Original Investigation

Association Between Duration of Overall and Abdominal Obesity Beginning in Young Adulthood and Coronary Artery Calcification in Middle Age

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IMPORTANCE Younger individuals are experiencing a greater cumulative exposure to excess adiposity over their lifetime. However, few studies have determined the consequences of long-term obesity.

OBJECTIVE To examine whether the duration of overall and abdominal obesity was associated with the presence and 10-year progression of coronary artery calcification (CAC), a subclinical predictor of coronary heart disease.

DESIGN, SETTING, AND PARTICIPANTS Prospective study of 3275 white and black adults aged 18 to 30 years at baseline in 1985-1986 who did not initially have overall obesity (body mass index [BMI] ≥30) or abdominal obesity (men: waist circumference [WC] >102 cm; women: >88 cm) in the multicenter, community-based Coronary Artery Risk Development in Young Adults (CARDIA) study. Participants completed computed tomography scanning for the presence of CAC during the 15-, 20-, or 25-year follow-up examinations. Duration of overall and abdominal obesity was calculated using repeat measurements of BMI and WC, respectively, performed 2, 5, 7, 10, 15, 20, and 25 years after baseline.

MAIN OUTCOMES AND MEASURES Presence of CAC was measured by computed tomography at the year 15 (2000-2001), year 20 (2005-2006), or year 25 (2010-2011) follow-up examinations. Ten-year progression of CAC (2000-2001 to 2010-2011) was defined as incident CAC in 2010-2011 or an increase in CAC score of 20 Agatston units or greater.

RESULTS During follow-up, 40.4% and 41.0% developed overall and abdominal obesity, respectively. Rates of CAC per 1000 person-years were higher for those who experienced more than 20 years vs 0 years of overall obesity (16.0 vs 11.0, respectively) and abdominal obesity (16.7 vs 11.0). Approximately 25.2% and 27.7% of those with more than 20 years of overall and abdominal obesity, respectively, experienced progression of CAC vs 20.2% and 19.5% of those with 0 years. After adjustment for BMI or WC and potential confounders, the hazard ratios for CAC for each additional year of overall or abdominal obesity were 1.02 (95% CI, 1.01-1.03) and 1.03 (95% CI, 1.02-1.05), respectively. The adjusted odds ratios for CAC progression were 1.04 (95% CI, 1.01-1.06) and 1.04 (95% CI, 1.01-1.07), respectively. Associations were attenuated but largely persisted following additional adjustment for potential intermediate metabolic factors during follow-up.

CONCLUSIONS AND RELEVANCE Longer duration of overall and abdominal obesity was associated with subclinical coronary heart disease and its progression through midlife independent of the degree of adiposity. Preventing or at least delaying the onset of obesity in young adulthood may lower the risk of developing atherosclerosis through middle age.

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Subclinical atherosclerosis, identified by the presence of coronary artery calcification (CAC),[1] progresses over time,[2] and predicts the development of coronary heart disease events.[3] In general, established risk factors for coronary heart disease are similar to those for CAC, including older age, male sex, elevated blood pressure, diabetes, cigarette smoking, and abnormal levels of low-density lipoprotein and high-density lipoprotein cholesterol.[2] The degree of overall and abdominal obesity, as reflected by an increased body mass index (BMI) and waist circumference, respectively, are also important risk factors for the presence and progression of CAC.[2,4,5] Less studied, however, is the influence of obesity duration as an independent risk factor for coronary atherosclerosis.

Understanding the influence of the duration of obesity on the presence or progression of atherosclerosis is critical, given the obesity epidemic. With a doubling of obesity rates for adults and a tripling of rates for adolescents during the last 3 decades, younger individuals are experiencing a greater cumulative exposure to excess adiposity during their lifetime.[6,7] However, few studies have determined the consequences of long-term obesity. Recent studies that have quantified the duration of overall obesity have found a longer duration to be associated with higher rates of diabetes[8-10] and mortality[11] independent of the degree of adiposity. With an increasing prevalence of abdominal obesity,[12,13] and its important role in the development of atherosclerosis independent of overall adiposity,[4,5] it also becomes essential to better understand the implications of a longer duration of abdominal obesity. However, to our knowledge, no study has examined whether the duration of overall or abdominal obesity contributes to the development or progression of atherosclerosis.

The present study was conducted to investigate whether the duration of overall and abdominal obesity determined prospectively using measured BMI and waist circumference, respectively, during a 25-year follow-up period beginning early in adulthood is associated with the presence of CAC as well as its 10-year progression in midlife.

Methods

Study Population

Participants were black and white adults recruited in 1985-1986 as part of the Coronary Artery Risk Development in Young Adults (CARDIA) study. The CARDIA study included a multicenter, community-based, longitudinal cohort to assess the development and determinants of cardiovascular disease over time in 5115 young adults initially aged 18 to 30 years in 1985-1986. Adults were recruited from 4 cities in the United States (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California) with population-based samples approximately balanced within center by sex, age (18-24 years and 25-30 years), race (white or black), and education (≤high school graduate or >high school graduate). To date, participants have been reexamined 2, 5, 7, 10, 15, 20, and 25 years after baseline. All participants provided written informed consent at each examination, and institutional review boards from each field center and the coordinating center approved the study annually.

