Association Between Adiposity in Midlife and Older Age and Risk of Diabetes in Older Adults

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Context Adiposity is a well-recognized risk factor for type 2 diabetes among young and middle-aged adults, but the relationship between body composition and type 2 diabetes is not well described among older adults.

Objective To examine the relationship between adiposity, changes in adiposity, and risk of incident type 2 diabetes in adults 65 years of age and older.

Design, Setting, and Participants Prospective cohort study (1989-2007) of 4193 men and women 65 years of age and older in the Cardiovascular Health Study. Measures of adiposity were derived from anthropometry and bioelectrical impedance data at baseline and anthropometry repeated 3 years later.

Main Outcome Measure Incident diabetes was ascertained based on use of antidiabetic medication or a fasting glucose level of 126 mg/dL or greater.

Results Over median follow-up of 12.4 years (range, 0.9-17.8 years), 339 cases of incident diabetes were ascertained (7.1/1000 person-years). The adjusted hazard ratio (HR) (95% confidence interval [CI]) of type 2 diabetes for participants in the highest quintile of baseline measures compared with those in the lowest was 4.3 (95% CI, 2.9-6.5) for body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]), 3.0 (95% CI, 2.0-4.3) for BMI at 50 years of age, 4.2 (95% CI, 2.8-6.4) for weight, 4.0 (95% CI, 2.6-6.0) for fat mass, 4.2 (95% CI, 2.8-6.2) for waist circumference, 2.4 (95% CI, 1.6-3.5) for waist-hip ratio, and 3.8 (95% CI, 2.6-5.5) for waist-height ratio. However, when stratified by age, participants 75 years of age and older had HRs approximately half as large as those 65 to 74 years of age. Compared with weight-stable participants (±2 kg), those who gained the most weight from 50 years of age to baseline (≥9 kg), and from baseline to the third follow-up visit (≥6 kg), had HRs for type 2 diabetes of 2.8 (95% CI, 1.9-4.3) and 2.0 (95% CI, 1.1-3.7), respectively. Participants with a greater than 10-cm increase in waist size from baseline to the third follow-up visit had an HR of type 2 diabetes of 1.7 (95% CI, 1.1-2.8) compared with those who gained or lost 2 cm or less.

Conclusion Among older adults, overall and central adiposity, and weight gain during middle age and after the age of 65 years are associated with risk of diabetes.

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INCIDENCE OF DIABETES IN THE United States has doubled in the past 15 years, and is highest among adults 65 to 79 years of age.[1] Approximately 70% of US men and women 60 years of age and older are overweight or obese (body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] ≥ 25).[2] Adiposity is a well-recognized risk factor for type 2 diabetes among young and middle-aged adults,[3-10] however, the relationships between different measures of body composition and diabetes in older adults (≥ 65 years of age) are not well described. Changes in body composition are known to occur with aging, including increase of fat mass, loss of muscle mass, redistribution of adipose tissue, and height shrinkage.

Given the high prevalence of obesity and diabetes in older adults, there is a need to clarify the relationship between adiposity and diabetes risk in this population. We examined the relationship between measures of overall body fat, fat distribution, changes in these measures, and diabetes risk among participants in the Cardiovascular Health Study, a large population-based study of adults 65 years of age and older.

METHODS

Study Population

The Cardiovascular Health Study is a prospective, population-based cohort

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study of cardiovascular disease in older adults. In 1989-1990, a group of 5201 ambulatory, noninstitutionalized men and women 65 years of age and older was recruited from a random sample of Medicare-eligible residents in 4 US communities: Forsyth County, North Carolina (Wake Forest University School of Medicine, Winston-Salem); Sacramento County, California (University of California, Davis); Washington County, Maryland (Johns Hopkins University, Hagerstown); and Allegheny County, Pennsylvania (University of Pittsburgh, Pittsburgh). To increase the number of African American participants, a supplemental cohort of 687 predominantly African American men and women was recruited during 1992 and 1993 from 3 of the same communities (excepting Washington County) using the same sampling and recruitment methods. Each center's institutional review committee approved the study and all participants gave informed written consent. Details of the study design, sampling, and recruitment are published.[11,12]

We excluded from the analysis participants who had prevalent diabetes at baseline (n=925), or for whom prevalent diabetes status could not be determined due to missing information on blood glucose levels (n=64) or diabetes medication use (n=6), or missing or inadequate fasting times (<8 hours; n=28). We also excluded participants who had no follow-up beyond baseline (n=111), were missing baseline measurements of body composition (weight, height, waist circumference, hip circumference, bioelectrical impedance, or weight at 50 years of age [n=303]), or were missing covariate data (n=250). An additional 8 participants were excluded due to fat-mass values outside the valid range. The final analysis sample included 4193 participants.

