Long-term Absolute Risk for Cardiovascular Disease Stratified by Fasting Glucose Level

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OBJECTIVE

To estimate the long-term absolute risk for cardiovascular disease (CVD) according to fasting glucose (FG) levels below the threshold of diabetes.

RESEARCH DESIGN AND METHODS

We pooled data from seven observational cohorts of U.S. black and white men and women followed from 1960 to 2015. We categorized FG as follows: <5.0, 5.0–5.5, 5.6–6.2, 6.3–6.9 mmol/L, and diabetes (FG ≥7.0 mmol/L or use of diabetes medications). CVD was defined as fatal/nonfatal coronary heart disease and fatal/nonfatal stroke. We estimated the risk of CVD by FG category at index age 55 years using a modified Kaplan-Meier survival analysis, adjusted for the competing risk of non-CVD death. We also assessed risk for incident CVD according to change in FG before 50 years of age, specifically among the categories <5.6 mmol/L, 5.6–6.9 mmol/L, and diabetes.

RESULTS

Our sample included 19,630 individuals (6,197 blacks and 11,015 women) without a prior CVD event. Risk for CVD through 85 years of age ranged from 15.3% (<5.0 mmol/L) to 38.6% (diabetes levels) among women and from 21.5% (5.0–5.5 mmol/L) to 47.7% (diabetes levels) among men. An FG of 6.3–6.9 mmol/L was associated with higher long-term CVD risk compared with the lowest FG among men but not women. Increases in glucose during midlife with conversion to diabetes were associated with higher cardiovascular risk (1.3- to 3.6-fold) than increases in glucose below the diabetes threshold.

CONCLUSIONS

Middle-age individuals with diabetes have high long-term absolute risk for CVD. These data strongly support the importance of blood glucose monitoring in midlife for CVD prevention.

Cardiovascular disease (CVD) is the leading cause of death in persons with diabetes and a significant source of morbidity and health care costs (1). Previous long-term absolute risk estimates for incident CVD among individuals with diabetes at midlife range from 49% to 67% for women and 62% to 78% for men (2,3). However, these estimates were limited to whites; the long-term absolute risk for CVD according to diabetes status has not been reported for black Americans. An update to these estimates to include black Americans is critically important for understanding health disparities in the U.S. Furthermore, absolute risk for CVD across the spectrum of glycemia from normal through diagnosed diabetes has not been reported. Some data

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suggest that elevated fasting glucose (FG) or glycated hemoglobin (HbA_{1c}) values in the prediabetes range (FG 5.6–6.9 mmol/L or HbA_{1c} 5.7–6.4% [39–47 mmol/mol]) are associated with higher relative CVD risk compared with normal glucose values over the shorter term (4–15 years) (4–6). Because roughly one-third of U.S. adults have prediabetes and prediabetes is associated with higher relative CVD risks, understanding the long-term absolute risk for CVD in these individuals is of substantial public health importance (7).

Using data from the Cardiovascular Disease Lifetime Risk Pooling Project (LRPP), we estimated the 30-year absolute risks for CVD by glucose level and by 4-year change in glucose level at midlife. We hypothesized that we would observe *1*) a positive graded association between higher level of glucose at midlife and 30-year risk for CVD and *2*) that compared with normal glucose levels over 4 years, higher and increasing glucose over 4 years would be associated with a positive graded association for 30-year risk for CVD.

RESEARCH DESIGN AND METHODS

Cohorts

Detailed methods for the LRPP have previously been published (8). Briefly, the LRPP was created by pooling individual-level data from 20 U.S.-based community epidemiological cohorts. For this analysis, we selected cohorts that had measurement of FG level and ascertainment of CVD outcomes, including fatal and nonfatal coronary heart disease (CHD) and fatal and nonfatal stroke. Because of our objective to update the long-term absolute risk estimates of CVD by glucose level to include black Americans, cohorts were eligible for inclusion if they had black or white participants. Data for each study were obtained from the National Heart, Lung, and Blood Institute or study investigators, and all study protocols and procedures for the LRPP were approved by the Institutional Review Board at Northwestern University.

Atherosclerosis Risk in Communities study

The Atherosclerosis Risk in Communities (ARIC) study was initiated in 1987, and its methods have been described previously (9). Probability sampling was used to select, recruit, and enroll individuals drawn from four U.S. communities: Forsyth County, NC; the city of Jackson, MS; seven suburbs of Minneapolis, MN; and Washington County, MD. Each field center enrolled men and women aged 45–64 years reflecting the racial/ethnic makeup of the community, with the exception of the Jackson cohort, which only enrolled blacks, for a cohort total of 15,792 study participants in 1987–1989. Participants have been invited to participate in five clinic examinations, with annual follow-up telephone calls to update health-related developments occurring since the last contact. Participants gave written informed consent, and the ARIC study procedures were reviewed and approved by each institution's review board.

Cardiovascular Health Study

The Cardiovascular Health Study (CHS) recruited participants between 1989 and 1990 from four U.S. communities including Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. The initial cohort of 5,201 individuals was identified using Medicare eligibility lists of the Health Care Finance Administration. Participants had to be 65 years of age, ambulatory and community dwelling, expected to remain in their communities for 3 years, and able to provide personal informed consent (10). In 1992 to 1993, an additional 687 predominantly African American participants were recruited, for a total of 5,888 participants.

