

Cardiometabolic Risk in Impaired Fasting Glucose and Impaired Glucose Tolerance

The Atherosclerosis Risk in Communities Study

JAMES S. PANKOW, PHD¹
DAVID K. KWAN, MPH¹
BRUCE B. DUNCAN, MD, PHD^{2,3}
MARIA I. SCHMIDT, MD, PHD^{2,3}

DAVID J. COUPER, PHD⁴
SHERITA GOLDEN, MD⁵
CHRISTIE M. BALLANTYNE, MD⁶

OBJECTIVE — We compared and contrasted cardiovascular disease (CVD) risk factors, subclinical manifestations of CVD, incident coronary heart disease (CHD), and all-cause mortality by categories of impaired glucose regulation in nondiabetic individuals.

RESEARCH DESIGN AND METHODS — The study included 6,888 participants aged 52–75 years who had no history of diabetes or CVD. All-cause mortality and incident CHD were ascertained over a median of 6.3 years of follow-up.

RESULTS — Agreement between fasting and postchallenge glucose impairment was poor: 3,048 subjects (44%) had neither impaired fasting glucose (IFG) nor impaired glucose tolerance (IGT), 1,690 (25%) had isolated IFG, 1,000 (14%) had isolated IGT, and 1,149 (17%) had both IFG and IGT. After adjustment for age, sex, race, and center, subjects with isolated IFG were more likely to smoke, consume alcohol, and had higher mean BMI, waist circumference, LDL cholesterol, and fasting insulin and lower HDL cholesterol than those with isolated IGT, while subjects with isolated IGT had higher mean triglycerides, systolic blood pressure, and white cell counts. Measures of subclinical CVD and rates of all-cause mortality and incident CHD were similar in isolated IFG and isolated IGT.

CONCLUSIONS — Neither isolated IFG nor isolated IGT was associated with a more adverse CVD risk profile.

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Type 2 diabetes imposes an increased burden of atherosclerotic cardiovascular disease (CVD), particularly of the coronary arteries, peripheral arteries, and cerebrovascular system (1). However, evidence of CVD risk can also be traced to glucose regulation abnormalities antecedent to diabetes status (2,3). The American Diabetes Association (ADA)

and the World Health Organization both recognize “impaired” glucose categories, metabolic stages of glucose homeostasis intermediary between normal and diabetes (4,5). Impaired glucose tolerance (IGT) is defined by both organizations as a 2-h postchallenge glucose level ≥ 7.8 mmol/l (140 mg/dl) but < 11.1 mmol/l (200 mg/dl). Although both organiza-

tions originally defined impaired fasting glucose (IFG) as a fasting glucose level between 6.1 mmol/l (110 mg/dl) and 6.9 mmol/l (125 mg/dl) (4,5), the ADA recommended in 2003 that the lower cut point for IFG be reduced to 5.6 mmol/l (100 mg/dl) (6). Studies (7,8) in diverse populations worldwide have reported substantial disagreement between fasting and postchallenge glucose impairment categories, although few studies (9–13) have investigated the impact of the lower cut point of 5.6 mmol/l for IFG.

Possible differences in CVD morbidity and mortality between IFG and IGT remain unclear, although the current evidence indicates that IGT entails greater risk of CVD (2,14). The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) investigators pooled data from a large number of prospective studies conducted in Europe and found that 2-h glucose was a better predictor than fasting glucose for all-cause and CVD mortality (15,16). Individual prospective studies (17–22) have reported similar findings. None of these studies investigated the impact of the lower cut point of 5.6 mmol/l for IFG on the association between glucose impairment and CVD risk.

The purpose of this investigation was to compare and contrast CVD risk factors, subclinical manifestations of CVD, incident coronary heart disease (CHD), and all-cause mortality by categories of fasting and postchallenge glucose impairment in nondiabetic individuals. Special attention was given to direct comparisons of discordant categories (i.e., isolated IFG and isolated IGT), as such comparisons are more likely to reveal possible differences in the etiology and risk associated with fasting and postchallenge glucose impairment (23).

RESEARCH DESIGN AND METHODS

The Atherosclerosis Risk in Communities (ARIC) Study is a multicenter, prospective investigation of CVD risk factors, subclinical atherosclerosis, and clinical CVD end points. The study was initiated between 1987 and

From the ¹Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, Minnesota; the ²Graduate Studies Program in Epidemiology, School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil; the ³Department of Epidemiology, University of North Carolina, Chapel Hill, North Carolina; the ⁴Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina; the ⁵Departments of Medicine and Epidemiology, Johns Hopkins University, Baltimore, Maryland; and the ⁶Department of Medicine, Baylor College of Medicine, Houston, Texas.

