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Impact of Impaired Fasting Glucose on Cardiovascular Disease

The Framingham Heart Study

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Objectives We sought to determine whether impaired fasting glucose (IFG) predicts cardiovascular disease (CVD) events.

Background It is unclear which glucose threshold should define prediabetes. We compared the 1997 and 2003 American Diabetes Association (ADA) definitions of IFG to predict CVD.

Methods Framingham offspring participants free of CVD, categorized by the 1997 ADA IFG definition (fasting plasma glucose 110 to 125 mg/dl; 6.1 to 6.9 mmol/l) or the 2003 definition (100 to 125 mg/dl; 5.6 to 6.9 mmol/l), were followed from 1983 to 2004. Pooled logistic regression was used to calculate multivariable-adjusted odds ratios (ORs) for incident coronary heart disease (CHD; 291 events) or CVD (423 events).

Results Four-year CHD event rates among women were 1.3% (100 to 109 mg/dl), 2.3% (110 to 125 mg/dl), and 2.9% (diabetes); whereas corresponding rates in men were 2.9%, 3.0%, and 8.7%. For the 2003 IFG definition, the OR for CHD among women was 1.7 (95% confidence interval [CI] 1.0 to 3.0, $p = 0.048$), whereas for the 1997 IFG definition, the OR for CHD in women was 2.2 (95% CI 1.1 to 4.4, $p = 0.02$), which was almost as high as for women with diabetes (OR 2.5, 95% CI 1.2 to 5.2, $p = 0.01$). For CVD, only the 1997 IFG definition yielded significantly greater odds of CVD in women (OR 2.1, 95% CI 1.2 to 3.6, $p = 0.01$). Men were not at increased odds of developing CVD or CHD by either definition.

Conclusions In women, both IFG definitions were associated with increased CHD risk, whereas neither IFG definition identified men at increased short-term risk for CHD or CVD. The finding that women with FPG 110 to 125 mg/dl had similar CHD risk compared with women with diabetes suggests that CHD risk in women may be elevated at a lower glucose level than for men. (J Am Coll Cardiol 2008;51:264–70) © 2008 by the American College of Cardiology Foundation

It has been recognized that prediabetic hyperglycemia confers an increased risk for cardiovascular disease (CVD) (1,2). In 1997, the American Diabetes Association (ADA) introduced the concept of impaired fasting glucose (IFG), a prediabetic state initially defined by fasting plasma glucose (FPG) of 110 to 125 mg/dl (6.1 to 6.9 mmol/l), in which those afflicted were significantly more likely to develop diabetes (3–5). The risk of developing CVD was not considered in establishing criteria for IFG.

Since the introduction of the concept of IFG, there has been considerable debate regarding where the lower limit should be set to achieve a reasonable balance between sensitivity and specificity for diabetes prediction. In 2003, the ADA lowered its threshold for diagnosis of IFG from 110 mg/dl (6.0 mmol/l) to 100 mg/dl (5.6 mmol/l) on the basis of evidence in selected samples that suggested diabetes prediction may be optimized at a lower threshold (6). The effect of this lowered cut point is that a much larger proportion of the population is now considered to have IFG. Using data from the Third National Health and Nutrition Examination Survey, Benjamin et al. (7) found that the prevalence of IFG among adults was estimated to increase from 8.3% to 30.2%.

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Since the publication of the 2003 IFG guidelines, relatively few studies have examined the impact of the 2003 IFG definition on CVD risk, and none have found a relation between FPG 100 to 125 mg/dl (5.6 to 6.9 mmol/l) and increased CVD risk or mortality (8–12). However, these studies have been limited by examination of samples with limited generalizability (9–11), relatively small samples with few CVD events during follow-up period (8), and potential inclusion of participants who develop diabetes in the IFG category (9,12).

Thus, on the basis of available data, it is uncertain whether the 2003 ADA definition of IFG offers improved risk prediction regarding cardiovascular disease as compared with the 1997 IFG definition. Therefore, the primary aims of this analysis were to characterize the new 2003 ADA definition of IFG in the Framingham Offspring study by examining incident CVD events as compared with the 1997 IFG definition. We also assessed the risk of developing diabetes based on the 2 IFG definitions.

