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Obesity

Excess Body Mass Index- and Waist Circumference-Years and Incident Cardiovascular Disease: The CARDIA Study

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Objective: To determine the influence of the total cumulative exposure to excess overall and abdominal adiposity on the incidence of cardiovascular disease (CVD).

Methods: Prospective study of 4,061 white and black adults without CVD at baseline in 1985-1986 (age 18-30 years) from the multicenter, community-based CARDIA study. Time-varying excess body mass index (BMI)- and waist circumference (WC)-years were calculated as products of the degree and duration of excess overall (BMI $\geq$ 25 kg/m^2) and abdominal adiposity [WC >94 cm (men) and >80 cm (women)], respectively, collected at up to eight examinations.

Results: During a median of 24.8 years, there were 125 incident CVD, 62 coronary heart disease (CHD), and 33 heart failure (HF) events. Adjusted hazard ratios for CVD, CHD, and HF for each additional 50 excess BMI-years were 1.20 (1.08, 1.34), 1.25 (1.07, 1.46), and 1.45 (1.23, 1.72), respectively. For each 50 excess WC-years, these hazard ratios were 1.10 (1.04, 1.18), 1.13 (1.03, 1.24), and 1.22 (1.11, 1.34), respectively. Akaike information criterion values were lowest in models containing time-varying excess BMI- or WC-years compared to those including time-varying BMI or WC only.

Conclusions: Excess BMI- and WC-years are predictors of the risk of CVD and may provide a better indicator of the cumulative exposure to excess adiposity than BMI or WC only.

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Introduction

Over the last 30 years, the prevalence of obesity has increased markedly in the United States, with a doubling of rates among adults, and a tripling of rates among children and adolescents (1,2). The acceleration of obesity trends among younger populations is particularly concerning given the persistence of obesity into adulthood (3). With obesity occurring at younger ages, the children and young adults of today will carry and express obesity-related risks for more of their lifetime than any other previous generation. This may have significant implications for an unprecedented acceleration of obesity-related morbidity and mortality. Yet few long-term studies have evaluated the consequences of a greater cumulative exposure to a higher degree of adiposity and longer duration of obesity in young adults during the obesity epidemic. Most available studies have focused on the degree of adiposity [either overall or abdominal adiposity reflected by body mass index (BMI) or waist circumference, respectively] as an important risk factor in the development of cardiovascular disease (CVD) and related conditions, but not the impact of the duration of excess adiposity (4). More recently, duration of obesity has been linked with progression to diabetes and subclinical atherosclerosis, as well as a higher risk of mortality, independent of the degree of adiposity (5-8).

In the current study, we sought to determine the influence of measures of the total cumulative exposure to excess overall and abdominal adiposity, expressed as excess BMI- and waist circumference-years, respectively, on the incidence of CVD in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Excess BMI and waist circumference-years are products of the degree of adiposity and duration of overweight/obesity, similar to the concept of pack-years, a frequently used cumulative measure of the quantity and duration of

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smoking (9). CARDIA provides a unique opportunity to study the cumulative impact of the obesity epidemic on the risk of incident CVD because the community-based cohort of young adults was recruited at the start of the obesity epidemic in the United States and has been followed continuously ever since with repeat assessments of anthropometry approximately every 2-5 years. We hypothesized that a greater cumulative exposure would be associated in a dose-response fashion with incident CVD. In addition, we hypothesized that excess BMI- and waist circumference-years would better predict CVD than only BMI or waist circumference attained over time.

Methods

Study population

CARDIA is a multicenter community-based longitudinal cohort study of the development and determinants of CVD in 5,115 young adults initially aged 18-30 years in 1985-1986 (10). To date, participants have been re-examined 2, 5, 7, 10, 15, 20, and 25 years after baseline and retention rates for the surviving cohort across examinations were 91%, 86%, 81%, 79%, 74%, 72%, and 72%, respectively. 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.

Of the 5,115 participants, we excluded those with missing BMI or waist circumference values at baseline ($n = 24$), women who were pregnant at any examination ($n = 239$), those who reported bariatric surgery during follow-up ($n = 68$), and those without BMI or waist circumference measured after baseline ($n = 723$). The remaining 4,061 participants formed the sample population for analysis.

Clinical measurements

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

Anthropometry

Weight and height were measured with participants wearing light examination clothes and no 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. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured with a Gulick 2 anthropometric tape with tensioning mechanism 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. Additional circumference measures (e.g., hip circumference) at all examinations were unavailable.

