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ORIGINAL ARTICLE

Association of prediabetes, defined by fasting glucose, HbA1c only, or combined criteria, with the risk of cardiovascular disease in Koreans

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Abstract

Background: The aim of the present study was to compare the association between cardiovascular diseases (CVD) and prediabetes defined by either fasting plasma glucose (FPG), HbA1c, or their combination in a Korean population.
Methods: In all, 76 434 South Koreans who voluntarily underwent a general health examination in the Health Screening & Promotion Center (Asan Medical Center) were analyzed after excluding patients with a previous history of CVD. Cardiovascular events and death due to CVD during a median follow-up period of 3.1 years (interquartile range 1.9–4.3 years) were identified from the Nationwide Health Insurance Claims Database and death certificates using ICD-10 codes.
Results: Age- and sex-adjusted hazard ratios (HRs) for overall CVD events were significantly greater for subjects with prediabetes defined by FPG only (HR 1.19; 95% confidence interval [CI] 1.08–1.31), HbA1c only (HR 1.28; 95% CI 1.16–1.42), and combined criteria (HR 1.20; 95% CI 1.09–1.32) compared with the normoglycemic group. After adjusting for multiple conventional risk factors (e.g. hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking status, family history of CVD, and BMI), the HRs for overall CVD were significantly increased only for participants with prediabetes defined by HbA1c. Age- and sex-adjusted HRs for major ischemic heart disease events were significantly increased for subjects with prediabetes defined either by HbA1c or combined criteria. Similarly, age- and sex-adjusted HRs for percutaneous coronary intervention were significantly higher for subjects with prediabetes defined by HbA1c only. For diabetes, the multivariate-adjusted HRs for all outcomes were significantly increased by all three criteria.
Conclusions: Adding an HbA1c criterion when defining prediabetes in Koreans can help identify individuals with an increased risk of CVD.

Keywords: cardiovascular disease, fasting glucose, HbA1c, Koreans, prediabetes.

Significant findings of the study: Prediabetes is associated with an increased overall risk of CVD in Koreans. After adjusting for multiple conventional risk factors, prediabetes defined by HbA1c was more strongly associated with the overall risk of CVD and ischemic heart disease compared with impaired fasting glucose.
What this study adds: The associations between prediabetes defined by HbA1c and CVD risk have been reported to vary according to race and/or ethnicity. This study adds significant longitudinal data confirming that individuals with prediabetes defined by HbA1c have an increased risk of CVD and coronary artery disease in a large cohort of an Asian population.

Introduction

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).[1–3] For non-diabetic dysglycemia, impaired fasting glucose (IFG) defined by fasting plasma glucose (FPG) alone has been reported to have only slightly increased hazard ratios (HRs) for CVD,[4–12] and some controversies remain.[13,14] In contrast, many studies have more consistently reported that impaired glucose tolerance (IGT) is associated with increased cardiovascular morbidity and mortality.[15–17] This discrepancy could result from the fact that a single glucose measurement used to define IFG has high intra-individual variation. In addition, IFG defined by FPG criteria only may include some patients with diabetes who have non-diabetic fasting but diabetic post-challenge glucose levels, and could exclude some individuals with prediabetes who have normal fasting but prediabetic post-challenge glucose levels (i.e. isolated IGT).[18] However, the definition of prediabetes using IGT is complicated because it is not easy to apply the oral glucose tolerance test in clinical practice or in epidemiological studies.[19]

A time-integrated marker of average blood glucose concentrations, HbA1c is easy to measure and has low intra-individual variation.[20] Therefore, in 2010, the American Diabetes Association (ADA) recommended the use of HbA1c as an alternative diagnostic criterion for diabetes (HbA1c ≥6.5% [48 mmol/mol]) and prediabetes (HbA1c 5.7%–6.4% [39 to 47 mmol/mol]).[21] Recently, several studies[22–28] have examined whether HbA1c is associated with CVD, including IHD, or mortality in apparently healthy, non-diabetic individuals. Of these, the EPIC-Norfolk (European Prospective Investigation into Cancer in Norfolk, United Kingdom) study,[23] Hoorn Study (Caucasians in The Netherlands),[22] ARIC (Atherosclerosis Risk in Communities; blacks and whites in the US) study,[24] the Nurses' Health Study and the Health Professionals Follow-up Study (mainly Caucasians in the US),[25] and a Japanese Study[26] have shown that HbA1c is independently and more strongly associated with CVD. However, the Finnish study[27] and Strong Heart Study (in American Indians)[28] did not show an additional role for HbA1c in predicting CVD risk in individuals with prediabetes. These studies were all performed in different populations and used various categories of HbA1c to examine the association between HbA1c and CVD risk. Therefore, the present study was designed to compare the association between CVD risk and prediabetes defined by FPG only, HbA1c only, or their combination in Koreans.