Address correspondence and reprint requests to James S. Pankow, Division of Epidemiology and Community Health, University of Minnesota, 1300 South Second St., Suite 300, Minneapolis, MN 55454. E-mail: pankow@epi.umn.edu.

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Abbreviations: ADA, American Diabetes Association; ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CVD, cardiovascular disease; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IMT, intima-media thickness; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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1989 with 15,792 men and women, aged 45–64 years, drawn from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; the northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland (24). In addition to the baseline exam (visit 1), a total of three follow-up exams (visits 2–4) were conducted at ~3-year intervals.

A standardized oral glucose tolerance test (OGTT) was administered during visit 4 between 1996 and 1998. Of 11,656 subjects attending visit 4 (74% of the original cohort), 1,183 were ineligible for the OGTT because they reported pharmacological treatment for diabetes, 237 because they had not fasted at least 10 h before the OGTT was scheduled to begin, and 192 because they had partial removal of the stomach or small intestine or were on kidney dialysis. Of the eligible subjects, 9,126 (86%) were willing to participate in the OGTT. We excluded 107 subjects because of technical difficulties with the OGTT or glucose assays and 65 subjects because they had not fasted at least 8 h before the initial (fasting) blood draw. Participants were also excluded from this analysis if they had prevalent diabetes, based on 2-h postchallenge glucose ≥ 11.1 mmol/l or fasting glucose ≥ 7.0 mmol/l ($n = 1,153$) or self-reported physician diagnosis ($n = 34$). Subjects with a history of CHD ($n = 630$) or stroke or transient ischemic attacks ($n = 207$) were excluded based on self-report and active surveillance of the cohort for hospitalized events between visits 1 and 4. Due to insufficient numbers, 18 participants of racial/ethnic groups other than black or white were excluded as well as 24 black subjects in either the Minneapolis and Washington County centers. After all exclusions, 6,888 participants were available for this study.

CVD risk factors and glucose

Unless otherwise indicated, CVD risk factors were measured at visit 4. Cigarette smoking and alcohol drinking status were categorized as current and not current (former and never). Current use of lipid-lowering and antihypertensive medications was determined by questionnaire. Educational attainment was categorized dichotomously as no college versus some college based on interviews at visit 1. BMI was derived from measured height and weight, and waist circumference was measured at the umbilical level. Blood samples were drawn from an antecubital vein with minimal trauma at fasting and

2-h postchallenge. Glucose levels were determined by a hexokinase assay procedure. The reliability coefficient was 0.99 based on blinded duplicate samples collected from 430 ARIC subjects at visit 4. Total cholesterol (25) and triglycerides (26) were measured by enzymatic methods. HDL cholesterol was measured after dextran-magnesium precipitation of non-HDL cholesterol lipoproteins (27), and LDL cholesterol was estimated (28). Insulin was measured by enzyme-linked immunosorbent assay (Boehringer Mannheim, Indianapolis, IN). Blood pressure was measured three times using a random-zero sphygmomanometer. The mean of the last two measurements was used for analysis. White cell counts were determined by local reference laboratories using automated particle counters. Only the Forsyth County and Washington County field centers elected to measure white cell counts. For each subject, we determined the number of metabolic syndrome abnormalities based on the National Cholesterol Education Program Adult Treatment Panel III definition (29). We excluded elevated fasting glucose from these counts because it was used to classify subjects into glucose impairment categories that formed the basis for comparison.

