Impact of Visit-to-Visit Fasting Plasma Glucose Variability on the Development of Type 2 Diabetes: A Nationwide Population-Based Cohort Study

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Diabetes Care 2018;41:2610–2616 | https://doi.org/10.2337/dc18-0802

OBJECTIVE

Although increasing evidence suggests the association between short-term variability of fasting plasma glucose (FPG) and diabetic complications or mortality, the impact of visit-to-visit variability of FPG on the development of type 2 diabetes (T2D) has not been evaluated.

RESEARCH DESIGN AND METHODS

Our analysis included 131,744 Korean men and women without diabetes using the Korean National Health Insurance System cohort with periodic health examination program. FPG variability was calculated using the coefficient of variation (FPG-CV), SD (FPG-SD), and variability independent of the mean (FPG-VIM).

RESULTS

During the median follow-up time of 8.3 years, Kaplan-Meier curves demonstrated lower disease-free probability in the higher FPG variability group compared with the lower FPG variability group. Multivariable Cox proportional hazards analysis exhibited that the hazard ratio for incident T2D was 1.67 (95% CI 1.58–1.77, $P < 0.001$) in the highest quartile of FPG-CV compared with the lowest quartile of FPG-CV after adjusting for confounding variables, including mean FPG. The association between FPG variability and the risk of T2D was consistent when modeling using FPG-SD and FPG-VIM in both normal and impaired fasting glucose groups. A 1 SD increase in the FPG-CV was associated with a 24% increased risk of T2D in the fully adjusted model.

CONCLUSIONS

Increased variability of FPG is associated with the development of T2D independently of diverse risk factors.

Glycemic variability has recently drawn attention as another aspect of glycemic control and may contribute to additional risk of diabetic complications independent of hemoglobin A_{1c} (HbA_{1c}) (1). Several human studies (2,3) suggested an association between glycemic variability and all-cause/cardiovascular mortality in patients with type 2 diabetes. Interestingly, mean fasting plasma glucose (FPG) level was not significantly associated with mortality in a multivariate analysis after adjusting for the coefficient of variation (CV) of FPG (3). In addition, long-term FPG variability was

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Received 16 April 2018 and accepted 28 August 2018.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-0802/-/DC1.

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reported as a risk factor for microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy in patients with type 2 diabetes (4–6).

The underlying mechanisms linking glycemic variability and diabetic complications are complex and not fully understood. Previous studies (7,8) demonstrated that fluctuations in blood glucose levels had a greater impact on oxidative stress, inflammatory cytokines, and endothelial function than sustained hyperglycemia. On the other hand, the oxidative stress–activated signaling pathway leads to both insulin resistance and impaired insulin secretion, which are the main pathogenic mechanisms of diabetes (9). Oxidative stress and subsequent activation of the c-Jun N-terminal kinase pathway are involved in the development of type 2 diabetes (10). In addition, many previous studies have supported the role of inflammatory factors in the pathogenesis of obesity-induced insulin resistance and the development of type 2 diabetes (11). Circulating biomarkers of inflammatory pathways and endothelial dysfunction are associated with the development of type 2 diabetes (12).

Although this evidence suggests a relationship between long-term glycemic variability and the development of type 2 diabetes, to the best of our knowledge, there has been no previous study of this issue. Therefore, we examined the impact of visit-to-visit FPG variability on the development of type 2 diabetes using a large population-based cohort's data from the National Health Insurance Service (NHIS)-National Health Screening Cohort (HEALS).