Data Collection

Comprehensive information on health-related variables was collected at baseline and annually thereafter in standardized fashion from Cardiovascular Health Study participants. Clinic examinations were performed annually from 1989-1990 (baseline) to 1998-1999, and again in 2005-2006. Telephone contact was made annually from 1989-1999 and 2005-2006 and twice per year from 2000-2004 and 2006-2007. Standardized questionnaires were administered at a baseline home interview, at annual clinic visits, and during telephone contacts. Descriptions of data collection methods, including instruments and protocols, have been reported previously.[12]

Body Composition Measures

Anthropometric measurements were performed by trained personnel using standardized protocols. Participants wore standard examination suits and no shoes. Standing height was measured using a stadiometer calibrated in centimeters. Body weight was measured using a balance beam scale calibrated in kilograms. Waist circumference was measured at the level of the umbilicus. Hip circumference was measured at the level of maximal protrusion of the gluteal muscles. Body weight was measured at each clinic examination. Standing height, waist circumference, and hip circumference were measured at the clinic examinations during 1989-1990, 1992-1993, and 1996-1997. Self-reported weight at 50 years of age was collected as part of the medical history questionnaire at baseline.

BMI at baseline was calculated using measured weight and height, but BMI at 50 years of age was calculated using self-reported weight at age 50 and measured height at baseline. Waist-hip ratio was calculated as the ratio of waist circumference to hip circumference. Waist-height ratio was calculated as the ratio of waist circumference to standing height.

Bioelectrical impedance was measured at baseline with participants in a supine position using a TVI-10 Body Composition Analyzer (Danninger Medical, Columbus, Ohio). Four adhesive electrocardiograph electrodes were placed in standard distal positions on the dorsum of the right hand and foot and resistance was measured at 50 kHz. Fat-free mass was calculated as $6710 \times ht^2/R + 3.1 \times S + 3.9$ (ht^2, standing height in meters squared; R, resistance in ohms; S, sex [0=women, 1=men]).[13] Fat mass was calculated as body weight minus fat-free mass.

Assessment of Type 2 Diabetes

Glucose was measured on fasting serum samples obtained during the annual clinic examinations in 1989-1990, 1992-1993, 1996-1997, and 2005-2006. Medication use was assessed at baseline and annually thereafter by medication inventory[14] through 2007. We classified participants as having diabetes if they used insulin or oral hypoglycemic agents, or had a fasting glucose level of 126 mg/dL or greater. We censored participants at the previous year's follow-up contact (last informative contact) if they had missing information on medication use or on fasting glucose levels at the 1992-1993, 1996-1997, or 2005-2006 examination.

Other Covariates

Age, sex, race, years of education, smoking status, physical activity, and diet (including alcohol consumption) were based on self-report. We assessed leisure-time physical activity as a weighted sum of kilocalories expended in specific physical activities.[15] To assess the influence of dietary habits, we adopted a dietary score, derived in prior studies, of dietary factors and diabetes.[16,17] To create the score, 4 dietary factors were selected based on their association with either an increased (higher intake of trans fat and higher glycemic load) or decreased (higher intake of cereal fiber and polyunsaturated fat) risk of diabetes. A dietary score for each participant was then computed by assigning a score from 1 to 5 corresponding with the participant's quintile of intake of higher dietary fiber, lower glycemic index, lower trans fat, and higher polyunsaturated to saturated fat ratio, and summing across the values (possible range for score, 5-20). Partici-

pants with higher composite diet scores were considered to be at lower risk of diabetes.

Statistical Analysis

We calculated Spearman correlation coefficients for each pair of body composition measures to assess the relationship between the measures. We categorized participants by sex-specific quintiles of BMI, BMI at 50 years of age, body weight, fat mass, waist circumference, waist-hip ratio, and waist-height ratio, and used Cox proportional hazards regression to estimate the relative risk (RR) of incident diabetes associated with these categories using the lowest quintile as the reference group. Estimates were also calculated for a 1 standard deviation change in the adiposity measures. Time at risk was calculated as the interval in days from the date of the baseline visit to the earliest of: date of the follow-up contact at which diabetes was ascertained, date of last informative contact, or date of the 2006-2007 telephone contact.

We tested for heterogeneity in the association of adiposity measures with incident diabetes by sex, race, and age by evaluating the statistical significance of multiplicative interaction terms in models that also included lower order terms. To evaluate whether age modified the risk of diabetes associated with adiposity, we categorized participants by sex-specific tertiles of each body composition measure and stratified the cohort by age group (<75 years; ≥75 years). The age of 75 years was selected a priori as the cutoff value to maximize the age difference between the groups while retaining adequate statistical power. In these analyses stratified by age group, categories were based on tertiles rather than quintiles to maximize statistical power. We assessed the joint association of body size at midlife (BMI at 50 years of age) and weight change since midlife with risk of diabetes, as well as the joint association of baseline BMI and baseline waist circumference with risk of diabetes. For these latter analyses, we classified participants using commonly used BMI (<25, 25-29, ≥30)[18] and waist circumference (women, <88 cm, ≥88 cm; men, <102 cm, ≥102 cm)[19] categories.

