Duration and Degree of Weight Gain and Incident Diabetes in Younger Versus Middle-Aged Black and White Adults: ARIC, CARDIA, and the Framingham Heart Study

Gina S. Wei,[1] Sean A. Coady,[1] Jared P. Reis,[1] Mercedes R. Carnethon,[2] Josef Coresh,[3,4] Ralph B. D'Agostino Sr.,[5] David C. Goff Jr.,[6] David R. Jacobs Jr.,[7] Elizabeth Selvin,[3,4] and Caroline S. Fox[8]

Diabetes Care 2015;38:2042–2049 | DOI: 10.2337/dc14-2770

OBJECTIVE

To determine whether duration and degree of weight gain are differentially associated with diabetes risk in younger versus middle-aged black and white adults.

RESEARCH DESIGN AND METHODS

We combined data from three cohort studies: Atherosclerosis Risk in Communities (ARIC), Coronary Artery Risk Development in Young Adults (CARDIA), and the Framingham Heart Study. A total of 17,404 participants (56% women; 21% black) were stratified by baseline age (younger: ≥30 and <45 years; middle-aged: ≥45 and <60 years) and examined for incident diabetes (median follow-up 9 years). Duration and degree of gain in BMI were calculated as "BMI-years" above one's baseline BMI.

RESULTS

Diabetes incidence per 1,000 person-years in the younger and middle-aged groups was 7.2 (95% CI 5.7, 8.7) and 24.4 (22.0, 26.8) in blacks, respectively, and 3.4 (2.8, 4.0) and 10.5 (9.9, 11.2) in whites, respectively. After adjusting for sex, baseline BMI and other cardiometabolic factors, and age and race interaction terms, gains in BMI-years were associated with higher risk of diabetes in the younger compared with middle-aged groups: hazard ratios for 1-unit increase in log BMI-years in younger versus middle-aged blacks were 1.18 (P = 0.02) and 1.02 (P = 0.39), respectively (P for interaction by age-group = 0.047), and in whites were 1.35 (P < 0.001) and 1.11 (P < 0.001), respectively (P for interaction by age-group = 0.008).

CONCLUSIONS

Although middle-aged adults have higher rates of diabetes, younger adults are at greater relative risk of developing diabetes for a given level of duration and degree of weight gain.

The young adulthood period is associated with the greatest gains in adiposity during the life course (1,2). Although middle-aged adults have the highest incidence of diabetes in the U.S., incidence in younger adults has risen steadily in recent years (3). Research on the clinical predictors of type 2 diabetes, however, has largely focused on middle-aged populations (4,5). Diabetes prediction rules derived from middle-aged

[1]Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD
[2]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL
[3]Department of Epidemiology and the Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
[4]Division of General Internal Medicine, Department of Medicine, Johns Hopkins University, Baltimore, MD
[5]Department of Mathematics and Statistics, Boston University, Boston, MA
[6]Office of the Dean, Colorado School of Public Health, Aurora, CO
[7]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN
[8]Framingham Heart Study, Center for Population Studies, National Heart, Lung, and Blood Institute, Bethesda, MD

Corresponding author: Gina S. Wei, weig@nhlbi.nih.gov.

Received 21 November 2014 and accepted 27 July 2015.

populations that incorporate measures of adiposity and other cardiometabolic variables have performed poorly in young adults (6), suggesting that risk factors are likely modified by age.

To our knowledge, no study has directly compared whether and how the impact of risk factors, including obesity, on incident diabetes might differ between middle-aged and young adults. Given the growing body of evidence suggesting the adverse effects of a greater cumulative obesity exposure (i.e., duration and degree) on the risk of developing diabetes (7–9), it is critical to account for both of these dimensions when assessing this question. Recent findings from a follow-up study of adolescents and young adults suggest that younger individuals are at greater risk of developing diabetes for a given cumulative level of excess weight gain (10). However, whether this age-related differential effect extends from young adulthood into middle age is unknown. It is also unknown whether the magnitude of any such association would vary between blacks and whites. Given prior evidence suggesting that other cardiometabolic factors affect diabetes risk differently in blacks and whites, further race-specific investigations appear warranted (11).