RESEARCH DESIGN AND METHODS

Study Design and Participants

Analysis was performed using data from the NHIS-HEALS database recorded from 1 January 2002 to 31 December 2013. The Korean NHIS is a government-operated mandatory social health insurance program, based on insurance claims, that covers ~98% of all Koreans (13). The Korean national health examination is conducted annually or biannually, and the attrition rate in this database over the time of follow-up was low (14). The NHIS-HEALS database includes ~10% of all participants who were >40 years old and who had undergone the national health examination provided by the NHIS. This database is composed of a set of health information databases, which includes an eligibility database (e.g., age, sex, socioeconomic variables), a health examination database (questionnaires on lifestyle and results of laboratory measurements), and a medical treatment database (diagnosis, medication, admission, and death). In the current study, data from a database of 209,226 Korean men and women who participated in health examinations in 2007 (index year) were examined. After the application of exclusion criteria, 131,744 individuals were finally included in our study (Supplementary Fig. 1). The median follow-up period was 8.3 (interquartile range 8.1–8.6) years. Blood samples were acquired after overnight fasting, and the quality control procedures followed the Korean Association of Laboratory Quality Control. The NHIS database was anonymized based on confidentiality guidelines. The Korea University institutional review board approved this study protocol in accordance with the Declaration of Helsinki of the World Medical Association.

Assessment of FPG Variability Indexes

Glycemic variability was determined as variability in FPG values measured in serial health examinations, and the following three indices of variability were calculated: *1*) CV; *2*) SD; and *3*) variability independent of the mean (VIM). VIM was defined as $100 \times \mathrm{SD}/\mathrm{mean}^{\beta}$, where β is the regression coefficient, on the basis of the ln of the SD over the ln of the mean. The number of FPG measurements per individual ranged from three to six: three measurements (n = 68,027, 52%); four measurements (n = 14,078, 11%); five measurements (n = 18,663, 14%); and six measurements (n = 30,976, 24%).

Definitions

The presence of type 2 diabetes was defined based on fasting glucose levels ≥7 mmol/L (126 mg/dL) or the presence of at least one claim per year for a prescription of antidiabetes medication under ICD-10 codes (E11–E14). Impaired fasting glucose (IFG) was defined as fasting glucose levels between 5.6 mmol/L (100 mg/dL) and 6.9 mmol/L (125 mg/dL) among individuals without diabetes. The presence of hypertension was defined based on systolic/diastolic blood pressure ≥140/90 mmHg or the presence of at least one claim per year for a prescription of an antihypertensive agent under ICD-10 codes (I10–I13, I15). The presence of dyslipidemia was defined based on a total cholesterol level of ≥6.2 mmol/L or the presence of at least one claim per year for a prescription of an antihyperlipidemic agent under ICD-10 codes (E78). Cardiovascular disease (CVD) was defined as a history of myocardial infarction, angina, ischemic heart disease, and ischemic stroke under ICD-10 codes (I20–222, I24, I63), and cancer was defined as any ICD-10 code starting with C (malignant neoplasm). Information on current smoking status, alcohol consumption, and family history of diabetes was obtained by questionnaire. Regular exercise was defined as physical activity that was performed at least five times per week. Income level was dichotomized at the lower 10%.

Statistical Analysis

Baseline characteristics were expressed as the mean (SD) or number of participants (%). Participants were classified into four groups according to the FPG variability quartiles. Differences in the distribution of baseline characteristics between FPG variability quartiles were identified using ANOVA or χ^2 test, as appropriate. The incidence rates of primary outcomes were calculated by dividing the number of incident cases by the total follow-up period (person-years). The disease-free probability of type 2 diabetes by quartiles of FPG variability was calculated by using the Kaplan-Meier method, and the log-rank test was performed to confirm differences across the groups. Hazard ratios (HRs) and 95% CI values of type 2 diabetes were analyzed using the Cox proportional hazards model for quartile or decile groups of FPG variability after adjusting for age, sex, BMI, alcohol consumption, smoking, regular exercise, income, hypertension, dyslipidemia, family history of diabetes, and mean FPG. The likelihood ratio test for trends was used to elucidate a relationship between the quartile of each FPG variability and the risk of type 2 diabetes. We tested the assumption of proportionality of hazards by the numerical method proposed by Lin et al. (15) derived from cumulative sums of martingale residuals. We found no evidence of violating the proportional hazards assumption. The HR (95% CI) of

the development of diabetes for every 1 SD increase in FPG variability was calculated after adjusting for confounding factors. All statistical results were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC), and P values <0.05 were considered statistically significant.