Excess BMI- and waist circumference-years

To account for BMI and waist circumference during follow-up years between examinations, we averaged values between adjacent examinations and assigned this value to each interim follow-up year. If BMI or waist circumference at an examination was missing, we used the value at the next available examination. For example, a participant with BMI values of 28, 30, and 32 kg/m^2 at baseline, year 2, and year 5, respectively, was assigned a BMI of 29 kg/m^2 at year 1 and 31 kg/m^2 at years 3 and 4. If the examined or interpolated BMI value for each follow-up year was $\geq$25 kg/m^2 (or for waist circumference >94 cm for men or >80 cm for women) (11,12), we subtracted a reference BMI of 24 kg/m^2 (for waist circumference 94 cm for men and 80 cm for women) from each value to calculate excess BMI (or waist circumference) at each year. If the examined or interpolated BMI was <25 kg/m^2 (or for waist circumference $\leq$94 cm for men and $\leq$80 cm for women), excess BMI (or waist circumference) was set to 0. For example, a participant with an examined BMI of 24 kg/m^2 at baseline, 25 at year 1, and 26 at year 2, would have excess BMI values of 0, 1, and 2 kg/m^2 for those years, respectively. We then accounted for duration of overweight/obesity by summing excess BMI and waist circumference over all years up to the development of a CVD event to calculate excess BMI- and waist circumference-years, respectively. For those who did not develop CVD, excess BMI and waist circumference were summed until the date of death or date of last contact.

Ascertainment of CVD

We recorded new CVD events through September 2011. During their scheduled study examinations and yearly telephone interviews, each participant or designated proxy was asked about interim hospital admissions, outpatient procedures, and deaths. Medical records were requested for participants who had been hospitalized or received an outpatient revascularization procedure. Vital status was assessed every 6 months; medical and other death records were requested after consent had been obtained from the next of kin.

Two physician members of the CARDIA endpoints surveillance and adjudication committee independently classified events and assigned incident dates. If they disagreed, the full committee made the final decision. For the purposes of this study, total CVD events comprised the incidence of coronary heart disease (CHD) (myocardial infarction, hospitalization for angina/acute coronary syndrome, or CHD death, including fatal myocardial infarction), heart failure (HF), stroke (fatal or non-fatal), transient ischemic attack, or peripheral arterial disease.

Other measurements

Detailed information on the collection of other measurements is available in the Supporting Information.

Statistical analysis

Participant characteristics overall, and according to excess BMI- and waist circumference-years were described using means, medians, or 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. We calculated the incidence rate of CVD, CHD, or HF (number of incident cases per person time at risk) per 1,000 person-years overall and according to excess BMI- and waist circumference-years accumulated. Follow-up time at risk was calculated as the difference between baseline and the incident date of CVD, CHD, or HF. For participants who did not experience a CVD, CHD, or HF event, follow-up time was censored at the date of death or the date of last contact.

Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI)

TABLE 1 Participant characteristics according to categories of excess body mass index (BMI)-years, The CARDIA study ($n = 4,061$)

