight loss was associated with increased risk of cardiovascular disease or total mortality, while mild-to-moderate weight gain did not increase or even decreased the risk of coronary events (19–21). The increased risk among weight losers has often been interpreted as a reflection of reverse causality due to unintentional weight loss from preexisting illness or cigarette smoking, or loss of lean mass rather than fat mass at older ages (22–24). Decreased risk with some weight gain has been dismissed as biologically implausible (23, 24). However, it is difficult to attribute our CAC findings on weight change to bias due to reverse causality, considering this generally healthy cohort who were young at baseline and successfully aged for 20 years (cumulative death rate = 4%; clinical heart disease was rare). First of all, the inverse trend was clearly observed across a broad range of weight changes, not just for the small group of participants who lost weight. In addition, all of these associations were similarly observed among never smokers.

It is also provocative that weight fluctuation appeared to increase CAC risk. It is generally thought that intentional weight loss is good for health, while unintentional weight loss is harmful. However, difficulties in maintaining reduced body weight after intentional weight loss commonly lead to repeated attempts and weight fluctuation. Thus, our findings on fluctuation suggest that even intentional weight loss may not always be good, if a person does not successfully maintain the intentional weight loss. An adverse effect of weight fluctuation has been regarded as biologically plausible, because weight fluctuation and associated adipose tissue remodeling can have detrimental effects on various cardiovascular disease risk factors (25). Similarly to our studies, weight fluctuation has been linked to some harmful consequences, including cardiovascular disease, in other studies (15, 26).

Many researchers think that higher risk of cardiovascular disease among weight losers and lower risk among weight gainers is not biologically plausible (23, 24). However, there are pathways that may be relevant; for example, lipophilic xenobiotics stored in adipose tissue may explain this surprising finding. In fact, in recent epidemiologic studies,

Table 5. Adjusted[a] Odds Ratios for Progression of Coronary Artery Calcification From Follow-up Year 15 to Year 20, According to 3 Indices of Year 15 Body Mass Index[b] and Its History, Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1985–2006

	BMI at Year 0					P_{trend}
	Q1 (19.8)[c]	Q2 (21.6)	Q3 (23.4)	Q4 (25.3)	Q5 (29.7)	
No. of cases/no. of participants	24/448	25/449	40/449	56/449	62/448	
Unadjusted %	5.4	5.6	8.9	12.5	13.8	
Model 1 OR (95% CI)	Referent	0.9 (0.5, 1.6)	1.1 (0.6, 1.9)	1.4 (0.8, 2.4)	2.0 (1.1, 3.4)	<0.01
Model 2 OR (95% CI)	Referent	0.8 (0.4, 1.5)	0.9 (0.5, 1.7)	1.2 (0.7, 2.0)	1.5 (0.8-2.6)	0.08
	Linear Slope of BMI From Year 0 to Year 15					
	Q1 (−0.01)	Q2 (0.12)	Q3 (0.22)	Q4 (0.36)	Q5 (0.61)	
No. of cases/no. of participants	51/448	50/449	43/449	41/449	22/448	
Unadjusted %	11.4	11.1	9.6	9.1	4.9	
Model 1 OR (95% CI)	Referent	1.0 (0.6, 1.5)	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)	0.4 (0.3, 0.8)	<0.01
Model 2 OR (95% CI)	Referent	0.9 (0.6, 1.4)	0.6 (0.4, 1.0)	0.6 (0.3, 0.9)	0.4 (0.2, 0.6)	<0.01
	Fluctuation in BMI During 15 Years					
	Q1 (0.40)	Q2 (0.69)	Q3 (0.96)	Q4 (1.35)	Q5 (2.17)	
No. of cases/no. of participants	31/448	35/449	42/449	51/449	48/448	
Unadjusted %	6.9	7.8	9.4	11.4	10.7	
Model 1 OR (95% CI)	Referent	1.1 (0.7, 1.9)	1.5 (0.9, 2.5)	2.1 (1.2, 3.5)	2.2 (1.3, 3.9)	<0.01
Model 2 OR (95% CI)	Referent	1.0 (0.6, 1.8)	1.4 (0.8, 2.3)	1.9 (1.1, 3.3)	2.0 (1.1, 3.6)	<0.01

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; Q, quintile.

[a] This table presents results from 2 separate models with different covariates. Each model included BMI at year 0, slope of BMI from year 0 to year 15, fluctuation in BMI from year 0 to year 15, and covariates measured at year 15. Covariates for model 1 were age, sex, race/ethnicity, study center, cigarette smoking, and physical activity. Covariates for model 2 were those for model 1 plus systolic blood pressure, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and fasting glucose.

[b] Weight (kg)/height $(m)^2$.

[c] Numbers in parentheses, median value.

investigators have reported that these xenobiotics were associated with various diseases, including cardiovascular disease in the US general population (27). These xenobiotics can be released from adipose tissue during weight loss, be redistributed to some critical organs, and cause some detrimental effects in vivo (28). On the other hand, weight gain could decrease disease risk by diluting or sequestering the xenobiotics, which are then less available for distribution to critical organs. In fact, in experimental studies, investigators have observed that polychlorinated biphenyls, one typical example of lipophilic xenobiotics, can disturb calcium homeostasis (29, 30). Thus, CAC may be more specifically associated with exposure to lipophilic xenobiotics than are other manifestations of subclinical cardiovascular disease. However, there may be other, unknown biologic mechanisms.

This study had several limitations. First, we could not assess whether the associations observed would hold for well-documented clinical outcomes such as incidence of coronary heart disease or stroke, for which we would need longer follow-up. Second, these analyses addressed only calcified coronary plaque; while carotid plaque may be noncalcified, other, possibly noncalcified coronary arterial changes should be studied separately. Third, these findings may not translate to older persons. Finally, as in all observational studies, residual unidentified confounding is possible.

In conclusion, this prospective study with repeated measures of body weight showed that associations with weight dynamics varied depending on which marker was used, with thicker IMT being associated with weight gain but greater coronary calcification being associated with weight loss, modest weight gain, and weight fluctuation.

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