RESULTS

Baseline Characteristics of Participants

The characteristics of the study participants according to FPG variability quartiles defined with CV (FPG-CV) are described in Table 1. Subjects in higher quartiles of FPG variability were older, mostly male, with a higher prevalence of hypertension, dyslipidemia, and low–income level status. Furthermore, higher quartiles of FPG variability tended to have poor health habits such as smoking, drinking, and lack of exercise. Similar associations were observed when two other FPG variability measurements (FPG-SD, FPG-VIM) were adopted (Supplementary Tables 1 and 2). The patterns of relationship were similar when classified into normal and IFG groups. However, BMI and total cholesterol levels were not significantly different according to quartiles of FPG variability, shown as FPG-CV.

Effect of FPG Variability on the Development of Type 2 Diabetes

HRs and 95% CIs of newly diagnosed type 2 diabetes across the FPG variability quartiles, calculated with the Cox proportional hazards model adjusted for various confounding factors, are demonstrated in Table 2. When CV was used as a marker of FPG variability, the HR for type 2 diabetes was 1.67 (95% CI 1.58–1.77, $P < 0.001$) in the highest quartile of FPG-CV, compared with the lowest quartile of FPG-CV, after adjusting for diverse confounding factors, including mean FPG values. Excluding subjects with a history of CVD or cancer did not attenuate the association between FPG variability and the incidence of type 2 diabetes (Supplementary Table 3). Very similar HR values were observed with the FPG-SD and FPG-VIM methods (FPG-SD: HR 1.63, 95% CI 1.54–1.73, $P < 0.001$; FPG-VIM: HR 1.65, 95% CI 1.56–1.75, $P < 0.001$). Kaplan-Meier curves demonstrated lower disease-free probability in the higher FPG variability quartile groups, shown as FPG-CV, FPG-SD, and FPG-VIM, compared with the lower FPG variability groups (Fig. 1). The effect of FPG variability on type 2 diabetes across the FPG variability deciles was evaluated (Supplementary Fig. 2). There were clear associations of FPG variability with increased risk of type 2 diabetes in total, normal, and IFG groups. Figure 2 shows the HRs and 95% CIs of type 2 diabetes for every 1 SD increase in FPG variability. The adjusted HRs for the development of type 2 diabetes with FPG variability using FPG-CV, FPG-SD, and FPG-VIM were 1.24 (95% CI 1.22–1.27, $P < 0.001$), 1.23 (95% CI 1.20–1.25, $P < 0.001$), and 1.23 (95% CI 1.21–1.26, $P < 0.001$), respectively, after adjusting for age, sex, BMI, income, family history of diabetes, hypertension, dyslipidemia, current smoking status, alcohol intake, exercise, and mean FPG.

CONCLUSIONS

In this study involving a large longitudinal population-based cohort, we showed that FPG variability, shown with three different indicators (FPG-CV, FPG-SD, and FPG-VIM), was a risk factor for the development of type 2 diabetes during a follow-up period of 8.3 years. Furthermore, we observed an independent association of FPG variability with increased risk of type 2 diabetes even after adjusting for lifestyle parameters and anthropometric and laboratory variables including mean FPG, indicating that our results might be robust.

HbA_{1c} and mean glucose levels are fundamental in the management of diabetes. Interestingly, recent studies and meta-analyses have emphasized that glycemic variability may be important in the macrovascular and microvascular complications and mortality in patients with type 2 diabetes. In the Verona Diabetes Study, Muggeo et al. (3) reported that long-term variability of FPG predicted the 10-year survival of patients with type 2 diabetes. Hirakawa et al. (16) investigated the relationship of

Table 1—Baseline characteristics of subjects according to the quartiles of FPG variability (FPG-CV)