	Excess BMI-years					
Variable[a]	0 ($n = 1,103$)	1-49 ($n = 986$)	50-99 ($n = 721$)	100-149 ($n = 494$)	≥150 ($n = 757$)	*P*-trend
Selected characteristics						
Baseline age (years)	24.7 (3.6)	24.9 (3.7)	24.9 (3.5)	25.1 (3.5)	24.7 (3.8)	0.6
Women, % (*n*)	57.1 (630)	45.5 (449)	44.5 (321)	40.3 (199)	55.2 (418)	0.06
Black race, % (*n*)	39.0 (430)	44.8 (442)	49.1 (354)	54.3 (268)	62.5 (473)	<0.001
Educational attainment (years)	15.3 (2.8)	15.5 (2.7)	15.3 (2.5)	15.3 (2.6)	15.0 (2.5)	0.002
Ever smoker, % (*n*)	78.8 (869)	70.5 (695)	71.0 (512)	69.8 (345)	71.5 (541)	<0.001
Physical activity (exercise units)[b]	363.7 (225.0-536.0)	347.5 (217.9-501.6)	341.9 (215.4-521.0)	349.5 (215.0-528.6)	279.2 (172.3-426.1)	<0.001
Alcohol (ml/day)[b]	7.2 (1.2-17.8)	7.5 (1.6-17.9)	6.4 (1.4-18.0)	6.2 (1.0-18.0)	3.3 (0.3-10.8)	<0.001
Clinical and physical characteristics						
Baseline BMI (kg/m^2)	20.6 (1.8)	22.5 (2.1)	23.6 (2.1)	24.8 (2.2)	26.2 (2.4)	<0.001
Baseline waist circumference (cm)	69.8 (6.1)	73.8 (7.0)	76.7 (7.7)	79.5 (8.0)	80.6 (7.8)	<0.001
Systolic blood pressure (mmHg)[b]	107.5 (9.5)	110.3 (9.5)	111.6 (9.0)	113.6 (9.7)	114.0 (9.5)	<0.001
Diastolic blood pressure (mmHg)[b]	67.7 (7.5)	69.6 (7.5)	70.7 (7.2)	72.2 (7.5)	73.3 (7.4)	<0.001
Ever antihypertensive medication, % (*n*)	7.9 (87)	17.4 (172)	20.3 (146)	24.9 (123)	36.6 (277)	<0.001
Ever lipid-lowering medication, % (*n*)	4.1 (45)	11.3 (111)	13.3 (96)	15.8 (78)	17.6 (133)	<0.001
Ever diabetes, % (*n*)[c]	2.4 (26)	6.0 (59)	8.3 (60)	14.2 (70)	20.9 (158)	<0.001
Fasting blood concentration[b]						
Glucose (mg/dl)	86.8 (14.6)	89.8 (14.8)	91.3 (13.4)	93.1 (10.7)	94.4 (14.2)	<0.001
Insulin (μU/ml)	8.8 (4.3)	10.5 (4.7)	12.0 (5.2)	14.0 (5.5)	17.0 (7.8)	<0.001
Total cholesterol (mg/dl)	173.1 (27.3)	181.5 (29.4)	184.0 (29.6)	185.2 (30.3)	183.2 (29.0)	<0.001
HDL-cholesterol (mg/dl)	58.3 (13.7)	54.8 (12.6)	51.6 (11.9)	49.3 (11.4)	49.4 (11.2)	<0.001
Triglycerides (mg/dl)	64.0 (51.0-82.8)	73.0 (56.3-98.4)	81.0 (59.5-106.6)	91.0 (67.1-121.0)	87.0 (63.9-118.8)	<0.001

[a]Presented as the mean (SD), median (IQR), or % (n) as appropriate.
[b]Based upon the average of all available values.
[c]Diabetes defined as a self-report of oral hypoglycemic medications or insulin at examination years 2, 5, 7, 10, 15, 20, and 25; fasting glucose levels ≥7.0 mmol/l (≥126 mg/dl) at examination years 7, 10, 15, 20, or 25; a 2-h postload glucose ≥11.1 mmol/l (≥200 mg/dl) at examination years 10, 20, and 25; or a glycated hemoglobin A_{1c} ≥6.5% at years 20 and 25.

TABLE 2 Hazard ratios (HR) and 95% confidence intervals (CI) for cardiovascular disease, coronary heart disease, and heart failure according to excess body mass index (BMI)-years, The CARDIA study ($n = 4,061$)

	Excess BMI-years						
	0 ($n = 1,103$)	1-49 ($n = 986$)	50-99 ($n = 721$)	100-149 ($n = 494$)	≥150 ($n = 757$)	P-trend	Per 50 excess BMI-years[a]
Cardiovascular disease							
No. of events	22	28	22	16	37		
Event rate[b]	0.86	1.12	1.27	1.33	2.02		
Model 1 HR (95% CI)[c]	1.00 (ref)	1.58 (0.94-2.67)	1.45 (0.79-2.65)	1.79 (0.92-3.51)	2.76 (1.49-5.09)	<0.001	1.20 (1.08-1.34)
Model 2 HR (95% CI)[d]	1.00 (ref)	1.14 (0.62-2.09)	0.89 (0.43-1.82)	0.74 (0.32-1.70)	0.90 (0.43-2.44)	0.82	0.98 (0.84-1.14)
Coronary heart disease							
No. of events	6	17	12	10	17		
Event rate[b]	0.23	0.71	0.69	0.83	0.92		
Model 1 HR (95% CI)[c]	1.00 (ref)	3.55 (1.45-8.72)	2.86 (1.05-7.78)	4.24 (1.48-12.11)	5.40 (1.91-15.26)	0.006	1.25 (1.07-1.46)
Model 2 HR (95% CI)[d]	1.00 (ref)	2.62 (0.87-7.93)	2.05 (0.60-7.01)	2.46 (0.67-8.99)	2.11 (0.53-8.48)	0.59	1.06 (0.86-1.32)
Heart failure							
No. of events	3	6	2	5	17		
Event rate[b]	0.12	0.25	0.11	0.41	0.92		
Model 1 HR (95% CI)[c]	1.00 (ref)	2.05 (0.53-7.96)	2.58 (0.61-11.01)	6.16 (1.53-24.81)	8.47 (2.17-33.08)	<0.001	1.45 (1.23-1.72)
Model 2 HR (95% CI)[d]	1.00 (ref)	3.25 (0.39-27.37)	4.11 (0.44-28.44)	4.23 (0.42-42.36)	5.99 (0.60-59.34)	0.02	1.32 (1.05-1.66)

