Impaired Fasting Glucose and Risk of Cardiovascular Disease in Korean Men and Women

The Korean Heart Study

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OBJECTIVE—The relationship between impaired fasting glucose (IFG) and risk of cardiovascular disease (CVD) or ischemic heart disease (IHD) varies widely according to sex and ethnicity. We evaluated the relationship between IFG and CVD or IHD among Korean men and women.

RESEARCH DESIGN AND METHODS—A total of 408,022 individuals who underwent voluntary private health examinations in 17 centers in South Korea were followed for 10 years. Data regarding CVD or IHD events were obtained from the Korean National Health Insurance database. IFG was categorized as grade 1 (fasting glucose 100–109 mg/dL) or grade 2 (110–125 mg/dL).

RESULTS—Incidence rates of CVD (per 100,000 person-years) were 2,203 for diabetes. Age-adjusted hazard ratios (HRs) for CVD were 1.17 (95% CI 1.13–1.20) for grade 1 IFG, 1.30 (1.24–1.35) for grade 2 IFG, and 1.81 (1.75–1.86) for diabetes. The increased risk for women was similar to that of men. Age-adjusted HRs for IHD and ischemic stroke were also significantly increased for men and women with IFG and diabetes. After multivariate adjustment of conventional risk factors (hypertension, dyslipidemia, smoking, obesity, and family history of CVD), the overall risk of CVD was greatly attenuated in all categories. However, the HRs for IHD and ischemic stroke remained significantly increased in men for grade 2 IFG but not in women.

CONCLUSIONS—In Korea, grade 2 IFG is associated with increased risk of IHD and ischemic stroke, independent of other conventional risk factors, in men but not in women.

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It is well-established that type 2 diabetes is associated with a marked increase in the risk of cardiovascular disease (CVD) and ischemic heart disease (IHD) (1–4). Studies suggest that atherosclerosis develops before the onset of clinical diabetes (5,6). Supporting this possibility, many studies have reported that impaired glucose tolerance (IGT) is associated with increased cardiovascular morbidity and mortality (7,8). However, the association between impaired fasting glucose (IFG) and risk of CVD and/or IHD remains unclear (7–18). Although some studies have reported that IFG was associated with a greater risk of IHD/CVD in women than in men (17,19), others have reported similar risks for men and women (18).

There has also been considerable debate regarding the threshold glucose level associated with increased CVD risk. In 2003, the American Diabetes Association (ADA) lowered the fasting plasma glucose (FPG) cutoff point for IFG from 110 to 100 mg/dL (20). Some studies have reported that FPG levels of 110–125 mg/dL were associated with significantly higher rates CVD morbidity or mortality, but that FPG levels of 100–109 mg/dL were not (12,13). However, other investigators reported that the relationship between CVD risk and fasting glucose was continuous or J-shaped rather than showing a threshold effect at high glucose levels (18,21). However, most studies were based mainly on Caucasian populations, and only a few studies have assessed the relationship between IFG and CVD risk in Asian populations (13,14,18). Furthermore, most of these studies analyzed IHD and stroke together as CVD, whereas few studies have analyzed IHD, ischemic stroke, and hemorrhagic stroke separately (14,22).

The primary purpose of this study was to determine whether IFG is associated with increased risk of CVD, IHD, and/or stroke in the Korean population. We also assessed potential sex differences, which have been shown in some previous studies (17,19). Finally, we evaluated whether the CVD risk associated with fasting serum glucose (FSG) levels of 100–109 mg/dL is similar to the risk associated with FSG levels of 110–125 mg/dL (the 1997 ADA definition of IFG).

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS—Participants for this study were drawn from a pool of 408,022 individuals (247,615 men and

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A complete list of the collaborators and principal investigators in the Korean Heart Study can be found in the APPENDIX.

160,407 women) who had voluntarily undergone private health examinations in 17 centers located in one capital and six provinces in South Korea from 1996–2004. The National Health Screening Program in Korea supports all men and women over the age of 20 years to receive basic health screening for hypertension, diabetes, hypercholesterolemia, proteinuria, pulmonary tuberculosis, and breast and cervical cancer (for women) biannually. However, many Korean companies provide more extensive private health examination program for their employees annually. Considerable proportions (varies from 40–80% depending on each health screening center) of private health examinations are for employees and their spouses. Remaining proportions are for individuals who voluntarily want to get more extensive health screening beyond the National Health Screening Program.