Abbreviations and Acronyms

ADA = American Diabetes Association
BMI = body mass index
CHD = coronary heart disease
CI = confidence interval
CVD = cardiovascular disease
FPG = fasting plasma glucose
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
OR = odds ratio
TIA = transient ischemic attack

Methods

Study sample. Participants for this study were drawn from the Framingham Offspring cohort. The design and inclusion criteria of the Framingham Heart Study have been described elsewhere (13). The current investigation included offspring participants who attended examinations (referred to as index examinations) in 1983 to 1987 (cycle 3), 1987 to 1991 (cycle 4), 1991 to 1995 (cycle 5), and 1995 to 1998 (cycle 6). Participants could contribute information to more than one examination cycle provided they reached the next examination cycle free of an outcome event of interest. All participants with CHD or CVD at the index examinations were excluded from further analyses. Participants were followed in approximately 4-year intervals, and events were accrued through December 31, 2004. Overall, 4,138 unique individuals contributed a total of 13,273 person-exams for analyses of incident CHD, and 4,058 unique individuals contributed 12,918 person-exams for analyses of incident CVD. For analyses involving incident diabetes, a total of 3,634 unique individuals free of diabetes and CHD at baseline were followed until diabetes or examination cycle 7 (1998 to 2001) contributing a total of 11,325 person-exams. The Institutional Review Board at Boston Medical Center approved the study protocol, and all participants gave written informed consent.

Baseline measurements and definitions. All Framingham clinic visits include a physician interview, physical examination, and laboratory tests. Participants who had a fasting plasma glucose ≥126 mg/dl (>7.0 mmol/dl) or were on insulin or oral hypoglycemic agents were considered to have diabetes. The 1997 ADA guidelines defined IFG as a FPG concentration of 110 to 125 mg/dl (6.1 to 6.9 mmol/l) (14), whereas the 2003 ADA guidelines define IFG as 100 to 125 mg/dl (5.6 to 6.9 mmol/l) (6).

Outcome ascertainment. The primary outcomes of interest were CHD, CVD, and diabetes. Coronary heart disease included cases of myocardial infarction, stable and unstable angina pectoris, and CHD death (15). Cardiovascular disease was defined as any CHD event, stroke, transient ischemic attack (TIA), intermittent claudication, congestive heart failure, or CVD death. Diabetes was defined as described previously in the previous section. A panel of 3 physicians reviewed each CHD and CVD event and adjudicated the end point according to pre-established criteria (16).

Covariates. Covariates were assessed and updated at all index examinations. Covariates included age, systolic blood pressure, hypertension treatment, total cholesterol to high-density lipoprotein cholesterol ratio, cigarette smoking within the past year, and body mass index (BMI). For incident diabetes, covariates were age, cigarette smoking within the past year, and BMI. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current treatment with antihypertensive medications. Current smoking was defined as at least 1 cigarette per day within 1 year of the index examination. Weight, measured to the nearest pound, was obtained with the participant wearing a gown without slippers or shoes. The BMI was calculated by dividing weight (kilograms) by square of height (meters^2).

Statistical analysis. A significant gender interaction was observed when age–gender-adjusted models were fit with an IFG-by-gender interaction. Therefore, all subsequent analyses were gender-specific.

All individuals with CHD or CVD at each index examination were excluded. Three separate models were used to examine incident CHD and CVD: 1) To examine the impact of the 1997 IFG definition on CHD and CVD risk, we compared FPG 110 to 125 mg/dl (6.1 to 6.9 mmol/l) to a referent group of FPG <110 mg/dl (<6.1 mmol/l). 2) To examine the impact of the 2003 IFG definition on CHD and CVD risk, we compared FPG 100 to 125 mg/dl (5.6 to 6.9 mmol/l) to a referent group of FPG <100 mg/dl (<5.6 mmol/l). 3) To directly compare the categorization and performance of the 1997 and 2003 IFG definitions, a multicategory model was created comparing both FPG 100 to 109 mg/dl (5.6 to 6.0 mmol/l) and 110 to 125 mg/dl (6.1 to 6.9 mmol/l) to a referent group of FPG <100 mg/dl (<5.6 mmol/l). This model ensured that the same referent group would be used to compare individuals in the 100 to 109 mg/dl category with those in the 110 to 125 mg/dl category.

