# Duration of Diabetes and Prediabetes During Adulthood and Subclinical Atherosclerosis and Cardiac Dysfunction in Middle Age: The CARDIA Study

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*Diabetes Care 2018;41:731–738 | https://doi.org/10.2337/dc17-2233*


## OBJECTIVE

**To determine whether the duration of diabetes and duration of prediabetes estimated during a 25-year period in early adulthood are each independently associated with coronary artery calcified plaque (CAC) and abnormalities in left ventricular structure and function later in life.**

## RESEARCH DESIGN AND METHODS

**Participants were 3,628 white and black adults aged 18–30 years without diabetes or prediabetes at baseline (1985–1986) in the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Durations of diabetes and prediabetes were estimated based on their identification at examinations 7, 10, 15, 20, and 25 years later. CAC was identified by computed tomography at years 15, 20, and 25. Left ventricular structure and function were measured via echocardiogram at year 25.**

## RESULTS

**Of the 3,628 individuals, 12.7% and 53.8% developed diabetes and prediabetes, respectively; average (SD) duration was 10.7 (10.7) years and 9.5 (5.4) years. After adjustment for sociodemographic characteristics and other cardiovascular risk factors, and mutual adjustment for each other, the hazard ratio for the presence of CAC was 1.15 (95% CI 1.06, 1.25) and 1.07 (1.01, 1.13) times higher for each 5-year-longer duration of diabetes and prediabetes, respectively. Diabetes and prediabetes duration were associated with worse subclinical systolic function (longitudinal strain [$P_{trend}$ < 0.001 for both]) and early diastolic relaxation (e′ [$P_{trend}$ 0.004 and 0.002, respectively]). Duration of diabetes was also associated with a higher diastolic filling pressure (E-to-e′ ratio [$P_{trend}$ 0.001]).**

## CONCLUSIONS

**Durations of diabetes and prediabetes during adulthood are both independently associated with subclinical atherosclerosis and left ventricular systolic and diastolic dysfunction in middle age.**


Diabetes is a major cause of morbidity and mortality in the U.S., costing an estimated $245 billion in 2012 as a result of increased medical costs and lost economic productivity (1). Over the last several decades, the prevalence of diabetes has increased considerably (2). The prevalence of prediabetes, an intermediate metabolic state

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*Received 24 October 2017 and accepted 13 December 2017.*

*This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-2233/-/DC1.*

*This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.*

between normoglycemia and diabetes, has also increased over this period (3). While these trends among adults have been shown to be consistent across every age-group, the increase in younger adults is especially concerning. Adults who develop diabetes or prediabetes at a younger age will be exposed to a longer duration of the condition over the course of their lifetime. As more people develop diabetes or prediabetes earlier, excess medical costs are likely to increase as well (4).

In addition to the significant clinical and public health–related implications of a longer duration of diabetes and prediabetes in the population, not accounting for these conditions may underestimate risk for cardiovascular disease (CVD), for example, since those with a longer duration are likely to have a longer exposure to chronic hyperglycemia. However, findings from previous studies that have examined this association have been inconclusive. Some studies have shown an association of a longer duration of diabetes with development of subclinical and clinical CVD (5–16), whereas others have not (17–19). Many existing studies have been limited by their inability to reliably estimate the onset of diabetes owing to a lack of preceding measures of glycemia. This limitation has also made it difficult to determine whether a prolonged duration of milder elevations in glycemia or prediabetes is associated with CVD. Controversy currently exists regarding the role of prediabetes in CVD risk, particularly whether proactive identification and management are warranted (20).

In the current study, we sought to determine whether the duration of diabetes and duration of prediabetes accumulated during a 25-year period beginning in early adulthood are each independently associated with the development of subclinical atherosclerosis as well as abnormalities in cardiac structure and function later in life in a population-based cohort study. We hypothesized that a longer duration of hyperglycemia both in the diabetes and in the prediabetes range during adulthood would each be associated with the presence of coronary artery calcified plaque (CAC) as well as adverse left ventricular remodeling and dysfunction in later adulthood.

## RESEARCH DESIGN AND METHODS

### Study Population

Participants were black and white adults recruited in 1985–1986 as part of the Coronary Artery Risk Development in Young Adults (CARDIA) Study. CARDIA is a multicenter population-based longitudinal cohort study of the development and determinants of CVD over time in 5,115 young adults initially aged 18–30 years at baseline. Participants were recruited from four cities in the U.S. (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA), with population-based samples approximately balanced within center by sex, age, race, and education. Participants have been reexamined 2, 5, 7, 10, 15, 20, 25, and 30 years after baseline, and retention rates across examinations were 91, 86, 81, 79, 74, 72, 72, and 71%, respectively. Data for this study come from years 0 through 25. All participants provided written informed consent at each examination.

Participants were excluded if they had diabetes ($n$ = 33) or prediabetes ($n$ = 101) at baseline or if we were unable to determine diabetes or prediabetes at baseline or during follow-up ($n$ = 703), and we also excluded those who experienced a study-validated clinical CVD event during follow-up because of our interest in subclinical disease ($n$ = 141), as well as those who did not complete a computed tomography (CT) scan (at follow-up years 15, 20, or 25) or echocardiogram (at year 25) ($n$ = 509). A total of 3,628 participants met inclusion criteria.