Participants enrolled during the first wave in 1989-1990 (N = 2807) were also classified according to change in weight and change in waist circumference between the baseline examination in 1989-1990 and the 1992-1993 examination. We calculated the RR of diabetes associated with categories of change in weight and waist using a stable range (±2 kg for weight, and ±2 cm for waist circumference) as the reference category. All multivariate models were adjusted for age, sex, race (African American, non-African American), current smoking status (yes, no), alcohol consumption (none, <7 drinks/week, ≥7 drinks/week), physical activity (kilocalories), and diet score (upper 2 quintiles vs lower 3). Covariates were selected a priori as potential confounders based on evidence from prior studies that they were associated with adiposity as well as with diabetes. Models of weight change were additionally adjusted for baseline BMI; and models of change in waist circumference were additionally adjusted for baseline BMI and baseline waist circumference. We evaluated the validity of the proportional hazards assumption using Schoenfeld residuals and found no evidence of nonproportionality.

All *P* values were based on 2-sided tests, were considered statistically significant at *P* less than .05, and were not adjusted for multiple comparisons. Because we tested highly correlated measures of a single exposure (adiposity) and a single outcome, adjustment for multiple comparisons would inappropriately reduce the power of our analy-

Table 1. Baseline Demographic and Lifestyle Characteristics by BMI Among Cardiovascular Health Study Participants

	No. (%) by BMI Category									
	Women (n = 2457)					Men (n = 1736)				
Characteristic	<22.2	22.2-24.4	24.5-26.6	26.7-29.6	≥29.7	<23.3	23.3-25.0	25.1-26.6	26.7-28.6	≥28.7
Age, mean (SD), y	73.3 (5.7)	72.3 (5.4)	72.2 (5.0)	72.2 (5.4)	71.3 (4.7)	74.7 (6.4)	73.2 (5.5)	72.8 (5.4)	72.7 (5.3)	71.8 (5.2)
African American	27 (5.5)	28 (5.7)	52 (10.6)	68 (13.9)	95 (19.4)	36 (10.3)	20 (5.8)	31 (8.9)	36 (10.4)	33 (9.5)
<High school education	105 (21.4)	107 (21.8)	110 (22.4)	135 (27.6)	171 (35.0)	87 (25.0)	92 (26.7)	90 (26.1)	101 (29.2)	96 (27.8)
Current smoker	88 (17.9)	75 (15.2)	56 (11.4)	40 (8.2)	47 (9.6)	59 (16.9)	39 (11.3)	35 (10.1)	31 (8.9)	24 (6.9)
≥7 Alcoholic drinks/wk	71 (14.4)	75 (15.2)	49 (10.0)	47 (9.6)	16 (3.3)	84 (24.1)	75 (21.7)	83 (23.9)	81 (23.3)	56 (16.1)
Dietary score upper 2 quintiles[a]	256 (52.0)	265 (53.9)	250 (50.9)	237 (48.3)	210 (42.8)	110 (31.5)	129 (37.3)	147 (42.4)	115 (33.1)	130 (37.5)
Physical activity, mean (SD), kcal	981.9 (1306.9)	990.3 (1322.9)	881.2 (1121.5)	870.4 (1235.5)	752.0 (1281.7)	1739.1 (2049.1)	1798.7 (1754.9)	1638.7 (1637.0)	1794.6 (2089.0)	1504.3 (1735.6)

Abbreviation: BMI, body mass index.
BMI is calculated as weight in kilograms divided by height in meters squared.
[a]Cut points for dietary score quintiles are 10, 12, 14, and 16.

ses. For the main analysis, we had 80% power to detect approximately a 70% increase in risk in women and 2-fold increase in risk in men, comparing any of quintiles 2, 3, or 4 to the lowest quintile. Statistical analysis was performed using Stata software version 10.1 (StataCorp, College Station, Texas).

RESULTS

The mean age (SD) of participants at baseline was 72.6 (5.4) years, 58.6% were women, and 10.2% were African American. Mean values of anthropometric measures for men and women were: BMI, 26.2 and 26.1; BMI at 50 years of age, 24.7 and 25.7; weight, 66.4 kg and 78.3 kg; fat mass, 33.7 kg and 30.0 kg; fat-free mass, 32.7 kg and 48.2 kg; waist-hip ratio, 0.89 and 0.96; waist-height ratio, 0.57 and 0.56, respectively. Measures of BMI, waist circumference, and fat mass were strongly correlated among both men and women with correlation coefficients ranging from 0.75 to 0.90. Waist-height ratio was strongly correlated with BMI (r=0.79), while waist-hip ratio was weakly correlated (r=0.33). BMI at 50 years of age was moderately correlated with baseline measures of BMI (r=0.70), waist circumference (r=0.58), and fat mass (0.50). BMI measured at baseline was positively associated with African American race, and inversely associated with age, education, current smoking, alcohol consumption, and physical activity (TABLE 1). Women with higher diet scores had lower average BMI, although there was no clear pattern between diet score and BMI among men. At baseline, 45% of participants had prediabetes (fasting glucose, 100-125 mg/dL).

