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Effects of long-term glycemic variability on incident cardiovascular disease and mortality in subjects without diabetes
A nationwide population-based study

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Abstract

Increased glycemic variability (GV) is an independent risk factor for cardiovascular complications in patients with diabetes. We evaluated the risk of future development of cardiovascular disease (CVD) and death according to GV in a general population without diabetes.

We used the National Health Insurance Service, providing a population-based, nationwide database of Koreans. We included individuals without diabetes who underwent glucose measurement at least 3 times during 2002 to 2006. GV was calculated as standard deviation (SD) of fasting plasma glucose (FPG) levels. We observed development of CVD or all-cause death from 2007 to 2015, and also evaluated the mortality within 1 year after CVD.

Among 3,211,319 people, we found 23,374 incident cases of myocardial infarction (MI), 27,705 cases of stroke, and 63,275 deaths during 8.3 years of follow-up. After multivariate adjustment, GV was found to be a significant predictor of MI, stroke and all-cause death for their highest quartile, with corresponding hazard ratios (HR) of 1.08 (95% confidence interval, CI 1.04–1.11), 1.09 (95% CI 1.06–1.13), and 1.12 (95% CI 1.10–1.15), respectively. The risk of death increased more in those who had both impaired fasting glucose and the highest quartile of GV (HR 1.24 [95% CI 1.21–1.28]). Moreover, early death rate after 1 year of CVD was higher in the highest quartile of GV compared to the lowest quartile (HR 1.21 [95% CI 1.03–1.41]).

Long-term FPG variation was independently associated with CVD and mortality in a general population without diabetes.

Abbreviations: ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation, BMI = body mass index, CI = confidence interval, CVD = cardiovascular disease, CV = coefficient of variance, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, GV = glycemic variability, HR = hazard ratio, HTN = hypertension, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, IRB = Institutional Review Board, ICD-10 = International Classification of Diseases, 10th revision, MAGE = mean amplitude of glycemic excursions, MI = myocardial infarction, MR = mortality rate, NGT = normal glucose tolerance, NHIS = National Health Insurance Service, SBP = systolic blood pressure, SD = standard deviation.

Keywords: cardiovascular disease, cardiovascular mortality, glycemic variability, mortality

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1. Introduction

Glycemic variability (GV) is fluctuation between high and low glucose levels and is a component of dysglycemia. In both type 1 and type 2 diabetes mellitus, prospective clinical studies show strong correlations between mean blood glucose values and diabetic complications.[1,2] GV is postulated to also contribute to development of diabetes complications.[3] Postprandial hyperglycemia has a harmful effect on the onset of cardiovascular complications in people with diabetes or impaired glucose tolerance (IGT).[4] The study to prevent type 2 diabetes (STOP-Noninsulin-Dependent Diabetes Mellitus [NIDDM] trial) demonstrated that decreasing postprandial plasma glucose level in patients with IGT using acarbose reduces risk of cardiovascular disease (CVD).[5] Studies have shown that GV might be important for the pathogenesis of atherosclerosis and could be an independent risk factor for cardiovascular complications in patients with diabetes.[6,7]

Short-term GV refers to within or between-day fluctuations in an individual and is usually measured by continuous glucose monitoring system.[8] On the other hand, long-term GV refers to glycemic fluctuations over months to years and is generally measured by visit-to-visit variability in either fasting plasma glucose (FPG) or glycated hemoglobin (HbA1c).[9] Long-term FPG or HbA1c variability is positively associated with microvascular and macrovascular complications and mortality independent of HbA1c level in patients with type 1 and type 2 diabetes.[8,10,11]

Intermittent high glucose level is reported to stimulate reactive oxygen species overproduction, leading to increased cellular apoptosis in human umbilical vein endothelial cells compared with cells in a stable high glucose environment.[12] Oscillating glucose compared to constant high glucose results in more deleterious effects on endothelial function and oxidative stress in people with and without type 2 diabetes.[13] These findings suggest that glucose fluctuations might be involved in development of vascular injury.