We have labeled this study as the Korean Heart Study. Individuals with previous history of coronary heart disease (CHD), cerebrovascular accident, or malignancy (n = 23,227) were excluded. Finally, data for 384,795 participants were collected for a mean follow-up of 10 years (median 9.4 years). This study was approved by the institutional review board of each participating center including Asan Medical Center.

Data collection

Of 80 health promotion centers in South Korea, around half routinely store their records electronically; of these, 17 agreed to provide data. Medical history and baseline laboratory data obtained during the health checkups were collected from the 17 participating centers. Data files were collected from centers that maintained electronic databases, and manual data coding was performed by trained personnel for data collected from centers that kept paper medical records.

Questionnaire. Questionnaires included items on smoking habits (current smoker, nonsmoker, or ex-smoker), alcohol consumption (yes/no), regular exercise (yes/no), education level, family history of CHD or cerebrovascular accident, and medication history.

Laboratory data standardization. Total cholesterol, triglyceride, HDL cholesterol, and FSG levels were measured at each center using autoanalyzers. LDL cholesterol was measured directly or calculated by the Friedewald equation. In 2006, the Korean Association of Quality Assurance for Clinical Pathology conducted a nationwide study of interlaboratory agreement, and the Department of Clinical Pathology at Asan Medical Center was in charge of the analysis. After receiving written permission, we reviewed interlaboratory correlations for the participating centers. The interlaboratory correlation coefficients for all measured variables exceeded 0.95.

Outcome ascertainment

Outcome variables were morbidity from: *1*) IHD alone (ICD-10 codes I20–I25); *2*) stroke alone (ICD-10 codes I60–I69); and *3*) total CVD. The latter category included hypertensive disease (ICD-10 codes I10–I15), IHD (ICD-10 codes I20–I25), hemorrhagic stroke (ICD-10 codes I60–I62), ischemic stroke (ICD-10 code I63), other stroke (ICD-10 codes I64–I69), other disease likely related to atherosclerotic CVD (ICD-10 codes I44–I51), sudden death (ICD-10 code R96), and other vascular disease (ICD-10 codes I70–I74). For individuals with more than one event, we used just the first event in our analysis. The follow-up period lasted 14 years, from January 1997 to December 2010.

Outcomes were ascertained from diagnosis on hospital discharge summaries and from the cause of death on death certificates. Computerized searches of death certificate data from the National Statistical Office in Korea were performed for each of the Korean National Health Insurance Corporation enrollees. For morbidity, which is defined exclusively by hospital discharge diagnosis, follow-up is likely to approach 100%, because all bills with discharge diagnosis are submitted to the National Health Insurance Corporation.

We conducted the IHD event validation study in collaboration with the Korean Heart Association through the formation of the Event Validation Committee (July 2008 to May 2009). For the participants who provided written permission for use of their personal information, 673 CHD events were confirmed with individual hospital medical records that 73% of myocardial infarction were valid (23). Another previous study reported that 83% of stroke diagnoses were valid (24).

Disease definitions (definition of dysglycemia)

Obesity was defined by the World Health Organization Asian reference as BMI >25 kg/m^2. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication. Diabetes was defined as FSG ≥126 mg/dL, use of glucose-lowering medication, or past medical history of diabetes. IFG was defined using the 2003 ADA criteria (20) and classified as grade 1 (FSG 100–109 mg/dL) or grade 2 (FSG 110–125 mg/dL).

Statistical analysis

Baseline characteristics of each group were compared by ANOVA or χ^2 tests. Incidence rates were expressed as cases per 100,000 person-years. The Cox proportional hazard model was used to calculate hazard ratios (HRs) of developing CVD. Models were initially age-adjusted and then adjusted for multiple covariates for each end point. The proportional hazards assumption in the Cox model was checked graphically and with the Schoenfeld residual test. All proportionality assumptions were generally appropriate. Statistical analyses were conducted using SAS software version 9.12 (SAS institute, Cary, NC). All tests were two-sided, and $P < 0.05$ was considered significant.