[a]50 excess BMI-years is approximately equal to a BMI of 30 kg/m^2 for 8 years, for example.
[b]Per 1,000 person-years.
[c]Adjusted for age, race (black/white), sex, study center, and time-varying education (maximum years), smoking (current or former/never), alcohol use (average ml/day), physical activity (average exercise units), and energy intake (average kcal).
[d]Adjusted additionally for time-varying systolic blood pressure (average mmHg), insulin (average μU/ml), total cholesterol (average mg/dl), HDL-cholesterol (average mg/dl), triglycerides (average mg/dl), diabetes (yes/no), and medication use for high blood pressure or high cholesterol (separately) (yes/no).

for CVD, CHD, and HF according to excess BMI- and waist circumference-years. Excess BMI- and waist circumference-years were included as time-dependent variables in one of two exposure forms: first as a continuous variable (per 50 excess BMI- and waist circumference-years) assuming a linear dose-response association, and second as a five-level categorical variable (i.e., 0, 1-49, 50-99, 100-149, and ≥150 excess BMI- and 0, 1-99, 100-199, 200-299, and ≥300 waist circumference-years). Fifty excess BMI-years (or waist circumference-years) is approximately equal to a BMI of 30 kg/m^2 (or a waist circumference of 100 cm for men and 86 cm for women) for 8 years, for example. Analyses were adjusted for age, sex, race, CARDIA field center, and the following time-dependent covariates: education, smoking, alcohol use, physical activity, and energy intake. A second model adjusted additionally for the following time-dependent variables: systolic blood pressure, fasting insulin, total cholesterol, HDL-cholesterol, triglycerides, diabetes, and antihypertensive and lipid-lowering medication, separately. Average values reflect the mean of all available measures up until the date of the event or censoring. The additional adjustment variables in the second model could be in the causal pathway between excess BMI- and waist circumference-years and CVD, CHD, and HF; we regarded these models as possibly explanatory. Given the strong correlation between BMI and waist circumference ($r > 0.80$), we did not mutually adjust for overall and abdominal adiposity.

To compare the predictive value of excess BMI- and waist circumference-years with BMI and waist circumference only, respectively, we divided each of these time-dependent variables into equal categories defined by a not overweight/obese category and deciles for the remaining categories. We used the Akaike information criterion (AIC), computed as -2*(log-likelihood) + 2*(number of estimated parameters), as a measure of goodness of fit, to compare the models (13). A lower AIC indicates better fit.

We performed two sensitivity analyses. In the first, we used alternate thresholds to define an excess degree of overall (BMI ≥22 and ≥30 kg/m^2) and abdominal adiposity (waist circumference >90 and >102 cm for men and >76 and >88 cm for women). In the second, we accounted for missing BMI and waist circumference values from the follow-up examinations (18% of all measurements for each) on the sample of 4,061 participants using the sequential regression imputation approach that is implemented in the software package IVEware (14). Five datasets were generated using all available BMI and waist circumference data. Each dataset was analyzed separately and results from the five analyses were combined using the rules of Little and Rubin (15).

Tests of statistical significance were two-tailed, with an alpha level of 0.05. SAS version 9.3 (SAS Institute, Cary, NC) was used to perform all analyses.