We therefore conducted pooled analyses using data from three large well-characterized community-based cohort studies in the U.S. Together, the Atherosclerosis Risk in Communities (ARIC) study, the Coronary Artery Risk Development in Young Adults (CARDIA) study, and the Framingham Heart Study provide a rich resource to compare the incidence of type 2 diabetes in younger versus middle-aged blacks and whites. We hypothesized that the association of prospective weight gain over approximately one decade, expressed as BMI-years to account for both the degree and duration of weight gain, would be more strongly associated with incident diabetes in younger than middle-aged adults independent of baseline BMI and other cardiometabolic risk factors. We secondarily investigated whether the magnitude of the associations would differ between blacks and whites.

RESEARCH DESIGN AND METHODS

Study Characteristics

ARIC is a longitudinal study of 15,792 adults aged 45–64 years at enrollment in 1987–1989 in four communities: Forsyth County, NC; Jackson, MS (black only); the northwestern suburbs of Minneapolis, MN; and Washington County, MD. Three subsequent examinations were conducted approximately every 3 years (1990–1992, 1993–1995, and 1996–1998). The fifth ARIC examination (2011–2013) was not used for this study due to its distance in time from the first four examinations.

CARDIA is also a longitudinal study in four communities: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. It enrolled 5,115 black and white men and women aged 18–30 years in 1985–1986, with the recruitment approximately balanced on age, sex, race, and education status within each community. Seven subsequent examinations were conducted every 2–5 years (1987–1988, 1990–1991, 1992–1993, 1995–1996, 2000–2001, 2005–2006, and 2010–2011).

The first examination of the offspring cohort of the Framingham Heart Study began in 1971–1975. A total of 5,124 offspring and spouses of the offspring (aged 5–70 years) of the Framingham Heart Study's original cohort were recruited. They were next examined 8 years later and then about every 4 years through the seventh examination, followed by the eighth examination ~6.5 years later (2005–2008).

Details of these three studies have been reported elsewhere (12–14). The studies were approved by their institutional review boards of the participating institutions. All participants provided written informed consent at each examination.

Participants

Initial eligibility criteria for our analysis included participants aged <60 years and without diabetes (defined as fasting blood glucose <126 mg/dL and no use of medication for diabetes) at their index or "baseline" examination. Additional exclusions included the following: not black or white (n = 34); did not have at least one follow-up visit to determine diabetes or weight status (n = 98); and at the index examination were either pregnant (n = 48), did not fast >8 h (n = 537), or had missing data on any of the following cardiometabolic traits: fasting blood glucose, HDL cholesterol (HDL-C), triglycerides, BMI, or blood pressure (n = 165). After these exclusions and with some participants meeting more than one exclusion criterion, 17,404 participants remained eligible for the current analysis.

To ensure a more contemporary sample while allowing for sufficient follow-up of approximately one decade, we chose the following examinations as the "baseline" for each study. For ARIC, its first examination (1987–1989) was considered the "baseline" examination and its fourth cycle (1996–1998) as the last examination for a follow-up period of ~9 years. For CARDIA, we considered either the year 10 (1995–1996) or year 15 (2000–2001) examination cycle as "baseline" depending on which exam a participant was first examined, for an approximate follow-up period of 10 years. For the Framingham Heart Study, the Offspring Cohort Examination 3 (1984–1987) or 4 (1987–1991) was considered the "baseline" depending on which exam a participant was first examined, for a follow-up period of ~12 years; Framingham Offspring Cohort participants at examination cycle 3 could re-enter the analysis at examination 6 (1995–1998) as "baseline" if they remained age eligible and diabetes free.

Assessment of BMI, BMI-Years, Baseline Covariates, and Incident Diabetes

Height and weight were measured with participants in light clothing. BMI was calculated as weight in kilograms divided by the square of height in meters. To calculate our primary predictor, which is the degree and duration of prospective weight gain, we estimated for each participant his/her "BMI-years" defined as the area of BMI units above or below his/her baseline BMI during follow-up. BMI-years was a time-dependent variable calculated for each participant using linear interpolation between measured BMI points at each interim examination across the entire follow-up period and the amount of time since the baseline exam. Only measured BMI points were used in the analysis; imputation was not used to adjust for missed visits or missing weight. BMI-years could range from a large negative to a large positive value; however, the relationship between BMI-years and incident diabetes may differ depending on

whether BMI-years was positive or negative. To allow for independent associations, the absolute value of BMI-years was split into two variables: BMI-years gained if BMI-years was positive and BMI-years lost if BMI-years was negative. A value for BMI-years gained would by definition imply a zero value for BMI-years lost and vice versa.