Coronary Artery Risk Development in Young Adults

The Coronary Artery Risk Development in Young Adults (CARDIA) study is an ongoing longitudinal observational study of individuals recruited from four U.S. metropolitan communities. In 1985 to 1986, a total of 5,115 black and white adults who were 18–30 years of age and free from CVD were enrolled. Participants have been contacted by telephone annually and invited to participate in follow-up examinations 2, 5, 7, 10, 15, 20, 25, and 30 (2015 to 2016) years after baseline. Participants have provided consent at each examination, and institutional review boards at each study site and coordinating center have granted approval for all examinations. Details regarding the study design have been published previously (11).

Framingham Heart Study

The Framingham Heart Study (FHS) is an ongoing community-based prospective cohort study initiated in 1948 with the enrollment of 5,209 women and men aged 28–74 years (original cohort) from the town of Framingham, MA (12). Participants have continued to return to the study every 2 years for in-person examinations that have consistently included detailed medical history, physical examination, and laboratory tests. The most recent, and 32nd, examination concluded in 2014. The study protocol was approved by the Institutional Review Board of the Boston University Medical Center, and all participants provided written informed consent.

Framingham Offspring Cohort Study

In 1971, 5,124 offspring (aged 5–70 years; 3,548 biological offspring and 1,576 offspring spouses) of the original FHS cohort were recruited to participate in the Framingham Offspring Study (FOS) (13). At each examination, participants underwent a standardized medical history and physical examination. The most recent, and ninth, follow-up examination concluded in 2014. The study protocol was approved by the Institutional Review Board of the Boston University Medical Center, and all participants provided written informed consent.

Jackson Heart Study

Between 2000 and 2004, 5,306 noninstitutionalized self-identified African Americans, aged ≥21 years, were enrolled in the Jackson Heart Study (JHS) (14). Participants were recruited from urban and rural areas of the three counties (Hinds, Madison, and Rankin) that comprise the Jackson, MS, metropolitan area and included participants in the ARIC study (22% of JHS participants), residents of households selected randomly from a commercial list, a volunteer sample, and family members of study participants. Participants were invited for in-person examinations in 2000–2004, 2005–2008, and 2009–2013, which included a clinical examination and questionnaires covering medical history, lifestyle, and psychosocial factors. Annual telephone interviews are conducted to update vital status, medical and medication history, and insurance, functional, and employment status. The current analysis was restricted to JHS participants who were not participants in the ARIC

study. All participants provided written informed consent, and the Institutional Review Board of the University of Mississippi Medical Center approved the JHS protocol.

Multi-Ethnic Study of Atherosclerosis

The general study design and objectives of the Multi-Ethnic Study of Atherosclerosis (MESA) have been described previously (15). From July 2000 to August 2002, 6,814 participants aged 45–84 years and free of clinical CVD were recruited and examined at six field centers located in Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and Saint Paul, MN. Participants were from four racial ethnic groups including non-Hispanic white (38%), African American (28%), Hispanic (22%), and Chinese American (12%). Only non-Hispanic white and African American participants were included in this analysis. All participants gave written informed consent at the baseline examination, and MESA study protocol and ancillary studies were approved by the Institutional Review Board at each site. Participants were contacted by telephone annually and invited to participate in four follow-up in-person clinic examinations, each ~2 years apart.

FG Measures

In ARIC, glucose was measured with the hexokinase/glucose-6-phosphate dehydrogenase method (9). Serum glucose levels were measured using a Kodak Ektachem 700 analyzer with reagents (Eastman Kodak, Rochester, NY) in CHS (16). CARDIA measured serum glucose using the hexokinase ultraviolet method by American Bio Science Laboratories (Van Nuys, CA) (17). For the Framingham cohorts, glucose measurements were performed with a hexokinase reagent kit (A-gent glucose test; Abbott Laboratories, South Pasadena, CA) (18). In JHS, plasma glucose was measured by the glucose oxidase colorimetric method using a Vitros 950 or 250 (Ortho Clinical Diagnostics analyzer; Ortho Clinical Diagnostics, Raritan, NJ) (19). Serum glucose was measured in MESA by the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Ortho Clinical Diagnostics) (20). For each study, we ascertained glucose according to index age groups of 45, 55, 65, and 75 years (±5 years). Glucose categories were defined as FG: <5.0, 5.0–5.5, 5.6–6.2, and 6.3–6.9 mmol/L and diabetes (FG ≥7.0 mmol/L or use of diabetes medications). A subset of 16,070 individuals had repeated assessment of glucose over an average of 4 years (range 2–12 years) at or before 50 years of age. For this subset, we also created 4-year change among normal FG (FG <5.6 mmol/L), impaired FG (IFG; 5.6–6.9 mmol/L), and diabetes (FG ≥7.0 mmol/L or use of diabetes medications) categories: normal-normal, normal-IFG, normal-diabetes, IFG-IFG, IFG-diabetes, and diabetes-diabetes. Due to small numbers, individuals who regressed in category over 4 years were collapsed into the respective stable category. On average, glucose measures were taken 3.8 years apart; so, for an index age of 50 years, glucose was first measured at mean age 46.