Methods

Data sources

In all, 114 698 consecutive South Korean individuals who had undergone a general health examination in the Health Screening and Promotion Center at Asan Medical Center between January 2007 and June 2011 were screened. Of these, 86 476 (75%) consented to participate in the study. Participants were excluded if the Health Insurance Review & Assessment Service (HIRA) database indicated that they had a history of CVD (codes I00–99 in the International Classification of Diseases, 10th Revision [ICD-10]; http://www.who.int/classifications/icd/en/, accessed on 5 January 2015) before the index day or if their data were not available in the HIRA database. The HIRA is a quasi-governmental organization that systematically reviews medical fees to minimize the risk of redundant and unnecessary medical services. South Korea has a National Health Insurance (NHI) system and it is mandatory that all healthcare providers join this system on a fee-for-service basis.[29] Consequently, all NHI claims are reviewed by the HIRA.[30] For the present study, the HIRA database was assessed up until December 2011. Patients with angina, myocardial infarction (MI), stroke, or structural heart disease; those who had undergone percutaneous coronary intervention (PCI), cardiac procedure, or open heart surgery before the index day; those who had a past medical history of angina, MI, stroke, or malignancy as determined by questionnaire; or those who <20 years of age were excluded from the study. Some subjects met more than two exclusion criteria. Thus, 76 434 participants were finally included in the analyses (Fig. 1).

This study was approved by the National Strategic Coordinating Center of Clinical Research and HIRA in Korea and the Institutional Review Board of Asan Medical Center, Seoul, Korea. It conforms to the provisions of the Declaration of Helsinki (as revised in Seoul, 2008). All participants enrolled in the study provided written informed consent.

Baseline demographic data of the participants were acquired from a database that is maintained by the Health Screening and Promotion Center at Asan Medical Center. The following data were collected via a systemized questionnaire prior to the general health examination: any medical history of angina, MI, stroke, structural heart disease, coronary revascularization, hypertension, diabetes mellitus, hyperlipidemia, or malignancy; family history of IHD; smoking status; physical activity; and education status. A family history of IHD was defined as IHD occurring in a first-degree relative of any age. Smoking habits were categorized as never, previous, or current smoker; drinking habits were simply