RESULTS—Table 1 shows the baseline characteristics of participants without CVD at baseline according to glycemic status. Incidence rates of CVD (per 100,000 person-years) were 1,084 for grade 1 IFG, 1,416 for grade 2 IFG, and 2,203 for type 2 diabetes (Table 2). Age-adjusted HRs for CVD were significantly increased for participants with grade 1 IFG (1.17 [95% CI 1.13–1.20]), grade 2 IFG (1.30 [1.24–1.35]), and type 2 diabetes (1.81 [1.75–1.86]). The HRs of CVD for men were similar to those for women (grade 1 IFG, 1.13 [1.09–1.18] vs. 1.21 [1.15–1.27]; grade 2 IFG, 1.32 [1.25–1.39] vs. 1.24 [1.15–1.34]; and type 2 diabetes, 1.80 [1.73–1.87] vs. 1.83 [1.74–1.93], respectively). In the total study population, the increased CVD risk associated with dysglycemia persisted after adjusting for multiple conventional risk factors such as systolic blood pressure, antihypertensive medications, LDL and HDL cholesterol levels, smoking status, BMI, and family history of CVD (grade 1 IFG, 1.02 [0.99–1.05]; grade 2 IFG, 1.05 [1.01–1.10]; and type 2 diabetes, 1.49 [1.45–1.54]). However, when we analyzed men and women separately, the multivariable-adjusted HR for CVD remained significantly increased in men but not in women with grade 2 IFG.

Table 1—*Baseline characteristics of subjects without CVD* (N = *384,795*)

FSG categories	Normoglycemia (<100 mg/dL)	Prediabetes		Diabetes (≥126 mg/dL or medication)	*P* value
		100–109 mg/dL	110–125 mg/dL		
No. of subjects (%)	289,511 (75.2)	49,921 (13.0)	17,975 (4.7)	27,388 (7.1)	
Sex (male) (%)	58.7	68.1	71.3	69.1	<0.0001
Age (years)	44.7 ± 9.7	47.7 ± 9.9	50.1 ± 9.7	52.0 ± 9.6	<0.0001
Smoking (%)					
Current smoker	33.6	34.7	34.9	34.8	
Ex-smoker	14.0	19.5	21.9	21.3	<0.0001
Alcohol (%)	61.9	67.8	69.4	65.5	<0.0001
Exercise (%)	56.1	55.5	55.0	49.4	<0.0001
CVD family history	7.4	7.2	6.8	7.2	0.0158
BMI (kg/m^2)	23.4 ± 2.9	24.4 ± 2.9	25.0 ± 3.0	24.6 ± 3.0	<0.0001
Obesity (BMI ≥25 kg/m^2, %)	28.6	41.7	49.7	43.0	<0.0001
Systolic BP (mmHg)	119.3 ± 16.8	126.1 ± 17.8	130.6 ± 18.8	129.2 ± 19.5	<0.0001
Diastolic BP (mmHg)	75.3 ± 11.5	79.1 ± 11.8	81.6 ± 12.1	80.1 ± 12.0	<0.0001
Hypertension (%)	21.7	33.4	43.6	45.0	<0.0001
Total cholesterol (mg/dL)	191.1 ± 34.5	201.0 ± 36.1	207.0 ± 37.8	204.7 ± 39.7	<0.0001
HDL cholesterol (mg/dL)	51.4 ± 11.9	50.0 ± 11.8	49.2 ± 11.7	48.3 ± 11.6	<0.0001
LDL cholesterol (mg/dL)	115.3 ± 31.9	122.2 ± 33.7	125.3 ± 35.6	123.7 ± 35.8	<0.0001
Triglyceride (mg/dL)	132.6 ± 86.9	157.6 ± 103.6	179.4 ± 121.7	185.8 ± 141.4	<0.0001
Fasting glucose (mg/dL)	87.0 ± 7.5	103.6 ± 2.8	115.5 ± 4.3	146.4 ± 52.9	<0.0001

Data are means ± SD unless otherwise indicated. BP, blood pressure.

The age-adjusted HR for IHD also increased significantly according to glycemic status (grade 1 IFG, 1.17 [1.11–1.24]; grade 2 IFG, 1.30 [1.21–1.40]; and type 2 diabetes, 1.95 [1.85–2.05]) (Table 2). After adjusting for other conventional risk factors, the increased HRs remained significant (grade 1 IFG, 1.06 [1.01–1.12]); grade 2 IFG, 1.11 [1.03–1.20]; and type 2 diabetes, 1.70 [1.61–1.79]). When we analyzed men and women separately, the association was significant in men with grade 2 IFG, but the multivariable-adjusted HRs for grade 1 and grade 2 IFG were not significant in women.