Results

Of the 4,061 eligible participants, 48.4% were black and 49.7% were women. The mean (standard deviation) and median (interquartile range) excess BMI-years were 76.6 (90.6) and 47.0 (0-121.0),

TABLE 3 Hazard ratios (HR) and 95% confidence intervals (CI) for cardiovascular disease, coronary heart disease, and heart failure according to excess waist circumference-years, The CARDIA study ($n = 4{,}061$)

	Excess waist circumference-years						
	0 ($n = 1{,}711$)	1-99 ($n = 1{,}210$)	100-199 ($n = 471$)	200-299 ($n = 273$)	≥300 ($n = 396$)	*P*-trend	Per 50 excess waist circumference-years[a]
Cardiovascular disease							
No. of events	36	40	18	15	16		
Event rate[b]	0.90	1.35	1.57	2.26	1.66		
Model 1 HR (95% CI)[c]	1.00 (ref)	1.78 (1.16-2.74)	2.13 (1.19-3.80)	2.16 (1.02-4.58)	2.58 (1.26-5.32)	0.003	1.10 (1.04-1.18)
Model 2 HR (95% CI)[d]	1.00 (ref)	1.30 (0.77-2.20)	1.09 (0.53-2.23)	1.01 (0.40-2.57)	0.66 (0.24-1.80)	0.51	0.97 (0.88-1.07)
Coronary heart disease							
No. of events	16	24	9	8	5		
Event rate[b]	0.40	0.81	0.78	1.19	0.52		
Model 1 HR (95% CI)[c]	1.00 (ref)	2.34 (1.26-4.35)	2.10 (0.85-5.17)	4.39 (1.74-11.03)	2.83 (0.89-8.99)	0.01	1.13 (1.03-1.24)
Model 2 HR (95% CI)[d]	1.00 (ref)	1.88 (0.88-4.06)	1.41 (0.47-4.20)	2.11 (0.62-7.21)	0.72 (0.13-4.00)	0.80	0.98 (0.85-1.13)
Heart failure							
No. of events	8	5	4	6	10		
Event rate[b]	0.20	0.17	0.35	0.90	1.04		
Model 1 HR (95% CI)[c]	1.00 (ref)	1.29 (0.46-3.62)	5.07 (1.83-14.05)	3.35 (0.83-13.57)	6.47 (1.94-21.50)	<0.001	1.22 (1.11-1.34)
Model 2 HR (95% CI)[d]	1.00 (ref)	0.93 (0.26-3.32)	2.30 (0.58-9.04)	1.27 (0.19-8.35)	2.07 (0.37-11.50)	0.28	0.99 (0.98-1.01)

[a]50 excess waist circumference-years is approximately equal to a waist circumference of 100 cm for men and 86 cm for women for 8 years, for example.
[b]Per 1,000 person-years.
[c]Adjusted for age, race (black/white), sex, study center, and time-varying education (maximum years), smoking (current or former/never), alcohol use (average ml/day), physical activity (average exercise units), and energy intake (average kcal).
[d]Adjusted additionally for time-varying systolic blood pressure (average mmHg), insulin (average μU/ml), total cholesterol (average mg/dl), HDL-cholesterol (average mg/dl), triglycerides (average mg/dl), diabetes (yes/no), and medication use for high blood pressure or high cholesterol (separately) (yes/no).

respectively, and 97.3 (153.3) and 9.0 (0-122.3) for excess waist circumference-years. Approximately 27.2% and 40.9% of participants never achieved a BMI ≥25.0 kg/m^2 or waist circumference >94 cm (men) or >80 cm (women), respectively, during follow-up, and therefore had 0 excess BMI- and waist circumference-years.

Table 1 shows the characteristics of participants according to categories of excess BMI-years accumulated. Those with greater exposure to excess BMI-years were more likely to be black, achieve less education, were less likely to smoke, report less physical activity, and consume less alcohol. In addition, participants with greater excess BMI-years had higher average blood pressures; higher glucose, insulin, and lipid levels; were more likely to use antihypertensive and lipid-lowering medication; and were more likely to develop diabetes during follow-up. Baseline age and sex were unrelated to excess BMI-years accumulation. Similar results were observed when excess BMI-years was substituted with excess waist circumference-years, except women were more likely to have higher excess waist circumference-years (data not shown).