Event Ascertainment and Definition

For this study, CVD was defined as fatal CHD, myocardial infarction, and fatal and nonfatal stroke by trained physician-adjudicators using all available medical records. For death events, many cohorts used linkage to the National Death Index for underlying cause of death from death certificate data, whereas others used adjudicated cause of death by study investigators after review of all available medical records and/or autopsy data. Vital status is known for 98% of the participants in the cohorts included in the LRPP. For the present analyses, deaths resulting from CVD (CHD or stroke, as adjudicated or indicated by ICD-8, ICD-9 codes 390–458, and ICD-10 codes I00–I99) were included. Nonfatal events of interest, including myocardial infarction and stroke, were obtained via trained physician-adjudicators, and methods for adjudication have been published for ARIC (9), CHS (21), CARDIA (22), FHS (23), FOS (24), JHS (25), and MESA (15).

Statistical Analysis

Long-term absolute CVD risk was calculated using a modified technique of survival analysis (26). Traditional survival analysis estimates base the probability of survival on an individual being event-free, but not necessarily alive. A more appropriate condition is survival free of the event and alive, in which individuals contribute information on the incidence of the event of interest for each age that they attain during follow-up. In this study, the risk set at any age j contained all participants who attained age j free of the event at some point during follow-up. Participants who developed an event, died, or were censored at age j were removed from the risk set for age j + 1 and older, whereas participants who were age j + 1 at entry were added to the risk set for age j + 1. Kaplan-Meier methods were used to calculate hazards, age-specific incidences, cumulative incidence, and survival probabilities for each age j. The cumulative incidence for each outcome applies to people who live through age j − 1. However, this method does not reflect the competing risk of death from other causes. Individuals who die are censored at the time of death and assumed to have the same future risk of CVD (the event) as those who are censored alive. Participants who die free of CVD before age j have escaped a diagnosis of CVD and have zero future risk of CVD. Therefore, we calculated a separate survival curve for the competing risk of death with death included alongside CVD as an event rather than as a withdrawal. This method yields a true remaining lifetime risk, is adjusted for the competing risk of death (27), and has been applied extensively (2,26,28,29).

Each individual was followed from study entry until the occurrence of a first CVD event, death, or 85 years of age. For the aim in which we assessed glucose level as determined at a single point in time, risk estimates for CVD, CHD, and stroke were calculated according to FG category, stratified by race and sex. Our primary analysis for this aim focused on index age 55 years in order to maximize the analytic sample and derive estimates comparable to prior studies. We also calculated risk estimates for index ages 45, 65, and 75 years. We estimated 30-year risk for CVD, CHD, and stroke according to 4-year change in normal FG, IFG, and diabetes category for the index age 50 years. For this aim, each individual was followed from 50 years of age until the occurrence of a first CVD event, death, or 80 years of age.

Because the use of FG as the sole laboratory criteria may result in misclassification of glycemic status, we conducted a sensitivity analysis for a subset of 5,180 individuals with concomitant HbA_{1c} measurement. We created

normal (FG <5.6 mmol/L and HbA_{1c} <5.7% [<39 mmol/mol]), prediabetes (FG 5.6–6.9 mmol/L or HbA_{1c} 5.7–6.4% [39–47 mmol/mol]), and diabetes categories (FG ≥7.0 mmol/L, HbA_{1c} ≥6.5% [≥48 mmol/mol], or use of diabetes medications) and assessed the risk for CVD, CHD, and stroke according to these categories. SAS software version 9.4 (SAS Institute Inc., Cary, NC) was used for all analyses.

RESULTS

Our primary sample included 19,630 individuals (6,197 blacks and 11,015 women) without a prior CVD event at an index age of 55 years (Table 1). The glucose category of 5.0–5.5 mmol/L was most prevalent, with the greatest percentage of white women (38%), white men (35%), and black men (32%), whereas the glucose category <5.0 mmol/L had the highest percentage of black women (29%) at index age 55. Greater age, BMI, and blood pressure, male sex, and black race were associated with higher FG category. Current diabetes medication use was higher in blacks than whites (black women: 63%; black men: 61%; white women: 48%; white men: 49%).

Over 272,124 person-years of follow-up from an index age of 55 years, we observed 2,217 incident CVD events, including 1,530 CHD and 877 stroke events. Similar patterns of incidence for CVD, CHD, and stroke according to FG categories were observed across index ages (Supplementary Table 1). For each index age, the incidence of CHD was higher than that of stroke within a given glucose category. In general, the incidence for each CVD end point was lowest among the FG category <5.0 mmol/L and highest among those meeting the criteria for diabetes.

Risk for CVD from 55 years through 85 years of age among women ranged from 15.3% (FG <5.0 mmol/L) to 38.6% (diabetes levels) and among men ranged from 21.5% (FG 5.0–5.5 mmol/L) to 47.7% (diabetes levels) (Table 2). Within each glucose category, after accounting for the competing risk of non-CVD death, the 30-year risk for CVD was similar for whites compared with blacks, but higher in men than women. When not accounting for the competing risk of death, black men had higher CVD risk estimates as compared with their white male counterparts, most pronounced in the diabetes category (Supplementary Table 2) (30-year risk for CVD for white men 53.5% compared with 67.8% for black men). This discrepancy in risk estimates for CVD was not observed between white and black women before and after adjustment for competing risk of death. CVD risk estimates for glucose categories <7.0 mmol/L were not statistically significantly greater than the reference (FG <5.0 mmol/L) for women. Among men, individuals in both the diabetes category and the FG 6.3–6.9 mmol/L category had significantly higher risk for CVD compared with those in the FG <5.0 mmol/L category.