### Clinical Measurements

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

### Duration of Diabetes and Prediabetes

Blood was drawn by venipuncture and processed at the central laboratory according to a standard protocol. Glucose was assayed at baseline using the hexokinase ultraviolet method by American Bio Science Laboratories (Van Nuys, CA) and at years 7, 10, 15, 20, and 25 using hexokinase coupled to glucose-6-phosphate dehydrogenase (Linco Research, St. Louis, MO). Glucose values at follow-up were recalibrated to year 0 glucose values. $HbA_{1c}$ was measured using the Tosoh G7 high-performance liquid chromatography method at years 20 and 25. Diabetes was determined based on a combination of measured fasting glucose levels ($\geq$7.0 mmol/L and $\geq$126 mg/dL) at examination years 0, 7, 10, 15, 20, or 25; self-report of oral hypoglycemic medications or insulin at years 0, 7, 10, 15, 20, or 25; a 2-h postload glucose $\geq$11.1 mmol/L ($\geq$200 mg/dL) during a 75-g oral glucose tolerance test at years 10, 20, and 25; or an $HbA_{1c}$ $\geq$6.5% at years 20 and 25 (21). Similarly, prediabetes was based on a combination of fasting glucose levels (5.6–6.0 mmol/L and 100–125 mg/dL) at years 0, 7, 10, 15, 20, or 25; a 2-h postload glucose 7.8–11.0 mmol/L (140–199 mg/dL) at years 10, 20, and 25; or an $HbA_{1c}$ 5.7–6.4% at years 20 and 25 (21).

For each participant, the number of years of diabetes and prediabetes were calculated based upon the presence (or absence) of diabetes or prediabetes at each examination beginning at year 7. For example, a participant who did not develop prediabetes at year 7 but did develop prediabetes at year 10 and all subsequent follow-up examinations through year 20 as well as diabetes at year 25 was assigned 0 years of prediabetes at year 7, 3 years at year 10, 5 years at year 15, and 5 years at year 20 and 5 years of diabetes at year 25 (for a total of 13 years of prediabetes and 5 years of diabetes). The cumulative duration of diabetes and prediabetes across examination years for each participant was calculated. For analyses of the presence of CAC, the duration of diabetes and prediabetes was summed until the examination when CAC was first identified. For those who did not develop CAC, cumulative duration was summed until the last known follow-up examination. For analyses of cardiac structure/function, duration was determined through year 25.

### CT

CAC was measured at years 15, 20, and 25 by CT of the chest (22). At years 15 and 20, electron beam CT (Chicago and Oakland centers) and multidetector CT (Birmingham and Minneapolis centers) scanners were used to obtain contiguous 2.5- to 3-mm-thick transverse images from the root of the aorta to the apex of the heart. At year 25, multidetector CT scanners were used at all centers. Participants were scanned while placed over a hydroxyl-apatite phantom to allow monitoring of image brightness and noise and to allow adjustment for scanner differences. Images were transmitted electronically to an independent reading center (Wake Forest University, Winston-Salem, NC). A calcium score in Agatston units (AU) (23) was calculated

for each calcified lesion, and the scores were summed across all lesions within a given artery and across all arteries (left anterior descending, left main, circumflex, and right coronary) to obtain the total calcium score. The presence of CAC was defined as a total calcified plaque score >0 AU measured at years 15, 20, or 25. Prior analyses in CARDIA have demonstrated the presence or absence of CAC to be a reliable measure, with observed agreement of 96% (22).

### Echocardiography

Echocardiography, including Doppler and tissue Doppler imaging, was performed at year 25 with an Artida cardiac ultrasound machine (Toshiba Medical Systems, Tokyo, Japan) by trained sonographers using a standardized protocol across all field centers. Experienced sonographers made measurements from digitized images using a standard software offline image analysis system (Digisonics, Inc., Houston, TX). The echocardiography protocol has previously been published and followed existing American Society of Echocardiography guidelines for study acquisition and measurement (24). Quality control and image analysis were performed at a core reading center (Johns Hopkins University, Baltimore, MD). Left ventricular mass was calculated using the Devereux formula (25). Relative wall thickness was calculated by dividing the sum of the posterior wall and interventricular septal thickness by the internal left ventricular diameter. Left ventricular systolic function was estimated with ejection fraction and global longitudinal strain and strain rate based on speckle-tracking echocardiography. Myocardial strain and strain rate measurements were analyzed on a 16-segment basis for the left ventricular midwall layer using two-dimensional Wall Motion Tracking software (UltraExtend, version 2.7; Toshiba Medical Systems, Otawara, Japan). Three cardiac cycles from each view were recorded for offline analyses. Strain was calculated as the change in segment length relative to its end-diastolic length, and the peak systolic value was recorded. More negative values of strain indicate greater shortening or better function.

Technical errors for intra- and intersonographer variability ranged from 5 to 11% and from 6to 12%, respectively. Intra- and interreader variability ranged from 3 to 9% and from 6 to 11%, respectively.