Subclinical CVD

Mean intima-media thickness (IMT) and presence of atherosclerotic plaque were both ascertained by B mode ultrasound at six 1-cm segments of the carotid artery: the left and right internal, bifurcation, and common. Trained ultrasound readers evaluated carotid IMT (in millimeters) for each site and secondarily indicated whether there was presence of a lesion (plaque) at any site, based on published criteria (30). Measurements of IMT at all six carotid segments were not attained for every participant and were imputed by maximum likelihood methods. The number (percentage) of subjects with imputed values for zero, one, two, three, four, and five segments was 1,129 (28%), 1,008 (25%), 771 (19%), 594 (15%), 396 (10%), and 191 (5%), respectively. Details of the measurement and imputation methods are described elsewhere (31,32). Resting ankle and brachial blood pressure were measured using a DINAMAP 1846 SX automated oscillometric device (Critikon, Tampa, FL), respectively, in the prone and supine position. Ankle-brachial index was calculated from the average of two ankle systolic blood pressure

readings divided by the average of two brachial systolic blood pressure readings (33). Peripheral arterial disease was defined as ankle-brachial index of ≤ 0.9 for men and ≤ 0.85 for women (34). The ultrasound and ankle-brachial measurements were obtained on approximately half of the ARIC cohort at visit 4. Left ventricular hypertrophy was determined electrocardiographically by Cornell voltage criteria ≥ 28 mm for men and ≥ 22 mm for women (35,36).

All-cause mortality and incident CHD

Vital status was determined through annual follow-up contacts with cohort members and searches of local hospital records and the National Death Index. Incident CHD was determined by contacting participants annually to identify hospitalizations during the previous year and by surveying discharge lists from local hospitals and death certificates from state vital statistics offices for potential CVD events and validated by computer algorithm and physician review. Details on quality assurance for ascertainment and classification of CHD events have been published elsewhere (24,37). For this analysis, incident CHD was defined as definite or probable myocardial infarction, fatal CHD, or cardiac procedure. Follow-up time was computed as the time between visit 4 and the first event (i.e., death or incident CHD, depending on analysis), loss to follow-up, or 31 December 2003, whichever was earliest.

Statistical analysis

Data management and analysis were performed with SAS version 9.1 (SAS Institute, Cary, NC). Adjusted means of demographic and behavioral factors, physiologic factors, and subclinical disease measures among glucose impairment categories were determined by ANCOVA using the LS MEANS option in SAS PROC GLM. Multiple logistic regression was performed to obtain adjusted proportions for dichotomous risk factors. Cox proportional hazards regression was used to evaluate associations between glucose categories and all-cause mortality or incident CHD.

RESULTS— Among 6,888 participants, 47% (3,255) were white women, 36% (2,461) were white men, 11% (776) were black women, and 6% (396) were black men. Over half of the participants (56%) were classified as having IFG, IGT,

Table 1—Distribution of fasting and postchallenge glucose impairment by sex and race

| | Glucose category | | | | Total |
|-------------|------------------|---------------|---------------|------------|-------|
| | Normal* | Isolated IFG† | Isolated IGT‡ | IFG/IGT§ | |
| White women | 1,623 (50) | 502 (15) | 649 (20) | 481 (15) | 3,255 |
| Black women | 334 (43) | 199 (26) | 86 (11) | 157 (20) | 776 |
| White men | 940 (38) | 834 (34) | 242 (10) | 445 (18) | 2,461 |
| Black men | 151 (38) | 155 (39) | 24 (6) | 66 (17) | 396 |
| Total | 3,048 (44) | 1,690 (25) | 1,001 (14) | 1,149 (17) | 6,888 |

Data are n (%). *Fasting glucose <5.6 mmol/l and postchallenge glucose <7.8 mmol/l. †Fasting glucose between 5.6 and 6.9 mmol/l and postchallenge glucose <7.8 mmol/l. ‡Fasting glucose <5.6 mmol/l and postchallenge glucose between 7.8 and 11.0 mmol/l. §Fasting glucose between 5.6 and 6.9 mmol/l and postchallenge glucose between 7.8 and 11.0 mmol/l.

or both (Table 1). IFG ($n = 2,839$, 42%) was more common, overall, than IGT ($n = 2,150$, 31%), with isolated IFG much more common than isolated IGT (25 vs. 14%, respectively). There were substantial differences in the distribution of glucose categories by sex and race: for example, the ratio of isolated IFG to isolated IGT was considerably higher in black women (2.3), white men (3.4), and black men (6.5) compared with white

women (0.77). Kappa coefficients evaluating agreement between IFG and IGT categories were highest for black women (0.24), followed by white women (0.20), black men (0.15), and white men (0.14). Kappa coefficients were slightly lower when the higher 6.1 mmol/l cut point for fasting glucose was used to define IFG. The Pearson correlation coefficient between fasting and 2-h glucose was 0.27.