In the subset of 5,180 individuals (2,463 blacks and 2,717 women) with concurrent HbA_{1c} measurement, 20-year absolute risk for CVD from 55 through 75 years of age was lowest for individuals with normal glucose for each race-sex group, with the exception of black women, for whom risk for CVD was lowest for those with prediabetes. For each race-sex group, 20-year risk for CVD was 3–10 times higher for individuals with diabetes than for those with normal glucose levels (Fig. 1). Risk estimates for CVD among individuals with diabetes, as determined by both FG and HbA_{1c}, were qualitatively higher in whites compared with blacks. Specifically, among those with diabetes, the 20-year risk for CVD was 31.6% (95% CI 10.1, 53.1) for white women, 19.5% (95% CI 9.6, 29.5) for black

Table 1—Participant characteristics at index age 55 years

	FG <5.0 mmol/L	FG 5.0–5.5 mmol/L	FG 5.6–6.2 mmol/L	FG 6.3–6.9 mmol/L	FG ≥7.0 mmol/L or diabetes medications (Rx)
Women					
N	3,314	3,816	2,313	528	1,044
Black, *n* (%)	1,083 (33)	1,072 (28)	773 (33)	221 (42)	623 (60)
Current smoker, *n* (%)	692 (21)	785 (21)	480 (21)	121 (23)	212 (20)
BMI, m/kg^2	27.0 (6.0)	28.0 (6.3)	29.9 (6.8)	32.5 (7.2)	34.5 (7.3)
Systolic blood pressure, mmHg	118 (18)	118 (18)	123 (19)	126 (19)	129 (20)
Diastolic blood pressure, mmHg	72 (11)	73 (10)	74 (11)	76 (11)	75 (11)
Total cholesterol, mmol/L	5.4 (1.0)	5.5 (1.0)	5.6 (1.1)	5.6 (1.1)	5.6 (1.3)
FG, mmol/L	4.7 (0.3)	5.2 (0.2)	5.8 (0.2)	6.6 (0.2)	10.0 (4.1)
HbA_{1c}, %*	5.4 (0.4)	5.6 (0.4)	5.9 (0.5)	6.4 (1.0)	8.0 (1.9)
HbA_{1c}, mmol/mol*	36 (4.4)	38 (4.4)	41 (5.5)	46 (10.9)	64 (20.8)
Rx use, *n* (%)	NA	NA	NA	NA	572 (55)
Men					
N	1,484	2,956	2,570	706	899
Black, *n* (%)	510 (34)	768 (26)	577 (22)	184 (26)	386 (43)
Current smoker, *n* (%)	355 (24)	696 (24)	619 (24)	169 (24)	200 (22)
BMI, m/kg^2	26.9 (4.2)	27.7 (4.4)	28.6 (4.6)	29.5 (5.0)	31.0 (5.6)
Systolic blood pressure, mmHg	121 (17)	121 (16)	122 (16)	126 (17)	129 (19)
Diastolic blood pressure, mmHg	77 (11)	76 (10)	76 (11)	78 (11)	79 (11)
Total cholesterol, mmol/L	5.1 (1.0)	5.3 (1.0)	5.4 (1.0)	5.4 (1.0)	5.2 (1.2)
FG, mmol/L	4.7 (0.2)	5.3 (0.2)	5.8 (0.2)	6.6 (0.2)	9.6 (3.6)
HbA_{1c}, %*	5.4 (0.4)	5.5 (0.4)	5.7 (0.5)	6.1 (0.7)	7.9 (1.9)
HbA_{1c}, mmol/mol*	36 (4.4)	37 (4.4)	39 (5.5)	43 (7.7)	63 (20.8)
Rx use, *n* (%)	NA	NA	NA	NA	452 (50)

Data are mean (SD) unless otherwise specified. NA, not applicable; Rx, diabetes medication. *Data on HbA_{1c} are on a subset of 5,180 individuals.

Table 2—Long-term risk for incident CVD (including fatal and nonfatal CHD and fatal and nonfatal stroke, adjusted for competing risk of death) according to FG category starting at index age 55 years