Over a median follow-up of 12.4 years (range, 0.9-17.8 years), 339 new cases of diabetes were ascertained among the 4193 participants in our analysis sample. BMI at baseline, BMI at 50 years of age, weight, fat mass, waist circumference, waist-hip ratio, and waist-height ratio were all strongly related to the risk of diabetes (TABLE 2, TABLE 3). For each measure, there was a graded increase in the risk of diabetes with increasing quintiles of adiposity. Participants in the highest category of adiposity had an approximately 2- to 6-fold increased risk of developing diabetes compared with those in the

Table 2. Association Between Measures of Adiposity and Risk of Incident Type 2 Diabetes in Women (n = 2457) by Measures of Adiposity, the Cardiovascular Health Study, 1989-2007

	Quintile				
Adiposity Measure	1	2	3	4	5
BMI[a]					
Quintile range	<22.2	22.2-24.4	24.5-26.6	26.7-29.6	≥29.7
No. person-years of follow-up	5610	6142	5959	6140	5614
No. cases type 2 diabetes	20	20	30	36	84
HR (95% CI)[b]	1.0	0.9 (0.5-1.6)	1.4 (0.8-2.5)	1.6 (0.9-2.7)	3.7 (2.3-6.2)
BMI at 50 years of age[a]					
Quintile range	<21.7	21.7-23.2	23.4-24.8	24.9-27.1	≥27.2
No. person-years of follow-up	5988	6101	6059	5917	5401
No. cases type 2 diabetes	19	22	38	49	62
HR (95% CI)[b]	1.0	1.1 (0.6-2.1)	2.0 (1.2-3.5)	2.5 (1.5-4.3)	3.2 (1.9-5.5)
Weight, kg					
Quintile range	<55.9	55.9-61.4	61.5-67.8	67.9-75.7	≥75.8
No. person-years of follow-up	5678	5832	6019	6243	5694
No. cases type 2 diabetes	20	21	32	39	78
HR (95% CI)[b]	1.0	1.0 (0.5-1.8)	1.5 (0.8-2.6)	1.7 (1.0-2.9)	3.5 (2.1-5.7)
Fat mass, kg					
Quintile range	<25.1	25.1-29.8	29.9-35.0	35.1-41.3	≥41.4
No. person-years of follow-up	5447	6041	6128	6111	5738
No. cases type 2 diabetes	19	20	31	43	77
HR (95% CI)[b]	1.0	0.9 (0.5-1.6)	1.4 (0.8-2.5)	1.9 (1.1-3.2)	3.3 (2.0-5.6)
Waist, cm					
Range	<78.6	78.6-86.0	86.1-93.0	93.1-101.0	≥101.1
No. person-years of follow-up	6048	6496	5467	5892	5563
No. cases type 2 diabetes	20	29	24	46	71
HR (95% CI)[b]	1.0	1.3 (0.8-2.4)	1.3 (0.7-2.4)	2.3 (1.4-4.0)	3.6 (2.2-6.0)
Waist-hip					
Quintile range	<0.81	0.81-0.85	0.86-0.90	0.91-0.95	≥0.96
No. person-years of follow-up	6380	5873	5895	5700	5617
No. cases type 2 diabetes	23	35	39	55	38
HR (95% CI)[b]	1.0	1.7 (1.0-2.8)	1.9 (1.1-3.2)	2.8 (1.7-4.6)	1.9 (1.1-3.2)
Waist-height					
Quintile range	<0.49	0.49-0.53	0.54-0.58	0.59-0.63	≥0.64
No. person-years of follow-up	6128	6077	5769	6091	5400
No. cases type 2 diabetes	22	22	31	43	72
HR (95% CI)[b]	1.0	1.0 (0.6-1.8)	1.5 (0.9-2.6)	1.9 (1.2-3.3)	3.6 (2.2-5.9)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a] BMI is calculated as weight in kilograms divided by height in meters squared.
[b] All hazard ratios are adjusted for age (continuous), race (African American, non-African American), current smoking (yes, no), physical activity (continuous), diet score (upper 2 quintiles vs lower 3), and alcohol consumption (none, <7 drinks/wk, ≥7 drinks/wk). HRs (95% CIs) per 1 standard deviation are: 1.5 (1.4-1.7) for BMI, 1.3 (1.2-1.5) for BMI at 50 years of age, 1.6 (1.4-1.9) for weight, 1.5 (1.4-1.7) for fat mass, 1.5 (1.4-1.7) for waist, 1.2 (1.1-1.3) for waist-hip ratio, and 1.5 (1.3-1.7) for waist-height ratio.

lowest category. We found no evidence of significant statistical interaction by sex or race.