### Other Measurements

After a 5-min rest, blood pressure was measured on the right arm of seated participants at three 1-min intervals using a Hawksley random zero sphygmomanometer (W.A. Baum Company, Copaigue, NY) at baseline through year 15. At years 20 and 25, blood pressure was measured using a standard automated blood pressure measurement monitor (IntelliSense Blood Pressure Monitor, model HEM-907XL; Omron) and standardized to the sphygmomanometer measures. Plasma total cholesterol concentrations were measured at all examinations by enzymatic methods at Northwest Lipids Research Laboratory (Seattle, WA). The insulin measurements were performed with the use of a radioimmunoassay (Linco Research, St Charles, MO) at baseline and years 7, 10, 15, and 20, and an Elecsys sandwich immunoassay (Roche Diagnostics Corporation, Indianapolis, IN) was performed at year 25. Weight and height were measured at all examinations 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 the square of height in meters. Standard questionnaires were used to maintain consistency in the assessment of demographic information across all CARDIA examination visits. Education was represented as years of schooling. Cigarette smoking behavior, queried at each exam, was used to estimate cumulative lifetime exposure to cigarettes in terms of pack-years. The use of antihypertensive and lipid-lowering medication was assessed by self-report at each examination. Diabetes diagnosed in an immediate family member (mother, father, sister, or brother) was queried at year 0 and updated at years 5, 10, and 25.

### Statistical Analyses

Participant characteristics overall, and according to the duration of diabetes and prediabetes, were described using means, medians, and proportions as appropriate. Trends were tested using linear regression models and $\chi^2$ analyses for continuous and categorical characteristics, respectively. The Kruskal-Wallis test was used for characteristics with skewed distributions. We calculated the rate of CAC (number of cases per person-time at risk) per 1,000 person-years beginning at year 15 overall and according to the duration of diabetes and prediabetes. Multivariable Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and 95% CI for the presence of CAC according to the duration of diabetes and prediabetes. Duration of diabetes and prediabetes was included (as time-dependent variables in analyses of the presence of CAC) in one of two exposure forms: first as a continuous variable assuming a linear dose-response association and second as a five-level categorical variable (i.e., 0, 1–5, 6–10, 11–15, and >15 years). Multivariable linear and logistic regression analyses were fit to examine the association between the 25-year cumulative duration of diabetes and prediabetes with measures of cardiac structure and function. Analyses were adjusted for age (years), sex, race (black/white), educational attainment (years), and CARDIA field center and simultaneously for either the duration of diabetes or the duration of prediabetes. A second model adjusted additionally for CVD risk factors, including lifetime pack-years of smoking, BMI (kg/m$^2$), systolic blood pressure (mmHg), antihypertensive medication use (yes/no), and total cholesterol level (mg/dL). Tests for a linear trend were performed by entering duration of diabetes or prediabetes as a continuous variable into the multivariable models. To test for the presence of nonlinearity, we added a quadratic duration of diabetes or prediabetes term to the multivariable models that also included a linear term. Potential effect modification by race and sex was evaluated by testing the statistical significance of a multiplicative interaction term including duration of diabetes or prediabetes as a continuous variable.

Tests of statistical significance were two tailed, with an $\alpha$ level of 0.05. SAS, version 9.4 (SAS Institute, Cary, NC), was used to perform all analyses.

## RESULTS

Of the 3,628 eligible participants, 47.3% were black and 56.5% were women. During follow-up, 12.7 and 53.8% developed diabetes and prediabetes, respectively. The average (SD) duration of diabetes and prediabetes was 10.7 (5.6) and 9.5 (5.2) years, respectively. Mean age at identification of diabetes was 42.4 (6.3) years and of prediabetes 39.4 (7.2) years. The prevalence of diabetes of 1–5, 6–10,

**Table 1—Participant characteristics according to duration of diabetes and prediabetes (the CARDIA Study) ($n$ = 3,628)**