		30-year risk for incident CVD								
		CVD			CHD			Stroke		
FG category	*N*	Events	Absolute risk, % (95% CI)†	RR (95% CI)	Events	Absolute risk, % (95% CI)†	RR (95% CI)	Events	Absolute risk, % (95% CI)†	RR (95% CI)
Women										
FG <5.0 mmol/L	3,314	205	15.3 (12.3, 18.3)	Reference	127	8.4 (6.4, 10.3)	Reference	96	8.5 (6.0, 11.0)	Reference
FG 5.0–5.5 mmol/L	3,816	247	15.6 (13.1, 18.2)	1.05 (0.87, 1.25)	153	9.1 (7.2, 10.9)	1.05 (0.83, 1.32)	108	7.9 (5.8, 9.9)	0.98 (0.75, 1.28)
FG 5.6–6.2 mmol/L	2,313	201	15.9 (13.3, 18.4)	1.40 (1.17, 1.69)	130	9.7 (7.8, 11.7)	1.47 (1.16, 1.86)	91	7.6 (5.7, 9.4)	1.36 (1.02, 1.80)
FG 6.3–6.9 mmol/L	528	54	18.6 (13.1, 24.1)	1.65 (1.24, 2.20)	31	11.9 (6.9, 16.9)	1.53 (1.05, 2.24)	26	8.0 (4.9, 11.1)	1.70 (1.11, 2.60)
FG ≥7.0 mmol/L or Rx	1,044	230	38.6 (33.4, 43.8)	3.56 (2.99, 4.24)	145	25.5 (21.0, 29.9)	3.62 (2.89, 4.55)	123	21.2 (17.0, 25.5)	4.07 (3.14, 5.26)
Men										
FG <5.0 mmol/L	1,484	180	23.5 (19.7, 27.3)	Reference	136	18.6 (14.5, 22.6)	Reference	58	8.4 (5.9, 10.9)	Reference
FG 5.0–5.5 mmol/L	2,956	337	21.5 (19.0, 24.1)	0.94 (0.79, 1.11)	244	16.0 (13.7, 18.3)	0.90 (0.74, 1.10)	112	7.2 (5.7, 8.8)	0.97 (0.71, 1.32)
FG 5.6–6.2 mmol/L	2,570	358	23.3 (20.6, 26.0)	1.15 (0.97, 1.36)	266	16.8 (14.5, 19.0)	1.13 (0.93, 1.37)	118	8.6 (6.7, 10.5)	1.17 (0.86, 1.60)
FG 6.3–6.9 mmol/L	706	138	31.0 (25.6, 36.3)	1.61 (1.32, 1.97)	104	24.1 (19.0, 29.2)	1.61 (1.27, 2.04)	44	9.6 (6.6, 12.6)	1.59 (1.09, 2.34)
FG ≥7.0 mmol/L or Rx	899	267	47.7 (42.8, 52.7)	2.45 (2.07, 2.90)	194	35.5 (30.8, 40.2)	2.35 (1.92, 2.88)	101	17.6 (14.1, 21.1)	2.87 (2.10, 3.93)
Subsample with concurrent FG and HbA_{1c}		20-year risk for incident CVD								
		CVD			CHD			Stroke		
FG and HbA_{1c} category	*N*	Events	Absolute risk, % (95% CI)†	RR (95% CI)	Events	Absolute risk, % (95% CI)†	RR (95% CI)	Events	Absolute risk, % (95% CI)†	RR (95% CI)
Women										
FG <5.6 mmol/L and HbA_{1c} <5.7% (<39 mmol/mol)	1,542	24	4.1 (2.0, 6.1)	Reference	10	1.5 (0.3, 2.7)	Reference	16	2.9 (1.2, 4.6)	Reference
FG 5.6–6.9 mmol/L or HbA_{1c} 5.7–6.4% (39–47 mmol/mol)	1,085	19	4.2 (2.1, 6.4)	1.13 (0.62, 2.04)	10	2.0 (0.7, 3.3)	1.42 (0.59, 3.40)	9	2.2 (0.5, 3.9)	0.80 (0.35, 1.80)
FG ≥7.0 mmol/L, HbA_{1c} ≥6.5% (≥48 mmol/mol), or Rx	386	29	25.8 (13.4, 38.3)	4.83 (2.84, 8.19)	18	17.1 (6.2, 28.0)	7.19 (3.35, 15.45)	12	11.2 (4.1, 18.3)	3.00 (1.43, 6.28)
Men										
FG <5.6 mmol/L and HbA_{1c} <5.7% (<39 mmol/mol)	901	31	8.1 (4.6, 11.6)	Reference	20	4.6 (2.4, 6.9)	Reference	27	3.6 (0.8, 6.4)	Reference
FG 5.6–6.9 mmol/L or HbA_{1c} 5.7–6.4% (39–47 mmol/mol)	957	40	10.7 (6.5, 15.0)	1.21 (0.77, 1.92)	27	8.1 (4.2, 12.1)	1.27 (0.72, 2.25)	26	3.6 (1.6, 5.7)	0.91 (0.53, 1.54)
FG ≥7.0 mmol/L, HbA_{1c} ≥6.5% (≥48 mmol/mol), or Rx	309	35	31.6 (20.7, 42.4)	3.29 (2.07, 5.25)	22	15.3 (9.2, 21.5)	3.21 (1.78, 5.80)	29	18.1 (8.3, 27.9)	3.13 (1.88, 5.20)

RR, relative risk; Rx, diabetes medication. †Absolute risk estimates can account for competing risk of death but cannot adjust for covariates.