In general, subjects with both IFG

and IGT had a more adverse CVD risk factor profile than those with neither condition (Table 2). However, neither isolated IFG nor isolated IGT was associated with a consistently worse pattern of CVD risk factors. Subjects with isolated IFG were younger, on average, than subjects with isolated IGT. After adjusting for age, sex, race, and center, subjects with isolated IFG were more likely to smoke, consume alcohol, and had higher mean BMI,

Table 2—Adjusted means \pm SEs or percentages of CVD risk factors and subclinical disease by fasting and postchallenge glucose impairment

| Risk factor * | Glucose category | | | | P value¶ |
|--|-------------------|-------------------|-------------------|-------------------|----------|
| | Normal† | Isolated IFG‡ | Isolated IGT§ | IFG/IGT | |
| <i>n</i> | 3,048 | 1,690 | 1,001 | 1,149 | |
| Age (years) | 61.8 \pm 0.1 | 61.8 \pm 0.1 | 63.5 \pm 0.2 | 63.3 \pm 0.2 | <0.01 |
| Smoking (% current smokers) | 15.1 | 15.0 | 11.6 | 11.8 | 0.01 |
| Alcohol intake (% current drinkers) | 55.2 | 56.6 | 50.3 | 53.1 | <0.01 |
| Education (% some college) | 44.7 | 39.9 | 38.3 | 38.2 | 0.43 |
| BMI (kg/m ²) | 26.9 \pm 0.1 | 29.2 \pm 0.1 | 28.1 \pm 0.2 | 30.4 \pm 0.1 | <0.01 |
| Waist circumference (cm) | 96.5 \pm 0.2 | 102.8 \pm 0.3 | 100.3 \pm 0.4 | 105.9 \pm 0.4 | <0.01 |
| HDL cholesterol (mmol/l) | 1.40 \pm 0.01 | 1.31 \pm 0.01 | 1.36 \pm 0.01 | 1.23 \pm 0.01 | <0.01 |
| LDL cholesterol (mmol/l) | 3.16 \pm 0.02 | 3.33 \pm 0.02 | 3.14 \pm 0.03 | 3.24 \pm 0.03 | <0.01 |
| Triglycerides (mmol/l)# | 1.20 | 1.39 | 1.51 | 1.61 | <0.01 |
| Lipid-lowering medication (%) | 8.4 | 9.5 | 13.2 | 12.6 | <0.01 |
| Fasting glucose (mmol/l) | 5.12 \pm 0.01 | 5.86 \pm 0.01 | 5.18 \pm 0.01 | 6.00 \pm 0.01 | <0.01 |
| 2-h glucose (mmol/l) | 5.73 \pm 0.02 | 6.12 \pm 0.03 | 8.91 \pm 0.03 | 9.13 \pm 0.03 | <0.01 |
| Fasting insulin (pmol/l)# | 57.0 | 72.7 | 61.5 | 86.5 | <0.01 |
| Systolic blood pressure (mmHg) | 123.5 \pm 0.3 | 125.4 \pm 0.4 | 127.7 \pm 0.6 | 129.0 \pm 0.5 | <0.01 |
| Diastolic blood pressure (mmHg) | 70.7 \pm 0.2 | 71.1 \pm 0.2 | 71.3 \pm 0.3 | 72.1 \pm 0.3 | 0.63 |
| Antihypertensive medication (%) | 23.1 | 28.7 | 31.4 | 39.4 | 0.15 |
| Metabolic syndrome abnormalities** | 1.50 \pm 0.02 | 1.92 \pm 0.03 | 1.95 \pm 0.04 | 2.35 \pm 0.03 | 0.46 |
| White cell count (10 ⁹ cells/l)†† | 6.0 \pm 0.1 | 6.3 \pm 0.1 | 6.6 \pm 0.1 | 6.5 \pm 0.1 | <0.01 |
| Carotid IMT (mm)†† | 0.760 \pm 0.005 | 0.781 \pm 0.007 | 0.779 \pm 0.008 | 0.802 \pm 0.008 | 0.85 |
| Carotid plaque at any site (%)†† | 35.4 | 39.2 | 37.0 | 35.9 | 0.40 |
| Peripheral artery disease (%)†† | 4.3 | 5.3 | 4.0 | 3.5 | 0.25 |
| Left ventricular hypertrophy (%)†† | 1.8 | 2.3 | 3.2 | 3.3 | 0.27 |