During a median 24.8 years of follow-up (35,478,786 person-years), there were 125 total CVD, 62 CHD, and 33 HF events. Table 2 shows adjusted HRs and 95% CIs for total CVD, CHD, and HF according to excess BMI-years. Rates per 1,000 person-years were higher with greater exposure to excess BMI-years. Adjusted HRs for CVD, CHD, and HF for each additional 50 excess BMI-years were 1.20 (95% CI: 1.08-1.34), 1.25 (95% CI: 1.07-1.46), and 1.45 (95% CI: 1.23-1.72), respectively. Associations were attenuated, but persisted for HF following further adjustment for potential intermediate factors (Table 2, model 2).

Table 3 shows adjusted HRs and 95% CIs for total CVD, CHD, and HF according to excess waist circumference-years. Similar to excess BMI-years, rates per 1,000 person-years were higher with greater excess waist circumference-years. Adjusted HRs for CVD, CHD, and HF for each additional 50 excess waist circumference-years were 1.10 (95% CI: 1.04-1.18), 1.13 (95% CI: 1.03-1.24), and 1.22 (95% CI: 1.11-1.34), respectively. Associations were attenuated and no longer statistically significant following further adjustment for potential intermediates (Table 3, model 2).

Table 4 shows AIC values comparing time-varying BMI and waist circumference with excess BMI- and waist circumference-years in the prediction of total CVD, CHD, and HF. Compared with models which included time-varying BMI only in the prediction of total CVD events and heart failure, models containing time-varying excess BMI-years exhibited lower AIC values. Similar results were observed in models which included waist circumference only vs. excess waist circumference-years, with the exception of CHD.

In the first sensitivity analysis, measures of association and AIC values were similar when we used alternative thresholds to define an excess degree of overall (BMI ≥22 and ≥30 kg/m^2) and abdominal adiposity (waist circumference >90 and >102 cm for men and >76 and >88 cm for women) (data not shown). In the second, when we imputed missing measurements of BMI and waist circumference

TABLE 4 Akaike information criterion values comparing time-varying body mass index (BMI) and waist circumference with time-varying excess BMI- and waist circumference-years in the prediction of total cardiovascular disease, coronary heart disease, and heart failure, The CARDIA study ($n = 4,061$)

	Time-varying exposures			
	BMI	Excess BMI-years	Waist circumference	Excess waist circumference-years
Cardiovascular disease	1,946	1,941	1,943	1,939
Coronary heart disease	939	938	944	945
Heart failure	521	516	519	512

from the follow-up examinations on the sample of 4,061 participants, HRs adjusted for model 1 covariates for each additional 50 excess BMI-years for CVD, CHD, and HF were 1.15 (95% CI: 1.03-1.29), 1.18 (95% CI: 1.00-1.79), and 1.40 (95% CI: 1.19-1.66), respectively, and 1.08 (95% CI: 1.01-1.16), 1.09 (95% CI: 0.98-1.21), and 1.22 (95% CI: 1.10-1.34) for each additional 50 excess waist circumference-years.

Neither excess BMI-years nor excess waist circumference-years were associated with incident stroke (32 events) [HRs adjusted for model 1 covariates for each additional 50 excess BMI- and waist circumference-years were 0.90 (95% CI: 0.70-1.17) and 0.95 (95% CI: 0.81-1.12), respectively].

Discussion

In this community-based longitudinal cohort study of young adults recruited and followed largely during the obesity epidemic over the last three decades in the United States, we found measures of the cumulative burden of excess overall and abdominal adiposity were strongly associated in a graded and similar fashion with incident CVD. As expected, this association was largely explained by several traditional metabolic CVD risk factors that may lie on the causal pathway between excess adiposity and the development of a CVD event. In addition, excess BMI- and waist circumference-years provided more discriminative power than those which included BMI or waist circumference alone. These findings suggest that the greater cumulative exposure to a higher degree and longer duration of excess adiposity will have important implications on the future burden of CVD in the United States.