	Q1 (n = 32,935)	Q2 (n = 32,937)	Q3 (n = 32,936)	Q4 (n = 32,936)	P
Age (years), mean (SD)	55.9 (8.8)	55.0 (8.4)	55.1 (8.5)	56.1 (9.0)	<0.0001
Sex (male)	16,493 (50.1)	18,555 (56.3)	19,481 (59.1)	19,947 (60.6)	<0.0001
BMI (kg/m^2), mean (SD)	23.8 (2.8)	23.8 (2.8)	23.8 (2.8)	23.9 (2.9)	0.9244
FPG (mg/dL), mean (SD)	92.0 (8.9)	91.2 (8.6)	90.9 (8.0)	90.9 (7.1)	<0.0001
FPG variability, mean (SD)					
CV (%)	4.19 (1.43)	7.75 (0.88)	10.99 (1.04)	16.69 (3.37)	<0.0001
SD (mg/dL)	3.85 (1.37)	7.07 (1.03)	9.99 (1.29)	15.17 (3.19)	<0.0001
VIM (%)	3.84 (1.32)	7.07 (0.87)	10.00 (1.05)	15.19 (3.07)	<0.0001
Family history of diabetes	3,663 (11.1)	3,817 (11.6)	3,591 (10.9)	3,307 (10.0)	<0.0001
Hypertension	17,572 (53.4)	18,316 (55.6)	18,914 (57.4)	20,004 (60.7)	<0.0001
Dyslipidemia	10,265 (31.2)	10,510 (31.9)	10,726 (32.6)	11,068 (33.6)	<0.0001
Current smoker	5,087 (15.4)	6,016 (18.3)	6,697 (20.3)	7,284 (22.1)	<0.0001
Alcohol consumption	12,731 (38.7)	14,028 (42.6)	14,442 (43.8)	14,202 (43.1)	<0.0001
Regular exercise	3,574 (10.9)	3,211 (9.7)	3,064 (9.3)	3,192 (9.7)	<0.0001
Income (lower 10%)	2,171 (6.6)	2,411 (7.3)	2,572 (7.8)	2,917 (8.9)	<0.0001

Data are number of participants (%) unless otherwise specified. Q, quartile.

Table 2—HR and 95% CI of subjects with newly diagnosed type 2 diabetes by quartiles of FPG variability

	Events (*n*)	Follow-up duration (person-years)	Incidence rate (per 1,000 person-years)	Unadjusted		Model 1		Model 2	
				HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
FPG variability (FPG-CV)									
Q1	2,083	264,236	7.88	1		1		1	
Q2	2,071	263,962	7.85	1.00 (0.94–1.06)	0.9121	1.03 (0.97–1.10)	0.3082	1.09 (1.03–1.16)	0.0047
Q3	2,303	263,039	8.76	1.11 (1.05–1.18)	0.0004	1.14 (1.07–1.21)	<0.0001	1.30 (1.22–1.38)	<0.0001
Q4	2,846	259,685	10.96	1.39 (1.32–1.47)	<0.0001	1.37 (1.30–1.45)	<0.0001	1.67 (1.58–1.77)	<0.0001
P for trend				<0.0001		<0.0001		<0.0001	
FPG variability (FPG-SD)									
Q1	1,770	265,631	6.66	1		1		1	
Q2	1,913	264,698	7.23	1.09 (1.02–1.16)	0.0119	1.13 (1.06–1.20)	0.0003	1.08 (1.01–1.15)	0.0220
Q3	2,367	262,534	9.02	1.36 (1.28–1.44)	<0.0001	1.39 (1.30–1.47)	<0.0001	1.29 (1.21–1.37)	<0.0001
Q4	3,253	258,058	12.61	1.90 (1.79–2.01)	<0.0001	1.85 (1.75–1.97)	<0.0001	1.63 (1.54–1.73)	<0.0001
P for trend				<0.0001		<0.0001		<0.0001	
FPG variability (FPG-VIM)									
Q1	1,920	264,952	7.25	1		1		1	
Q2	2,000	264,292	7.57	1.05 (0.98–1.11)	0.1606	1.08 (1.02–1.15)	0.0125	1.10 (1.03–1.17)	0.0040
Q3	2,332	262,817	8.87	1.23 (1.16–1.30)	<0.0001	1.25 (1.18–1.33)	<0.0001	1.28 (1.21–1.36)	<0.0001
Q4	3,051	258,860	11.79	1.63 (1.54–1.73)	<0.0001	1.60 (1.51–1.69)	<0.0001	1.65 (1.56–1.75)	<0.0001
P for trend				<0.0001		<0.0001		<0.0001	