JACC Vol. 51, No. 3, 2008
January 22, 2008:264–70

Table 1 Baseline Characteristics of Cohort*

Characteristic	Women (n = 2,163)	Men (n = 1,895)
Age, yrs	48 (10)	49 (10)
Glucose, mmol/l	5.1 (1.2)	5.4 (1.4)
Current smoker, %	29	28
Body mass index, kg/m^2	25.6 (5.4)	27.3 (3.9)
Systolic blood pressure, mm Hg	122 (18)	127 (16)
Hypertension treatment, %	14	16
Hypertension, %	26	35
Total/high-density lipoprotein cholesterol, ratio	4.0 (1.4)	5.0 (1.6)

Values are mean (SD) or percent. *Data represent unique individuals based on first exam attended and is based on the sample free of cardiovascular disease (n = 4,058).

For analyses of diabetes prediction, individuals with diabetes at each index examination were excluded and 3 similar models (1 to 3 as described in the previous paragraph) were constructed. Age-adjusted incidence rates of CHD, CVD, and diabetes were calculated for each FPG group (17). Pooled logistic regression was used to calculate the odds of developing CHD, CVD, or diabetes over the follow-up intervals using SAS version 9.1 (SAS Institute, Cary, North Carolina) (18). Pooled logistic regression has been shown to provide estimates similar to those generated from time-dependent Cox regression analysis (19).

Models were initially age-adjusted and then adjusted for covariates for each end point. To compare the predictive capacity of the 2003 versus 1997 IFG definition, we examined the c-statistics of all multivariable models. The c-statistic is a measure of model discrimination or concordance between the predictions and outcomes (20). Crude Kaplan-Meier curves were constructed using time to CVD stratified by glycemic category (FPG <100 mg/dl; 100 to 109 mg/dl; 110 to 125 mg/dl; diabetes).

Results

The overall sample (n = 4,058) consisted of 53% women, and the mean age was 49 years (Table 1).

Impact of the IFG definition on incident CHD and CVD. The 4-year rates of developing CHD are presented in Table 2. There were 291 cases of incident CHD. Four-year CHD event rates among women were 1.3% (100 to 109 mg/dl), 2.3% (110 to 125 mg/dl), and 2.9% (diabetes), whereas corresponding rates in men were 2.9%, 3.0%, and 8.7%. The odds ratio for CHD in women for the 2003 definition was 1.7 (95% confidence interval [CI] 1.0 to 3.0)

Table 2 4-Year Age-Adjusted Event Rates of CHD, CVD, and Diabetes by Baseline Glycemic Status Category

	Multicategory Model (mg/dl)			
Outcome	≤99	100 to 109	110 to 125	Diabetes
Any CHD event				
Women				
Events, n	39	14	12	13
Person-exams, n	5,563	882	365	318
4-year event rate (%) with 95% CI	0.8 (0.5–1.1)	1.3 (0.7–2.2)	2.3 (1.3–4.3)	2.9 (1.6–5.3)
Men				
Events, n	106	38	19	50
Person-exams, n	3,960	1,235	516	434
4-year event rate (%) with 95% CI	2.9 (2.3–3.7)	2.9 (2.0–4.0)	3.0 (1.9–4.8)	8.7 (6.4–11.7)
Any CVD event				
Women				
Events, n	71	19	18	20
Person-exams, n	5,457	850	352	299
4-year event rate (%) with 95% CI	1.4 (1.1–1.9)	1.8 (1.1–2.9)	3.6 (2.2–5.9)	4.8 (3.0–7.6)
Men				
Events, n	138	60	31	66
Person-exams, n	3,876	1,198	495	391
4-year event rate (%) with 95% CI	3.9 (3.2–4.8)	4.6 (3.5–6.0)	5.0 (3.4–7.1)	12.5 (9.7–16.0)
Diabetes				
Women				
Events, n	17	31	87	—
Person-exams, n	5,049	780	317	—
4-year event rate (%) with 95% CI	0.3 (0.2–0.6)	4.0 (2.7–6.0)	27.8 (21.6–35.1)	—
Men				—
Events, n	23	52	92	—
Person-exams, n	3,608	1,129	442	—
4-year event rate (%) with 95% CI	0.6 (0.4–1.0)	4.5 (3.3–6.1)	20.0 (15.8–25.1)	—

CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease.