The risk of diabetes associated with adiposity was modified by age; the RR of diabetes associated with being in the upper third of the distribution for each adiposity measure was approximately half as large in participants 75 years of age and older compared with those younger than 75 years of age (TABLE 4).

The mean (SD) change in weight from 50 years of age to study entry (baseline) was 4.3 (8.8) kg for women and 1.3 (8.1) kg for men. The risk of diabetes increased monotonically with the amount of weight gained between 50 years of age and baseline (TABLE 5). Compared with participants whose weight remained stable (±2 kg) over the time period, those who gained 9 kg or more between the age of 50 years and study entry had an approximately 3-fold greater risk of developing diabetes during follow-up, regardless of their BMI at 50 years of age. Participants who were obese (BMI ≥30) at 50 years of age and who experienced the most weight gain (>9 kg) between the age of 50 years and study entry had 5 times the risk of developing diabetes compared with weight-stable participants with normal BMI (<25) at 50 years of age. We did not observe a decrease in diabetes risk with weight loss between 50 years of age and baseline except in participants in the lowest tertile of BMI at the age of 50 years who had a 40%-decreased risk of diabetes, which was not statistically significant (RR, 0.6; 95% CI, 0.3-1.3).

In a joint model of BMI (<25, 25-29, ≥30) and waist circumference (men, <102 cm vs ≥102 cm; women, <88 cm vs ≥88 cm), the risk of diabetes was independently associated with both measures. However, examination of waist circumference estimates stratified by BMI revealed that the association was driven primarily by a strong association of waist circumference and diabetes in participants with a BMI of less than 25. Compared with participants with low waist circumference, the hazard ratios (HRs) for diabetes for those with high waist circumference were 1.8 (95% CI, 1.1-3.0) for BMI less than 25, 1.2 (95% CI, 0.9-1.6) for BMI 25-29, and 1.4 (95% CI, 0.5-3.9) for BMI ≥30. Participants in the highest categories of both BMI and waist circumference had

Table 3. Association Between Measures of Adiposity and Risk of Incident Type 2 Diabetes in Men (n = 1736), the Cardiovascular Health Study, 1989-2007

	Quintile				
Adiposity Measure	1	2	3	4	5
BMI[a]					
Quintile range	<23.3	23.3-25.0	25.1-26.6	26.7-28.6	≥28.7
No. person-years of follow-up	3445	3597	3757	3551	3639
No. cases type 2 diabetes	9	18	28	41	53
HR (95% CI)[b]	1.0	1.9 (0.9-4.3)	2.9 (1.3-6.1)	4.4 (2.1-9.1)	5.6 (2.7-11.4)
BMI at 50 years of age[a]					
Quintile range	<23.3	23.3-24.7	24.8-26.0	26.1-27.9	≥28.0
No. person-years of follow-up	3769	3669	3508	3686	3358
No. cases type 2 diabetes	21	25	22	32	49
HR (95% CI)[b]	1.0	1.2 (0.6-2.1)	1.1 (0.6-2.0)	1.5 (0.9-2.6)	2.6 (1.5-4.3)
Weight, kg					
Quintile range	<68.5	68.5-74.8	74.9-80.5	80.6-87.1	≥87.2
No. person-years of follow-up	3434	3450	3656	3871	3579
No. cases type 2 diabetes	9	29	22	33	56
HR (95% CI)[b]	1.0	3.1 (1.5-6.5)	2.3 (1.0-5.0)	3.1 (1.5-6.6)	6.0 (2.9-12.2)
Fat mass, kg					
Quintile range	<22.9	22.9-27.4	27.5-31.5	31.6-36.8	≥36.9
No. person-years of follow-up	3429	3566	3765	3736	3494
No. cases type 2 diabetes	9	23	35	34	48
HR (95% CI)[b]	1.0	2.5 (1.1-5.3)	3.6 (1.7-7.5)	3.5 (1.7-7.3)	5.2 (2.5-10.7)
Waist, cm					
Quintile range	<89.1	89.1-94.0	94.1-99.0	99.1-104.5	≥104.6
No. person-years of follow-up	3712	3827	3924	3242	3286
No. cases type 2 diabetes	11	24	26	37	51
HR (95% CI)[b]	1.0	2.1 (1.0-4.2)	2.2 (1.1-4.4)	3.9 (2.0-7.7)	5.1 (2.7-9.9)
Waist-hip ratio					
Quintile range	<0.92	0.92-0.94	0.95-0.96	0.97-1.00	≥1.01
No. person-years of follow-up	3793	3700	3569	3535	3393
No. cases type 2 diabetes	16	28	25	35	45
HR (95% CI)[b]	1.0	1.8 (1.0-3.3)	1.7 (0.9-3.1)	2.4 (1.3-4.4)	3.1 (1.8-5.5)
Waist-height ratio					
Quintile range	<0.51	0.51-0.53	0.54-0.56	0.57-0.59	≥0.60
No. person-years of follow-up	3733	3775	3657	3357	3468
No. cases type 2 diabetes	14	19	25	39	52
HR (95% CI)[b]	1.0	1.3 (0.7-2.7)	1.8 (1.0-3.5)	3.2 (1.7-5.8)	3.9 (2.2-7.1)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a] BMI is calculated as weight in kilograms divided by height in meters squared.
[b] All hazard ratios are adjusted for age (continuous), race (African American, non-African American), current smoking (yes, no), physical activity (continuous), diet score (upper 2 quintiles vs lower 3), and alcohol consumption (none, <7 drinks/wk, ≥7 drinks/wk). HRs (95% CIs) per 1 standard deviation are: 1.7 (1.4-2.0) for BMI, 1.4 (1.2-1.6) for BMI at 50 years of age, 1.7 (1.4-2.0) for weight, 1.5 (1.3-1.8) for fat mass, 1.7 (1.4-2.1) for waist, 1.5 (1.2-1.8) for waist-hip ratio, and 1.7 (1.4-2.0) for waist-height ratio.