| Variable | Duration of diabetes (years) | | | | | | Duration of prediabetes (years) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 ($n$ = 3,168) | 1–5 ($n$ = 155) | 6–10 ($n$ = 168) | 11–1 ($n$ = 64) | >15 ($n$ = 73) | $P_{trend}$ | 0 ($n$ = 1,678) | 1–5 ($n$ = 792) | 6–10 ($n$ = 657) | 11–15 ($n$ = 282) | >15 ($n$ = 219) | $P_{trend}$ |
| Baseline age (years) | 24.9 (3.6) | 25.5 (3.4) | 25.5 (3.8) | 25.2 (3.6) | 25.6 (3.4) | 0.004 | 24.6 (3.6) | 25.1 (3.6) | 25.3 (3.6) | 25.3 (3.7) | 25.3 (3.5) | <0.001 |
| Women | 56.4 | 58.7 | 60.1 | 54.7 | 50.7 | 0.83 | 65.6 | 58.5 | 50.1 | 32.6 | 30.1 | <0.001 |
| Black race | 44.6 | 63.2 | 67.9 | 73.4 | 60.3 | <0.001 | 42.4 | 48.1 | 56.0 | 53.6 | 47.5 | <0.001 |
| Educational attainment (years) | 15.7 (2.6) | 15.2 (2.4) | 15.1 (2.5) | 14.7 (2.2) | 14.6 (2.6) | <0.001 | 15.7 (2.6) | 15.7 (2.6) | 15.3 (2.4) | 15.4 (2.5) | 15.2 (2.6) | <0.001 |
| Ever smoker | 48.2 | 50.3 | 47.6 | 54.7 | 57.5 | 0.12 | 48.2 | 46.7 | 49.6 | 49.3 | 54.3 | 0.14 |
| Lifetime pack-years† | 2.5 (1.3, 3.8) | 2.8 (1.8, 5.0) | 2.8 (1.3, 5.0) | 1.8 (1.0, 3.8) | 2.5 (1.3, 3.8) | 0.20 | 2.0 (1.3, 3.8) | 2.5 (1.3, 3.8) | 2.5 (1.3, 3.8) | 2.5 (1.4, 4.4) | 2.5 (1.3, 4.8) | 0.41 |
| Family history of diabetes | 33.1 | 52.9 | 59.5 | 57.8 | 49.3 | <0.001 | 30.6 | 39.8 | 42.0 | 39.0 | 40.6 | <0.001 |
| Clinical and physical characteristics | | | | | | | | | | | | |
| BMI (kg/m$^2$)‡ | 26.3 (5.0) | 30.8 (6.4) | 32.3 (7.2) | 34.3 (7.1) | 31.8 (5.8) | <0.001 | 26.0 (5.4) | 27.4 (5.5) | 28.4 (6.1) | 28.4 (5.3) | 28.4 (5.3) | <0.001 |
| Glucose (mg/dL)‡ | 88.7 (6.3) | 98.8 (10.8) | 104.9 (16.7) | 118.5 (22.3) | 130.7 (35.4) | <0.001 | 87.9 (12.7) | 91.4 (10.0) | 95.2 (12.7) | 96.6 (8.1) | 97.8 (7.0) | <0.001 |
| $HbA_{1c}$ (%)‡ | 5.4 (0.4) | 6.2 (0.8) | 6.9 (1.4) | 7.8 (1.5) | 7.7 (2.0) | <0.001 | 5.2 (0.9) | 5.6 (0.8) | 5.8 (0.8) | 5.8 (0.6) | 5.7 (0.4) | <0.001 |
| 2-h postload glucose (mg/dL)‡ | 100.0 (22.7) | 146.8 (50.0) | 164.5 (73.0) | 148.5 (66.0) | 220.3 (113.3) | <0.001 | 96.1 (35.8) | 110.3 (36.0) | 117.3 (39.6) | 117.9 (34.1) | 119.4 (34.0) | <0.001 |
| Insulin (μU/mL)‡ | 8.0 (6.3, 10.5) | 13.2 (9.9, 16.9) | 13.0 (9.9, 16.4) | 15.9 (12.5, 22.6) | 14.3 (10.6, 19.3) | <0.001 | 7.4 (6.0, 9.8) | 8.8 (6.9, 11.8) | 9.8 (7.1, 13.6) | 10.2 (7.6, 13.2) | 10.1 (7.8, 12.5) | <0.001 |
| Systolic blood pressure (mmHg)‡ | 110.4 (9.3) | 115.5 (10.0) | 115.2 (10.4) | 118.0 (10.6) | 116.7 (9.5) | <0.001 | 109.2 (9.4) | 111.1 (9.3) | 113.2 (9.5) | 114.7 (9.6) | 115.2 (9.0) | <0.001 |
| Diastolic blood pressure (mmHg)‡ | 70.2 (7.2) | 74.0 (7.0) | 74.6 (7.2) | 76.5 (8.2) | 74.5 (6.6) | <0.001 | 69.4 (7.3) | 70.9 (7.1) | 72.2 (7.4) | 72.7 (7.4) | 72.9 (6.9) | <0.001 |
| Ever hypertension medication | 20.0 | 56.1 | 58.3 | 64.1 | 57.5 | <0.001 | 10.3 | 14.7 | 18.4 | 14.2 | 14.2 | <0.001 |
| Total cholesterol (mg/dL)‡ | 181.0 (27.5) | 186.2 (28.5) | 184.2 (28.6) | 182.8 (27.7) | 187.4 (28.2) | 0.008 | 178.6 (26.5) | 182.4 (28.1) | 185.4 (28.3) | 185.2 (28.2) | 184.9 (28.8) | <0.001 |
| Ever cholesterol medication | 9.8 | 28.4 | 35.7 | 51.6 | 45.2 | <0.001 | 10.3 | 14.7 | 18.4 | 14.2 | 14.2 | <0.001 |

Data are presented as mean (SD), median (interquartile range), or % as appropriate. †Among ever smokers. ‡Average of all available measures during follow-up.

11–15, and >15 years was 4.3, 4.6, 1.8, and 2.0%, respectively, and of prediabetes 21.8, 18.1, 7.8, and 6.0%. As expected, those who accumulated a longer duration of diabetes and prediabetes during follow-up had higher average fasting and 2-h glucose levels and higher $HbA_{1c}$ and insulin levels (Table 1). They also were more likely to be older at baseline, to be black, to have a family history of diabetes, to have a lower educational attainment, and to have worse CVD risk factor levels. Men were more likely to have a longer duration of prediabetes but not diabetes. Smoking was not associated with duration of diabetes or prediabetes.