Although GV increases in people with diabetes or impaired blood glucose regulation, a certain degree of variability is also observed in people with normal glucose tolerance (NGT).[14,15] A study[16] found significant increases in GV with aging in a general adult population. However, the prognostic implications of long-term GV in people without diabetes have not been investigated in a population-based study. Therefore, we evaluated the risk of future development of CVD and death for a general population and the risk of death 1 year after development of CVD according to variation in FPG in individuals without diabetes. We used the National Health Insurance Service (NHIS), which is a population-based database of a nationwide cohort.

2. Methods

2.1. Study population

The NHIS has information about health insurance utilization and periodic health examinations that cover almost all Korean adults.[17] The NHIS is a mandatory, government-operated, social health insurance program that covers about 97% of the Korean population. The remaining 3% are covered by the medical aid program. The NHIS in Korea is a comprehensive set of health information including around 50 million Koreans with eligibility, health examination database, medical treatment, and medical care institution databases.[17,18] NHIS contains claims and mortality data and is open to any researchers whose

protocols are approved by both an NHIS review committee and an Institutional Review Board (IRB). The Korea University IRB approved the study protocol in accordance with the Declaration of Helsinki of the World Medical Association.

The NHIS recommends that all eligible Korean adults and their dependents undergo a standardized health examination if they are insured employees or self-employed and over the age of 40. The examination is recommended to occur at least biennially. Anthropometric and laboratory measurements include fasting glucose, lipid profile, creatinine, liver enzymes, and urinalysis. Health-related behavioral variables such as smoking, alcohol consumption, physical activity, and detailed medical history are gathered. Blood samples are collected after an overnight fast, and quality control procedures follow the Korean Association of Laboratory Quality Control.

From a database of 16,094,237 Korean residents who participated in at least 1 health examination provided by the NHIS, we selected 3,691,136 subjects who underwent glucose measurements at least 3 times during 2002 to 2006. It has been measured an average of 4.2 ± 1.2 times (median 4) per participant. We excluded people who had been diagnosed with diabetes (n=279,141) or with CVD (n=21,897) between 2002 and 2006, or missing information (n=178,749) or aged <20 years (n=30). As a result, a total of 3,211,319 subjects were analyzed in this study (Supplementary Fig. 1, http://links.lww.com/MD/D116). We observed the development of CVD or all-cause death from 2007 to 2015.

To examine the effect of GV on the prognosis of incident CVD, we analyzed people who developed CVD during follow-up and underwent a glucose measurement during the year before the incident CVD. They should have at least 2 more blood glucose measurements over 5 years before CVD development. Therefore, records on 24,031 people were analyzed. We examined mortality 1 month and 1 year after the CVD event.

2.2. Outcome ascertainment and definition

We examined myocardial infarction (MI), stroke, and all-cause mortality as primary outcomes. Diagnosis of MI was defined using the International Classification of Diseases, 10th revision (ICD-10) codes (I21–I22) and admission records. Diagnosis of stroke was based on ICD-10 codes (I63–I64), computed tomography or magnetic resonance imaging claim data, and admission records. We also examined mortality from all causes. Impaired fasting glucose (IFG) was defined as FPG $\geq$6.1 mmol/L. The presence of diabetes was defined using the criterion of fasting glucose $\geq$7.0 mmol/L or presence of at least 1 claim per year for prescription of antidiabetic medication based on ICD-10 codes (E11–E14). The presence of hypertension was defined using criteria of systolic/diastolic blood pressure $\geq$140/90 mm Hg or presence of at least 1 claim per year for prescription of an antihypertensive agent using ICD-10 codes (I10–I15). The presence of dyslipidemia was defined using the criteria of total cholesterol $\geq$6.21 mmol/L or presence of at least 1 claim per year for prescription of an antihyperlipidemic agent using ICD-10 codes (E78).