Model 1, adjusted for age and sex. Model 2, adjusted for age, sex, BMI, alcohol consumption, smoking, regular exercise, income, family history of diabetes, hypertension, dyslipidemia, and mean FPG. Q, quartile.

visit-to-visit variability in FPG and HbA_{1c} with the risks of microvascular and macrovascular events and all-cause mortality among patients with type 2 diabetes using data from the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial. In that study, glucose variability (GV) was clearly associated with microvascular and macrovascular events ($P = 0.005$ and $P < 0.001$, respectively). In a Chinese study (17) including 8,871 patients with type 2 diabetes, FPG variability was an important predictor of mortality, particularly in patients with poor glycemic control. Recently, Lin et al. (18) demonstrated that visit-to-visit variability of FPG is an independent predictor of ischemic stroke in patients with type 2 diabetes. Yang et al. (19) showed that visit-to-visit variability of FPG predicted the development of end-stage renal disease in 31,841 Chinese patients with type 2 diabetes. In addition, FPG variability, as measured by CV, was a potent predictor of the development of diabetic polyneuropathy in patients with type 2 diabetes during an average follow-up period of 7.2 years (6). In a recent meta-analysis (20), the low-GV group was associated with improved insulin resistance and reduced carotid intima-media thickness in patients with type 2 diabetes. Another meta-analysis (21) reported that long-term glycemic variability was positively associated with microvascular and macrovascular complications and mortality in patients with diabetes independent of the HbA_{1c} levels.

However, previous studies examining the prognostic significance of long-term glycemic variability in individuals without diabetes are scarce. In the general population, elevated visit-to-visit FPG variability predicted the risk of CVD and all-cause mortality independent of mean FPG and other baseline variables in 53,607 Chinese participants during a mean follow-up time of 4.9 years (22). Our study demonstrated the consistent association between glycemic variability and the development of type 2 diabetes in both normal and IFG groups after adjusting for confounding factors. We examined whether mean FPG modifies the association of FPG variability with the development of type 2 diabetes disease by including an interaction term between the mean FPG value and FPG variability in a Cox proportional hazards regression model. Results demonstrated no quantitative interactions because the effects of the three indexes were similar in low and high mean FPG and did not show a clear trend. This result is in line with the Verona study (3). There have been several studies investigating the possible mechanisms linking glycemic variability with the development of type 2 diabetes. Accumulating evidence has supported the role of oxidative stress in insulin resistance, impaired glucose secretion, and ultimately overt type 2 diabetes through the activation of diverse inflammatory pathways. Acute hyperglycemia increases circulating inflammatory cytokines through an oxidative mechanism in humans, and this effect is more prominent in individuals with impaired glucose tolerance (23). Intermittent hyperglycemia exaggerates reactive oxygen species production relative to chronic hyperglycemia. Monnier et al. (7) reported that stronger activation of oxidative stress occurs in glucose fluctuations than in sustained chronic hyperglycemia in patients with type 2 diabetes. Ceriello et al. (8) found that glycemic fluctuation has more deleterious effects on endothelial function and oxidative stress than stable constant hyperglycemia in both healthy individuals and patients with type 2 diabetes. Furthermore, Gillard et al. (24) reported that functioning β-cell mass negatively correlated with the CV of fasting plasma glycemia ($r = -0.78$). Kohnert et al. (25) showed that glycemic variability correlated with postprandial β-cell dysfunction in patients with type 2 diabetes. Women with previous