Among those who completed a CT scan ($n$ = 3,577), 26.7% developed CAC during follow-up (11.7 per 1,000 person-years). The median CAC score among those who developed CAC was 23 AU (interquartile range 6–75). Among those with CAC, the proportion with a CAC score of 1–50, 51–100, and >100 AU was 67.0, 14.2, and 18.7%, respectively. Table 2 displays adjusted HRs and 95% CIs for the presence of CAC according to the duration of diabetes and prediabetes. Rates per 1,000 person-years of CAC were higher with a longer duration of diabetes (11.4 for those with 0 years to 12.5 for those with >15 years) and prediabetes (11.0 for those with 0 years to 14.5 for those with >15 years). A longer duration of diabetes and duration of prediabetes were each independently associated with risk for CAC in models adjusted for sociodemographic characteristics and each other (model 1), as well as models adjusted further for time-varying CVD risk factor levels (model 2). In fully adjusted models, the HRs for CAC were 1.15 (95% CI 1.06, 1.25) and 1.07 (95% CI 1.01, 1.13) for each 5-year increment in diabetes and prediabetes duration, respectively. In comparison of categories of increasing duration of prediabetes with 0 years duration, the HR for CAC was significantly elevated only among those with >15 years of prediabetes (HR 1.57 [95% CI 1.18, 2.08]). There was no evidence of nonlinearity ($P_{quadratic} > 0.05$ [for all]).

Tables 3 and 4 display the adjusted mean left ventricular structural and functional outcomes at year 25 according to the duration of diabetes and prediabetes, respectively, during the 25-year follow-up period. In analyses adjusted for sociodemographic characteristics, CVD risk factors, and each other (model 2), durations of diabetes

**Table 2—Adjusted HRs (95% CI) for presence of CAC according to the time-varying duration of diabetes and prediabetes during follow-up (the CARDIA Study)**

| | 0 years | 1–5 years | 6–10 years | 11–15 years | >15 years | $P_{trend}$ | Per each additional 5 years |
|---|---|---|---|---|---|---|---|
| Diabetes duration | | | | | | | |
| Person-years | 72,025 | 3,410 | 3,200 | 1,360 | 1,355 | | |
| No. of cases | 821 | 51 | 42 | 24 | 17 | | |
| Incidence rate* | 11.4 | 15.0 | 13.1 | 17.6 | 12.5 | | |
| Model 1 | 1 (Ref.) | 1.59 (1.19, 2.12) | 2.07 (1.50, 2.84) | 2.56 (1.70, 3.85) | 2.17 (1.33, 3.54) | <0.001 | 1.31 (1.21, 1.41) |
| Model 2 | 1 (Ref.) | 1.11 (0.83, 1.50) | 1.57 (1.13, 2.18) | 1.69 (1.10, 2.59) | 1.50 (0.92, 2.46) | 0.001 | 1.15 (1.06, 1.25) |
| Prediabetes duration | | | | | | | |
| Person-years | 40,065 | 17,760 | 13,540 | 5,820 | 4,420 | | |
| No. of cases | 442 | 208 | 169 | 71 | 64 | | |
| Incidence rate* | 11.0 | 11.7 | 12.5 | 12.2 | 14.5 | | |
| Model 1 | 1 (Ref.) | 1.28 (1.08, 1.51) | 1.39 (1.15, 1.67) | 1.31 (1.01, 1.70) | 2.07 (1.57, 2.73) | <0.001 | 1.17 (1.11, 1.24) |
| Model 2 | 1 (Ref.) | 1.04 (0.88, 1.24) | 1.08 (0.90, 1.31) | 0.97 (0.75, 1.27) | 1.57 (1.18, 2.08) | 0.03 | 1.07 (1.01, 1.13) |

Model 1 was adjusted for age, sex, race, educational attainment, study center, and mutual adjustment for duration of diabetes or prediabetes. Model 2 was adjusted for model 1 variables in addition to time-varying lifetime pack-years of smoking, BMI, systolic blood pressure, use of blood pressure–lowering medication, and total cholesterol level during follow-up. Ref., reference. *Per 1,000 person-years.

and prediabetes were not associated with left ventricular mass ($P_{trend}$ 0.88 and 0.54, respectively) or relative wall thickness ($P_{trend}$ 0.89 and 0.59). Among the systolic function parameters, longitudinal strain ($P_{trend}$ <0.001 and <0.001), but not ejection fraction ($P_{trend}$ 0.57 and 0.13), was significantly worse, with a longer duration of diabetes and prediabetes, and this association persisted after further adjustment for CVD risk factor levels during follow-up. Longer durations of diabetes and prediabetes were associated with worse levels for both diastolic function parameters. Participants with longer durations of diabetes and prediabetes exhibited worse left ventricular relaxation (e′ [$P_{trend}$ < 0.001 for both]) and a greater left ventricular filling pressure (E-to-e′ ratio [$P_{trend}$ < 0.001 for both]) (model 1). These associations were attenuated somewhat after adjustment for CVD risk factor levels (model 2) but remained significant for both diastolic function

**Table 3—Adjusted mean (SE) left ventricular structural and functional outcomes at year 25 according to the duration of diabetes during follow-up (the CARDIA Study)**