more than 4 times the risk of those in the lowest category of both measures (HR, 4.5; 95% CI, 3.3-6.1).

Estimates of the risk of diabetes associated with changes in weight and waist circumference were similar when we used measured weight and waist circumference change between the 1989-1990 and 1992-1993 examinations (TABLE 6). Compared with participants with stable measures, those who gained 6 kg or greater or in whom waist circumference increased more than 10 cm had a 2-fold increased risk of diabetes.

Table 4. Association Between Measures of Adiposity and Risk of Incident Type 2 Diabetes by Age Group, the Cardiovascular Health Study, 1989-2007

	Patient Age Group by Tertile						
	<75 y (n = 2840)			≥75 y (n = 1353)			
Adiposity Measure	1	2	3	1	2	3	*P* Value Interaction[a]
BMI[b]							
No. person-years of follow-up	10 466	12 377	12 238	4878	4027	3469	
No. cases type 2 diabetes	36	66	168	17	28	24	.005
HR (95% CI)[c]	1.0	1.6 (1.1-2.4)	4.0 (2.8-5.7)	1.0	2.0 (1.1-3.6)	1.9 (1.0-3.6)	
BMI at 50 years of age[d]							
No. person-years of follow-up	11 893	12 097	11 092	4388	4080	3906	
No. cases type 2 diabetes	49	77	144	25	17	27	.02
HR (95% CI)[c]	1.0	1.5 (1.1-2.2)	3.0 (2.2-4.2)	1.0	0.8 (0.4-1.5)	1.3 (0.7-2.3)	
Weight[e]							
No. person-years of follow-up	9902	12 078	13 101	5252	4188	2933	
No. cases type 2 diabetes	40	61	169	25	21	23	.08
HR (95% CI)[c]	1.0	1.3 (0.8-1.9)	3.2 (2.3-4.5)	1.0	1.1 (0.6-1.9)	1.5 (0.9-2.7)	
Fat mass[f]							
No. person-years of follow-up	10 164	12 254	12 664	5025	4270	3079	
No. cases type 2 diabetes	38	68	164	20	32	17	<.001
HR (95% CI)[c]	1.0	1.5 (1.0-2.3)	3.5 (2.4-4.9)	1.0	1.8 (1.0-3.2)	1.3 (0.7-2.5)	
Waist[g]							
No. person-years of follow-up	11 706	11 758	11 617	4716	3911	3747	
No. cases Type 2 diabetes	43	77	150	21	21	27	.07
HR (95% CI)[c]	1.0	1.7 (1.2-2.5)	3.5 (2.5-4.9)	1.0	1.2 (0.7-2.3)	1.6 (0.9-2.9)	
Waist-hip ratio[h]							
No. person-years of follow-up	12 497	11 601	10 983	4052	4290	4031	
No. cases type 2 diabetes	59	94	117	22	21	26	.11
HR (95% CI)[c]	1.0	1.8 (1.3-2.4)	2.3 (1.7-3.1)	1.0	0.9 (0.5-1.7)	1.3 (.7-2.3)	
Waist-height ratio[i]							
No. person-years follow-up	12 210	11 622	11 249	4190	4240	3944	
No. cases type 2 diabetes	43	75	152	19	20	30	.06
HR (95% CI)[c]	1.0	1.8 (1.2-2.6)	3.8 (2.7-5.4)	1.0	1.1 (0.6-2.1)	1.7 (1.0-3.1)	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, harzard ratio.
[a] *P* value for interaction compares participants younger than 75 years of age with participants 75 years of age or older.
[b] BMI is calculated as weight in kilograms divided by height in meters squared. Cut points for BMI are: women, 23.8, 27.5; men, 24.5, 27.3.
[c] All hazard ratios are adjusted for sex, race (African American, non-African American), current smoking (yes, no), physical activity (continuous), diet score (upper 2 quintiles vs lower 3), and alcohol consumption (none, <7 drinks/wk, ≥7 drinks/wk).
[d] Cut points for BMI at 50 years of age are 22.8 and 25.5 for women; 24.3 and 26.5 for men.
[e] Cut points for weight (kg) are 59.7 and 70.5 for women; 72.8 and 82.6 for men.
[f] Cut points for fat mass (kg) are 28.3 and 36.9 for women; 25.9 and 33.0 for men.
[g] Cut points for waist circumference (cm) are 83.5 and 95.4 for women; 92.5 and 100.4 for men.
[h] Cut points for waist-hip ratio are 0.84 and 0.93 for women; 0.94 and 0.98 for men.
[i] Cut points for waist-height ratio are 0.53 and 0.60 for women; 0.54 and 0.58 for men.