Clinical Measurements

Standardized protocols for data collection were used across study centers and examinations. Before each examination, participants were asked to fast for at least 12 hours and avoid smoking or engaging in heavy physical activity for at least 2 hours.

Anthropometry

Weight and height were measured with participants wearing light examination clothes but not shoes. Body weight was measured to the nearest 0.2 kg with a calibrated, balance-beam scale. Height was measured with a vertical ruler to the nearest 0.5 cm. Body mass index was calculated as weight in kilograms divided by height in meters squared. Waist circumference was determined using a tape measure in duplicate to the nearest 0.5 cm around the minimal abdominal girth identified laterally midway between the iliac crest and the lowest portion of the rib cage and anteriorly midway between the xiphoid process and the umbilicus.

Duration of Overall and Abdominal Obesity

For each participant, the number of years of overall and abdominal obesity was calculated separately based on the presence of overall or abdominal obesity at each follow-up examination and the preceding examination. For example, a participant who was not overall obese at year 2, but was overall obese at year 5 and all subsequent follow-up examinations was assigned 0 years of overall obesity at year 2, 3 years at year 5, 2 years at year 7, 3 years at year 10, and so on. This scoring method was applied at each follow-up examination and the cumulative duration of obesity across examination years for each participant was then calculated. For analyses of the presence of CAC, the duration of overall and abdominal obesity was summed until the examination when CAC was first identified. For those who did not develop CAC, cumulative duration was summed until the last known follow-up examination. For analyses of the extent and progression of CAC, duration was determined through year 25.

Computed Tomography

The presence and level of CAC was measured at year 15 (2000-2001), year 20 (2005-2006), or year 25 (2010-2011) using computed tomography (CT) of the chest.[14] At years 15 and 20, an electron-beam CT scanner (at the Chicago and Oakland centers) and a multidetector CT scanner (at the Birmingham and Minneapolis centers) were used to obtain contiguous 2.5- to 3-mm-thick transverse images from the root of the aorta to the apex of the heart. At year 25, multidetector CT scanners were used at all centers. Participants were scanned over a hydroxyapatite phantom to allow monitoring of image brightness and noise and to allow adjustment for scanner differences. Images were transmitted electronically to an independent reading center. A calcium score in Agatston units[15] was calculated for each calcified lesion and the scores were summed across all lesions within a given artery and across all arteries (left anterior descending, left main, circumflex, and right coronary) to obtain the total calcium score. The presence of CAC was defined as a total calcification score greater than 0 Agatston units measured at year 15, 20, or 25. Prior analyses in the CARDIA

study have demonstrated CAC to be a reliable measure with observed agreement of 96%.[14] For analyses of the extent of CAC, we averaged all available nonzero CAC scores. For those with CT scans at both 15 and 25 years, we also examined the association of duration of overall and abdominal obesity with 10-year progression of CAC. Because of the challenges posed by the large number of zeros and the skewed distribution for CAC change data and because no consensus exists in the literature, we defined CAC progression a priori as incident CAC at year 25 or an increase in CAC score of 20 Agatston units or greater.[16]

Other Measurements

After a 5-minute rest, blood pressure was measured on the right arm of seated participants at three 1-minute intervals using a Hawksley random zero sphygmomanometer (WA Baum Company) at baseline through year 15. At years 20 and 25, blood pressure was measured using a standard automated blood pressure measurement monitor (Omron model HEM907XL). Blood was drawn by venipuncture according to a standard protocol.[17] Plasma concentrations of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured at all examinations using enzymatic methods at Northwest Lipids Research Laboratory. High-density lipoprotein cholesterol was measured after dextran-magnesium precipitation. Glucose was assayed at baseline using the hexokinase UV method by American Bio-Science Laboratories and hexokinase coupled to glucose-6-phosphate dehydrogenase (Millipore Inc) at years 7, 10, 15, 20, and 25. The insulin measurements were performed with the use of a radioimmunoassay (Linco Research) at baseline and years 7, 10, 15, and 20 and an Elecsys sandwich immunoassay (Roche Diagnostics Corporation) at year 25. Diabetes was determined based on a combination of measured fasting glucose levels (≥7.0 mmol/L [≥126 mg/dL]) at baseline and years 7, 10, 15, 20, and 25, self-report of oral hypoglycemic medications or insulin (all examinations), a 2-hour postload glucose level of 11.1 mmol/L or higher (≥200 mg/dL) at years 20 and 25, or a glycated hemoglobin A_{1c} level of 6.5% or higher at years 20 and 25.[18] Plasma C-reactive protein was measured using high-sensitivity nephelometry-based methods at years 7, 15, 20, and 25 (BNII nephelometer, Dade Behring).

Standard questionnaires were used to maintain consistency in the assessment of demographic (age, sex, race, and education) and behavioral (physical activity, cigarette smoking, and alcohol use) information across all study examination visits. Education was represented as years of schooling. The CARDIA physical activity history questionnaire queried the amount of time spent per week in 13 categories of leisure, occupational, and household physical activities during the prior 12 months.[19] Cigarette smoking status was classified as ever or never. Total daily alcohol consumption was calculated from an interviewer-administered questionnaire. Energy intake was measured with the interviewer-administered, validated CARDIA dietary history at years 0, 7, and 20.[20] Extreme values of energy intake (high: >8000 kcal/d in men and >6000 kcal/d in women; low: <800 kcal/d in men and <600 kcal/d in women) were excluded as unreliable. The use of antihypertensive and lipid-lowering medications was assessed by self-report at each examination.