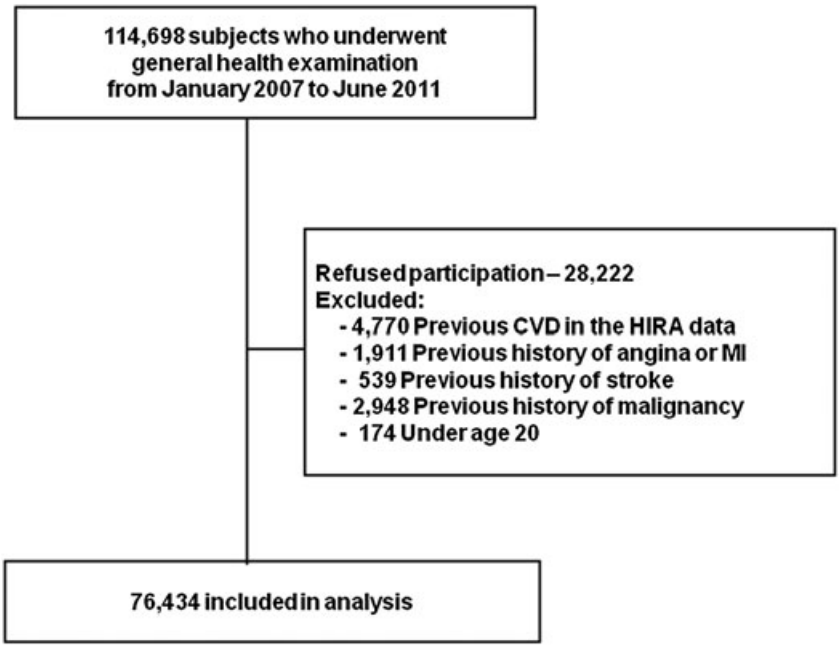

Figure 1 Overview of the study population with inclusion and exclusion criteria. CVD, cardiovascular disease; HIRA, the Health Insurance Review & Assessment Service; MI, myocardial infarction.

categorized according to frequency per week (≤3 times/week or ≥4 times/week); and physical activity was classified according to exercise frequency (≤2 days/week or ≥3 days/week).

Height and weight were measured with participants wearing light clothing without shoes. Blood pressure was measured with an electric sphygmomanometer on the right arm with participants in a sitting position after a 5-min rest. Body mass index (BMI) was calculated as weight in kilograms divided by height (in meters) squared. Blood samples were obtained in the morning after an overnight fast. Plasma glucose was measured by the hexokinase method using an autoanalyzer (Toshiba, Tokyo, Japan). Standard liver function testing and total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were also measured using an autoanalyzer (Toshiba). Ion-exchange HPLC using an automated analyzer (Variant II; Bio-Rad Laboratories, Hercules, CA, USA) was used to determine HbA1c.

Disease definitions

Obesity and hypertension

Obesity was defined by the World Health Organization (WHO) Asian reference as BMI >25 kg/m^2.[31] Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or the use of antihypertensive medications.

Definitions of dysglycemia

Prediabetes was defined by FPG only (100–125 mg/dL), HbA1c only (5.7%–6.4% [39–47 mmol/mol]), or a combination of FPG and HbA1c (FPG 100–125 mg/dL or HbA1c 5.7%–6.4% [39–47 mmol/mol]). Similarly, diabetes was defined by FPG only (≥126 mg/dL), HbA1c only (≥6.5% [48 mmol/mol]), or their combination (FPG ≥126 mg/dL or HbA1c ≥6.5% [48 mmol/mol]).

Outcome definitions

Three major outcomes were assessed. The overall CVD event was defined as a composite of cardiovascular death, MI, stroke (hemorrhagic and ischemic), coronary revascularization, hospitalization or out-patient visit with IHD, other vascular disease, or congestive heart failure. Cardiovascular death, MI, revascularization, and hospitalization with IHD were classified as major IHD events. Major CVD events were also defined as a composite of cardiovascular death, MI, stroke (hemorrhagic and ischemic), coronary revascularization, and hospitalization with IHD. In participants with multiple events, the first event was considered to be the component of the composite outcome. Deaths up to 31 December 2011 were confirmed by matching the information to the death records. To this end, death certificates in the National Statistical Office were identified by using personal identification numbers that were assigned to the participants at birth. The abstractors coded the recorded

underlying causes of death according to the ICD-10. The causes of death were classified as cardiovascular if ICD-10 codes I00–99 and R96 were recorded. Myocardial infarction and stroke were ascertained by the hospital discharge databases of the HIRA (ICD-10 codes I21–22 and I60–69). Coronary revascularizations in the HIRA database were identified using the procedure codes of PCI (M6551, M6552, M6561–4, M6571, and M6572) and coronary artery bypass surgery (O1641, O1642, O1647, OA641, OA642, and OA647). Hospitalizations with IHD other than MI (ICD-10 codes I20, 23–25), other vascular disease (ICD-10 code I70), or congestive heart failure (ICD-10 code I50) were defined by the hospital discharge databases of the HIRA. Out-patient visits with IHD, other vascular disease, or congestive heart failure were also identified using the HIRA database.