The relationship between dysglycemia and risk of ischemic stroke was similar to that of IHD (Table 2). Age-adjusted HRs were significantly increased for all three dysglycemic groups, but the HR for grade 1 IFG was not significant after adjusting for multiple risk factors. When we analyzed men and women separately, these associations were similar between men and women, but the multivariate-adjusted HR was significant for grade 2 IFG in men. In contrast, the risk of hemorrhagic stroke was not increased in men or women with IFG.

To control for the effect of hypertension, the major CVD risk factor most commonly associated with IFG, we separately analyzed incidence rates and HRs of IHD and ischemic stroke in prediabetic participants with or without hypertension (Table 3). The increased risk of IHD associated with IFG remained significant independent of hypertension in both men and women. However, the risk of ischemic stroke was significantly increased in men, but not in women, with IFG without hypertension.

To examine the association between FSG and CVD in detail, the fasting glucose range was further divided into smaller categories (10-mg/dL intervals). In the total study population, multivariate-adjusted HR for IHD was significantly increased in categories of FSG >100 mg/dL, but those for CVD and ischemic stroke were increased only in FSG >120 mg/dL (Fig. 1 and Supplementary Table 1). When we analyzed men and women separately, the risks of CVD, IHD, and ischemic stroke were increased significantly above the FSG levels of 110, 100, and 126 mg/dL, respectively, in men (Fig. 1 and Supplementary Table 2), and 120, 126, and 120 mg/dL, respectively, in women (Fig. 1 and Supplementary Table 3) after additional adjustment for menopause status.

CONCLUSIONS—In this large Korean cohort, the 2003 ADA definition of IFG (FSG 100–125 mg/dL) is associated with an increased risk of CVD, although the risk was lower for grade 1 IFG (FSG 100–109 mg/dL) than for grade 2 IFG (FSG 110–125 mg/dL). Although diabetes and prediabetes are frequently associated with other cardiovascular risk factors (e.g., hypertension, obesity, smoking, and dyslipidemia), the association between IFG and CVD, IHD, and ischemic stroke remained significant after adjusting for those potential confounders.

Our findings are in general agreement with previous studies in other populations (18,19,25,26), which showed that IFG is associated with CVD risk independent of other CVD risk factors. Although there have been a number of studies on this issue, most studies were performed in Europe and North America, and adjustments for confounding factors were heterogeneous among studies. In a recent meta-analysis of 102 prospective studies involving ~700,000 participants of multiethnic background (26), only <4% (~23,000) of the participants were Asians (all from Japan). In addition, fasting glucose level was available only in ~40% (~288,000 of 699,000) of the participants.

In Korean population, a large study utilizing data of ~650,000 individuals was also conducted previously (22), but the participants were limited to male public servants aged 30–64 years. Our study could analyze the relationship between

Table 2—*Incidence rates (1/100,000 person-years), HRs, and 95% CIs of CVDs by different traits of dysglycemia*