Statistical Analysis

Participant characteristics overall and according to CT examination status and duration of overall and abdominal obesity were described using means, medians, and proportions as appropriate. Differences and trends were tested using linear regression models and χ^2 analyses for continuous and categorical characteristics, respectively. The Kruskal-Wallis test was used for characteristics with skewed distributions. Multivariable Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% confidence interval for the presence of CAC according to the duration of overall and abdominal obesity. Duration of overall and abdominal obesity was included as a time-dependent variable (in analyses of the presence of CAC) in 1 of 2 exposure forms: first as a continuous variable assuming a linear dose-response association, and second as a 6-level categorical variable (ie, 0, 1-5, 6-10, 11-15, 16-20, and >20 years). Analyses were adjusted for age, sex, race, CARDIA field center, and the following time-dependent covariates: BMI or waist circumference, education, physical activity, energy intake, smoking (current, former, or never), and alcohol consumption.

A second model adjusted additionally for the following time-dependent variables: systolic blood pressure level, antihypertensive and lipid-lowering medication use separately (yes or no), diabetes (yes or no), C-reactive protein, and levels of fasting insulin, total cholesterol, high-density lipoprotein cholesterol, and triglycerides. The additional adjustment variables in the second model could be in the causal pathway between overall and abdominal obesity duration and CAC; we regarded these models as possibly explanatory. Multivariable logistic regression models were used to estimate the odds ratio (OR) and 95% confidence interval for the progression of CAC according to the duration of overall and abdominal obesity.

Tests for a linear trend were performed by entering overall or abdominal obesity duration into the multivariable models as a continuous variable. We also examined the joint association by classifying participants according to the duration of both overall and abdominal obesity because each may have independent effects on the development of atherosclerosis. Potential effect modification by race and sex was evaluated by testing the statistical significance of a multiplicative interaction term including race, sex, and duration of overall or abdominal obesity as a continuous variable.

We also performed a number of sensitivity analyses. First, we defined presence of CAC as greater than 10 Agatston units. Second, we defined progression of CAC as incident CAC at year 25 or an increase of 1 Agatston units or greater. Third, we determined the influence of missing BMI and waist circumference values (10.2% of all measurements for each) on the association between the duration of overall and abdominal obesity and CAC as well as its progression. Multiple imputation was used for missing BMI and waist circumference values using the sequential regression imputation approach,[21] which was implemented using the software package IVEware version 0.2 (University of Michigan; http://www.isr.umich.edu/src/smp/ive/). Five data sets were generated using all available BMI and waist circumference data. Each data set was analyzed separately and results from the 5 analyses were combined using the rules of Little and Rubin.[22]

Tests of statistical significance were 2-tailed, with an α level of .05. SAS version 9.2 (SAS Institute Inc) was used to perform all statistical analyses.

Results

The retention rates across examinations conducted 2, 5, 7, 10, 15, 20, and 25 years after baseline were 91%, 86%, 81%, 79%, 74%, 72%, and 72% of the surviving cohort, respectively. A CT examination was performed on 3043 participants at year 15, 3141 at year 20, and 3189 at year 25. We included participants with CAC data from at least 1 examination (n = 3980). Participants who never had a CT examination were slightly younger and more likely to be male, black, less educated, and have higher levels of systolic blood pressure, glucose, and insulin and lower levels of total cholesterol at baseline (eTable 1 in the Supplement). However, there was no difference in BMI or waist circumference between those who ever had a CT examination and those who did not. We excluded those at baseline who were obese (BMI ≥30; n = 452), abdominally obese (waist circumference >102 cm in men and >88 cm in women[23]; n = 31), or were missing BMI or waist circumference data (n = 15), had bariatric surgery during follow-up (n = 27), or women who were pregnant during any examination (n = 180). The remaining 3275 participants formed the sample population for analysis.

Of the 3275 eligible participants, 45.7% were black and 50.6% were women. During follow-up, 40.4% and 41.0% developed overall and abdominal obesity, respectively; the mean (SD) duration of obesity was 13.3 (6.5) years and 12.2 (6.2) years for those who developed overall and abdominal obesity, respectively. The mean (SD) age at initiation of obesity was 35.4 (8.0) years and 37.7 (7.6) years, respectively. The prevalence of the duration of overall obesity for 1-5, 6-10, 11-15, 16-20, and more than 20 years was 8.7%, 7.6%, 8.5%, 8.6%, and 6.9%, respectively. For abdominal obesity, these estimates were 11.1%, 9.3%, 8.2%, 7.8%, and 4.5%, respectively.

Table 1 shows the characteristics of the participants according to the duration of overall obesity in 5-year increments. Those with a longer exposure to obesity were more likely to be younger at baseline, female, black, achieve less education, have a higher waist circumference at baseline and during follow-up, and were less physically active and consumed less alcohol. In addition, a longer duration of obesity was associated with higher levels (averaged during follow-up) of blood pressure, glucose, insulin, C-reactive protein, high-density lipoprotein cholesterol, and triglycerides. Presence of diabetes and medication use for hypertension and dyslipidemia also were more frequent among those with a longer duration of obesity. Smoking and total cholesterol level were unrelated to obesity duration. Similar results were observed when duration of abdominal obesity was substituted for overall obesity, except total cholesterol level was positively associated and age was unrelated to abdominal obesity duration (eTable 2 in the Supplement).