Blood pressure was measured with participants seated after a 5-min rest using a random-zero mercury sphygmomanometer in ARIC and CARDIA and a standard mercury-column sphygmomanometer in the Framingham Heart Study. The average of two readings was used. Participants were instructed to fast overnight before providing blood specimens for measuring glucose and lipid levels. Age, race, and medication use were self-reported and verified with prescriptions brought to the clinic for that purpose.

Incident diabetes was defined when any of the following were present at a follow-up examination: fasting blood glucose ≥126 mg/dL, casual blood glucose ≥200 mg/dL, or use of insulin or oral hypoglycemic medication. Time to diabetes was estimated using a previously described method by Duncan et al. (15). In brief, for cases ascertained based on blood glucose value, the incident date was estimated by linear interpolation using the glucose values at the ascertaining and previous examinations. For cases ascertained based on the use of diabetic medications (~15% of the observed cases), the time to diabetes was estimated by using their fasting glucose at the earlier visit and a slope estimated using information from all subjects with diabetes who had been unaware of their status (because the fasting glucose at ascertainment for those who were on diabetic medication may have been affected by their knowledge of their diabetes status).

Statistical Analysis

We pooled individual participant-level data from the three studies and stratified the results by baseline age-groups (younger: ≥30 and <45 years; middle-aged: ≥45 and <60 years) and race. Cox proportional hazards models were used for the multivariable analyses, in which the BMI-years (positive and negative) were included as time-dependent variables (accumulated net recalculated at time of each event), and adjustment for all other covariates was based solely on baseline values. The cardiometabolic covariates were selected a priori as potential confounders based on prior evidence that they were associated with adiposity as well as with diabetes (11,16–19). The absolute values of BMI-years and baseline triglycerides were natural-log transformed due to their skewed distribution or range from zero to large numbers. BMI-years was assigned a small positive number (0.00001) if BMI-years was zero to allow for natural logarithmic transformation. Interaction terms between the age cohort indicator variable and the covariates were used to test for differences in associations by baseline age-groups. Additional two-way and three-way interaction terms were used to test for differences by race and for age-group differences within race.

BMI-years, particularly natural log–transformed BMI-years, is difficult to translate into a clinically meaningful result. To help readers more easily interpret and quantify the association between this exposure variable and its interactions with age and race, we used the coefficients derived from our primary model to generate a table of hazard ratios (HRs) that illustrates the results for a given set of baseline BMI values and alternative uniform increases in BMI over a fixed follow-up period. Namely, we calculated for each race and age-group the HRs and 95% CIs for incident diabetes associated with a prespecified baseline BMI and a prespecified constant linear increase in BMI over 9 years of follow-up. We chose the following baseline BMI values: 22, 27, and 32 kg/m^2 to be within the approximate midrange of normal, overweight, and obese BMI categories, respectively. We chose the following cumulative increases in BMI over the 9 years: 1, 2, 5, and 10 kg/m^2 to correspond to approximately the 25th, 50th, 90th, and 99th percentile values, respectively, among all participants who had increased BMI (13,087 participants) during follow-up. Within each race and age-group, a baseline BMI of 22 kg/m^2 and no weight gain over 9 years were used as the referent.

In a sensitivity analysis, we examined the robustness of our primary finding by removing baseline fasting glucose as a covariate from our primary multivariable model. We did this because of its likely role in the causal pathway in the development of diabetes (20) and to address any potential concerns of overadjustment, given that our primary outcome is partly defined by subsequent fasting glucose levels.