*All means or proportions except age adjusted for age, sex, race, and center. †Fasting glucose <5.6 mmol/l and postchallenge glucose <7.8 mmol/l. ‡Fasting glucose between 5.6 and 6.9 mmol/l and postchallenge glucose <7.8 mmol/l. §Fasting glucose <5.6 mmol/l and postchallenge glucose between 7.8 and 11.0 mmol/l. ||Fasting glucose between 5.6 and 6.9 mmol/l and postchallenge glucose between 7.8 and 11.0 mmol/l. ¶Test for difference in mean or percentage between isolated IFG and isolated IGT. #Geometric means. **Number of metabolic syndrome abnormalities (between 0 and 4), excluding elevated fasting glucose. ††Only measured on a subset of subjects at visit 4. Sample sizes are 3,587 for white cell count, 4,089 for carotid IMT, 3,716 for carotid plaque, 3,895 for peripheral artery disease, and 4,950 for left ventricular hypertrophy.

Table 3—All-cause mortality and CHD incidence by fasting and postchallenge glucose impairment

| Outcome | Glucose category | | | |
|---------------------------------|------------------|------------------|------------------|------------------|
| | Normal* | Isolated IFG† | Isolated IGT‡ | IFG/IGT§ |
| All-cause mortality | | | | |
| Deaths | 135 | 81 | 56 | 61 |
| Person-years | 19,417 | 10,697 | 6,298 | 7,201 |
| Rate (per 1,000 person-years) | 7.0 | 7.6 | 8.9 | 8.5 |
| Hazard ratio (95% CI), model 1 | 1.00 (reference) | 0.92 (0.70–1.22) | 1.19 (0.87–1.63) | 0.98 (0.72–1.32) |
| Hazard ratio (95% CI), model 2¶ | 1.00 (reference) | 0.93 (0.70–1.24) | 1.16 (0.83–1.60) | 1.03 (0.75–1.42) |
| Incident CHD | | | | |
| Events | 151 | 104 | 46 | 73 |
| Person-years | 18,984 | 10,359 | 6,185 | 6,988 |
| Rate (per 1,000 person-years) | 8.0 | 10.0 | 7.4 | 10.4 |
| Hazard ratio (95% CI), model 1 | 1.00 (reference) | 1.02 (0.79–1.31) | 0.94 (0.67–1.31) | 1.14 (0.86–1.51) |
| Hazard ratio (95% CI), model 2¶ | 1.00 (reference) | 0.87 (0.67–1.12) | 0.83 (0.59–1.17) | 0.90 (0.66–1.21) |

*Fasting glucose <5.6 mmol/l and postchallenge glucose <7.8 mmol/l. †Fasting glucose between 5.6 and 6.9 mmol/l and postchallenge glucose <7.8 mmol/l. ‡Fasting glucose <5.6 mmol/l and postchallenge glucose between 7.8 and 11.0 mmol/l. §Fasting glucose between 5.6 and 6.9 mmol/l and postchallenge glucose between 7.8 and 11.0 mmol/l. ||Adjusted for age, sex, race, and center. ¶Adjusted for model 1 variables and smoking status, hypertension, LDL cholesterol, HDL cholesterol, triglycerides, use of lipid-lowering medications, BMI, and waist circumference.

waist circumference, LDL cholesterol, and fasting insulin and lower HDL cholesterol than those with isolated IGT. By contrast, subjects with isolated IGT had higher triglyceride levels, systolic blood pressure, white cell counts, and were more likely to use lipid-lowering medications than those with isolated IFG. Further adjustment for BMI and waist circumference did not substantially change the patterns of nonanthropometric risk factors across glucose impairment categories (data not shown). There were no material differences between men and women or between whites and blacks in the relation between glucose categories and CVD risk factors (data not shown). Subclinical manifestations of CVD were generally similar between glucose categories. Mean common carotid IMT and the proportions with carotid plaque, peripheral artery disease, or left ventricular hypertrophy did not differ significantly between isolated IFG and isolated IGT.