Overall, CAC was present in 27.5% (n = 902); the median CAC score of 25 Agatston units (interquartile range, 6-87 Agatston units) was based on the average of a maximum of 3 nonzero measurements at years 15, 20, or 25. The percentage of participants with a CAC score of 1-50, 51-100, and more than 100 Agatston units was 17.7%, 3.9%, and 5.9%, respectively. The presence and extent of CAC were strongly associated with duration of overall and abdominal obesity (P<.001 for both; **Figure**). Approximately 38.2% and 39.3% of participants with more than 20 years of overall and abdominal obesity, respectively, had CAC compared with 24.9% and 24.7% of those who never developed overall or abdominal obesity. For those with more than 20 years of overall and abdominal obesity, 28.4% and 28.3%, respectively, had a CAC score of 1-50 Agatston units compared with 15.2% and 15.5% with 0 years of overall and abdominal obesity, respectively. Extensive CAC (>100 Agatston units) was present in 6.5% and 9.0% of those with more than 20 years of overall and abdominal obesity, respectively, compared with 5.7% and 5.3% of those who never developed overall or abdominal obesity, respectively.

The adjusted HRs (AHRs) and 95% confidence intervals for presence of CAC according to duration of overall and abdominal obesity appear in **Table 2**. The rates per 1000 person-years of CAC were higher with a longer duration of overall obesity (11.0 for those with 0 years vs 16.0 for those with >20 years) and abdominal obesity (11.0 for those with 0 years vs 16.7 for those with >20 years). The AHRs for CAC for each additional year of overall and abdominal obesity were 1.02 (95% CI, 1.01-1.03) and 1.03 (95% CI, 1.02-1.05), respectively. The AHR was 1.02 (95% CI, 1.00-1.04) for both overall and abdominal obesity when presence of CAC was defined as greater than 10 Agatston units. Associations were attenuated, but persisted for abdominal obesity duration after further adjustment for potential intermediate factors (Table 2). The AHRs for CAC according to time-varying BMI and waist circumference were 1.03 (95% CI, 1.02-1.04) and 1.02 (95% CI, 1.01-1.02), respectively, before and 1.02 (95% CI, 1.01-1.03) and 1.01 (95% CI, 1.00-1.02), respectively, after adjustment for duration of overall or abdominal obesity.

Among those with CT scans at both years 15 and 25 (n = 2042), 21.6% (n = 441) experienced progression of CAC (defined as incident CAC at year 25 or an increase of ≥20 Agatston units). The adjusted ORs (AORs) and 95% confidence intervals for 10-year progression of CAC according to duration of overall and abdominal obesity appear in **Table 3**. Approximately 25.2% and 27.7% of those with more than 20 years of overall and abdominal obesity, respectively, experienced progression of CAC compared with 20.2% and 19.5% of those with 0 years. The AORs for CAC progression according to each additional year of overall and abdominal obesity were 1.04 (95% CI, 1.01-1.06) and 1.04 (95% CI, 1.01-1.07), respectively. When we alternatively defined CAC progression as incident CAC at year 25 or an increase of at least 1 Agatston units, the AOR was 1.03 for (95% CI, 1.00-1.05) for overall obesity and 1.03 (95% CI, 1.01-1.06) for abdominal obesity. Associations were attenuated, but largely persisted after additional adjustment for potential intermediate factors. The AORs for BMI and waist circumference were 1.03 (95% CI, 1.01-1.05) and 1.02 (95% CI, 1.01-1.02), respectively, before and 0.99 (95% CI, 0.96-1.03) and 1.00 (95% CI, 1.00-1.02) after adjustment for duration of overall or abdominal obesity.

Table 1. Characteristics of Participants in the CARDIA Study According to Duration of Overall Obesity in 5-Year Increments (N=3275)