Table 3 Odds Ratios and 95% Confidence Intervals by Glucose Subgroup for 4-Year Incidence of CHD According to 1997 and 2003 IFG Definitions

	Multicategory Model (mg/dl)*						2003 IFG (mg/dl)*		1997 IFG† (mg/dl)	
	100 to 109	p Value	110 to 125	p Value	Diabetes	p Value	100 to 125	p Value	110 to 125	p Value
Women										
Age-adjusted	1.7 (0.9–3.1)	0.11	3.1 (1.6–6.1)	0.001	4.0 (2.1–7.6)	<0.001	2.1 (1.3–3.5)	0.005	2.7 (1.4–5.2)	0.002
MV-adjusted‡	1.4 (0.7–2.7)	0.30	2.5 (1.2–5.0)	0.01	2.5 (1.2–5.2)	0.01	1.7 (1.0–3.0)	0.048	2.2 (1.1–4.4)	0.02
Men										
Age-adjusted	1.0 (0.7–1.4)	0.92	1.0 (0.6–1.7)	0.91	3.2 (2.2–4.6)	<0.001	1.0 (0.7–1.4)	0.99	1.0 (0.6–1.7)	0.89
MV-adjusted‡	0.9 (0.6–1.4)	0.66	0.9 (0.5–1.5)	0.60	2.6 (1.7–3.8)	<0.001	0.9 (0.6–1.3)	0.55	0.9 (0.5–1.5)	0.67

*Referent group is <100 mg/dl (<5.6 mmol/l). †Referent group is <110 mg/dl (<6.1 mmol/l). ‡Covariates: age, systolic blood pressure, hypertension treatment, total cholesterol/high-density lipoprotein ratio, current smoking, and body mass index.

CHD = coronary heart disease; IPG = impaired fasting glucose; MV = multivariable.

and for the 1997 definition was 2.2 (95% CI 1.1 to 4.4) (Table 3). In the multicategory model, women with FPG 110 to 125 mg/dl (6.1 to 6.9 mg/dl) had a 2.5-fold increased odds ratio (OR) of CHD (95% CI 1.2 to 5.0, p = 0.01), whereas women with FPG 100 to 109 mg/dl (5.6 to 6.0 mmol/l) had a nonsignificantly increased OR of CHD (OR 1.4, 95% CI 0.7 to 2.7, p = 0.30), suggesting that much of the increase in CHD is driven primarily by those with FPG 110 to 125 mg/dl (6.1 to 6.9 mmol/l). Among women with FPG 110 to 125 mg/dl, the OR was similar to the OR for CHD in women with diabetes (OR 2.5, 95% CI 1.2 to 5.2, p = 0.01). The c-statistic was essentially unchanged between models based on the 1997 versus the 2003 IFG definition (0.798 vs. 0.800, respectively).

In men, there was no significant difference in the OR of developing CHD among those categorized by either the 1997 IFG definition or the 2003 IFG definition (Table 3). There was a significant gender interaction with incident CHD (p = 0.04), indicating that the OR of developing CHD in women was significantly greater than for men.

Similar trends were observed for CVD (Table 4) (423 incident events). The OR for CVD in women for the 2003 definition was 1.4 (95% CI 0.9 to 2.1) and for the 1997 definition was 2.1 (95% CI 1.2 to 3.6) (Table 4). In the multicategory model for women, no significantly increased OR was observed in the 100 to 109 mg/dl (5.6 to 6.0 mmol/l) group, whereas significantly increased OR were observed among women with FPG 110 to 125 mg/dl (6.1 to 6.9 mmol/l). The multivariable-adjusted c-statistics for the 1997 and 2003 definitions were similar (0.785 vs. 0.787, respectively).

In men, there was no significant difference in the OR of developing CVD in those with IFG as categorized by either the 1997 definition or 2003 definition; similar results were observed in the multicategory model (Table 4). The multivariable-adjusted c-statistics were identical for the 1997 and 2003 definitions (0.763). The formal sex-interaction was not significant (p = 0.19), although the trends observed were overall similar to the CHD results. The results are presented as Kaplan-Meier curves in Figure 1.

Impact of the IFG definition on incident diabetes. The 4-year age-adjusted rates of developing diabetes by glycemic category are presented in Table 2. Among women, the OR of developing diabetes was elevated in multivariable-adjusted models for both the 1997 and 2003 definitions (Table 5). Among men, the differences between the 1997 and 2003 definitions were less striking than in women (Table 5).