Statistical analyses

Baseline characteristics of participants by sex and each of the three different criteria for prediabetes were compared by analysis of variance or Chi-squared tests. To estimate incidence rates of CVD according to prediabetes and diabetes, we calculated the person-years at risk of all the participants included in the study. For participants who had events related to outcomes, the affected time was time to events, and for participants who had no events, the individual time at risk was the follow-up time. The incidence rate was estimated by the total number of events divided by 100 000 person-years at risk. In addition, to evaluate the association of CVD according to different prediabetes criteria, we constructed multivariate logistic regression models weighted with the person-year data of the participants.[32] Based on the model, we estimated the odds ratios (ORs) for developing CVD of the prediabetes and diabetes groups compared with participants with normal glucose regulation. Models were initially adjusted for age and sex, and then adjusted for multiple covariates for each endpoint. Statistical analyses were conducted using SAS version 9.13 (SAS Institute, Cary, NC, USA). All tests were two-sided and $P < 0.05$ was considered significant.

Results

Table 1 lists the baseline characteristics of participants. Figure 2 shows the prevalence of prediabetes and diabetes by different criteria at baseline. The prevalence of prediabetes by FPG only, HbA1c only, and combined criteria was 26.4%, 19.3%, and 35.2%, respectively. The prevalence of diabetes using these criteria was 8.3%, 8.3%, and 9.2%, respectively.

During a median follow-up of 3.1 (interquartile range [IQR] 1.9–4.3) years, 5800 overall CVD events were recorded, including 782 major CVD events and 430 major IHD events. Incidence rates of overall CVD (per 100 000 person-years) in prediabetes were estimated to be 3460 by FPG only, 3684 by HbA1c only, and 3434 using combined criteria (Table 2). Age- and sex-adjusted HRs for the overall CVD events were significantly higher for participants with IFG (HR 1.19; 95% confidence interval [CI] 1.08–1.31) and diabetes (HR 2.11; 95% CI 1.88–2.37) by FPG only, prediabetes (HR 1.28; 95% CI 1.16–1.42) and diabetes (HR 2.12; 95% CI 1.89–2.37) by HbA1c only, and prediabetes (HR 1.20; 95% CI 1.09–1.32) and diabetes (HR 2.15; 95% CI 1.91–2.41) using combined criteria. After adjusting for multiple conventional risk factors, such as hypertension, low-density lipoprotein cholesterol (LDL-C) and HDL-C levels, smoking status, and family history of CVD, the HRs for overall CVD were significantly higher for participants with prediabetes defined only by HbA1c (HR 1.12; 95% CI 1.01–1.24).

Age- and sex-adjusted HRs for major IHD events were significantly higher for participants with prediabetes defined by HbA1c only (HR 1.54; 95% CI 1.20–1.98) and combined criteria (HR 1.28; 95% CI 1.01–1.62). For PCI, age- and sex-adjusted HRs were significantly higher

Table 1 Baseline characteristics of the study participants

No. subjects	76 434
No. men	43 749 (57.2%)
Age (years)	47.5 ± 10.5
BMI (kg/m^2)	23.7 ± 2.9
Obesity (BMI ≥ 25 kg/m^2)	31.5%
Waist circumference (cm)	
Men	85.8 ± 7.6
Women	76.4 ± 8.0
Smoking status	
Current smoker	24.1%
Ex-smoker	30.6%
Alcohol use	40.6%
Exercise	37.0%
Hypertension	20.2%
SBP (mmHg)	121.4 ± 13.4
DBP (mmHg)	73.6 ± 9.9
Total cholesterol (mmol/L)	4.97 ± 0.89
HDL-C (mmol/L)	1.45 ± 0.36
LDL-C (mmol/L)	3.11 ± 0.77
Triglycerides (mmol/L)	1.40 ± 0.81
FPG (mmol/L)	5.48 ± 1.07
HbA1c	
%	5.5 ± 0.7
mmol/mol	37 ± 6
Family history of CVD	5.5%

Unless indicated otherwise, data are given as the mean ± SD.
SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; CVD, cardiovascular disease.