	Duration of Overall Obesity[a]						
	0 y (n = 1952)	1-5 y (n = 286)	6-10 y (n = 250)	11-15 y (n = 279)	16-20 y (n = 283)	>20 y (n = 225)	*P* Value for Trend
Age at baseline, mean (SD), y	25.1 (3.5)	24.6 (3.6)	25.1 (3.6)	24.8 (3.8)	24.5 (3.8)	24.9 (3.6)	<.001
Female sex, No. (%)	9 (48.8)	146 (51.1)	132 (52.8)	143 (51.3)	153 (54.1)	130 (57.8)	<.001
Black race, No. (%)	740 (37.9)	139 (48.6)	136 (54.4)	165 (59.1)	166 (58.7)	150 (66.7)	<.001
Educational attainment, mean (SD), y	15.8 (2.6)	15.6 (2.4)	15.4 (2.5)	15.3 (2.5)	15.3 (2.5)	15.0 (2.4)	<.001
Ever smoker, No. (%)	1363 (67.7)	183 (65.4)	173 (65.6)	191 (63.8)	160 (68.2)	118 (64.0)	.26
Physical activity, median (IQR), exercise units[b]	366.0 (233.8-524.5)	324.2 (200.4-504.3)	314.8 (208.4-480.1)	294.7 (180.5-448.3)	299.5 (179.7-453.0)	265.5 (155.9-413.3)	<.001
Alcohol consumption, median (IQR), mL/d[b]	7.5 (1.7-17.7)	5.3 (0.9-15.6)	7.3 (1.0-16.5)	3.7 (0.3-12.3)	3.1 (1.7-5.4)	3.2 (0.3-11.0)	<.001
Body mass index, mean (SD)[c]							
At baseline	21.8 (2.3)	23.6 (2.3)	24.1 (2.4)	24.9 (2.5)	25.7 (2.3)	27.4 (2.0)	<.001
Final[d]	25.0 (2.9)	30.3 (2.3)	31.7 (2.7)	34.0 (3.4)	36.0 (4.2)	38.9 (5.7)	<.001
Waist circumference, mean (SD), cm							
At baseline	73.0 (7.4)	76.2 (8.0)	77.0 (8.0)	78.5 (8.5)	80.0 (8.0)	82.3 (7.5)	<.001
Final[d]	84.1 (9.9)	96.0 (8.1)	98.8 (9.1)	102.8 (9.8)	107.2 (10.3)	111.3 (121.3)	<.001
Blood pressure, mean (SD), mm Hg[b]							
Systolic	109.6 (9.4)	111.3 (9.2)	111.9 (9.4)	113.8 (9.4)	113.3 (8.9)	115.1 (9.0)	<.001
Diastolic	69.3 (7.3)	70.6 (6.7)	71.6 (7.6)	72.8 (7.0)	72.7 (7.0)	74.2 (6.7)	<.001
Medication use ever, No. (%)							
Antihypertensive	311 (15.9)	80 (28.0)	65 (26.0)	89 (31.9)	104 (36.8)	103 (45.8)	<.001
Lipid-lowering	213 (10.9)	40 (14.0)	33 (13.2)	55 (19.7)	63 (22.3)	46 (20.4)	<.001
Ever diabetes, No. (%)[e]	103 (5.3)	35 (12.2)	30 (12.0)	47 (16.9)	62 (21.9)	70 (31.1)	<.001
Fasting blood concentration[b]							
Glucose, mean (SD), mg/dL	89.4 (10.0)	92.5 (15.6)	92.1 (10.5)	93.4 (11.6)	94.2 (13.3)	97.5 (14.6)	<.001
Insulin, mean (SD), μIU/mL	9.8 (4.0)	13.0 (5.8)	14.0 (6.8)	15.2 (6.1)	16.7 (7.4)	17.8 (7.7)	<.001
C-reactive protein, median (IQR), mg/L	1.0 (0.5-2.0)	1.8 (1.0-3.2)	2.1 (1.1-4.3)	2.7 (1.4-5.2)	3.1 (1.7-5.4)	3.5 (1.7-6.2)	<.001
Cholesterol, mean (SD), mg/dL							
Total	180.6 (28.5)	183.7 (26.6)	182.0 (28.3)	185.2 (28.2)	181.9 (26.6)	184.8 (27.6)	.14
High-density lipoprotein	55.8 (13.1)	50.9 (12.1)	51.6 (11.6)	50.1 (11.7)	48.8 (10.8)	50.1 (11.9)	<.001
Triglycerides, median (IQR), mg/dL	71.6 (55.6-94.6)	82.9 (62.8-111.5)	88.7 (65.1-112.5)	85.8 (65.4-119.3)	89.7 (64.5-116.6)	95.3 (66.5-125.3)	<.001

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; IQR, interquartile range.

SI conversion factors: To convert C-reactive protein to nmol/L, multiply by 9.524; glucose to mmol/L, multiply by 0.0555; HDL and total cholesterol to mmol/L, multiply by 0.0259; insulin to pmol/L, multiply by 6.945; triglycerides to mmol/L, multiply by 0.0113.

[a] Defined as a body mass index of 30 or greater.

[b] Based on average values during follow-up.

[c] Calculated as weight in kilograms divided by height in meters squared.