FSG categories	Normoglycemia (<100 mg/dL)	Prediabetes		Diabetes (≥126 mg/dL or on medication)
		100–109 mg/dL	110–125 mg/dL	
CVD				
Total				
Person-years	2,750,034	471,013	166,657	247,025
Cases (*n*)	20,463	5,107	2,360	5,443
Incidence rates	744	1,084	1,416	2,203
Age-adjusted HR	1.0	1.17 (1.13–1.20)	1.30 (1.24–1.35)	1.81 (1.75–1.86)
MV-adjusted HR*	1.0	1.02 (0.99–1.05)	1.05 (1.01–1.10)	1.49 (1.45–1.54)
Men				
Person-years	1,586,798	319,255	118,161	169,987
Cases (*n*)	11,658	3,209	1,611	3,615
Incidence rates	735	1,005	1,363	2,127
Age-adjusted HR	1.0	1.13 (1.09–1.18)	1.32 (1.25–1.39)	1.80 (1.73–1.87)
MV-adjusted HR*	1.0	1.01 (0.97–1.05)	1.10 (1.05–1.17)	1.52 (1.46–1.58)
Women				
Person-years	1,163,237	151,758	48,496	77,038
Cases (*n*)	8,805	1,898	749	1,828
Incidence rates	757	1,251	1,544	2,373
Age-adjusted HR	1.0	1.21 (1.15–1.27)	1.24 (1.15–1.34)	1.83 (1.74–1.93)
MV-adjusted HR*	1.0	1.04 (0.99–1.09)	0.96 (0.89–1.04)	1.45 (1.38–1.53)
IHD				
Total				
Person-years	2,813,023	486,835	174,127	263,667
Cases (*n*)	6,650	1,712	801	2,018
Incidence rates	236	352	460	765
Age-adjusted HR	1.0	1.17 (1.11–1.24)	1.30 (1.21–1.40)	1.95 (1.85–2.05)
MV-adjusted HR*	1.0	1.06 (1.01–1.12)	1.11 (1.03–1.20)	1.70 (1.61–1.79)
Men				
Person-years	1,618,678	328,417	122,948	108,209
Cases (*n*)	4,277	1,186	604	1,456
Incidence rates	264	361	491	1,346
Age-adjusted HR	1.0	1.14 (1.07–1.22)	1.34 (1.23–1.46)	1.93 (1.82–2.05)
MV-adjusted HR*	1.0	1.06 (0.99–1.13)	1.18 (1.08–1.29)	1.71 (1.61–1.82)
Women				
Person-years	1,194,344	158,418	51,179	83,458
Cases (*n*)	2,373	526	197	562
Incidence rates	199	332	385	673
Age-adjusted HR	1.0	1.23 (1.11–1.35)	1.19 (1.03–1.38)	1.98 (1.81–2.18)
MV-adjusted HR*	1.0	1.09 (0.99–1.20)	0.97 (0.84–1.13)	1.67 (1.52–1.84)
Ischemic stroke				
Total				
Person-years	2,834,609	492,472	176,439	269,404
Cases (*n*)	2,457	648	347	954
Incidence rates	87	132	197	354
Age-adjusted HR	1.0	1.13 (1.04–1.24)	1.38 (1.23–1.55)	2.14 (1.98–2.31)
MV-adjusted HR*	1.0	1.02 (0.93–1.11)	1.18 (1.05–1.33)	1.85 (1.71–2.00)
Men				
Person-years	1,633,131	332,544	124,836	184,560
Cases (*n*)	1,402	410	238	628
Incidence rates	86	123	191	340
Age-adjusted HR	1.0	1.12 (1.01–1.25)	1.41 (1.23–1.62)	2.10 (1.91–2.32)
MV-adjusted HR*	1.0	1.03 (0.92–1.16)	1.24 (1.08–1.43)	1.87 (1.70–2.06)
Women				
Person-years	1,201,478	159,928	51,603	84,844
Cases (*n*)	1,055	238	109	326

Continued on p. 332

Table 2—*Continued*

FSG categories	Normoglycemia (<100 mg/dL)	Prediabetes		Diabetes (≥126 mg/dL or on medication)
		100–109 mg/dL	110–125 mg/dL	
Incidence rates	88	149	211	384
Age-adjusted HR	1.0	1.14 (0.99–1.31)	1.31 (1.07–1.59)	2.21 (1.95–2.51)
MV-adjusted HR*	1.0	1.00 (0.87–1.16)	1.07 (0.88–1.31)	1.82 (1.59–2.07)
Hemorrhagic stroke				
Total				
Person-years	2,841,964	494,557	177,633	273,004
Cases (*n*)	1,241	306	135	293
Incidence rates	44	62	76	107
Age-adjusted HR	1.0	1.15 (1.01–1.30)	1.21 (1.01–1.45)	1.53 (1.35–1.75)
MV-adjusted HR*	1.0	1.05 (0.93–1.20)	1.05 (0.88–1.27)	1.34 (1.17–1.53)
Men				
Person-years	1,637,434	333,840	125,659	186,811
Cases (*n*)	685	192	99	205
Incidence rates	42	58	79	110
Age-adjusted HR	1.0	1.16 (0.98–1.36)	1.36 (1.10–1.68)	1.67 (1.42–1.95)
MV-adjusted HR*	1.0	1.05 (0.89–1.23)	1.17 (0.94–1.45)	1.45 (1.23–1.72)
Women				
Person-years	1,204,530	160,717	51,974	86,193
Cases (*n*)	556	114	36	88
Incidence rates	46	71	69	102
Age-adjusted HR	1.0	1.14 (0.93–1.40)	0.94 (0.67–1.32)	1.31 (1.05–1.65)
MV-adjusted HR*	1.0	1.06 (0.86–1.30)	0.82 (0.59–1.16)	1.14 (0.90–1.44)

MV, multivariate. *Covariates: age, systolic blood pressure, antihypertensive medication, LDL cholesterol, HDL cholesterol, current smoking, BMI, and family history of CVD.