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

RESULTS

Baseline Characteristics, Incident Diabetes, and Change in BMI-Years

The age ranges in ARIC, CARDIA, and the Framingham Heart Study were 44–59, 30–46, and 30–59 years, respectively. More than half (55.6%) of the total participants in the analysis were women. One-fifth (21.0%) were black, all from ARIC and CARDIA. Among blacks, mean baseline BMI was similar in both age-groups (Table 1). Those in the younger age-group (between 30 and 45 years old) had significantly more favorable blood pressure profile and fasting triglyceride and glucose levels, but less favorable HDL-C levels, than those in the middle-aged group (between 45 and 60 years old). Among whites, the younger group had significantly lower baseline BMI and more favorable blood pressure profile and fasting triglyceride and glucose levels.

During a median follow-up of 9 years, there were 1,509 newly identified cases of diabetes among all age-race groups. Diabetes incidence (per 1,000 person-years) in the younger and middle-aged groups among blacks was 7.2 (95% CI 5.7, 8.7) and 24.4 (22.0, 26.8), respectively, and among whites was 3.4 (2.8, 4.0) and 10.5 (9.9, 11.2), respectively.

The distribution of the cumulative BMI-years over the follow-up period is shown in Table 2. Cumulative BMI-years for each participant was calculated by summing for each interim exam the area defined by the time between exams and the linear interpolation of starting BMI and interim-exam BMI from baseline to incident diabetes or the censored exam. Each participant was then classified as having a net gain in BMI-years (i.e., area ≥1), net loss in BMI-years (i.e., area ≤−1), or no change in BMI-years (i.e., area between −1 and 1). The cumulative distribution for

Table 1—Baseline characteristics by race and age-group

	Blacks			Whites		
	≥30 and <45 years old (*n* = 1,359)	≥45 and <60 years old (*n* = 2,297)		≥30 and <45 years old (*n* = 3,266)	≥45 and <60 years old (*n* = 10,482)	
Characteristic	Mean (SD) or %	Mean (SD) or %	*P* value*	Mean (SD) or %	Mean (SD) or %	*P* value*
Age (years)	35.7 (3.5)	51.1 (4.3)	—	37.5 (3.8)	52.0 (4.2)	—
Women (%)	58.7%	62.9%	0.06	52.9%	54.5%	<0.001
SBP (mmHg)	113.5 (13.8)	125.7 (19.8)	0.11	111.0 (12.6)	118.1 (16.2)	<0.001
DBP (mmHg)	75.2 (10.5)	80.0 (11.9)	<0.001	73.2 (9.8)	73.5 (10.2)	<0.001
Normal BP (%)†	61.1%	26.3%	0.008	67.6%	48.4%	<0.001
Prehypertensive (%)†	25.6%	25.6%		24.3%	27.7%	
Hypertensive (%)†	13.3%	48.1%		8.1%	23.9%	
HDL-C (mg/dL)	51.5 (14.2)	56.3 (17.8)	<0.001	50.4 (13.9)	51.6 (16.5)	0.29
Triglycerides (mg/dL)‡	83.2 (60.9)	104.8 (72.0)	0.003	100.4 (79.8)	128.0 (81.4)	<0.001
Fasting glucose (mg/dL)	90.2 (8.7)	98.5 (10.2)	<0.001	89.4 (8.0)	97.1 (9.3)	<0.001
BMI (kg/m^2)	29.1 (7.0)	29.3 (6.0)	0.27	25.7 (5.0)	26.7 (4.7)	<0.001

Data are mean (SD) or percent, unless otherwise indicated. SD is from the unadjusted distribution. BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure. *P value from a simple χ^2 or Student t test after adjustment for age and sex where appropriate. †Blood pressure categories: normal, SBP <120 and DBP <80 mmHg and not using antihypertensive medication; prehypertension, not hypertension and SBP 120–139 or DBP 80–89 mmHg; hypertension, SBP ≥140, DBP ≥90 mmHg, or using antihypertensive medication. P values provided reflect the distribution of the three blood pressure categories between the two age-groups within each race. ‡Means and SD from the untransformed distribution. Student t test P value is from the natural log–transformed distribution.

BMI-years is shown for each race and age-group. Among blacks, the proportions of younger and middle-aged adults with a net gain of at least 1 BMI-year at end of follow-up were 72 and 60%, respectively. Among the younger and middle-aged whites, the proportions were 76 and 67%, respectively. Within each race, the median gain in BMI-years over the follow-up time also tended to be greater in the younger as opposed to the middle-aged adults.