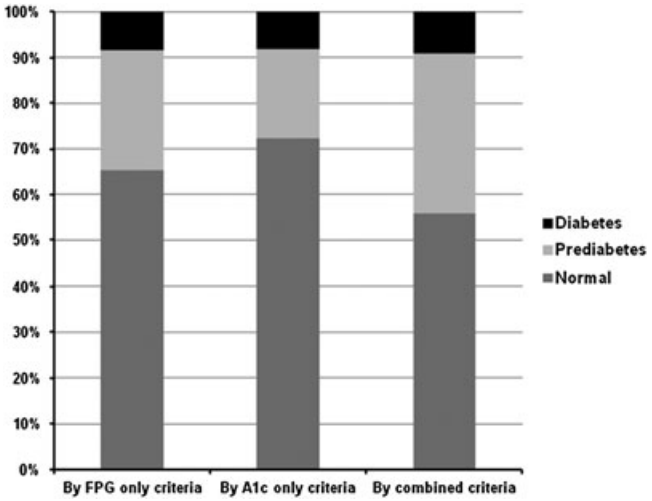

Figure 2 Prevalence of prediabetes and diabetes according to fasting plasma glucose (FPG) only, HbA1c only, or combined criteria at baseline.

for participants with prediabetes defined by HbA1c only (HR 1.57; 95% CI 1.12–2.20). Age- and sex-adjusted and multivariate-adjusted HRs for out-patient visits with IHD were significantly higher for prediabetes defined by HbA1c only and combined criteria (data not shown). For diabetes, age- and sex-adjusted and multivariate-adjusted HRs for overall CVD events, major IHD events, major CVD events, stroke, and all-cause mortality were significantly higher using all three criteria (Table 2).

When we analyzed men and women separately to see whether there is a gender difference in risk, no significant differences were observed for HRs for overall CVD, major IHD, and major CVD events between men and women by each criterion (Table 3).

Discussion

The results of the present study show that prediabetes and diabetes are associated with an increased overall risk of CVD. Following adjustment for age and sex, overall CVD risk was increased by 19%, 28%, and 20% for prediabetes defined by IFG only, HbA1c only, and combined criteria, respectively. After further adjustments for other conventional risk factors, participants with prediabetes defined by HbA1c only had a 12% increased overall risk of CVD events. For major IHD events, prediabetes defined by either HbA1c only or combined criteria had increased risks of 54% and 28%, respectively, after adjustment for age and sex. These results suggest that prediabetes defined by HbA1c seems to be more strongly and independently associated with the overall risk of CVD. These results are consistent with those of previous studies[22–24] showing that HbA1c is more strongly associated with CVD risk than FPG.

Because previous studies[33,34] suggested that atherosclerosis develops before the onset of clinical diabetes, we wanted to know whether non-diabetic dysglycemia could initiate an atherosclerotic process and to determine which criteria would be more useful for early recognition of the risk in clinical practice. Therefore, we compared the three criteria of prediabetes that were already defined (IFG, prediabetes by HbA1c, and combined criteria), instead of the quartile or quintile categories of HbA1c used in other studies.[6,22–25] We could not compare prediabetes by post-challenge plasma glucose (IGT) because oral glucose tolerance tests are not usually performed in general health check-ups or in routine clinical practice, although post-challenge hyperglycemia has been reported to be a better predictor of CVD.[15–17] Therefore, adding HbA1c criteria when defining prediabetes could more reasonably detect people at high risk of CVD than the previously used IFG, which is based only on the FPG level. Our results suggest that physicians should try to identify other CVD risk factors and to actively control those factors when prediabetes has been diagnosed, especially when it has been diagnosed in accordance with HbA1c criteria. When people are diagnosed with prediabetes, they are usually recommended to start lifestyle modifications, including diet and exercise. Therefore, detecting prediabetes with proper criteria may be helpful in reducing the risk of not only diabetes, but also CVD as a result of lifestyle improvements. Recently, a 5-year follow-up cohort study[35] showed that both overall level of daily ambulatory activity and change in ambulatory activity over 12 months exhibited a graded inverse association with the risk of CVD in individuals with IGT at baseline.