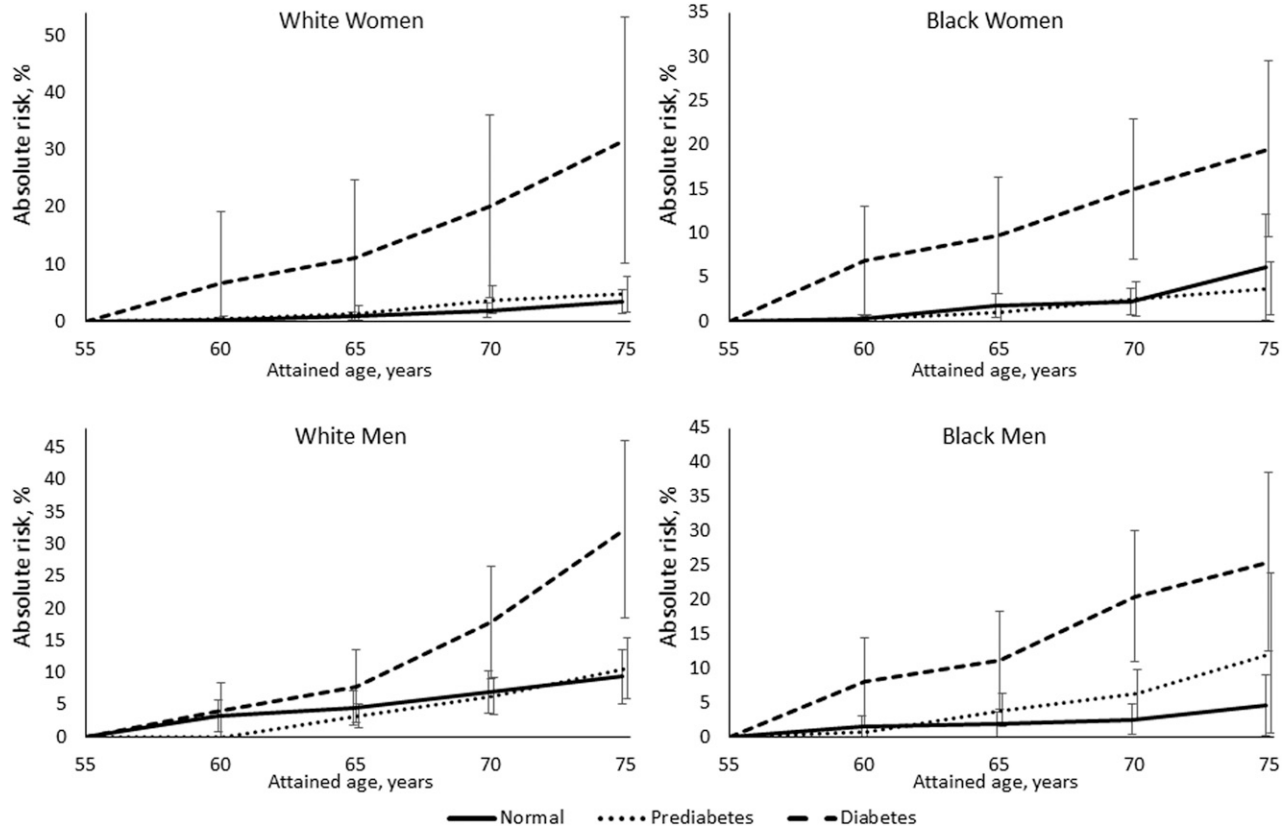

Figure 1—Absolute risk (with 95% confidence limits) for incident CVD over 20 years from 55 years of age according to subgroup of normal (FG <5.6 mmol/L and HbA_{1c} <5.7 [<39 mmol/mol]), prediabetes (FG 5.6–6.9 mmol/L or HbA_{1c} 5.7–6.4% [39–47 mmol/mol]), and diabetes (FG ≥7.0 mmol/L or HbA_{1c} ≥6.5% [≥48 mmol/mol] or diabetes medication use) for black and white women and men.

women, 32.3% (95% CI 18.6, 46.1) for white men, and 25.5% (95% CI 12.4, 38.6) for black men. We observed a similar pattern of association between glucose category and 30-year absolute risk for CHD and stroke by sex and race each, as found for CVD. Among women with diabetes by 55 years of age, the 30-year risk for CHD was 25.5% (95% CI 21.0, 29.9) and for stroke was 21.1% (95% CI 17.0, 25.5). For men with diabetes by 55 years of age, the 30-year risk for CHD was 35.5% (95% CI 30.8, 40.2) and for stroke was 17.6% (95% CI 14.1, 21.1). Patterns of associations were similar for the other index ages (Supplementary Tables 3–5), when stratifying by the presence of other CVD risk factors (Supplementary Table 6), and across cohorts (Supplemental Table 7).

Four-Year Change in Glucose Category

In the subset of 16,070 individuals (5,228 blacks and 9,187 women) with repeated measurement of FG, the greatest percentage of individuals had normal FG values at both assessments for all race-sex groups (white women: 62%; black women: 52%; white men: 40%; and black men: 44%). Due to similar risk between race groups, we present sex-stratified results (Table 3). Risk for CVD through 80 years of age was lowest for individuals who had normal FG values at both examinations (reference) for both women (14.2% [95% CI 11.5, 16.8]) and men (23.4% [95% CI 19.8, 27.0]). However, even for individuals who increased from normal FG to IFG over 4 years or had IFG at both examinations, the 30-year risk for CVD was not significantly higher than the reference level. The highest risk was observed for individuals who had diabetes at both examinations (women 57.2% and men 55.5%) followed by the groups who transitioned from normal FG to diabetes (women 25.5% and men 42.8%) and IFG to diabetes (women 35.7% and men 38.0%). We observed a similar pattern of association between change in glucose category and 30-year risk for CHD and stroke by sex and race each, as was found for CVD.