Multivariable Analyses

As shown in the upper half of Table 3, after adjusting for sex, baseline covariates, race and age interaction terms, and loss in BMI-years, gain in BMI-years was associated with significantly higher risk of diabetes in the younger compared with middle-aged groups in both racial groups. In contrast, although baseline BMI was positively associated with incident diabetes within each of the four

Table 2—Net changes in BMI-years at end of follow-up by race and age-group*

	Age-group at baseline					
	≥30 and <45 years old			≥45 and <60 years old		
	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile
Blacks		*n* = 1,359			*n* = 2,297	
Net gain of >1 BMI-years at end of follow-up						
n (%)		976 (71.8)			1,366 (59.5)	
BMI-years/follow-up time†	1.58	0.86	2.62	1.09	0.61	1.81
Net stable (±1) BMI-years at end of follow-up						
n (%)		108 (7.9)			389 (16.9)	
BMI-years/follow-up time	0.01	−0.05	0.07	0.00	−0.10	0.11
Net loss of >1 BMI-years at end of follow-up						
n (%)		275 (20.2)			542 (23.6)	
BMI-years/follow-up time	−0.80	−1.59	−0.44	−0.69	−1.20	−0.40
Whites		*n* = 3,266			*n* = 10,482	
Net gain of >1 BMI-years at end of follow-up						
n (%)		2,478 (75.9)			6,995 (66.7)	
BMI-years/follow-up time	1.27	0.69	2.13	1.05	0.58	1.77
Net stable (±1) BMI-years at end of follow-up						
n (%)		203 (6.2)			1,222 (11.7)	
BMI-years/follow-up time	0.03	−0.04	0.07	0.02	−0.05	0.09
Net loss of >1 BMI-years at end of follow-up						
n (%)		585 (17.9)			2,265 (21.6)	
BMI-years/follow-up time	−0.64	−1.18	−0.33	−0.64	−1.10	−0.35

*Results stratified by net gain in BMI (cumulative BMI-years >1), no net change in BMI (cumulative BMI-years ±1), and net loss in BMI (cumulative BMI-years less than −1). †BMI-years/follow-up time: cumulative area calculated based on time to each recorded examination (x-axis) and connected BMI measurements (y-axis) divided by the total amount of follow-up time in years.

Table 3—HRs by age-group for the association of prospective gains in BMI with incident diabetes, after adjusting for covariates*

	Age-group at baseline				
	≥30 and <45 years old		≥45 and <60 years old		
	HR	*P* value	HR	*P* value	*P* value for interaction‡
Primary model					
Blacks					
n (events)	1,359 (89)		2,297 (391)		
Baseline BMI (5 units)	1.29	<0.001	1.25	<0.001	0.69
Log(BMI-years over baseline BMI)† (1 unit)	1.18	0.02	1.02	0.39	0.047
Whites					
n (events)	3,266 (110)		10,482 (919)		
Baseline BMI (5 units)	1.37	<0.001	1.38	<0.001	0.92
Log(BMI-years over baseline BMI) (1 unit)	1.35	<0.001	1.11	<0.001	0.008
Sensitivity analysis (excluding baseline fasting glucose from the primary model)					
Blacks					
n (events)	1,359 (89)		2,297 (391)		
Baseline BMI (5 units)	1.41	<0.001	1.25	<0.001	0.69
Log(BMI-years over baseline BMI)† (1 unit)	1.13	0.08	0.99	0.56	0.065
Whites					
n (events)	3,266 (110)		10,482 (919)		
Baseline BMI (5 units)	1.60	<0.001	1.60	<0.001	0.96
Log(BMI-years over baseline BMI) (1 unit)	1.27	<0.001	1.06	0.001	0.006