FSG and CVD in both men and women, and we included more aged people (up to 74 years) with broad range of socioeconomic status enrolled on a nationwide scale from 17 centers. In addition, we could further adjust the data for important potential confounders such as LDL- and HDL-cholesterol levels and antihypertensive medications. Therefore, our study could provide additional information on the relationship between fasting glucose level and cardiovascular risk in a large number of Asian population. Furthermore, thorough health checkup data at baseline allowed us more accurate adjustments for other cardiovascular risk factors.

A study conducted in China (14) also reported that IFG (FSG 100–125 mg/dL) was significantly associated with an increased 10-year risk of CVD, CHD, and ischemic stroke, although they did not separately analyze FSG levels of 100–109 mg/dL (designated as grade 1 IFG in our study). However, hyperglycemia without any other metabolic syndrome component was not associated with increased risk of CVD, suggesting that the increased CVD risk in individuals with IFG or diabetes was largely driven by the coexistence of multiple metabolic disorders rather than hyperglycemia per se. However, only a small percentage of participants in their study exhibited IFG without other metabolic syndrome components. In our results, HRs were substantially lower after adjusting for multiple cardiovascular risk factors, but remained significant. Considerable evidence has shown that hyperglycemia induces inflammation, oxidative stress, endothelial dysfunction (4), and fibrinolytic and thrombotic processes that could destabilize an atherosclerotic plaque, leading to eventual thrombosis and clinical CHD (12).

There has been considerable debate regarding whether the 2003 ADA definition of IFG (FSG 100–125 mg/dL) predicts the risk of CVD as well as the 1997 ADA definition of IFG (FSG 110–125 mg/dL). A study conducted in Taiwan (13) reported that the 1997 definition of IFG was associated with a significant increase in mortality related to CVD and/or diabetes, but that the 2003 definition of IFG did not have predictive value for CVD or diabetes mortality. However, this Taiwanese study did not report the relationship between IFG and incidence of CVD. In a study of postmenopausal women in the U.S. (12), IFG according to the 1997 definition was associated with an increased risk for any CHD event, but IFG according to the 2003 definition was not associated with increased risk. However, the study included only postmenopausal women with established CHD, and the sample size was small; therefore, it is difficult to generalize their results. In contrast, studies in China (14) and the U.S. (25) showed that IFG defined as FSG 100–125 mg/dL was associated with increased risk of CHD. In the Asia Pacific Cohort Studies (18), a positive log-linear association was reported between FSG and the risk of total stroke and IHD. Continuous positive associations were observed down to at least 4.9 mmol/L (88 mg/dL), without evidence of a threshold level. A meta-analysis of previous studies (19) indicated that FPG showed a possible threshold effect at ~100 mg/dL (5.6 mmol/L). Although we did not analyze for a specific threshold level, our results support the lower 2003 IFG cutoff point as a predictor of increased IHD risk.

In our study, the increased risk for IHD associated with IFG persisted after adjusting for other conventional risk factors in men but not in women. In contrast, the Framingham Heart Study (17) reported that hyperglycemia was associated with a greater CVD risk in women

Table 3—*Incidence rates (1/100,000 person-years), HRs, and 95% CIs of IHD and ischemic stroke of prediabetes (fasting glucose 100–125 mg/dL) with or without hypertension* (N = 357,407)