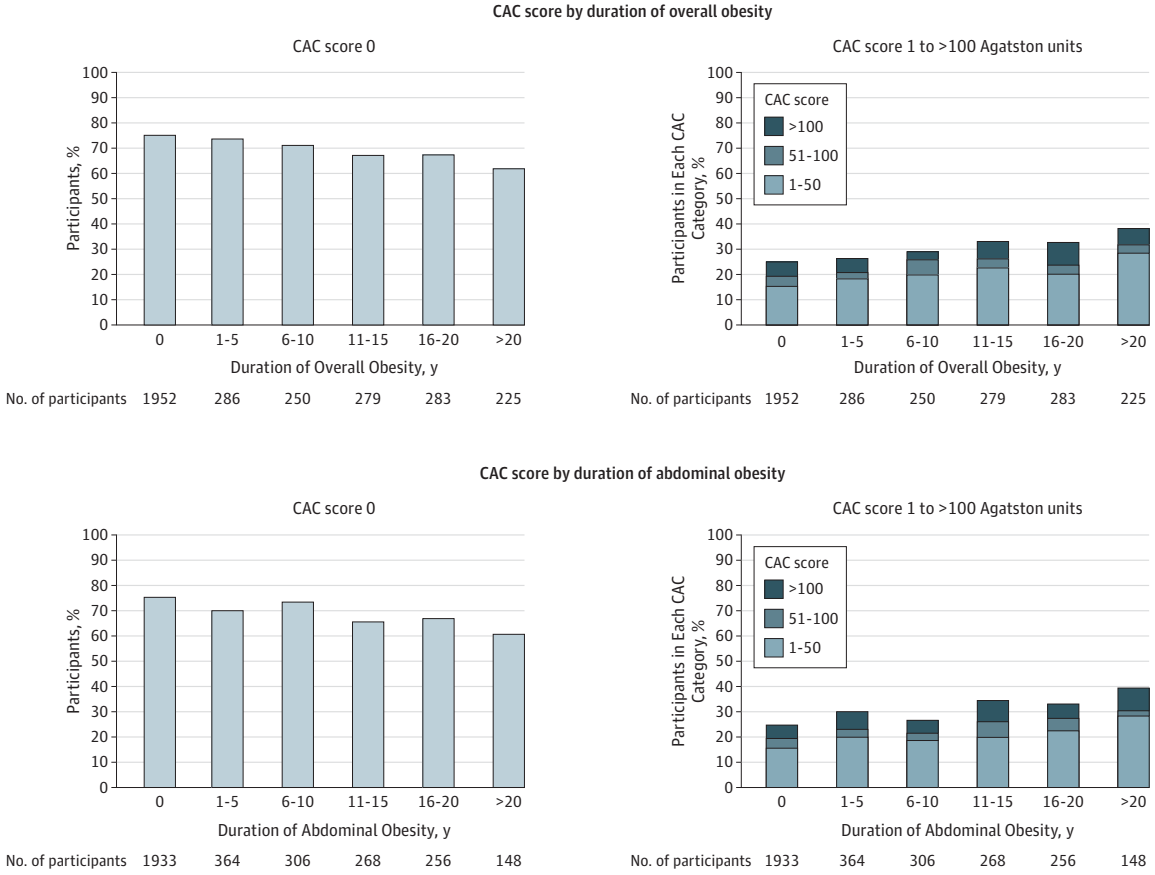
[d] Last observed measurement.

[e] Defined as a self-reported use of oral hypoglycemic medications or insulin at examination years 2, 5, 7, 10, 15, 20, or 25; fasting glucose levels of 7.0 mmol/L or higher (≥126 mg/dL) at examination years 7, 10, 15, 20, or 25; a 2-hour postload glucose level of 11.1 mmol/L or higher (≥200 mg/dL) at examination years 10, 20, or 25; or a glycated hemoglobin A_{1c} level of 6.5% or higher at years 20 or 25.

eFigures 1 and 2 in the Supplement show the joint association between duration of both overall and abdominal obesity and presence and 10-year progression of CAC, respectively. Compared with those who never developed overall or abdominal obesity (event rate: 10.7/1000 person-years), a trend was observed for a higher risk for CAC among those with the longest duration (>10 years) of both overall and abdominal obesity (event rate: 15.3/1000 person-years) (HR, 1.54 [95% CI, 0.96-2.50]; *P* = .07) (eFigure 1 in the Supplement). Compared with those who never developed overall or abdominal obesity (19.5% of participants), the ORs for progression of CAC for those with the longest duration of both overall obesity (>10 years; 27.8%) and abdominal obesity (1-10 and >10 years; 26.3%) were 1.99 (95% CI, 1.13-3.49) and 2.32 (95% CI, 1.32-4.05), respectively (eFigure 2 in the Supplement).

When we imputed missing values using all available measures of BMI and waist circumference during follow-up on the sample of 3275 participants, the HRs for CAC according to each additional year of overall obesity were 1.02 (95% CI, 1.01-1.03) and 1.03 (95% CI, 1.02-1.05) for each additional year of abdominal obesity. Similar ORs for CAC progression were 1.04 (95% CI, 1.01-1.07) for overall obesity and 1.02 (95% CI, 1.00-1.05) for abdominal obesity. We also assessed whether the association between the duration of overall and abdominal obesity and the presence or progression of CAC differed by race and sex. The race × sex interaction terms yielded *P* values of .86 and .53 for

Figure. Coronary Artery Calcification (CAC) Score Distribution According to Duration of Overall and Abdominal Obesity (N=3275)



Coronary artery calcification score is based on the average of a maximum of 3 nonzero measurements at years 15, 20, or 25.

presence and progression of CAC, respectively, for overall obesity duration, and .90 and .80, respectively, for abdominal obesity duration.

Discussion

In this community-based, longitudinal cohort study of adults recruited and followed up largely during the obesity epidemic over the past 3 decades in the United States, we found a longer duration of overall and abdominal obesity starting in young adulthood to be important factors associated with CAC and its progression during middle age independent of the degree of adiposity. Each additional year of overall or abdominal obesity beginning in early adulthood was associated with a HR or OR of 1.02 to 1.04 for CAC and its progression later in life. In addition, compared with those who were never obese, those with the longest duration of both overall and abdominal obesity had the highest odds for progression of CAC. These findings suggest that the longer duration of exposure to excess adiposity as a result of the obesity epidemic and an earlier age at onset will have important implications on the future burden of coronary atherosclerosis and potentially on the rates of clinical cardiovascular disease in the United States.