Secondary analyses. When glucose was modeled as a continuous variable, for CVD, significant results were observed for women (p = 0.007) as well as for men (p = 0.0001). However, when individuals with diabetes were excluded from the models, results were no longer significant (women p = 0.16; men p = 0.89). For CHD, similar findings were observed (data not shown). Additional adjustment for triglycerides in men did not result in any material changes to the results (data not shown).

Table 4 Odds Ratios and 95% Confidence Intervals by Glucose Subgroup for 4-Year Incidence of Cardiovascular Disease According to 1997 and 2003 IFG Definitions

	Multicategory Model, mg/dl*						2003 IFG, mmol/l*		1997 IFG, mmol/l†	
	100 to 109	p Value	110 to 125	p Value	Diabetes	p Value	100 to 125	p Value	110 to 125	p Value
Women										
Age-adjusted	1.3 (0.8–2.1)	0.38	2.6 (1.5–4.5)	<0.001	3.6 (2.1–6.0)	<0.001	1.7 (1.1–2.5)	0.01	2.5 (1.5–4.2)	<0.001
MV-adjusted‡	1.1 (0.6–1.8)	0.84	2.1 (1.2–3.7)	0.01	2.3 (1.3–4.1)	0.007	1.4 (0.9–2.1)	0.16	2.1 (1.2–3.6)	0.01
Men										
Age-adjusted	1.2 (0.9–1.6)	0.32	1.3 (0.8–1.9)	0.25	3.6 (2.6–5.0)	<0.001	1.2 (0.9–1.6)	0.19	1.2 (0.8–1.8)	0.35
MV-adjusted‡	1.1 (0.8–1.5)	0.51	1.0 (0.7–1.6)	0.85	2.8 (2.0–4.0)	<0.001	1.1 (0.8–1.4)	0.56	1.0 (0.7–1.5)	0.98

*Referent group is <5.6 mmol/l (<100 mg/dl). †Referent group is <6.1 mmol/l (<110 mg/dl). ‡Covariates: age, systolic blood pressure, hypertension treatment, total cholesterol/HDL ratio, current smoking, and BMI.

Abbreviations as in Table 3.

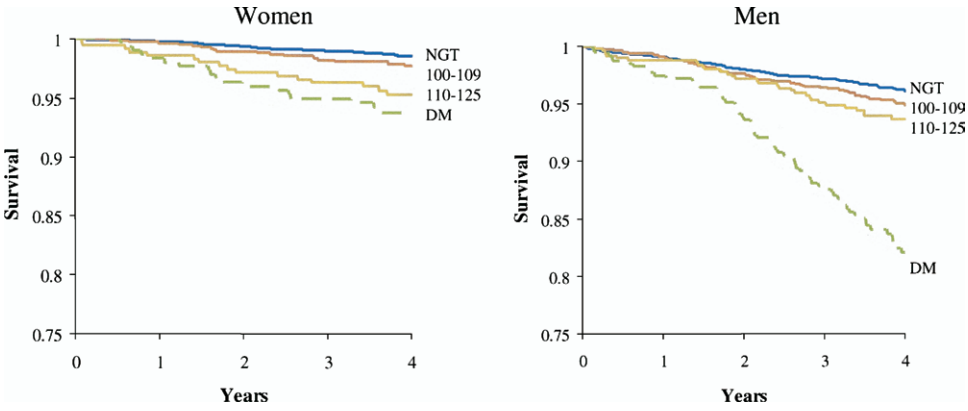

Figure 1 Kaplain-Meier Plots of CVD-Free Survival by Glycemic Category

CVD = cardiovascular disease; DM = diabetes mellitus; NGT = normal glucose tolerance; 100–109 = 100 to 109 mg/dl; 110–125 = 110 to 125 mg/dl.

Discussion

Principal findings. The 1997 and 2003 IFG definitions are predictive of CHD in women but not in men. The odds of developing CHD among women with IFG in the 110 to 125 mg/dl (6.1 to 6.9 mmol/l) range approach the risk conferred by having diabetes. C-statistics were essentially unchanged between the 1997 and 2003 IFG definitions, suggesting no improvement in overall risk prediction when one uses the new IFG definition. For CVD, only the 1997 IFG definition was associated with a statistically significant increased odds among women, whereas no increased odds of CVD was observed in men for either IFG definition. Ultimately, however, men have greater absolute rates of events as compared with women. With respect to diabetes, the 1997 IFG definition is associated with a greater risk of developing diabetes compared with the 2003 IFG definition.