*Additional covariates in the primary multivariate analyses include sex, baseline HDL-C (15 mg/dL), log(baseline triglycerides), baseline fasting glucose, baseline prehypertension, baseline hypertension, log(BMI-years below baseline BMI), as well as interaction terms for age-group × baseline covariates, race × baseline covariates, and age-group × race × baseline covariates. The referent group for hypertension and prehypertension is those with normal blood pressure, defined as systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg and not using antihypertensive medication. In the sensitivity analyses, baseline fasting glucose was removed as a covariate from the primary multivariable model. †BMI-years is a time-dependent variable calculated using linear interpolation between measured BMI points and the amount of time above or below baseline BMI. ‡*P* value for interaction is the test of effect modification between age-group at baseline and the risk factor on incident diabetes.

race and age subgroups, significant interactions by age-group within each race were not observed. Among blacks, HRs of diabetes risk for 1-unit increase in natural-log BMI-years in younger versus middle-aged adults were 1.18 (P = 0.02) and 1.02 (P = 0.39), respectively (P for interaction by age-group = 0.047). Among whites, HRs of diabetes risk for 1-unit increase in natural-log BMI-years in younger versus middle-aged adults were 1.35 ($P < 0.001$) and 1.11 ($P < 0.001$), respectively (P for interaction by age-group = 0.008). The P values for interactions between race and increase in natural-log BMI-years on incident diabetes in the younger and middle-aged groups were 0.14 and <0.001, respectively (results not shown).

Results of the sensitivity analysis in which baseline fasting glucose was removed from the multivariable model are shown on the lower half of Table 3. The primary finding that BMI gain was more strongly associated with incident diabetes in younger compared with middle-aged adults remained statistically significant in whites (P for interaction = 0.006) but was no longer significant in blacks (P for interaction = 0.065). The interaction between race and increase in natural-log BMI-years on incident diabetes in the younger and middle-aged cohorts remains largely unchanged (P for interaction = 0.78 and 0.007, respectively) (results not shown).

Table 4 translates the model results into HRs and 95% CIs for incident diabetes according to baseline BMI and constant linear change in BMI over 9 years. Using a baseline BMI of 22 kg/m^2 and no weight gain as the referent, the HR for incident diabetes in younger blacks with a BMI of 32 and a gain of 10 additional BMI units is 3.10 (95% CI 1.70, 5.65). This is in contrast to an HR of 1.68 (1.37, 2.07) in their older counterparts with the same baseline BMI and weight gain. Among whites, the HR of diabetes risk in the younger individuals with the same baseline BMI and weight gain is 5.91 (3.38, 10.32), compared with 2.91 (2.43, 3.49) in the older group.

CONCLUSIONS

Although middle-aged black and white adults had higher rates of incident diabetes than their young-adult counterparts, young adults had a greater relative risk of developing diabetes for a given level of gain in BMI-years, independent of any differences in baseline BMI and other cardiometabolic factors. Younger adults also had an overall higher prevalence and larger degree of net gain in BMI-years. Our finding supports continued efforts to prevent weight gain in both younger and middle-aged adults. It further highlights the importance of accounting for the age at which weight gain occurs when assessing obesity's impact on diabetes risk. A cautionary message to young adults might be that gaining weight at their age may be more strongly associated with developing diabetes than if a similar degree and duration of weight gain were to occur in their middle-aged counterparts.

Although previous studies have also brought forth the need to consider the age in which weight gain occurs when assessing diabetes risks (10,19,21–23), these studies were cross-sectional (21), limited to a single ethnic population (19,22), and/or relied on self-reported

Table 4—Matrix of HRs (95% CI) for incident diabetes associated with a specific baseline BMI and increase in BMI over 9 years*