Among 6,888 participants there were 333 deaths and 374 incident CHD events over a median of 6.3 years of follow-up. Subjects in the four glucose categories had similar rates of death and incident CHD in minimally adjusted and more fully adjusted models (Table 3). Neither fasting glucose level (hazard ratio per 1 SD increment: 0.98 [95% CI 0.88–1.10]) nor postchallenge glucose level (hazard ratio per 1 SD: 1.03 [0.92–1.14]) was associated with all-cause mortality in a minimally adjusted model that included the glucose measures as continuous variables (data not shown). Similarly, neither fast-

ing glucose (hazard ratio per 1 SD: 1.07 [0.97–1.19]) nor postchallenge glucose (hazard ratio per 1 SD: 1.07 [0.96–1.18]) was associated with incident CHD in a minimally adjusted model. Addition of a quadratic term for fasting glucose or postchallenge glucose did not improve the fit of models for all-cause mortality or incident CHD ($P > 0.10$). Hazard ratios for glucose impairment categories were not consistently higher or lower in analyses restricted to the first 3 years of follow-up and analyses excluding the first 3 years (data not shown). Associations between IFG and IGT categories and total mortality or incident CHD were similar across strata of potential effect modifiers including sex, race, age (< or ≥ 65 years), and BMI (< or ≥ 30 kg/m²) (data not shown).

Reanalyses using the old ADA criteria for IFG (cut point 6.1 mmol/l) led to reclassification of nearly one-third of the subjects, with 4,382 classified as normal (versus 3,048 under the newer criteria), 356 as isolated IFG (1,690 under the newer criteria), 1,735 as isolated IGT (1,001 under the newer criteria), and 415 as IFG/IGT (1,149 under the newer criteria). However, patterns of association between categories of glucose regulation and CVD risk factors, subclinical disease, all-cause mortality, and incident CHD were largely similar under the older and newer criteria. For example, hazard ratios for incident CHD (model 2) were 1.14 (95% CI 0.77–1.70) for isolated IFG, 0.94 (0.73–1.21) for isolated IGT, and 0.94 (0.62–1.43) for IFG/IGT when the older criteria were used.

CONCLUSIONS — We observed poor agreement between IFG and IGT using current ADA definitions for glucose impairment in nondiabetic individuals. Approximately 39% of subjects in the ARIC cohort without diabetes or a history of CVD were discordant on glucose impairment categories (i.e., isolated IFG or isolated IGT). In cross-sectional analysis, subjects with combined glucose impairment (IFG/IGT) had the least favorable pattern of CVD risk factors. Isolated IFG and isolated IGT had differing patterns of risk factors, but neither category had a consistently worse CVD risk profile or excess of metabolic syndrome abnormalities. Measures of subclinical CVD and rates of all-cause mortality and incident CHD did not differ significantly between isolated IFG and isolated IGT.

In 2003 the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recommended that the cut point for IFG be lowered from 6.1 to 5.6 mmol/l (6). The primary rationale for the change was to make the sensitivity and specificity of IFG similar to that of IGT in predicting future risk of type 2 diabetes (6,38). The change has been controversial (9,38–42). Population-based data from the U.S. and other countries indicate that the prevalence of IFG increased two- to fourfold upon application of the new criteria (9,12,39,43,44), with the largest increases in IFG in younger age-groups (39). A recent report from the National Health and Nutrition Examination Survey 1999–2002 estimated that 26 million U.S. adults have IFG using the lower cut

point (45). In the present study, the overall prevalence of isolated IFG was higher than the prevalence of isolated IGT among subjects without a history of CVD, suggesting that the new definition of IFG does not necessarily produce equivalent numbers of subjects in the IFG and IGT categories. Furthermore, the lower cut point for IFG produced only slightly better agreement between IFG and IGT categories.

The prevalence of isolated IFG and isolated IGT differed by sex and, to a lesser extent, by race. More specifically, isolated IFG was more common than isolated IGT among black men and women and white men but not among white women. Studies with the higher (11,46) and lower (11,13) cut point for IFG have reported, at least in relative terms, that women are more likely to have isolated IGT and men are more likely to have isolated IFG. Whether there are important differences according to race or ethnicity is less clear. Based on World Health Organization definitions, IGT was more common than IFG in both non-Hispanic white and non-Hispanic black subjects in the U.S., but discrepancies between IGT prevalence and IFG prevalence were most evident in non-Hispanic white women (47).