A possible explanation for the difference between CVD and CHD is that the CHD end point contains primarily hard diagnoses that are known to be highly associated with diabetes and pre-diabetes, such as myocardial infarction, whereas CVD contains end points which are potentially more heterogeneous, such as intermittent claudication and TIA. Nonetheless, women in our sample with FPG 110 to 125 mg/dl (6.1 to 6.9 mmol/l) are at significantly increased risk of both CHD and CVD.

In the context of current literature. Conflicting data exist regarding the effect of nondiabetic fasting hyperglycemia on cardiovascular risk. Whereas several studies have found that the 1997 IFG definition is associated with significantly increased risk for CVD (2,9,11,21), at least 5 studies have shown no significantly increased risk for CVD with the 1997 IFG definition (5,8,10,22,23).

Relatively fewer studies have examined the 2003 IFG cut point and its predictive capacity for CVD, and none have demonstrated an increased risk (8–10,24). Kanaya et al. (9) examined data from the Heart and Estrogen/Progestin Replacement Study, which enrolled women with known coronary disease, grouped them by fasting glucose status, and followed them for CVD events, stroke, TIA, and CHF hospitalization for an average of 6.8 years. They found that women with FPG 100 to 125 mg/dl (5.6 to 6.9 mmol/l) were at no increased risk for any end point as compared with women with normal levels of fasting glucose. In contrast, we found that women categorized by the 2003 IFG definition do not have a statistically significant increased risk of CVD

Table 5 Odds Ratios and 95% Confidence Intervals for 4-Year Incidence of Diabetes Examining the 1997 and 2003 IFG Definitions in Age- and Multivariable-Adjusted Models

	Multicategory Model, mmol/l				2003 IFG Glucose Category, mmol/l		1997 IFG Glucose Category, mmol/l	
	5.6 to 6.0*	p Value	6.1 to 6.9*	p Value	5.6 to 6.9*	p Value	6.1 to 6.9†	p Value
Women								
Age-adjusted	12.4 (6.8–22.8)	<0.001	114.5 (65.4–200.5)	<0.001	33.9 (20.1–57.3)	<0.001	42.3 (28.5–62.9)	<0.001
MV-adjusted‡	9.1 (4.9–17.0)	<0.001	72.5 (40.5–129.8)	<0.001	22.3 (13.0–38.1)	<0.001	26.3 (17.4–39.8)	<0.001
Men								
Age-adjusted	7.2 (4.4–11.9)	<0.001	38.5 (23.8–62.1)	<0.001	14.6 (9.3–22.8)	<0.001	14.9 (10.7–20.8)	<0.001
MV-adjusted‡	6.4 (3.9–10.6)	<0.001	32.4 (20.0–52.6)	<0.001	12.7 (8.1–20.0)	<0.001	12.9 (9.3–18.1)	<0.001

*Referent group is <5.6 mmol/l (<100 mg/dl). †Referent group is <6.1 mmol/l (<110 mg/dl). ‡Covariates: age, body mass index, smoking.
Abbreviations as in Table 3.

(OR 1.4, 95% CI 0.9 to 2.1) but do have significantly increased odds of CHD (OR 1.7, 95% CI 1.0 to 3.0, p = 0.048). A potential explanation for the differences in our findings may be the result of differences in our study sample, which included only individuals free of CVD at baseline, which is especially important when comparing our findings to those of Kanaya et al. (9), who used a sample of women with pre-existing CVD, and followed their participants for new events.

In a recent publication from the Hoorn Study in which participants (n = 1,428) were categorized according to 1997 and 2003 criteria based on OGTT measured in 1989 and 1996 with 10-year follow-up for all-cause and CVD mortality, there was no significant increased risk for CVD unless participants developed diabetes (12). These data are distinctly incongruent with our current findings, possibly in part because of the lack of gender-specific analyses in the Hoorn study.

The Hoorn investigators used oral glucose tolerance testing to diagnose impaired fasting glucose as compared with our use of FPG, which may also be pertinent to understanding why our findings differed. However, researchers using data from the Atherosclerosis Risk in Communities Study recently have confirmed that there is poor congruence between IFG (defined as 100 to 125 mg/dl; 5.6 to 6.9 mmol/l) and impaired glucose tolerance (IGT). They also demonstrate that neither IFG nor IGT are associated with an increased risk of all-cause mortality or incident CHD after a median follow-up of 6.3 years in fully-adjusted models (25). Therefore, we believe that our findings using FPG to diagnose IFG is an acceptable and clinically applicable method by which to conduct these analyses. Finally, a recent study from a community-based medical center examined CVD risk factor prevalence and prevalent CVD events among individuals with the 1997 as compared with the 2003 IFG definition (26) and found that the 2003 definition was not associated with an elevated level of CVD risk factors or CVD as compared to the 1997 definition.