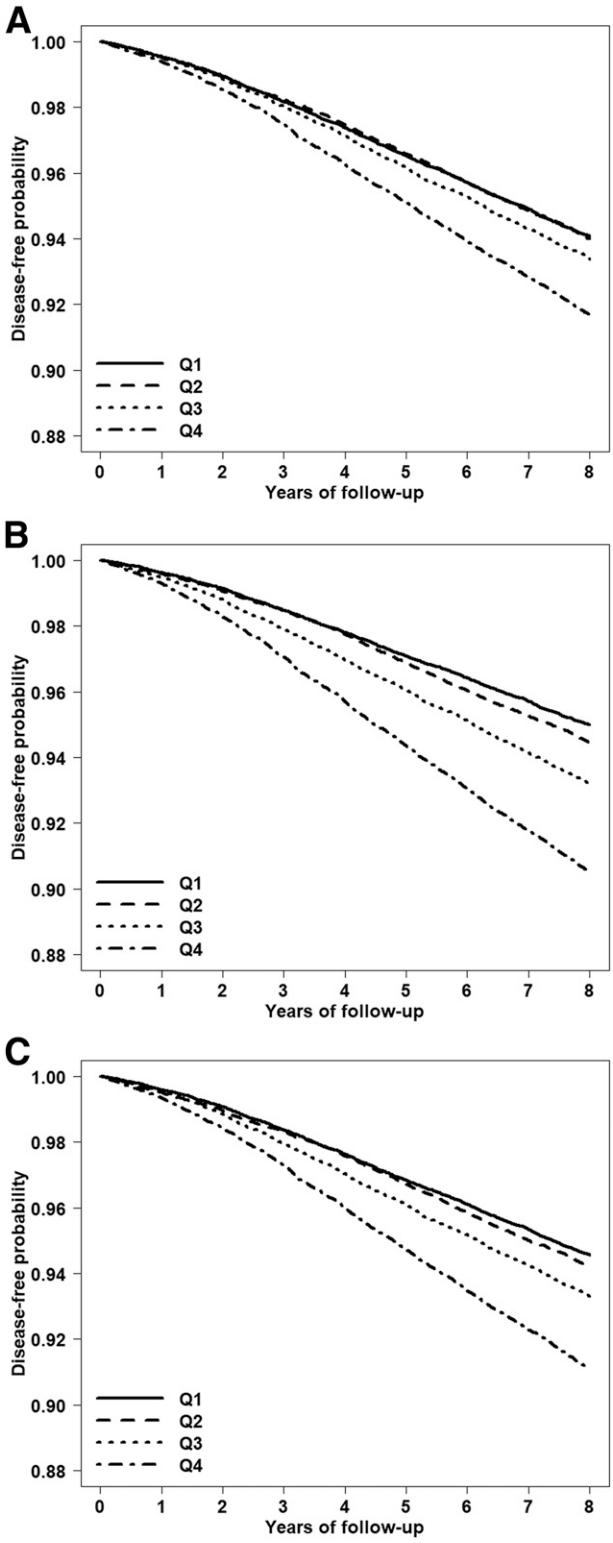

Figure 1—Kaplan-Meier estimates of disease-free probability in the risk of type 2 diabetes by quartiles of FPG variability: FPG-CV (*A*), FPG-SD (*B*), and FPG-VIM (*C*). Q, quartile.

gestational diabetes mellitus and postpartum normal glucose tolerance showed elevated glycemic variability, which is associated with impaired β-cell dysfunction (26). Furthermore, glycemic variability can be reduced by improving β-cell function with intensive insulin therapy in early type 2 diabetes (27). These results suggest the possibility that glycemic variability may consist of one marker of β-cell dysfunction in at-risk individuals before diabetes onset or in early type 2 diabetes. Exercise significantly reduced glycemic variability and oxidative stress markers in individuals with obesity with type 2 diabetes/impaired glucose tolerance (28). Another hypothesis related to the mechanism suggests that patients with higher FPG variability tend to have a higher prevalence of other risk factors for type 2 diabetes, such as old age, male sex, obesity, hypertension, dyslipidemia, and bad lifestyle habits. In this study, we tried to adjust for these confounding factors using multivariate model analyses.

There are various definitions of GV, including intraday GV, day-to-day GV, and visit-to-visit GV. Intraday GV or day-to-day GV could be assessed by self-monitoring of blood glucose or continuous glucose monitoring means, and visit-to-visit GV could be assessed by FPG or HbA_{1c} levels (29). SD is the most commonly reported index for GV. However, SD is significantly influenced by the mean value; thus, CV (SD divided by mean $\times$ 100 [%]) has been proposed to assess GV (30). There is no gold standard for quantifying FPG variability; therefore, in the current study we used three different indicators, namely FPG-SD, FPG-CV, and FPG-VIM, to evaluate the effect of long-term FPG variability.