COMMENT

In this prospective analysis of a population-based sample of older adults, we found that measures of overall and central adiposity were strongly associated with the risk of incident diabetes in both men and women. Using longitudinal measures of weight from midlife, at study entry, and over follow-up, we were able to demonstrate that weight gain during midlife (after 50 years of age) and in late life (after 65 years of age) is an important risk factor for diabetes among older adults. Although the risk associated with adiposity appeared to wane with age, individuals in the highest category of BMI remained at twice the risk of diabetes compared with those in the lowest category among participants 75 years of age and older.

In the current analysis, simple anthropometric measures such as BMI, body weight, and waist circumference were as strongly associated with the risk of diabetes as were fat mass estimates derived from bioelectrical impedance measures. The 2 composite measures, waist-hip ratio and waist-height ratio, had RR estimates for diabetes that were similar to those of waist circumference alone. While in certain populations, waist circumference[6,20,21] or waist-to-hip ratio[22] may offer better predictive power for diabetes risk than BMI, our findings are generally consistent with the findings of a meta-analysis of 32 population-based studies that found that RRs for diabetes were equivalent for standardized differences in BMI, waist circumference, and waist-to-hip ratio.[23]

Age modified the risk of diabetes associated with adiposity in this analysis. For each of the various adiposity measures evaluated at baseline, RR estimates associated with higher adiposity were appreciably lower in individuals 75 years of age and older compared with those 65 to 74 years of age. The presence of effect modification by age has been noted for the relationship between body composition measures and outcomes such as mortality[24-26] and coronary heart disease risk,[27] but we are unaware of previous studies reporting an age interaction of the association of adiposity with diabetes risk.

There are a number of potential explanations for a weaker association of body composition measures with diabetes risk among individuals 75 years of age and older. Among older adults, standard anthropometric measures may not adequately quantify body fat due to age-related changes in body composition, including decreases in skeletal muscle mass and height.[28] However, the RRs associated with fat mass estimates from bioelectrical impedance measures showed reductions in magnitude similar to those of anthropometric measures among those 75 years of age and older. A second possibility is that regional fat distribution is more important in the etiology of diabetes than absolute fat mass. Visceral fat and intermuscular thigh fat are associated with

Table 5. Association Between BMI at Midlife, Change in Weight Between Midlife and Older Age, and Risk of Incident Type 2 Diabetes, the Cardiovascular Health Study

Weight Change Between 50 years of Age and Baseline, kg	No. Person-Years of Follow-up	No. Cases Type 2 Diabetes	Incident Diabetes HR (95% CI)[a]
<25 BMI at 50 years of age[b]			
Loss of >2	4336	10	0.6 (0.3-1.3)
Gain/loss of ≤2	6965	26	1 [Reference]
Gain of >2-<6	7172	26	1.0 (0.6-1.7)
Gain of ≥6-<9	3568	17	1.3 (0.7-2.5)
Gain of ≥9	4340	50	3.2 (2.0-5.1)
25-29 BMI at 50 years of age[b]			
Loss of >2	4435	39	2.3 (1.4-3.8)
Gain/loss of ≤2	3450	18	1.3 (0.7-2.4)
Gain of >2-<6	4162	33	2.0 (1.2-3.4)
Gain of ≥6-<9	1978	22	2.9 (1.7-5.2)
Gain of ≥9	3689	57	4.0 (2.5-6.4)
≥30 BMI at 50 years of age[b]			
Loss of >2	1471	13	2.3 (1.2-4.6)
Gain/loss of ≤2	524	6	2.4 (1.0-5.9)
Gain of >2-<9[c]	719	10	3.5 (1.7-7.2)
Gain of ≥9	645	12	5.0 (2.5-10.0)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a] All HRs are adjusted for age (continuous), sex, race (African American, non-African American), current smoking (yes, no), physical activity (continuous), diet score (upper 2 quintiles vs lower 3), and alcohol consumption (none, <7 drinks/wk, ≥7 drinks/wk).
[b] BMI is calculated as weight in kilograms divided by height in meters squared.
[c] The greater than 2 kg to less than 6 kg and the 6 kg or greater to less than 9 kg categories for weight gain were pooled due to small numbers.