	Normoglycemia		Prediabetes	
	Without hypertension	With hypertension	Without hypertension	With hypertension
IHD				
Total				
Person-years	2,206,350	603,679	423,847	236,418
Cases (*n*)	4,005	2,636	1,233	1,276
Incidence rates	182	437	291	540
Age-adjusted HR	1.0	1.60 (1.52–1.68)	1.23 (1.16–1.31)	1.70 (1.59–1.81)
MV-adjusted HR*	1.0	1.48 (1.41–1.56)	1.14 (1.07–1.22)	1.51 (1.41–1.62)
Men				
Person-years	1,237,881	379,741	291,251	159,766
Cases (*n*)	2,626	1,645	889	897
Incidence rates	212	433	305	561
Age-adjusted HR	1.0	1.52 (1.42–1.61)	1.18 (1.09–1.27)	1.68 (1.55–1.82)
MV-adjusted HR*	1.0	1.45 (1.36–1.54)	1.11 (1.03–1.20)	1.56 (1.44–1.69)
Women				
Person-years	968,469	223,938	132,595	76,652
Cases (*n*)	1,379	991	344	379
Incidence rates	142	443	259	494
Age-adjusted HR	1.0	1.74 (1.60–1.90)	1.35 (1.20–1.52)	1.70 (1.51–1.91)
MV-adjusted HR*	1.0	1.58 (1.45–1.73)	1.22 (1.08–1.38)	1.46 (1.29–1.65)
Ischemic stroke				
Total				
Person-years	2,220,269	611,294	428,163	240,025
Cases (*n*)	1,283	1,173	388	606
Incidence rates	58	192	91	252
Age-adjusted HR	1.0	1.88 (1.73–2.04)	1.14 (1.02–1.28)	2.07 (1.87–2.29)
MV-adjusted HR*	1.0	1.85 (1.70–2.01)	1.10 (0.98–1.23)	2.00 (1.80–2.21)
Men				
Person-years	1,247,413	384,624	294,400	162,606
Cases (*n*)	738	663	273	374
Incidence rates	59	172	93	230
Age-adjusted HR	1.0	1.88 (1.69–2.09)	1.19 (1.04–1.37)	2.05 (1.80–2.32)
MV-adjusted HR*	1.0	1.91 (1.71–2.13)	1.17 (1.02–1.35)	2.07 (1.81–2.36)
Women				
Person-years	972,856	226,670	133,763	77,419
Cases (*n*)	545	510	115	232
Incidence rates	56	225	86	300
Age-adjusted HR	1.0	1.86 (1.64–2.11)	1.03 (0.84–1.26)	2.09 (1.78–2.46)
MV-adjusted HR*	1.0	1.77 (1.56–2.02)	0.96 (0.78–1.18)	1.91 (1.62–2.25)

MV, multivariate. *Covariates: age, LDL cholesterol, HDL cholesterol, current smoking, BMI, and family history of CVD.

than in men. The meta-analysis (19) also reported that the relative risk for CVD was greater in cohorts that included women than in cohorts of men. However, few studies have examined this relationship in cohorts of women only. Although most Asian studies (13,14) did not analyze men and women separately, the Asian Pacific Cohort Study (18) showed that fasting glucose in prediabetes and diabetes was an important determinant of CVD, without a significant difference between men and women. It is unclear that whether these discrepancies are due to ethnic differences or to differences in risk factor management between populations.

Although diabetes is strongly associated with increased risk for stroke (27,28), less is known about the risk associated with prediabetic states. In previous cross-sectional (29) and longitudinal studies (12), IGT or IFG was not associated with risk of stroke. However, many previous studies (12,17,18) did not perform separate analyses for ischemic and hemorrhagic strokes. Our study showed that IFG was associated with increased risk for ischemic stroke but not hemorrhagic stroke, which is consistent with results of a longitudinal study conducted in China (14). However, the association between IFG and risk of ischemic stroke appears weak compared with the association between IFG and IHD, as increased risk of ischemic stroke was seen only in men with grade 2 IFG (FSG 110–125 mg/dL) after multivariate adjustment.

Our study has several limitations that must be acknowledged. First, results of oral glucose tolerance testing (OGTT) were not available; therefore the 1997 and 2003 IFG definitions could not be