We are unaware of longitudinal studies that have simultaneously measured and combined information regarding both the degree and duration of excess adiposity in the prediction of CVD. However, we note that our findings are consistent with a limited number of studies that have suggested the construct of excess BMI-years is associated with other adverse health-related outcomes, including diabetes, and may provide a better indicator of the health risks of increasing body weight than simply the degree of adiposity. In the National Longitudinal Survey of Youth 1979, excess BMI-years based on repeat reports of height and weight from 1981 through 2006 was strongly associated with the development of diabetes (16). In addition, models which contained excess BMI-years had areas under the receiver operator characteristic curve that were larger than those that included only baseline BMI (16). However, no additional measures of adiposity were available. In the Framingham Heart Study, each additional 10 excess BMI-years calculated from repeat measurements of BMI over 48 years beginning in 1948 was associated with a 7% higher incidence of diabetes (17). AIC values were lowest in models containing excess BMI-years than those which contained BMI only (17). However, rates of obesity were much lower in the United States over six decades ago and no other measures of adiposity were available. The primary strengths of the current study include the replicate assessments of both BMI and waist circumference collected every 2-5 years via a standardized protocol during a long follow-up period over the course of the obesity epidemic in the United States.

In the current study, we found that models predicting risk of CVD containing time-varying excess BMI- and waist circumference-years had lower AIC values than similar models that evaluated time-varying BMI and waist circumference only, results that were largely due to enhanced prediction of HF. Although it was not possible to perform a statistical comparison between models since they were non-nested, the AIC provides an objective way of determining which model among a set of models is most parsimonious. The exact value of the AIC for a given set of data has no meaning; however, when the AIC of a series of models is compared, the model with the lowest AIC is often referred to as the best model among all models specified. As a rule of thumb, models with a difference in AIC values of ≤ 2, 3-10, and >10 have little, considerable, and substantial evidence, respectively, for a difference between models (18). Thus, differences in the AIC values for CVD, which ranged from 4 to 5, suggest considerable support for both excess BMI- and waist circumference-years as improved predictors of CVD (18). To estimate the cumulative effects of a greater degree and longer duration of exposure to excess overall and abdominal adiposity as a result of the obesity epidemic, future studies should attempt to measure both the degree and duration of excess adiposity.

Our findings showed that greater exposure to excess BMI- and waist circumference-years was associated with higher levels of blood pressure, insulin, triglycerides, and total cholesterol, greater use of antihypertensive and lipid-lowering medications, higher rates of diabetes, and lower levels of HDL-cholesterol during follow-up. As expected, these potential intermediate metabolic CVD risk factors largely explained the association between excess BMI- and waist circumference-years and the development of CVD. However, the association of excess BMI-years with HF remained following adjustment for these factors. Additional mechanisms that may explain, at least in part, the association of excess overall adiposity with HF include sustained expression and secretion of proinflammatory adipocytokines, myocyte hypertrophy, myocardial fibrosis, sleep disordered breathing, and alterations in cardiac structure and function (19).

Strengths of the current study include a community-based sampling method; cohort recruitment and follow-up largely during the obesity epidemic of the last three 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 and waist circumference (and potential confounding and intermediate factors) starting at a young age, minimizing the potential for reverse causation; a high retention rate; verification and adjudication of CVD events; and the standardized data collection protocols and rigorous quality control of the CARDIA study. Nevertheless, at least four limitations deserve mention. First, our estimation of excess overall and abdominal adiposity during follow-up was based on the measurement of BMI and waist circumference, respectively, every 2-5 years. It is likely that a more frequent number of assessments would have led to a more accurate estimation; however, to the extent that there was random misclassification due to this assessment schedule, we may have underestimated the true association in our cohort. Second, because our study collected data over a 25-year follow-up period, some participants were missing at least one eligible measurement of BMI and waist circumference. However, we noted similar results (except for the association of excess waist circumference-years and CHD) between our multiple imputed datasets and our primary dataset that accounted for missing BMI and waist circumference using the average value from adjacent follow-up examinations. Third, although we defined an excess degree of overall and abdominal adiposity using recommended cut-points, it is unlikely that the adverse metabolic effects of excess adiposity begin to occur only at these levels. However, we noted no appreciable differences in models that set alternative definitions for these thresholds. Fourth, the relatively small number of outcomes in our study limited the precision of our estimates and our ability to perform stratified analyses.

In conclusion, our findings indicate that combined measures of the degree and duration of excess overall and abdominal adiposity strongly predict risk of new-onset CVD in a dose-response fashion. In addition, in nearly all instances, excess BMI- and waist circumference-years better predicted risk of CVD than BMI or waist circumference alone. This information is critical to understanding the consequences of a greater cumulative exposure to excess adiposity over the life course as a result of the obesity epidemic. These findings suggest that future public health interventions focused on CVD prevention should focus on younger populations to prevent or at least delay the development of excess adiposity. O

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