Table 2 Incidence rates and hazard ratios (95% confidence intervals) of cardiovascular disease according to degree of dysglycemia by different definitions

	By FPG only			By HbA1c only			Combined criteria		
	Normal	Prediabetes (IFG)	Diabetes	Normal	Prediabetes	Diabetes	Normal	Prediabetes	Diabetes
Total no. subjects	49 779	20 256	6399	55 261	14 821	6 352	42 538	26 966	6930
Overall CVD events									
Person-years	136 961	52 769	14 671	156 352	33 755	14 293	121 173	67 394	15 834
No. cases	2642	1826	1332	3117	1355	1328	2083	2314	1403
Incidence rate	1929	3460	9079	1906	3684	7671	1719	3434	8861
Unadjusted HR	1	1.60 (1.46–1.75)	3.61 (3.23–4.03)	1	1.79 (1.61–1.98)	3.56 (3.19–3.97)	1	1.67 (1.52–1.82)	3.82 (3.42–4.27)
Age- and sex-adjusted HR	1	1.19 (1.08–1.31)	2.11 (1.88–2.37)	1	1.28 (1.16–1.42)	2.12 (1.89–2.37)	1	1.20 (1.09–1.32)	2.15 (1.91–2.41)
MV-adjusted HR*	1	1.05 (0.95–1.15)	1.72 (1.52–1.93)	1	1.12 (1.01–1.24)	1.75 (1.55–1.96)	1	1.05 (0.95–1.15)	1.70 (1.51–1.92)
Major IHD events									
Person-years	143 356	57 052	17 776	163 931	36 895	17 377	126 242	72 879	19 082
No. cases	198	120	112	206	112	112	143	168	119
Incidence rate	138	210	630	126	304	645	113	231	624
Unadjusted HR	1	1.60 (1.26–2.04)	4.33 (3.36–5.57)	1	2.33 (1.83–2.98)	4.72 (3.68–6.05)	1	2.08 (1.64–2.63)	5.18 (3.98–6.74)
Age- and sex-adjusted HR	1	1.00 (0.79–1.27)	1.87 (1.44–2.42)	1	1.54 (1.20–1.98)	2.20 (1.70–2.85)	1	1.28 (1.01–1.62)	2.15 (1.64–2.82))
MV-adjusted HR*	1	0.88 (0.69–1.12)	1.52 (1.16–1.98)	1	1.24 (0.97–1.60)	1.76 (1.35–2.29)	1	1.08 (0.85–1.38)	1.67 (1.26–2.20)
Major CVD events									
Person-years	142 816	56 777	17 513	163 350	36 648	17 107	125 821	72 482	18 803
No. cases	373	222	187	408	191	183	284	303	195
Incidence rate	261	391	1068	250	521	1070	226	418	1037
Unadjusted HR	1	1.54 (1.26–1.88)	3.61 (2.89–4.50)	1	1.86 (1.51–2.30)	3.55 (2.85–4.42)	1	1.75 (1.44–2.12)	3.89 (3.10–4.89)
Age- and sex-adjusted HR	1	1.05 (0.86–1.28)	1.76 (1.40–2.21)	1	1.23 (0.99–1.53)	1.79 (1.42–2.25)	1	1.14 (0.94–1.39)	1.80 (1.42–2.28)
MV-adjusted HR*	1	0.94 (077–1.15)	1.48 (1.17–1.87)	1	1.05 (0.84–1.30)	1.49 (1.18–1.88)	1	0.99 (0.81–1.22)	1.46 (1.14–1.86)
Stroke									
Person-years	143 170	56 980	17 708	163 722	36 831	17 305	126 080	72 768	19 010
No. cases	185	105	89	209	85	85	147	141	91
Incidence rate	129	184	503	128	231	491	117	194	479
Unadjusted HR	1	1.60 (1.22–2.07)	3.83 (2.87–5.11)	1	1.72 (1.30–2.29)	3.46 (2.59–4.61)	1	1.66 (1.29–2.15)	3.01 (2.01–5.26)
Age- and sex-adjusted HR	1	1.15 (0.88–1.50)	2.01 (1.49–2.72)	1	1.12 (0.84–1.49)	1.80 (1.33–2.43)	1	1.12 (0.86–1.45)	1.92 (1.41–2.62)
MV-adjusted HR*	1	1.05 (0.80–1.37)	1.70 (1.25–2.32)	1	1.00 (0.74–1.33)	1.51 (1.11–2.06)	1	1.00 (0.77–1.30)	1.58 (1.15–2.17)
NH stroke									
Person-years	143 324	67 029	17 742	163 869	36 887	17 340	126 199	72 850	19 047
No. cases	80	58	54	102	40	50	67	70	55
Incidence rate	56	87	304	62	108	288	53	96	289
Unadjusted HR	1	1.72 (1.20–2.47)	4.22 (2.85–6.24)	1	1.74 (1.18–2.56)	3.40 (2.28–5.06)	1	1.68 (1.18–2.39)	4.18 (2.80–6.24)
Age- and sex-adjusted HR	1	1.19 (0.83–1.72)	2.09 (1.39–3.15)	1	1.14 (0.77–1.68)	1.70 (1.12–2.57)	1	1.10 (0.77–1.57)	1.94 (1.28–2.96)
MV-adjusted HR*	1	1.06 (0.73–1.54)	1.73 (1.34–2.62)	1	1.00 (0.67–1.49)	1.41 (0.92–2.14)	1	0.96 (0.67–1.39)	1.56 (1.01–2.39)
PCI									
Person-years	143 102	56 941	17 651	163 672	36 772	17 249	126 051	72 695	18 947
No. cases	169	98	90	172	95	90	123	139	95
Incidence rate	118	172	510	105	258	522	98	191	501