| | Duration of diabetes (years) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 1–5 | 6–10 | 11–15 | >15 | $P_{trend}$ | Per each additional 5 years |
| Structural outcomes | | | | | | | |
| Left ventricular mass (g) | | | | | | | |
| No. of participants | 2,465 | 115 | 134 | 47 | 56 | | |
| Model 1 | 170.5 (1.1) | 186.8 (4.1) | 187.1 (3.8) | 186.7 (6.4) | 198.1 (5.9) | <0.001 | 7.4 (1.02) |
| Model 2 | 169.3 (1.2) | 171.6 (3.7) | 166.9 (3.6) | 158.8 (5.8) | 173.8 (5.4) | 0.88 | −0.14 (0.96) |
| Relative wall thickness | | | | | | | |
| No. of participants | 2,463 | 115 | 134 | 46 | 56 | | |
| Model 1 | 0.35 (0.002) | 0.36 (0.006) | 0.37 (0.006) | 0.36 (0.010) | 0.36 (0.001) | 0.13 | 0.0025 (0.002) |
| Model 2 | 0.35 (0.002) | 0.36 (0.007) | 0.36 (0.006) | 0.35 (0.010) | 0.35 (0.010) | 0.89 | −0.0002 (0.002) |
| Systolic function outcomes | | | | | | | |
| Ejection fraction (%) | | | | | | | |
| No. of participants | 2,465 | 115 | 134 | 47 | 56 | | |
| Model 1 | 69.7 (0.2) | 69.2 (0.7) | 69.5 (0.7) | 69.2 (1.1) | 69.1 (1.1) | 0.50 | −0.12 (0.18) |
| Model 2 | 69.8 (0.2) | 69.2 (0.7) | 69.8 (0.7) | 69.5 (1.2) | 69.3 (1.1) | 0.57 | −0.11 (0.19) |
| Longitudinal strain (%) | | | | | | | |
| No. of participants | 2,419 | 114 | 129 | 45 | 49 | | |
| Model 1 | −15.0 (0.1) | −14.6 (0.2) | −14.0 (0.2) | −14.3 (0.3) | −13.8 (0.3) | <0.001 | 0.34 (0.06) |
| Model 2 | −15.0 (0.1) | −14.8 (0.2) | −14.4 (0.2) | −14.7 (0.3) | −14.1 (0.3) | <0.001 | 0.21 (0.06) |
| Diastolic function outcomes | | | | | | | |
| e′ (cm/s) | | | | | | | |
| No. of participants | 2,685 | 134 | 153 | 54 | 60 | | |
| Model 1 | 11.8 (0.1) | 10.6 (0.2) | 11.0 (0.2) | 11.2 (0.4) | 10.4 (0.3) | <0.001 | −0.36 (0.06) |
| Model 2 | 11.7 (0.1) | 11.0 (0.2) | 11.3 (0.2) | 11.8 (0.4) | 10.9 (0.3) | 0.004 | −0.18 (0.06) |
| E-to-e′ ratio | | | | | | | |
| No. of participants | 2,669 | 131 | 153 | 53 | 59 | | |
| Model 1 | 7.0 (0.05) | 8.2 (0.19) | 7.7 (0.18) | 7.8 (0.30) | 8.0 (0.29) | <0.001 | 0.32 (0.05) |
| Model 2 | 7.0 (0.06) | 7.8 (0.19) | 7.3 (0.18) | 7.3 (0.30) | 7.5 (0.29) | 0.001 | 0.17 (0.05) |

Model 1 was adjusted for age, sex, race, educational attainment, study center, and duration of prediabetes. Model 2 was adjusted for model 1 variables in addition to lifetime pack-years of smoking, use of blood pressure–lowering medication, and mean BMI, systolic blood pressure, and total cholesterol level during follow-up.

**Table 4—Adjusted mean (SE) left ventricular structural and functional outcomes at year 25 according to the duration of prediabetes during follow-up (the CARDIA Study)**

| | Duration of prediabetes (years) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 1–5 | 6–10 | 11–15 | >15 | $P_{trend}$ | Per each additional 5 years |
| Structural outcomes | | | | | | | |
| Left ventricular mass (g) | | | | | | | |
| No. of participants | 1,273 | 619 | 527 | 223 | 175 | | |
| Model 1 | 178.9 (2.2) | 181.9 (2.6) | 188.9 (2.7) | 189.5 (3.5) | 189.9 (4.0) | <0.001 | 3.8 (0.69) |
| Model 2 | 168.0 (2.1) | 166.5 (2.4) | 170.9 (2.5) | 168.2 (3.3) | 166.8 (3.6) | 0.54 | 0.39 (0.64) |
| Relative wall thickness | | | | | | | |
| No. of participants | 1,272 | 619 | 526 | 222 | 175 | | |
| Model 1 | 0.35 (0.004) | 0.36 (0.004) | 0.36 (0.004) | 0.36 (0.006) | 0.35 (0.006) | 0.08 | 0.0019 (0.001) |
| Model 2 | 0.35 (0.004) | 0.35 (0.004) | 0.36 (0.004) | 0.36 (0.006) | 0.35 (0.006) | 0.53 | 0.0007 (0.001) |
| Systolic function outcomes | | | | | | | |
| Ejection fraction (%) | | | | | | | |
| No. of participants | 1,273 | 619 | 527 | 223 | 175 | | |
| Model 1 | 68.6 (0.4) | 69.9 (0.5) | 70.0 (0.5) | 69.8 (0.6) | 68.4 (0.7) | 0.10 | 0.20 (0.12) |
| Model 2 | 68.8 (0.4) | 70.1 (0.5) | 70.2 (0.5) | 70.0 (0.7) | 68.6 (0.7) | 0.13 | 0.20 (0.13) |
| Longitudinal strain (%) | | | | | | | |
| No. of participants | 1,224 | 611 | 519 | 229 | 173 | | |
| Model 1 | −14.7 (0.1) | −14.4 (0.1) | −14.3 (0.1) | −14.2 (0.2) | −14.1 (0.2) | <0.001 | 0.17 (0.04) |
| Model 2 | −14.9 (0.1) | −14.6 (0.1) | −14.6 (0.1) | −14.5 (0.2) | −14.5 (0.2) | <0.001 | 0.13 (0.04) |
| Diastolic function outcomes | | | | | | | |
| e′ (cm/s) | | | | | | | |
| No. of participants | 1,357 | 685 | 585 | 256 | 203 | | |
| Model 1 | 11.4 (0.1) | 10.9 (0.1) | 10.9 (0.2) | 11.1 (0.2) | 10.8 (0.2) | <0.001 | −0.20 (0.04) |
| Model 2 | 11.6 (0.1) | 11.2 (0.1) | 11.2 (0.2) | 11.5 (0.2) | 11.3 (0.2) | 0.002 | −0.12 (0.04) |
| E-to-e′ ratio | | | | | | | |
| No. of participants | 1,345 | 681 | 584 | 253 | 202 | | |
| Model 1 | 7.5 (0.11) | 7.8 (0.12) | 7.8 (0.13) | 7.6 (0.17) | 8.0 (0.18) | <0.001 | 0.12 (0.03) |
| Model 2 | 7.3 (0.11) | 7.5 (0.12) | 7.4 (0.13) | 7.2 (0.17) | 7.4 (0.19) | 0.20 | 0.04 (0.03) |