The current study has several limitations. First, although we tried to adjust for diverse confounding variables using multivariate analyses, the possibility of residual confounding factors cannot be completely excluded. Second, our study included only Korean men and women, so our findings should be confirmed in independent populations. Third, the NHIS-HEALS database does not include data from oral glucose tolerance tests, HbA_{1c} values, or diet habit questionnaire. The major strengths of our study are the huge sample size, the sufficient follow-up period, the inclusion of information about diverse potential confounding factors, and the use of a standardized and validated database provided by the Korean government. In addition, we analyzed the impact of 1 SD of FPG variability on the risk of type 2 diabetes, using three different indicators of glycemic variability, revealing a consistent and a similar degree of association after adjusting for

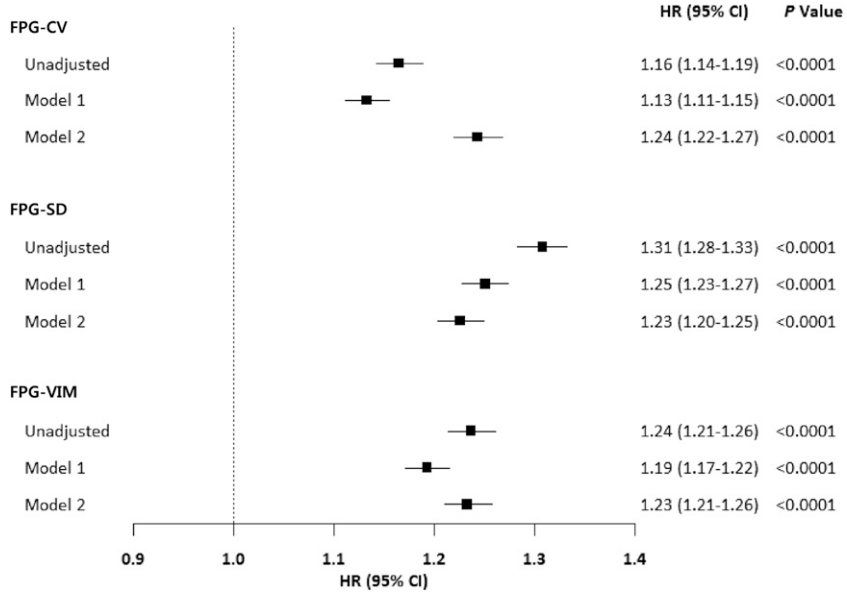

Figure 2—HR and 95% CI for every 1 SD increase of FPG variability. Model 1: adjusted for age, sex, income, family history of diabetes, hypertension, dyslipidemia, BMI, smoking, alcohol intake, and exercise; Model 2: adjusted for age, sex, income, family history of diabetes, hypertension, dyslipidemia, BMI, smoking, alcohol intake, exercise, and mean FPG.

various confounding factors. Furthermore, to the best of our knowledge, this is the first study evaluating the role of FPG variability in the development of type 2 diabetes.

In conclusion, our study demonstrated that visit-to-visit glycemic variability is a risk factor for the development of type 2 diabetes independent of other risk variables, including mean FPG. Further research is required to explore the pathophysiological mechanisms of glycemic variability mediating the development of diabetes and to examine the possibility of FPG variability as a target for intervention to prevent type 2 diabetes.

Funding. This study used the NHIS-HEALS data (grant NHIS-2018-2-023). This study was supported by the Korea University Research Fund (grant Q1625561).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. J.A.K., J.S.L., and K.M.C. contributed to the acquisition, analysis, and interpretation of the data; study concept and design; and drafting of the manuscript. H.S.C. contributed to the acquisition, analysis, and interpretation of data and study concept and design. E.R., Y.-B.L., S.-h.H., and H.J.Y. contributed to the analysis and interpretation of the data. Nam H.K., J.A.S., S.G.K., Nan H.K., and S.H.B. contributed to the critical revision of the manuscript. K.M.C. 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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