Gender differences. For any given glycemic category, women had greater relative odds of CHD and CVD as compared with men, although men had greater absolute event rates for cardiovascular disease. In fact, the cardiovascular disease event rates and odds ratios for women in the 110 to 125 mg/dl group were similar to those for women with diabetes in our sample. These findings build upon those from a recent meta-analysis that included more than 33,000 women and 172,000 men in examining nondiabetic hyperglycemia as a risk factor for CVD; results demonstrate that the risk of CVD events was markedly greater in cohorts that included women (27). However, gender-specific data for women in this meta-analysis were not presented. Taken together with our findings, CVD and diabetes risk in women may occur at lower glucose thresholds as compared with men, which raises several potentially interesting questions. Whether gender differences are due to intrinsic biologic differences or differences in risk factor management is uncertain. These differences also raise the question of whether gender-specific cut points for impaired fasting glucose should exist.

Implications. In the absence of a clear glucose threshold that is predictive of CVD, the debate continues regarding what should define IFG to maximize sensitivity and specificity for predicting cardiovascular events. In examining the effect of IFG categorization with respect to cardiovascular disease, we uncovered gender differences, raising the question of whether a lower glycemic threshold should be used to diagnose IFG or diabetes in women. It is important to remember, however, that men have a greater absolute rate of events as compared with women. Further, IFG is not a CHD risk-equivalent. In addition, whether the effect of identifying individuals with this diagnosis in clinical practice encourages lifestyle modification including weight loss and increased physical activity is uncertain. Fasting blood sugar is often associated with other adverse CVD risk factors and may serve to identify patients with hypertension and dyslipidemia. Finally, it is uncertain whether identifying an individual with IFG results in aggressive CVD risk factor modification; randomized clinical trials among individuals with IFG would be necessary to assess this.

Strengths and study limitations. The strength of our analysis lies in our population-based cohort and long-term follow-up. We assessed the glycemic status of our participants every 4 years and were able to remove those who developed incident diabetes from the IFG category, which is particularly important when trying to understand the risk of cardiovascular disease associated with IFG independently of developing diabetes.

Our study has several limitations which must be acknowledged. Oral glucose tolerance testing was not available at each index examination cycle, thereby precluding comment on how the 1997 and 2003 IFG definitions compare with IGT for prediction of CVD. Further, this unavailability may have resulted in cases of undiagnosed diabetes in our exposure group. However, the primary point of our paper is to analyze the current ADA recommendations for IFG, and current guidelines do not recommend the routine use of oral glucose tolerance testing (28).

Next, although we found no increased risk in men for CHD and CVD, we examined short-term risk, and application to long-term risk, which allows for transition to diabetes over many years of follow-up, is uncertain. However, the consideration of short-term risk is congruent with the ADA's recommendation that all individuals over 45 years of age be screened for diabetes every 3 years and even more frequently if additional risk factors are present (29). Third, the Framingham Heart Study at its inception in 1948 included only white participants. Therefore, the generalizability to other ethnic groups is uncertain. However, the Framingham risk score has been validated in other ethic groups and has been found to be applicable in other populations (30,31). Although we used data from our study that spans several decades, we do not believe that temporal

trends would have an important effect on our results, because we have previously shown that the relative risk between cardiovascular disease and diabetes has not changed over time (32). Finally, we only evaluated cardiovascular complications of IFG and diabetes and were not able to assess retinopathy, neuropathy, and nephropathy, which may yield different findings.

Conclusions

Our data suggest that for prediction of CHD and CVD events, neither IFG definition identifies a group of men at increased short-term risk. In women, there is a significantly increased risk of CHD in the 2003 IFG group, but this risk is driven primarily by the high event rate in participants with FPG 110 to 125 mg/dl (6.1 to 6.9 mmol/l). In comparing women and men, for any given prediabetic category, women have a greater relative risk of CHD than men. The 2003 IFG definition does not offer substantive advantages over the 1997 definition for prediction of CVD or diabetes.

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