2.3. Measurements

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). At the time of weight measurement, systolic and diastolic pressure were also measured; serum

Table 1

Baseline characteristics according to quartiles of fasting plasma glucose standard deviation.

| | Quartiles of FPG-SD | | | | |
	Q1	Q2	Q3	Q4	P
n	802,066	803,483	802,555	803,215	
Age	44.4±13.1	42.9±11.6	43.3±11.7	44.3±12.2	<.001
Sex, male (%)	474,442 (59.2)	541,702 (67.4)	556,830 (69.4)	576,995 (71.8)	<.001
Current smoker (%)	205,587 (25.6)	237,096 (29.5)	248,435 (31.0)	269,591 (33.6)	<.001
Alcohol					
1–2/week (%)	369,609 (46.1)	406,740 (50.6)	405,144 (50.5)	398,024 (49.6)	<.001
≥3/week (%)	48,687 (6.1)	53,756 (6.7)	58,608 (7.3)	66,748 (8.3)	<.001
Exercise					
No	392,894 (49.0)	375,900 (46.8)	377,648 (47.1)	384,388 (47.9)	<.001
≤4/week	352,354 (43.9)	376,319 (46.8)	373,087 (46.5)	365,654 (45.5)	<.001
≥5/week	56,818 (7.1)	51,264 (6.4)	51,820 (6.5)	53,173 (6.6)	<.001
Income (the lowest decile, %)	68,178 (8.5)	60,652 (7.6)	63,862 (8.0)	72,842 (9.1)	<.001
HTN (%)	156,437 (19.5)	146,342 (18.2)	156,524 (19.5)	173,820 (21.6)	<.001
Dyslipidemia (%)	96,778 (12.1)	91,246 (11.4)	94,748 (11.8)	99,991 (12.5)	<.001
BMI (kg/m^2)	23.4±3.0	23.4±3.0	23.5±3.0	23.6±3.0	<.001
SBP (mm Hg)	121.2±14.5	121.4±14.1	122.0±14.2	123.1±14.4	<.001
DBP (mm Hg)	76.0±9.8	76.4±9.7	76.8±9.7	77.3±9.8	<.001
Total cholesterol (mg/dL)	192.5±35.1	192.1±34.8	192.2±34.8	192.6±35.2	<.001
FPG (mmol/L)	5.0±0.6	5.0±0.6	5.0±0.6	5.1±0.7	<.001
FPG (mg/dL)	90.0±11.0	90.2±11.1	90.7±11.3	91.5±11.9	<.001

Data are mean±SD or N (%).

BMI = body mass index, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HTN = hypertension, SBP = systolic blood pressure, SD = standard deviation.

samples for fasting glucose, hemoglobin, and total cholesterol levels were obtained at examination sites after overnight fast. Detailed histories of smoking status, alcohol consumption, and physical activity were obtained via questionnaire. Questionnaires at health examinations categorized smoking status as nonsmokers, ex-smokers, or current smoker and alcohol use as 0, 1 to 2, or ≥3 times/week. Participants were graded as exercising 0, 1 to 4, or ≥5 times/week. Income level was dichotomized at the lower 10%.

2.4. Statistical analysis

Data are expressed as mean±standard deviation (SD) or percentage. Differences between groups were analyzed using Student *t*-test or Chi-squared test to assess differences in the distribution of categorical variables. SD of FPG was calculated only when more than 3 FPG measurements were performed. Participants were grouped into quartiles according to FPG-SD. Incidence or mortality rate per 1000 person-years, Kaplan–Meier curves, and adjusted hazard ratio (HR) were analyzed according to FPG-SD quartiles. To see the joint effect of FPG-SD and IFG, we collapsed the first, second, and third quartiles (Q1–3) of FPG-SD into a single group for participants with NGT or IFG. We conducted a 4-group comparison to calculate HRs for MI, stroke, and all-cause death for Q1–3 and Q4 for the NGT and IFG groups. A multiple Cox proportional hazard model was used after adjusting for age, sex, BMI, smoking status, alcohol drinking, exercise, dyslipidemia, hypertension, and FPG or the change of FPG level between 2002 and 2006 (ΔFPG). Forest plots for incident MI, stroke, and mortality according to risk factor subgroups were evaluated. A *P* < .05 was considered statistically significant. All statistical analyses used SAS software package version 9.3 (SAS Institute Inc, Cary, NC).