Table 6. Risk of Incident Diabetes During 1994-2007 Associated With Change in Waist Circumference and Weight Between 1989-1990 and 1992-1993, Among Participants Free of Diabetes at 1992-1993 Examination

	Waist Change Between 1989-1990 and 1992-1993				
	Loss	Gain/Loss		Gain	
Range, cm	>2	≤2	3-4	5-10	>10
Cases No.	24	43	37	28	42
HR (95% CI)[a]	0.8 (0.5-1.3)	1 [Reference]	1.3 (0.9-2.1)	1.0 (0.6-1.6)	1.7 (1.1-2.8)
	Weight Change Between 1989-1990 and 1992-1993				
Range, kg	>2	≤2	3-5	≥6	
Cases No.	42	73	46	13	
HR (95% CI)[b]	1.1 (0.7-1.6)	1 [Reference]	1.1 (0.8-1.6)	2.0 (1.1-3.6)	

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age, sex, race, current smoking, physical activity, alcohol consumption, body mass index at 1989-1990 examination, and waist circumference at 1989-1990 examination.
[b] Adjusted for age, sex, race, current smoking, physical activity, diet, alcohol consumption, and body mass index at 1989-1990 examination.

impaired glucose tolerance and diabetes in older adults independent of total adiposity.[29,30] Waist circumference is highly correlated with visceral fat in older adults in some[31,32] but not all[33] studies, and the strength of association may vary according to age, sex, race, overall adiposity, and cardiorespiratory fitness.[34,35] This raises some uncertainty about whether waist circumference is a reliable surrogate for direct measurement of visceral fat. Intermuscular thigh fat can be measured reliably only through an imaging modality such as computed tomography. To the extent that these fat depots become more important to diabetes etiology as individuals age, the inability of the adiposity measures included in our study to measure such depots could explain the observed effect modification by age.

Another explanation for the effect modification by age is that the pathophysiology of diabetes in older adults differs from that of young and middle-aged adults. If, for instance, defects in insulin secretion played a larger role than insulin resistance in the development of diabetes in older individuals, one might expect there to be less of an association with adiposity. While possible, we know of no data that support a different pathophysiology of diabetes in older adults.

In addition, the observed age-adiposity interaction with diabetes risk may result from selective survival among older adults.[36] Individuals who are more susceptible to adverse health outcomes associated with adiposity may be less likely to survive into old age. Such an effect would be consistent with the uniform attenuation of all adiposity measures among the older age group observed in the current analysis.

We did not observe a reduction in diabetes risk associated with measured weight loss over a 3-year period. This contrasts with the results of studies in younger populations that found weight loss to be associated with a decreased risk of diabetes.[37,38] Older adults may lose proportionately more muscle mass with weight loss than younger ones,[39] decreasing the accuracy of weight loss as a surrogate for loss of adipose tissue in older adults. Furthermore, the loss of skeletal muscle mass may decrease insulin sensitivity,[40] negating the benefit derived from fat loss. Alternatively, weight loss associated with insulin resistance[41] that preceded the onset of clinical diabetes may have obscured an association between weight loss and decreased diabetes risk. Because of these complexities, our results do not preclude the possibility that voluntary weight loss reduces the risk of diabetes in older adults.

Our analysis showed an association between waist circumference and diabetes risk in individuals with a BMI of less than 25, suggesting that measurement of waist circumference may add important information beyond BMI regarding diabetes risk in normal-weight individuals. The observation that waist circumference was less strongly associated with diabetes risk at higher BMIs may reflect the fact that waist circumference is a better measure of visceral fat at a low BMI.[35]

This study has several strengths. We used data from a well-characterized population-based cohort with long-term follow-up. Aside from self-reported weight at 50 years of age, all our anthropometry was based on direct measurement rather than self-report. We were able to examine both incident diabetes and body composition changes prospectively, analyzed both men and women, and had extensive covariate data. We examined multiple measures of adiposity—particularly valuable in light of heterogeneity among previous studies of adiposity, the marked changes in body composition that occur with aging, and the paucity of studies of this type in older adults.

Potential limitations should also be noted. The measurement of fasting glucose at limited time points may have resulted in misclassification of participants with untreated diabetes. Such misclassification would likely be nondifferential and result in attenuation of risk estimates. Despite the wealth of covariate data that allowed us to adjust for well-known confounders, residual confounding due to unknown factors related to both adiposity and diabetes may be present.

Results of this study affirm the importance of maintaining optimal weight during middle age for prevention of diabetes and, while requiring confirmation, suggest that weight control remains important in reducing diabetes risk among adults 65 years of age and older.

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Analysis and interpretation of data: Biggs, Mukamal, Ix, Luchsinger, Newman, de Boer, Newman, Siscovick, Strotmeyer, Mozaffarian.
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