CONCLUSIONS

In this study of seven pooled cohorts, we estimated the long-term absolute risk for developing CVD according to multiple glucose categories in middle age and by change in glucose category during middle age. We observed several important findings. First, long-term absolute CVD risks were similar among FG categories below the threshold for diabetes for women, ~16%. For men, long-term risk for CVD was similar among FG categories <6.3 mmol/L, ~22%. We did observe that high normal FG was associated with higher long-term CVD risk compared with the lowest FG among men but not women. However, risk among middle-aged participants with diabetes was approximately twice as high as among those with the lowest glucose levels: 39% for women and 48% for men. This strongly supports current diabetes diagnostic thresholds and an emphasis for diabetes prevention among individuals with prediabetes (1). Among a subsample of participants with concomitant FG and HbA_{1c} data, the disparity in

Table 3—Long-term risk for incident CVD (including fatal and nonfatal CHD and fatal and nonfatal stroke, adjusted for competing risk of death) through 80 years of age according to 4-year change in FG category before 50 years of age

		30-year risk for incident CVD								
		CVD			CHD			Stroke		
4-year change category†	*N*	Events	Absolute risk, % (95% CI)‡	RR (95% CI)	Events	Absolute risk, % (95% CI)‡	RR (95% CI)	Events	Absolute risk, % (95% CI)‡	RR (95% CI)
Women										
Normal-normal	5,402	233	14.2 (11.5, 16.8)	Reference	130	7.4 (5.6, 9.1)	Reference	115	7.8 (5.5, 10.1)	Reference
Normal-IFG	1,291	75	16.9 (11.0, 22.9)	1.35 (1.05, 1.73)	53	12.0 (7.1, 16.9)	1.71 (1.25, 2.33)	25	5.8 (1.6, 9.9)	0.91 (0.59, 1.40)
Normal-diabetes	80	3	25.5 (0.0, 59.0)	0.87 (0.28, 2.66)	0	NA§	NA§	3	25.5 (0.0, 59.0)	1.76 (0.57, 5.42)
IFG-IFG	1,425	99	16.1 (8.0, 24.2)	1.61 (1.28, 2.02)	68	12.0 (3.9, 20.1)	1.98 (1.49, 2.64)	40	5.4 (2.8, 8.0)	1.32 (0.92, 1.88)
IFG-diabetes	293	31	35.7 (11.2, 60.2)	2.45 (1.72, 3.50)	19	27.8 (1.3, 54.3)	2.69 (1.69, 4.30)	16	11.8 (3.3, 20.4)	2.57 (1.54, 4.27)
Diabetes-diabetes	696	140	57.2 (43.0, 71.3)	4.66 (3.84, 5.66)	85	32.7 (22.6, 42.8)	5.07 (3.91, 6.59)	79	39.6 (21.9, 57.3)	5.33 (4.05, 7.02)
Men										
Normal-normal	2,815	215	23.4 (19.8, 27.0)	Reference	158	17.7 (14.4, 21.1)	Reference	69	7.3 (5.2, 9.4)	Reference
Normal-IFG	1,194	136	29.3 (23.4, 35.2)	1.49 (1.22, 1.83)	102	21.0 (16.2, 25.9)	1.52 (1.20, 1.93)	41	10.6 (5.7, 15.4)	1.40 (0.96, 2.05)
Normal-diabetes	61	6	42.8 (7.2, 78.3)	1.29 (0.60, 2.78)	5	40.6 (4.1, 77.2)	1.46 (0.62, 3.43)	3	10.9 (0.0, 22.9)	2.01 (0.65, 6.20)
IFG-IFG	1,835	232	29.8 (23.9, 35.6)	1.66 (1.39, 1.97)	180	24.2 (18.6, 29.7)	1.75 (1.42, 2.15)	64	7.9 (4.5, 11.3)	1.42 (1.02, 1.99)
IFG-diabetes	326	56	38.0 (24.6, 51.4)	2.25 (1.72, 2.95)	35	23.3 (11.4, 35.3)	1.91 (1.35, 2.71)	24	19.8 (10.0, 29.7)	3.00 (1.91, 4.71)
Diabetes-diabetes	652	162	55.5 (46.6, 64.3)	3.25 (2.70, 3.92)	114	42.6 (33.3, 51.9)	3.12 (2.49, 3.90)	58	19.9 (11.9, 28.0)	3.63 (2.59, 5.09)

NA, not applicable; RR, relative risk. †Normal: FG <5.6 mmol/L and HbA_{1c} <5.7 (<39 mmol/mol); IFG: FG 5.6–6.9 mmol/L or HbA_{1c} 5.7–6.4% (39–47 mmol/mol); and diabetes: FG ≥7.0 mmol/L or HbA_{1c} ≥6.5% (≥48 mmol/mol) or diabetes medication use. ‡Absolute risk estimates can account for competing risk of death but cannot adjust for covariates. §Risk estimates for CHD for women with 4-year change in group "normal-diabetes" were inestimable due to 0 events.