Table 2 (Continued)

	By FPG only			By HbA1c only			Combined criteria		
	Normal	Prediabetes (IFG)	Diabetes	Normal	Prediabetes	Diabetes	Normal	Prediabetes	Diabetes
Unadjusted HR	1	1.40 (1.00–1.94)	3.86 (2.73–5.47)	1	1.74 (1.18–2.56)	3.40 (2.28–5.06)	1	1.85 (1.35–2.55)	4.57 (3.19–6.55)
Age- and sex-adjusted HR	1	0.88 (0.63–1.22)	1.72 (1.20–2.46)	1	1.57 (1.12–2.20)	2.21 (1.55–3.16)	1	1.16 (0.84–1.61)	1.97 (1.36–2.87)
MV-adjusted HR*	1	0.74 (0.53–1.04)	1.37 (0.95–1.97)	1	1.20 (0.85–1.69)	1.72 (1.20–2.48)	1	0.94 (0.67–1.30)	1.48 (1.01–2.16)
All-cause mortality									
Person-years	143 058	56 893	17 709	163 566	36 781	17 313	125 990	72 664	19 005
No. cases	140	88	54	166	65	51	110	113	59
Incidence rate	98	155	305	101	177	295	87	156	310
Unadjusted HR	1	1.87 (1.18–2.96)	4.51 (2.74–7.44)	1	1.90 (1.16–3.09)	3.85 (2.35–6.33)	1	1.99 (1.26–3.15)	5.08 (3.05–8.46)
Age- and sex-adjusted HR	1	1.29 (0.81–2.05)	2.19 (1.30–3.68)	1	1.21 (0.74–1.99)	1.87 (1.12–3.13)	1	1.29 (0.81–2.06)	2.32 (1.36–3.96)
MV-adjusted HR*	1	1.37 (0.85–2.18)	2.10 (1.23–3.60)	1	1.21 (0.73–2.00)	1.73 (1.02–2.95)	1	1.35 (0.84–2.17)	2.25 (1.30–3.91)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease; NH, non-hemorrhagic; PCI, percutaneous coronary intervention; MV, multivariate.

*Note, MV-adjusted HRs were adjusted for age, sex, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking, a family history of CVD, and body mass index.

However, other studies[27,28] did not show an additional role of HbA1c to conventional CVD risk factors for predicting CVD risk in people with prediabetes. Although the reasons for these discrepancies are currently unclear, different ethnicities of the study participants could be one of the reasons, because disparities in HbA1c levels among different ethnicities have been reported[36,37] and the association between non-diabetic HbA1c levels and all-cause and CVD mortality were reported to vary according to race and/or ethnicity.[39] Other possible explanations for these discrepancies include different methodologies, such as outcome definitions and/or duration of follow-up. In the present study, the risks for prediabetes defined by HbA1c were higher for the composite endpoints, such as overall CVD or major IHD and CVD events. However, the risks for prediabetes defined by HbA1c were not higher than those defined by FPG for individual endpoints, such as stroke or mortality. In the case of mortality, its incidence may be too low to reach statistical significance during the relatively short follow-up period. Among individual endpoints, the superiority of HbA1c seems to come primarily from the difference in PCI. However, in addition to cardiovascular death and MI, composite endpoints, including revascularization and hospitalization with IHD, have also been used as major outcomes in several studies.[39,40] Although the causal relationship between HbA1c and atherosclerosis is unclear and the mechanism by which HbA1c is associated with increased risk for CVD is not simple, HbA1c as a precursor of advanced glycation end-products (AGEs) could be related to a low degree of inflammation and future atherosclerosis.[41,42]