Cross-sectional studies (11,13,48–51), most using the higher IFG cut point, have found inconsistent differences in CVD risk factors between isolated IFG and isolated IGT categories. Although we found statistically significant differences between isolated IFG and isolated IGT for most CVD risk factors, absolute differences were generally small and not consistently higher in one category or the other. An Expert Consensus Workshop of the International Diabetes Federation recently concluded that IFG is characterized by raised hepatic glucose output and deficits in early insulin secretion, while IGT is characterized by peripheral insulin resistance (2). Data from the present study suggest that subjects with IFG are more insulin resistant if fasting insulin is interpreted as a surrogate measure of insulin resistance. However, studies using direct measures of insulin resistance (i.e., euglycemic-hyperinsulinemic clamp or frequently sampled intravenous glucose tolerance test) have found that subjects with isolated IGT have similar (51), if not greater (48,50), deficiencies in insulin action compared with subjects with isolated IFG.

Neither isolated IFG nor isolated IGT

was more strongly associated with measures of subclinical CVD in the ARIC cohort. Our data appear to contrast with that of the RIAD (Risk Factors in IGT for Atherosclerosis and Diabetes) Study, which found that carotid IMT was more strongly associated with IGT than IFG in middle-aged subjects (52). We are unsure why patterns of association between IFG, IGT, and carotid IMT differ in the two studies. Associations between fasting glucose and carotid IMT among nondiabetic subjects were weak in ARIC at visit 1 (53); our data corroborate those earlier findings.

Unlike the present study, a meta-regression analysis of 20 prospective studies found a significant graded relationship between CVD events and glucose level, both fasting and postchallenge (3). Some studies (44,54,55) have reported a J-shaped relation between fasting or 2-h postchallenge glucose and CVD or total mortality, with subjects having the lowest glucose levels having slightly increased risk relative to those in low-normal categories. However, the lack of association between fasting glucose and incident CHD in our study is consistent with earlier reports from the ARIC cohort. In one analysis, fasting glucose levels <6.4 mmol/l at the baseline exam (visit 1) were not associated with incident CHD over 4–7 years of follow-up (56). In another analysis, fasting glucose measured at visit 2 was not associated with incident CHD over 8–10 years of follow-up among nondiabetic subjects (57). By contrast, A1C levels $>4.6\%$ at visit 2 demonstrated a positive, graded association with incident CHD among individuals without diabetes (57).

It is unclear why the present study failed to find an association between postchallenge glycemia and all-cause mortality or incident CHD that has been reported elsewhere (13,15–22,58,59). The median follow-up of 6.3 years may have been too short for an association to emerge, as many earlier studies had longer follow-up for nonfatal and fatal outcomes. In the Whitehall Study of British men, decreased survival among glucose-intolerant subjects only became apparent between 5 and 10 years of follow-up (58). However, in an analysis of 14 European cohorts by the DECODE group, hazard ratios for CVD death associated with IGT and/or IFG were lower after 10 years of follow-up compared with 5 years of follow-up (60). It is possible that in studies with longer follow-up, a high proportion of individuals with IGT

at baseline develop diabetes as an intermediate condition before onset of CHD or death. Associations between baseline IGT and these long-term outcomes may therefore be explained by greater risk of diabetes among those with IGT. However, development of diabetes during follow-up was not found to be an intermediate factor linking baseline IGT and incident CHD in a Finnish cohort study (61).

Approximately 14% of subjects without prevalent CVD and diabetes were excluded from our analysis for other reasons, mainly because they refused the OGTT. Our results may have underestimated the association between glucose impairment and all-cause mortality or incident CHD if subjects with glucose impairment who developed these outcomes were more likely to be excluded. Subjects who were excluded were more likely to be African American and smoke and had lower BMI, higher HDL cholesterol, and higher systolic blood pressure than those not excluded. After adjusting for age, sex, race, and center, subjects who were excluded had higher rates of all-cause mortality (hazard ratio 1.53 [95% CI 1.21–1.94]) but similar rates of incident CHD (1.16 [0.88–1.52]) compared with subjects not excluded. However, mean fasting glucose was similar in excluded subjects compared with those not excluded, and the magnitude of association between fasting glucose and all-cause mortality or incident CHD was similar in the two groups, suggesting that the results are representative for all subjects in the cohort without CVD and diabetes.

Possible differences in the etiology and long-term risk associated with IFG and IGT are important to delineate in light of the population impact of CVD morbidity and mortality and inconsistent use of the OGTT in clinical settings. However, neither IFG nor IGT were important predictors of incident CHD or all-cause mortality in the ARIC cohort. The relatively poor agreement between fasting and postchallenge glucose levels and differing patterns of association with CVD risk factors suggest that IFG and IGT do not represent metabolically equivalent categories.

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