	Increase in BMI over 9 years†: ≥30 and <45 years old at baseline					Increase in BMI over 9 years†: ≥45 and <60 years old at baseline				
Baseline BMI†	0	1	2	5	10	0	1	2	5	10
Blacks										
22	1 (ref)	1.28 (1.04, 1.57)	1.43 (1.06, 1.94)	1.66 (1.08, 2.55)	1.86 (1.10, 3.15)	1 (ref)	1.03 (0.97, 1.09)	1.04 (0.95, 1.13)	1.06 (0.93, 1.20)	1.07 (0.92, 1.24)
27	1.29 (1.14, 1.47)	1.65 (1.28, 2.12)	1.85 (1.32, 2.59)	2.15 (1.36, 3.39)	2.40 (1.39, 4.16)	1.25 (1.17, 1.35)	1.29 (1.17, 1.41)	1.30 (1.17, 1.46)	1.32 (1.15, 1.53)	1.34 (1.14, 1.58)
32	1.67 (1.30, 2.15)	2.13 (1.52, 2.99)	2.39 (1.59, 3.59)	2.77 (1.66, 4.64)	3.10 (1.70, 5.65)	1.57 (1.37, 1.81)	1.62 (1.39, 1.88)	1.64 (1.39, 1.93)	1.66 (1.38, 2.00)	1.68 (1.37, 2.07)
Whites										
22	1 (ref)	1.58 (1.29, 1.93)	1.95 (1.45, 2.62)	2.57 (1.69, 3.91)	3.17 (1.90, 5.30)	1 (ref)	1.18 (1.12, 1.25)	1.28 (1.18, 1.39)	1.42 (1.26, 1.60)	1.54 (1.33, 1.77)
27	1.37 (1.18, 1.58)	2.15 (1.70, 2.72)	2.66 (1.94, 3.63)	3.51 (2.29, 5.37)	4.33 (2.58, 7.25)	1.38 (1.30, 1.46)	1.63 (1.51, 1.77)	1.76 (1.60, 1.95)	1.95 (1.72, 2.22)	2.11 (1.81, 2.46)
32	1.86 (1.39, 2.51)	2.94 (2.10, 4.12)	3.63 (2.45 5.36)	4.79 (2.96, 7.75)	5.91 (3.38, 10.32)	1.90 (1.68, 2.13)	2.25 (1.97, 2.55)	2.43 (2.11, 2.80)	2.69 (2.29, 3.17)	2.91 (2.43, 3.49)

*Increase in BMI is assumed to be a constant linear function over time. Within each race and age-group, a baseline BMI of 22 kg/m^2 and no weight gain over 9 years was used as the referent. Adjusted for baseline BMI, HDL-C, natural log–transformed triglycerides, fasting glucose, and hypertension group, as well as interaction terms for age-group × baseline covariates, race × baseline covariates, and age-group × race × baseline covariates. †BMI units expressed as kg/m^2.

data of weight change or diabetes status (10,22). Furthermore, only one accounted for both degree and duration of weight gain when examining the age differentials in obesity-related incidence of diabetes (10). That study, by Lee e al. (10), used data from the National Longitudinal Survey of Youth 1979 and evaluated a younger cohort, specifically adolescents and young adults. Using excess weight calculated as self-reported BMI over a reference BMI (25 kg/m^2 for adults or 85th percentile for adolescents), they found younger individuals to have greater risks of self-reported diabetes for a given level of excess BMI-years exposed. Our study, which used objectively measured BMI and diabetes status, supports and extends this age effect modification from young adulthood to middle age, the latter being a time period with the highest incidence of diabetes in the U.S. (24). We further found that these associations were independent of any differences in baseline cardiometabolic risk factors.

It is unclear why adiposity gained in young adulthood is associated with greater relative risk for developing diabetes than if the same level of adiposity were gained in middle age. This might be explained in part by the greater absolute risks for developing diabetes in the older age-group, such that each additional risk factor is likely to contribute only an incremental effect to the overall risk. Such decreases in relative risks with aging have been observed in studies assessing other predictors and/or outcomes (25,26). Another potential explanation is survival bias. Those in the middle-aged group who were most susceptible to diabetes may have already developed the disease by the time of the study index examination and were thus excluded from the analyses, leaving in those who may be more protected from developing the disease. Reverse causality is another possibility given that outcomes associated with BMI are likely to be especially pronounced in young adults since older individuals experience age-related loss of height and muscle mass. Alternatively, there may be a pathophysiologic explanation. Type 2 diabetes results when pancreatic β-cells are unable to match insulin secretion in the face of insulin resistance over time. Obesity is a known

determinant of insulin resistance. Aging, on the other hand, is largely independently associated with impaired β-cell function (27,28). In young adulthood, when one's overall β-cell function is still relatively intact, perhaps adiposity exerts greater harmful effects on insulin resistance than in middle age, when one may instead be more sensitive to age-accelerated β-cell function decline. More basic research is needed to test this mechanistic hypothesis. Other potential mechanisms associated with worsened insulin resistance should also be explored, including whether weight gain in younger age leads to greater increases in visceral adiposity tissue compartments (29), hepatic fat (30), and/or inflammation (31) as compared with their older counterparts.