We did not observe any significant differences in HRs for overall CVD, major IHD, and major CVD events between men and women. The HRs for the IHD events seemed to be higher in women than in men, but the difference did not reach statistical significance, probably because the numbers of events were small. In general, it has been thought that CVD or IHD events occur more often among men than women. However, there have been several reports that women show increased risk for IHD and related mortality.[43–46]

The present study has several limitations. First, the study participants were not a random sample of the general population. Therefore, the results may not be generalizable to the entire Korean population. Second, we could not exclude participants who developed incident diabetes before CVD events because we only assessed baseline FPG or HbA1c levels. However, most other studies also used only baseline measures of glycemia. Third, the follow-up period may be too short to obtain sufficient outcomes. This could have led to an underestimation of outcomes, although the confounding effects from incident

Table 3 Hazard ratios (95% confidence intervals) of cardiovascular disease according to degree of dysglycemia by different definitions in men and women

	By FPG only criteria			By HbA1c-only criteria			By combined criteria		
	Normal	Prediabetes (IFG)	Diabetes	Normal	Prediabetes	Diabetes	Normal	Prediabetes	Diabetes
Overall CVD events									
Men	1	1.09 (0.96–1.26)	2.21 (1.93–2.53)	1	1.34 (1.17–1.52)	2.31 (2.03–2.64)	1	1.11 (0.99–1.25)	2.24 (1.96–2.57)
Women	1	1.40 (1.19–1.64)	1.72 (1.36–2.18)	1	1.14 (0.95–1.36)	1.58 (1.25–2.00)	1	1.314 (1.12–1.54)	1.75 (1.38–2.21)
Major IHD events									
Men	1	0.92 (0.71–1.21)	1.80 (1.35–2.39)	1	1.54 (1.17–2.03)	2.12 (1.59–2.82)	1	1.17 (0.89–1.52)	2.00 (1.49–2.70)
Women	1	1.97 (0.97–3.99)	2.62 (1.11–6.17)	1	2.27 (1.10–4.70)	3.21 (1.375–7.48)	1	3.01 (1.36–6.68)	4.17 (1.59–10.91)
Major CVD events									
Men	1	0.95 (0.75–1.22)	1.87 (1.43–2.43)	1	1.22 (0.94–1.59)	1.95 (1.50–2.54)	1	1.99 (0.78–1.26)	1.87 (1.42–2.46)
Women	1	1.39 (0.95–2.04)	1.11 (0.61–2.02)	1	1.18 (0.79–1.77)	0.93 (0.50–1.71)	1	1.48 (1.02–2.16)	1.09 (0.58–2.02)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; CVD, cardiovascular disease.

diabetes would be minimized. Finally, including data from out-patient visits may have led to an overestimation of the outcomes. However, any possible underestimation of outcomes because of the short duration of follow-up could be partly balanced through this analysis.

Despite these limitations, our results suggest that HbA1c can be used during health screenings to help identify individuals who will need more follow-up for potential CVD development in the future. In South Korea, health screenings are widely practiced and may be more successful in identifying individuals with prediabetes than more traditional physician–patient office visits. However, in other countries there may be cultural or social system differences in seeing a healthcare provider and screening large numbers of the population with HbA1c may not be applicable.

In conclusion, the present study showed that prediabetes defined by HbA1c only was associated with increased overall risk of CVD and major IHD events, and adding HbA1c in defining prediabetes has a certain role in detecting individuals at high risk of CVD in Korea. Further long-term follow-up studies should be performed to confirm this association and to determine whether intensive control of risk factors at an early stage can reduce the actual risk of CVD events in individuals with prediabetes identified by HbA1c criteria.

Disclosure

There are no potential conflicts of interest relevant to this article for any of the authors.

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