3. Results

Table 1 shows baseline demographic and clinical characteristics of participants grouped according to FPG-SD quartile. The mean FPG-SD value (median, minimum, maximum) of each quartile group was 2.55 (2.83, 0.00, and 4.50), 6.07 (6.10, 4.51, and 7.68), 9.38 (9.22, 7.68, and 11.32), and 15.76 (14.71, 11.32, and 55.15) mg/dL, respectively. Higher FPG-SD was associated with higher proportions of current smokers, heavy drinkers, and men. During an average 8.3 years of follow-up, we observed 23,374 incident occurrences of MI, giving a crude incidence rate of 0.88/1000 person-years; 27,705 of stroke, an incidence rate of 1.04/1000 person-years; 63,275 of all-cause death, a mortality rate of 2.37/1000 person-years.

Table 2 shows HRs for MI, stroke, and all-cause death grouped by FPG-SD quartile. After adjustment for age, sex, BMI, smoking, alcohol, exercise, hypertension, dyslipidemia, and FPG, HRs for the highest FPG-SD quartile was 1.08 (95% CI 1.04–1.11) for MI, 1.09 (95% CI 1.06–1.13) for stroke, and 1.12 (95% CI 1.10–1.15) for all-cause death compared to the lowest FPG-SD quartile. In model 5, the results were similar even after further adjustment for the change of FPG level.

Figures present the Kaplan–Meier cumulative risk for MI (Fig. 1), stroke (Fig. 2), and all-cause death (Fig. 3) according to FPG-SD quartile. People in the highest quartile showed a higher risk for MI, stroke, and all-cause death than those in the lowest quartile of FPG-SD (log-rank test *P* < .001, Figs. 1–3).

We also evaluated risk of MI, stroke, and all-cause death according to GV and FPG categories (Table 3). Compared with Q1–3 in the NGT group, Q4 in the NGT and IFG groups had comparable risks for MI and stroke. In contrast, HRs for Q1–3 in the IFG group did not increase for MI or stroke. The impact of higher GV and IFG was evident for mortality. HR for all-cause death increased by 12% in the Q4 group with NGT and 10% in

Table 2

Hazard ratios for death, myocardial infarction, and stroke according to quartiles of fasting plasma glucose standard deviation.

	Quartiles of FPG-SD			
	Q1	Q2	Q3	Q4
MI				
n	6049	5203	5429	6693
Model 1	1	0.86 (0.83–0.89)	0.90 (0.87–0.93)	1.11 (1.07–1.15)
Model 2	1	1.00 (0.96–1.04)	1.00 (0.96–1.04)	1.11 (1.07–1.15)
Model 3	1	1.00 (0.96–1.04)	0.99 (0.95–1.02)	1.07 (1.04–1.11)
Model 4	1	1.00 (0.96–1.04)	0.99 (0.95–1.02)	1.08 (1.04–1.11)
Model 5	1	1.00 (0.96–1.04)	0.99 (0.95–1.02)	1.07 (1.04–1.11)
Stroke				
n	7371	5842	6568	7924
Model 1	1	0.79 (0.76–0.82)	0.89 (0.86–0.92)	1.08 (1.04–1.11)
Model 2	1	1.01 (0.97–1.04)	1.07 (1.04–1.11)	1.13 (1.09–1.16)
Model 3	1	1.00 (0.97–1.04)	1.06 (1.03–1.10)	1.09 (1.06–1.13)
Model 4	1	1.00 (0.97–1.04)	1.06 (1.03–1.10)	1.09 (1.06–1.13)
Model 5	1	1.00 (0.97–1.04)	1.06 (1.03–1.10)	1.09 (1.06–1.13)
Death				
n	16,597	13,204	14,463	19,011
Model 1	1	0.80 (0.78–0.81)	0.87 (0.85–0.89)	1.15 (1.12–1.17)
Model 2	1	0.99 (0.97–1.02)	1.02 (1.00–1.05)	1.16 (1.13–1.18)
Model 3	1	0.99 (0.97–1.02)	1.02 (0.99–1.04)	1.13 (1.10–1.15)
Model 4	1	0.99 (0.97–1.02)	1.01 (0.99–1.04)	1.12 (1.10–1.15)
Model 5	1	0.99 (0.97–1.02)	1.02 (0.99–1.04)	1.13 (1.10–1.15)