Model 1 was adjusted for age, sex, race, educational attainment, study center, and duration of diabetes. Model 2 was adjusted for model 1 variables in addition to lifetime pack-years of smoking, use of blood pressure–lowering medication, and mean BMI, systolic blood pressure, and total cholesterol level during follow-up.

parameters with the duration of diabetes ($P_{trend}$ 0.004 and 0.001 for e′ and E-to-e′ ratio, respectively) and with e′ only for prediabetes ($P_{trend} < 0.001$). The prediabetes duration and ejection fraction relation showed evidence for an inverse U-shaped association ($P_{quadratic} < 0.001$); no other evidence for nonlinearity was identified.

In terms of the clinical definitions of adverse left ventricular structure and function, a longer duration of diabetes was independently associated with a low ejection fraction, worse longitudinal strain, and impaired left ventricular relaxation and filling pressure (Supplementary Table 1). Duration of prediabetes was associated with worse longitudinal strain and impaired relaxation (Supplementary Table 2). Neither duration of diabetes nor duration of prediabetes showed an association with left ventricular mass or relative wall thickness.

The associations between the duration of diabetes and prediabetes with the presence of CAC did not vary significantly by race or sex (data not shown). There was also no evidence of effect modification for the measures of left ventricular structure and function, except for prediabetes duration, left ventricular mass, and race ($P_{interaction}$ = 0.02); prediabetes duration, E-to-e′ ratio, and sex ($P_{interaction}$ = 0.03); and diabetes duration, relative wall thickness, and sex ($P_{interaction}$ = 0.04). However, when these associations were observed in stratified analyses, the only significant association was among women, for whom each 5-year-longer duration of prediabetes was associated with a 0.12 (0.05) unit higher E-to-e′ ratio ($P$ = 0.02) (men: $\beta = -0.02$ [SE 0.04]; $P$ = 0.61). In addition, findings were similar in a sensitivity analysis that defined diabetes and prediabetes with the use of fasting glucose only (data not shown).

## CONCLUSIONS

In this long-term population-based study, longer durations of diabetes and prediabetes during early adulthood were each independently associated with subclinical atherosclerosis and measures of systolic and diastolic dysfunction later in life. The associations of prediabetes with these subclinical outcomes remained even after simultaneous adjustment for the duration of diabetes. Furthermore, these associations were independent of smoking behavior and several potentially important metabolic factors such as adiposity, blood pressure, and cholesterol. In addition, there was relatively little evidence to suggest that associations varied in subgroups defined by race or sex.

An independent association of the duration of diabetes with subclinical atherosclerosis is in agreement with many, but not all, existing studies. In a cross-sectional study of 933 patients with type 2 diabetes without known coronary artery disease, Kim et al. (6) reported that the duration of diabetes was associated with a higher CAC score as well as a higher rate of obstructive coronary artery disease determined via coronary angiography. Among 54 patients with diabetes who underwent coronary angiography and intravascular ultrasound, those with a longer duration of diabetes were more likely to have thin-cap fibroatheroma,

a vulnerable plaque morphology associated with myocardial infarction and sudden death (8). In a cross-sectional study of 275 patients, Kawamori et al. (26) reported a positive association of the duration of diabetes with carotid intima-media thickness determined via B-mode ultrasound. However, findings from the Insulin Resistance Atherosclerosis study (19) and others have shown no evidence for an association of the duration of diabetes with carotid intima-media thickness (27,28) or degree of coronary stenosis (29). The reasons for the differences in results across studies are unknown but may be due, at least in part, to methodological differences pertaining to the study design or sampling procedure, referral bias, demographic characteristics of the sample populations, or a greater reliance in the null studies on carotid intima-media thickness as a measure of atherosclerosis versus more precise measures of subclinical disease (e.g., cardiac CT, intravascular ultrasound).