risk between individuals with the normal and prediabetes glucose levels compared with diabetes was even greater in magnitude. Second, greater 4-year change in glucose category before 50 years of age was associated with higher 30-year risk for CVD through 80 years of age. Although not statistically significant, we did observe qualitatively high risk for CVD for all groups who developed diabetes over 4 years before middle age compared with those who had normal glucose through 50 years of age. Third, the incidence of CVD, CHD, and stroke was higher for men than women. However, within sex groups, blacks and whites had similar risk for CVD by glucose level. Although a greater proportion of blacks had diabetes compared with whites, long-term CVD risks were similar among this group after accounting for competing risk of death. In contrast, black men with diabetes had greater long-term CVD risks compared with their white counterparts when not accounting for this competing risk of death. This methodological consideration is important in this analysis given that black men have significantly higher risk for death due to diseases of noncardiovascular origin relative to white men; notably, some of these are directly attributable to diabetes (i.e., diseases of the kidneys) (30).

The long-term risks for developing CVD according to diabetes status in the current study are 20% lower than previously reported in the original and offspring cohorts of the FHS. Lloyd-Jones et al. (2) observed that of the traditional CVD risk factors present at 50 years of age, the development of diabetes by this age was associated with the highest risk for CVD: 57% for women and 67% for men through 95 years of age from the combined cohorts. In the separate cohorts, diabetes by midlife was associated with higher risk for CVD among the original Framingham participants (risk of 67% for women and 78% for men) than among the offspring cohort (risk for women 49% and for men 62%) (3). In addition to demographic differences, longer follow-up and a broader definition for CVD events including intermittent claudication and congestive heart failure may contribute to differences in risk estimates compared with our current work (3). Further, trends in better CVD risk factor control and lower diabetes complications may

contribute to differences in findings (31). In contrast, our 30-year risk for CHD estimates for individuals with diabetes are 2.5 times higher than those observed by Turin et al. (32) among urban Japanese women at 10.1% (95% CI 1.6, 18.5) and men at 15.2% (95% CI 6.6, 23.8). We believe the differences in risk estimates are due to differences in CHD case definition and higher incidence of CHD in the U.S. study populations.

The results presented on change in FG and long-term absolute risk for CVD, CHD, and stroke are novel. We observed that changes in FG during middle age are associated with higher risk for CVD, most notably for individuals who develop diabetes, 1.5–4 (26–57%) times higher than individuals who are able to maintain FG below the threshold for diabetes (14–30%). The most striking finding was that men and women who were identified as having diabetes at multiple time points exceeded a 55% 20-year probability of developing CVD. In contrast to our hypothesis was the finding of similar long-term CVD risk for 4-year FG change groups that did not exceed the threshold for diabetes.

Prior studies have estimated the long-term absolute risk for CVD according to the presence or absence of diabetes at a single point in adulthood in racially homogenous cohorts of 5,000–11,000 individuals (2,3,32). The larger sample size of this current study allowed for multiple novel aspects including finer stratification by glucose level than previously reported and assessment of long-term absolute risks for CVD, CHD, and stroke according to change in glucose level during middle age. Another novel aspect to our work compared with prior studies is that we are the first to include both black and white Americans from varied geographic origin, which also provides more representative estimates. Limitations of this study also merit consideration. FG was used as the primary biochemical test to determine diabetes status. This may result in low sensitivity to detect hyperglycemia and misclassification of exposure and may bias our estimates toward the null. However, in a subsample with FG and HbA_{1c} data (given average FG over 90 days), we observed similar risk estimates between the normal group and and group with prediabetes. We lack data on glucose tolerance testing, which would improve the classification of exposure further. We pooled cohorts of various birth epochs and demographic makeup, and there is potential for heterogeneity in our estimates resulting from these differences. However, although diabetes prevalence may vary by cohort, and secular trends in treatment patterns occur, the relationship between glucose level and risk for CVD did not, and our findings were consistent across cohorts. We observed qualitative differences in long-term CVD risk according to category in FG change, but the magnitude of these differences did not reach statistical significance. This suggests that we may not have had adequate statistical power to detect an association and may contribute to nonsignificant differences reported in this study. Interpretation of our findings should be done with caution when small event numbers are present. Traditional adjustment approaches are not feasible with the absolute risk estimation methods used in this study, though we did present results stratified by important demographic characteristics and when accounting for the competing risk of non-CVD death. Further, we also present consistent findings when stratifying by the number of concurrent traditional CVD risk factors.

Conclusion

Our results suggest a threshold effect in glucose level for the long-term absolute risk for CVD, including both CHD and stroke. Long-term absolute risk for CVD was similar for middle-age adults who had glucose levels below diabetes diagnostic criteria and markedly higher for individuals with diabetes. Increases in glucose during middle age that include conversion to diabetes are associated with higher cardiovascular risk than maintaining or increasing glucose below the diabetes threshold. These data strongly support the monitoring of glucose levels during middle age and the importance of public health and clinical strategies that target prevention of incident diabetes by midlife.

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