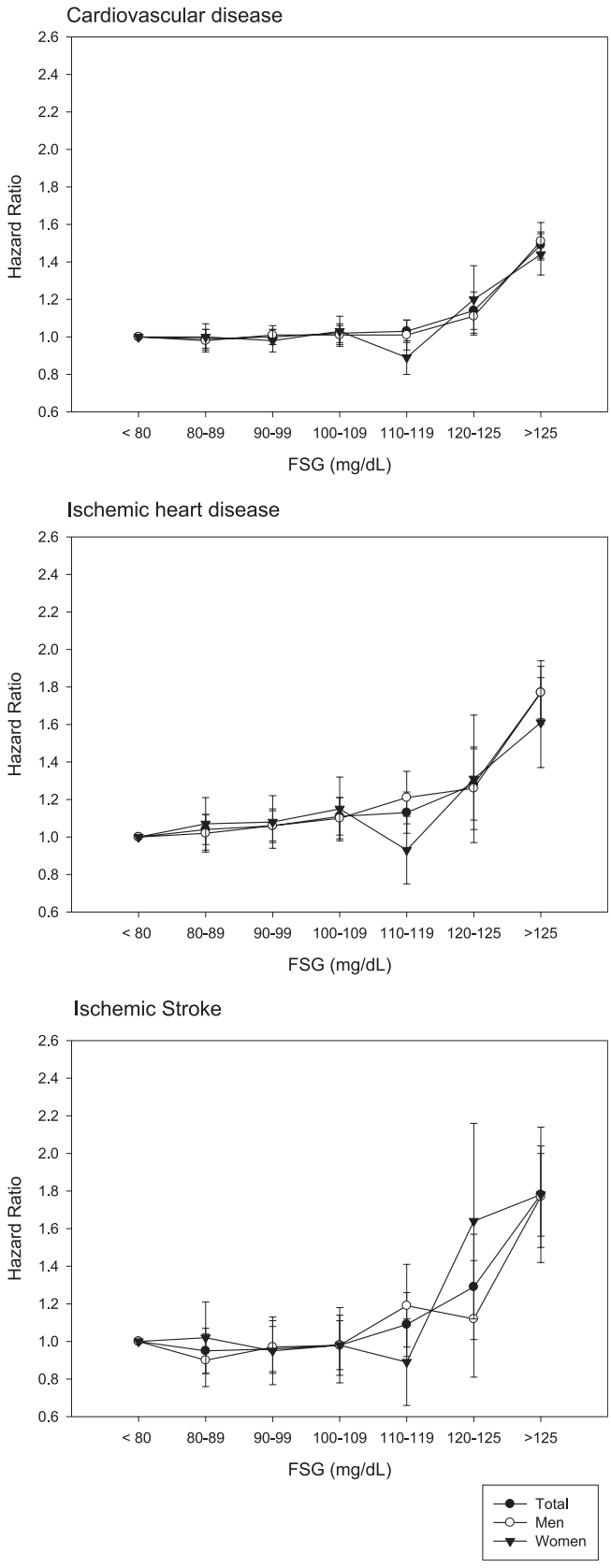

Figure 1—*HRs (95% CIs) for the risk of CVD* (top)*, IHD* (middle)*, and ischemic strokes* (bottom) *associated with FPG in Korean men and women adjusted for age, systolic blood pressure, antihypertensive medication, LDL cholesterol, HDL cholesterol, current smoking, BMI, and family history of CVD.*

compared with IGT for prediction of CVD. Further, this lack of OGTT results may have lead to the inclusion of participants with undiagnosed diabetes in the IFG group. However, OGTT is more complicated and expensive to perform than FSG measurement (30), and the current ADA guidelines do not recommend the routine use of OGTT (31). Second, we could not exclude participants who developed incident diabetes before CVD events from IFG groups, because we used only baseline FSG levels. However, most other studies (13,14,18,25) also used only baseline glucose values, except one study (17) that excluded incident diabetes. Third, our cohort was not based on a general population sample that could represent the Korean population. However, the large number of participants from 19 centers located throughout the country may alleviate potential selection bias. Considering that we often encounter individuals who are found to have IFG during routine health examinations, our results are applicable to clinical and public health practice. Fourth, the outcome definition was based on hospital admissions only. Although it was more accurate than outpatient-based diagnosis, there were possibilities of underestimation for the outcomes. Finally, although many important clinical and laboratory variables were adjusted for the risk analysis in this study, several relevant factors such as use of lipid-lowering drugs could not be adjusted properly because of incomplete data at baseline.

In conclusion, our study showed that IFG, defined as FPG levels of 100–125 mg/dL, is associated with increased risk of CVD (including IHD and ischemic stroke) in the Korean population. This association is independent of other conventional risk factors in men but not in women. Further studies are needed to identify subgroups with IFG for whom prevention efforts in reducing cardiovascular events are cost-effective.

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H.-K.K. drew the conception, researched data, and wrote the manuscript. C.-H.K. discussed, reviewed, and edited the manuscript. E.H.K., S.J.B., J.C., J.-Y.P., and S.-W.P. contributed to discussion and reviewed the manuscript.

Y.D.Y., S.-J.B., and Y.M. provided input to data analysis and reviewed and edited the manuscript. S.H.J. analyzed data and edited the manuscript. S.H.J. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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