Data are HR (95% CI).
Model 1: No adjustment.
Model 2: Adjusted for age and sex.
Model 3: Adjusted for age, sex, BMI, smoking, alcohol, exercise, HTN, and dyslipidemia.
Model 4: Adjusted for age, sex, BMI, smoking, alcohol, exercise, HTN, dyslipidemia, and FPG.
Model 5: Adjusted for age, sex, BMI, smoking, alcohol, exercise, HTN, dyslipidemia, and ΔFPG.
BMI = body mass index, CI = confidence interval, FPG = fasting plasma glucose, HR = hazard ratio, HTN = hypertension, MI = myocardial infarction, SD = standard deviation.
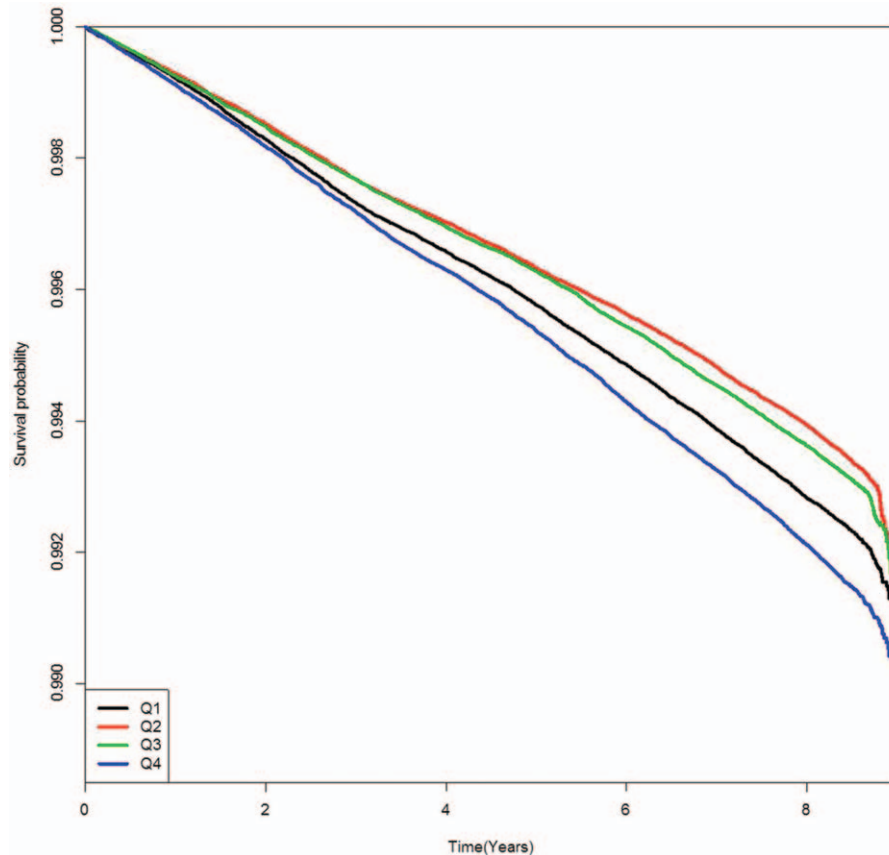