Although other studies have shown associations between the degree of overall or abdominal adiposity and the presence and progression of CAC,[2,4,5] this is the first study, to our knowledge, to provide evidence that the duration of overall and abdominal obesity are also independently associated with CAC and its progression. Studies estimating the association of obesity duration with health-related outcomes are limited.[8-11,24-27] Existing studies have relied primarily on the recall of body weight at previous ages or the self-reported duration of obesity,[24-27] methods that may be susceptible to a substantial amount of measurement error. The primary strength of the current study was the replicate objective assessments of BMI and waist circumference collected every 2 to 5 years via a standardized protocol during a long follow-up period over the course of the obesity epidemic as well as during the period of greatest gain in adiposity during the life course.[6,28] Our findings suggest that to estimate the cumulative exposure to excess overall and abdominal adiposity, future studies should measure both the degree of adiposity and duration of obesity.

In the current study, we found that a longer duration of overall and abdominal obesity was associated with higher levels of systolic blood pressure, insulin, C-reactive protein, and triglycerides, greater use of antihypertensive and lipid-lowering medications, higher rates of diabetes, and lower

Table 2. Adjusted Hazard Ratios (AHRs) for Presence of Coronary Artery Calcification According to Duration of Overall and Abdominal Obesity During Follow-up (N = 3275)[a]

	Duration of Obesity						*P* Value for Trend	Per Each Additional Year
	0 y	1-5 y	6-10 y	11-15 y	16-20 y	>20 y		
Overall obesity[b]								
No. of participants	1952	286	250	279	283	225		
No. of events	486	78	73	91	89	85		
Event rate[c]	11.0	12.0	13.0	14.6	13.9	16.0		
AHR (95% CI)[d]	1 [Reference]	1.05 (0.81-1.36)	1.27 (0.99-1.63)	1.34 (1.04-1.73)	1.32 (0.97-1.81)	1.84 (1.25-2.70)	.001	1.02 (1.01-1.03)
AHR (95% CI)[e]	1 [Reference]	0.96 (0.74-1.25)	1.16 (0.88-1.51)	1.16 (0.87-1.54)	1.13 (0.80-1.60)	1.52 (1.00-2.32)	.10	1.01 (1.00-1.03)
Abdominal obesity[f]								
No. of participants	1933	364	306	268	256	148		
No. of events	478	112	81	92	81	58		
Event rate[c]	11.0	13.5	11.8	15.4	13.6	16.7		
AHR (95% CI)[d]	1 [Reference]	1.17 (0.91-1.51)	1.31 (0.99-1.74)	1.56 (1.13-2.15)	1.76 (1.20-2.57)	2.48 (1.53-4.01)	<.001	1.03 (1.02-1.05)
AHR (95% CI)[e]	1 [Reference]	1.09 (0.85-1.41)	1.25 (0.94-1.67)	1.47 (1.06-2.05)	1.55 (1.06-2.28)	2.26 (1.39-3.69)	.001	1.03 (1.01-1.05)

[a] Presence of coronary artery calcification defined as a total calcification score of greater than 0 Agatston units measured at year 15, 20, or 25.

[b] Defined as a body mass index (calculated as weight in kilograms divided by height in meters squared) of 30 or higher.

[c] Per 1000 person-years.

[d] Adjusted for age, sex, race, study center, and the following time-dependentcovariates: body mass index (or waist circumference), education, physical activity, energy intake, smoking, and alcohol consumption.

[e] Adjusted for variables listed in footnote d and the following time-dependent covariates: systolic blood pressure, antihypertensive medication, lipid-lowering medication, diabetes, C-reactive protein, fasting insulin, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.

[f] Defined as a waist circumference of greater than 102 cm for men and greater than 88 cm for women.[23]

Table 3. Adjusted Odds Ratios (AORs) for 10-Year Progression of Coronary Artery Calcification According to Duration of Overall and Abdominal Obesity During Follow-up (n = 2042)[a]

	Duration of Obesity						*P* Value for Trend	Per Each Additional Year
	0 y	1-5 y	6-10 y	11-15 y	16-20 y	>20 y		
Overall obesity[b]								
No. of noncases	943	163	132	125	124	114		
No. of cases	238	35	38	46	45	39		
Percentage	20.2	17.7	22.4	26.9	26.6	25.5		
AOR (95% CI)[c]	1 [Reference]	0.97 (0.62-1.52)	1.39 (0.88-2.21)	1.72 (1.05-2.82)	1.97 (1.16-3.36)	1.98 (1.06-3.71)	.005	1.04 (1.01-1.06)
AOR (95% CI)[d]	1 [Reference]	0.84 (0.53-1.35)	1.40 (0.86-2.28)	1.48 (0.88-2.49)	1.71 (0.97-3.04)	1.95 (1.00-3.79)	.02	1.03 (1.01-1.06)
Abdominal obesity[e]								
No. of noncases	936	195	164	115	118	73		
No. of cases	226	64	44	45	34	28		
Percentage	19.5	24.7	21.2	28.1	22.4	27.7		
AOR (95% CI)[c]	1 [Reference]	1.53 (1.03-2.26)	1.43 (0.89-2.28)	2.22 (1.31-3.77)	1.76 (0.96-3.23)	2.85 (1.40-5.83)	.008	1.04 (1.01-1.07)
AOR (95% CI)[d]	1 [Reference]	1.29 (0.85-1.94)	1.31 (0.81-2.13)	1.87 (1.07-3.25)	1.37 (0.72-2.61)	2.26 (1.06-4.82)	.06	1.03 (1.00-1.06)

[a] For those with measures of coronary artery calcification at follow-up examinations at years 15 and 25, 10-year progression was defined as incident coronary artery calcification at year 25 or an increase in score of 20 Agatston units or greater.