Our finding that whites had significantly greater relative risks of diabetes than blacks for a given level of gain in BMI-years, particularly among the middle-aged, is in contrast to results from Lee et al. (10), which reported blacks as having higher odds of diabetes than whites, albeit only at lower levels of excess BMI-years. As aforementioned, that study included a much younger cohort and did not account for any potential effects of other baseline cardiometabolic factors, the profiles of which are typically disproportionately worse in blacks (4,11,32). Rather, our finding is consistent with those by Taylor et al. (32), which found that despite higher prevalence of obesity and other cardiometabolic factors in blacks, obesity is more strongly associated with diabetes in whites. The mechanism is unclear, but as noted by Taylor et al. (32), biological factors related to insulin insensitivity might differ between blacks and whites (29,33). Blacks also have less visceral abdominal fat and lower prevalence of hepatic steatosis than whites (30,34). As further research is conducted to explain this differential relative risk, one should not lose sight of the fact that blacks still have an unduly greater absolute risk for developing diabetes than whites (4,11).

Strengths of this study include the population-based biracial cohorts and objectively measured weight, blood glucose, and cardiometabolic covariates. Weight was measured objectively and prospectively, and we took into account both the duration and degree of weight gain over time. Limitations should also be noted. First, black participants were recruited in only two cohorts (CARDIA and ARIC) with very little overlap in age. It is possible that the observed age differential effects in blacks might have been due to differences between studies. However, the standardized data collections and protocols and rigorous quality control measures within each study make this concern less likely. Second, the duration of weight gain during follow-up was based on measurements ascertained over a range of 3–6 years. Perhaps more frequent measurements would improve the accuracy of estimations of BMI-years to capture sudden fluctuations in weight that can result from life events such as postpregnancy or acute illnesses. Third, relying on laboratory measurements and use of diabetes medications to ascertain diabetes may have missed cases controlled by lifestyle alone. Finally, we lacked data to evaluate the potential impact of cumulative obesity burden prior to the index examination, which would likely be greater in the older participants simply because they have lived longer and because of age-related loss in muscle mass. Rather, our focus was on comparing differences in the incremental increase in diabetes risk for a given level of weight gained prospectively within a specified follow-up period. It might be more generalizable to settings such as new patient encounters in which only current information is available, yet one wishes to estimate future risks based on various possible scenarios of weight gain. Certainly future studies that examine the effects of lifetime obesity burden on diabetes incidence starting from early childhood and across the life span are still needed.

In summary, in this combined analysis of three population-based cohorts, a given degree and duration of weight gained in young-adult blacks and whites are more strongly associated with risk of diabetes than if similar weight was gained in middle age, even after accounting for baseline weight and other cardiometabolic risk factors. Our findings support continued efforts to prevent weight gain in both younger and middle-aged adults. Additionally, a cautionary message to young adults might be that gaining weight at their age may be more strongly associated with developing diabetes than if similar weight gain were to occur in their middle-aged counterparts.

Acknowledgments. The authors thank the staff and participants of these studies for their important contributions.

Funding. The ARIC study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute (NHLBI) contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). CARDIA is supported by NHLBI contracts HHSN268201300025C, HHSN268201300026C, HHSN268201300027C, HHSN268201300028C, HHSN268201300029C, and HHSN268200900041C; the Intramural Research Program of the National Institute on Aging (NIA); and an intra-agency agreement between the NIA and NHLBI (AG0005). The Framingham Heart Study is conducted and supported by the NHLBI in collaboration with Boston University (contract N01-HC-25195).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. G.S.W. contributed to the discussion and wrote the manuscript. S.A.C. conducted the statistical analysis, contributed to the discussion, and reviewed and edited the manuscript. J.P.R., M.R.C., J.C., R.B.D., D.C.G., D.R.J., E.S., and C.S.F. contributed to the discussion and reviewed the manuscript. G.S.W. and S.A.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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