In general, the findings of the current study are consistent with an earlier report from CARDIA, which found that diabetes diagnosed during the early part of the follow-up period (a duration of $\geq$10 years vs. $<$10 years) is associated with measures of subclinical left ventricular systolic and diastolic function in middle age (16). The current study confirms and extends these observations across a more detailed range of the duration of diabetes while also examining whether the duration of prediabetes is associated with these and other outcomes. Consistent with previous results that suggest that ejection fraction may not be a sensitive measure of subclinical systolic dysfunction (30), we found that a longer duration of diabetes was associated with worse longitudinal strain but not ejection fraction (31). Our findings are also in agreement with a limited number of available studies showing that a longer duration of diabetes is associated with measures of left ventricular diastolic function (7,32). These results suggest that long-term diabetes during adulthood may lead to overt left ventricular dysfunction in later life.

To our knowledge, the current study represents the first comprehensive report on the characterization of the cumulative effects of a longer duration of prediabetes. It is important to note that associations with prediabetes were generally of a more modest magnitude when compared with the duration of diabetes. However, given the sizeable and growing percentage of adults who have prediabetes in the U.S. (3), a small increase in risk assuming a causal relationship between prediabetes and subclinical CVD might still translate into a substantial number of adults developing subclinical or clinical CVD. Furthermore, it has been estimated that only 2% of those with prediabetes progress to diabetes per year, suggesting that a considerable number of individuals are exposed to long-term glycemic elevations that do not reach the level of diabetes (33). A recent meta-analysis of $>$50 prospective cohort studies found that prediabetes was associated with a higher risk of heart disease, stroke, and all-cause mortality (34). Other studies have shown that persons with prediabetes have a higher prevalence of subclinical atherosclerosis (35,36). Our results confirm these findings and suggest that a longer cumulative exposure to prediabetes may lead to the development of subclinical atherosclerosis and cardiac dysfunction independent of any time spent with diabetes.

Our findings suggest either a direct effect of long-term glycemic elevations and/or an indirect effect due to the multiple metabolic abnormalities associated with diabetes and prediabetes. Importantly, we have shown that both prediabetes and diabetes may contribute to future target organ damage. Atherosclerosis and left ventricular dysfunction, in the setting of prolonged diabetes or prediabetes, may share common antecedents. Autopsy studies have shown an association of diabetes duration and the extent of atherosclerosis and myocardial lesions (37). Extended exposure to hyperglycemia leads to the nonenzymatic glycosylation of proteins in the arterial wall and myocardium (38,39). Other potential mechanisms for atherosclerosis or cardiac dysfunction include autonomic dysfunction, interstitial fibrosis, impaired calcium homeostasis, upregulation of the renin-angiotensin system, endothelial dysfunction, increased oxidative stress, altered substrate metabolism, LDL cholesterol, and mitochondrial dysfunction (39,40).

Strengths of the current study include a population-based sampling method; a biracial cohort; serial screening of multiple measures of glycemic status, which allowed for the identification and mutual adjustment of diabetes and prediabetes duration over 25 years; extensive data on potential confounders measured concurrently with the diagnosis of diabetes and prediabetes; a large sample size well balanced with respect to race and sex that increased precision and permitted adjustment and stratification; a high retention rate; and the standardized data collection protocols and rigorous quality control of the CARDIA Study. Nevertheless, our estimation of the duration of diabetes and prediabetes during follow-up was based on the measurement of fasting glucose and other measures of glycemia every 3-7 years. It is likely that a more frequent number of assessments would have led to a more accurate estimation of the duration of diabetes and prediabetes during follow-up; however, to the extent that there was random misclassification as a result of this assessment schedule, we may have underestimated the true association between the duration of diabetes and prediabetes and subclinical CVD in our cohort. In addition, 2-h glucose and $HbA_{1c}$ levels were not available at baseline, although our findings were similar when fasting glucose only was used to define diabetes and prediabetes.

In conclusion, both the duration of diabetes and the duration of prediabetes during adulthood are associated with CAC and left ventricular systolic and diastolic dysfunction in later life, suggesting that the cumulative exposure to chronic hyperglycemia even in the prediabetes range may lead to increased risk of atherosclerosis and impaired cardiac function. These data emphasize the importance of early identification and management of those at risk for diabetes and prediabetes in order to limit exposure to the adverse cardiovascular effects of a longer duration of these conditions.

**Acknowledgments.** The authors thank the staff and participants of the CARDIA Study for their important contributions. This manuscript was reviewed by CARDIA for scientific content.

**Funding.** The CARDIA Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201300025C and HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and The Johns Hopkins University School of Medicine (HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging (NIA) and an intra-

agency agreement between NIA and NHLBI (AG0005). M.P.B. was supported by NHLBI (T32HL069771).

The views expressed in this article are those of the authors and do not necessarily represent the views of the NHLBI, the National Institutes of Health, or the U.S. Department of Health and Human Services.

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

**Author Contributions.** J.P.R. developed the study concept and design, performed analysis and interpretation of data, and drafted the manuscript. N.B.A., M.P.B., J.S.R., and S.S.G. performed analysis and interpretation of data and critically revised the manuscript for important intellectual content. J.J.C. and J.A.L. obtained funding, performed analysis and interpretation of data, and critically revised the manuscript for important intellectual content. C.E.L. and P.J.S. obtained funding, acquired data, performed analysis and interpretation of data, and critically revised the manuscript for important intellectual content. J.P.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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