[b] Defined as a body mass index (calculated as weight in kilograms divided by height in meters squared) of 30 or higher.

[c] Adjusted for age, sex, race, educational attainment, study center, body mass index (or waist circumference), ever smoking, and average energy intake, physical activity, and alcohol consumption.

[d] Adjusted for variables listed in footnote c and antihypertensive medication, lipid-lowering medication, diabetes, average systolic blood pressure, C-reactive protein, fasting insulin, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.

[e] Defined as a waist circumference of greater than 102 cm for men and greater than 88 cm for women.[23]

levels of high-density lipoprotein cholesterol during follow-up. Despite these associations, we found that these potential intermediate factors attenuated, but did not statistically explain the association between the duration of overall and abdominal obesity and the presence and progression of CAC in all instances. A number of studies have shown the deleterious metabolic effects of a higher degree of overall and abdominal adiposity on CAC and its progression that may be explained at least in part by these intermediate factors.[2,4,5] It is possible that a longer duration of overall or abdominal obesity may influence the development and progression of CAC through any of these variables because statistical adjustment may not completely account for long-term influence. A prolonged duration of overall and abdominal obesity may also promote atherosclerosis through sustained expression and secretion of proinflammatory adipocytokines.[29,30] Extended impairment of the fibrinolytic system via increased markers of hypercoagulability and hypofibrinolysis may also contribute to atherosclerotic vascular disease.[31,32] Additional mechanisms that may explain, at least in part, the association between a longer duration of overall and abdominal obesity and CAC and its progression include impaired nitric oxide-dependent endothelial function, oxidative stress, and upregulation of vasoconstrictor proteins.[33,34]

Previous studies have shown that the prevalence of overall and abdominal obesity and CAC differ significantly between white and black men and women.[13,35] In general, among these race-sex groups in the United States, black women have the highest prevalence of overall and abdominal obesity, whereas white and black men have the lowest prevalence, respectively.[13] For CAC, white men and black women have the highest and lowest prevalence, respectively.[13,35] Despite these differences, we found little evidence to suggest that the association between the duration of overall or abdominal obesity and CAC or its progression differed significantly between white and black men and women. These findings are in agreement with an earlier report from the CARDIA study investigators[5] in which no evidence was found to suggest that the association observed between the degree of abdominal adiposity in early adulthood and CAC in later life varied according to race and sex. Future studies should verify that the association of overall or abdominal obesity duration with atherosclerosis does not differ between white and black men and women.

Strengths of the current study include a community-based sampling method; cohort recruitment and follow-up largely during the obesity epidemic of the past 3 decades; a biracial cohort; extensive data on potential confounders; a large sample size well balanced with respect to age, sex, race, and education that increased precision and permitted simultaneous adjustment by multiple variables; repeat assessments of BMI, waist circumference, CAC, and potential confounding factors; a high retention rate; and the standardized data collection protocols and rigorous quality control of the CARDIA study.

Nevertheless, there are some limitations that deserve mention. First, our estimation of the duration of overall and abdominal obesity during follow-up was based on the measurement of BMI and waist circumference, respectively, every 2 to 5 years. It is likely that a more frequent number of assessments would have led to a more accurate estimation of the duration of obesity during follow-up; however, to the extent that there was random misclassification due to this assessment schedule, we may have underestimated the true association between the duration of obesity and CAC in our cohort. Second, waist circumference was used as an estimate of central obesity even though it does not distinguish between subcutaneous and visceral fat. Nevertheless, waist circumference has been shown to be strongly correlated with visceral fat, and offers widespread appeal due to its relative ease of measurement.[36] Third, because our study collected data during a 25-year follow-up period, some participants were missing at least 1 eligible measurement of BMI and waist circumference. However, we noted similar results between our multiple imputed data sets and our primary data set that did not account for missing BMI and waist circumference values. Fourth, our study was limited to those who completed at least 1 coronary CT examination during follow-up. This may have induced a selection bias if duration of obesity was associated with participation in a CT examination differentially by presence of CAC. However, we noted no difference in baseline BMI or waist circumference between those who ever had a CT examination and those who did not.

In conclusion, in this study a longer duration of overall and abdominal obesity beginning in young adulthood was associated with CAC and its 10-year progression through middle age independent of the degree of adiposity. This information may help understanding the consequences of a greater prevalence and cumulative exposure to excess adiposity over the life course as a result of the obesity epidemic. Our findings suggest that preventing or at least delaying the onset of obesity in young adulthood may substantially reduce the risk of coronary atherosclerosis and limit its progression later in life.

ARTICLE INFORMATION

Author Contributions: Dr Reis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Reis, Loria.
Acquisition of data: Lewis, Wei, Carr, Terry.
Analysis and interpretation of data: Reis, Loria, Powell-Wiley, Wei, Carr, Liu.
Drafting of the manuscript: Reis, Carr.
Critical revision of the manuscript for important intellectual content: Reis, Loria, Lewis, Powell-Wiley, Wei, Terry, Liu.
Statistical analysis: Reis, Liu.
Obtained funding: Reis, Loria, Lewis, Carr, Liu.
Administrative, technical, or material support: Reis, Lewis, Powell-Wiley, Carr, Terry.
Study supervision: Reis, Carr.

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