Figure 1. Kaplan–Meier event-free survival curves for myocardial infarction according to glycemic variability quartile.
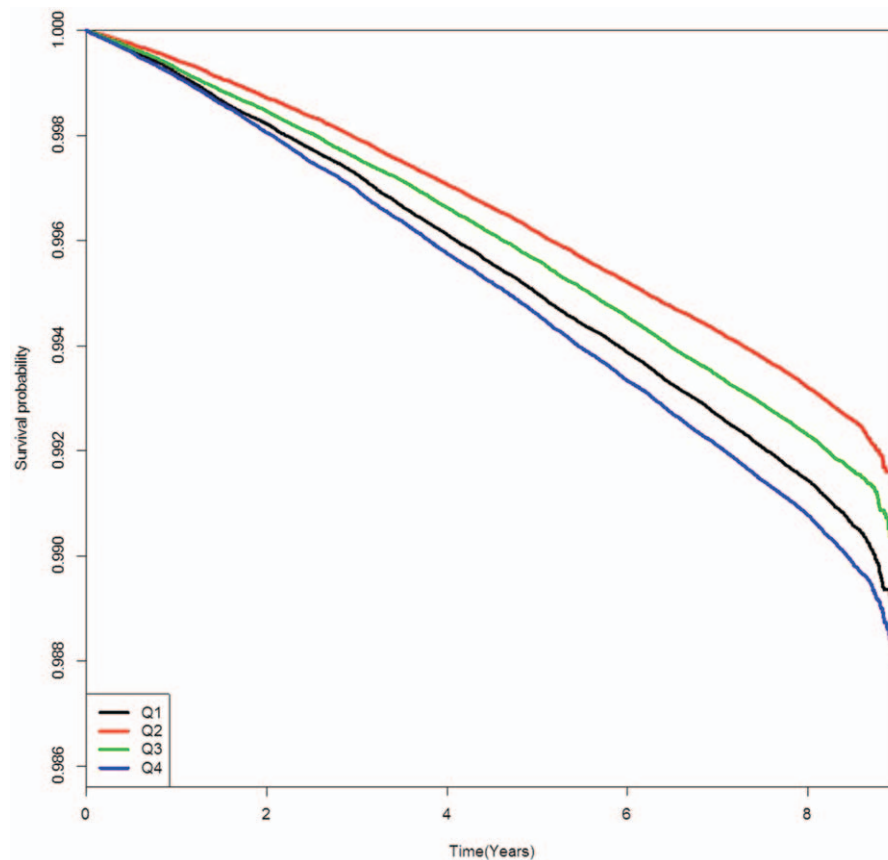
Figure 2. Kaplan–Meier event-free survival curves for stroke according to glycemic variability quartile.

the Q1–3 IFG group. HR was highest in the Q4 group with IFG (24%) compared to the Q1 to Q3 group with NGT.

We analyzed prognosis of incident CVD according to FPG-GV. After MI or stroke events, 541 people died within 1 month and 1253 within 1 year (Table 4). HR for death within 1 month after a CVD event did not increase for Q4 compared to Q1. However, HR for death within 1 year after a CVD event was 1.21 (95% CI 1.03–1.41) for Q4 versus Q1. It was 1.22 (1.04–1.43) even after further adjustment for the change of FPG level.

4. Discussion

This study demonstrated that long-term FPG variation was independently associated with CVD and death in individuals without diabetes. We found that a high GV was associated with significantly increased risk for future cardiovascular events and all-cause mortality in a general population and poor prognosis for people with CVD without diabetes. The results suggested that elevated GV might be associated with greater risk of CVD and all-cause death, even in people without diabetes.

Several studies have shown that FPG variation is an independent predictor of total, cancer, and cardiovascular mortality in patients with diabetes.[11,19,20] Post hoc analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) dataset showed that visit-to-visit GV of FPG or HbA1c is associated with macrovascular events and mortality for patients with type 2

diabetes.[21] In the national cohort of the Taiwan Diabetes Study, visit-to-visit GV predicted the development of ischemic stroke[22] and end-stage renal disease[23] in patients with type 2 diabetes. These results suggest that GV over a long period is an important risk factor for vascular events and mortality.

However, to the best of our knowledge, no study found an association between GV and CVD or mortality in a general population without diabetes. The importance of high GV was shown in people with CVD regardless of diabetes. Higher GV measured by continuous glucose monitoring system compared to conventional glucose indicators is more strongly associated with larger plaque burden, plaque instability,[4] and rapid progression in patients with acute coronary syndromes.[5] Furthermore, elevated GV appears to be a more important risk factor than glucose or HbA1c level for predicting 1-year major adverse cardiac events in patients with acute MI.[8]

Several possible mechanisms might be involved in generating the associations between long-term GV and outcomes. First, glucose fluctuations can trigger adverse biological events and independently trigger oxidative stress, a key factor of atherosclerosis.[24] In patients with type 2 diabetes, daily blood glucose fluctuations are strong predictors of higher generation of oxidative stress.[24] Control of mean amplitude of glycemic excursions (MAGE) reduces markers of systemic inflammation and oxidative stress.[25] Oscillating glucose can have more deleterious effects than constant high glucose on endothelial function and oxidative stress in people with and without type 2
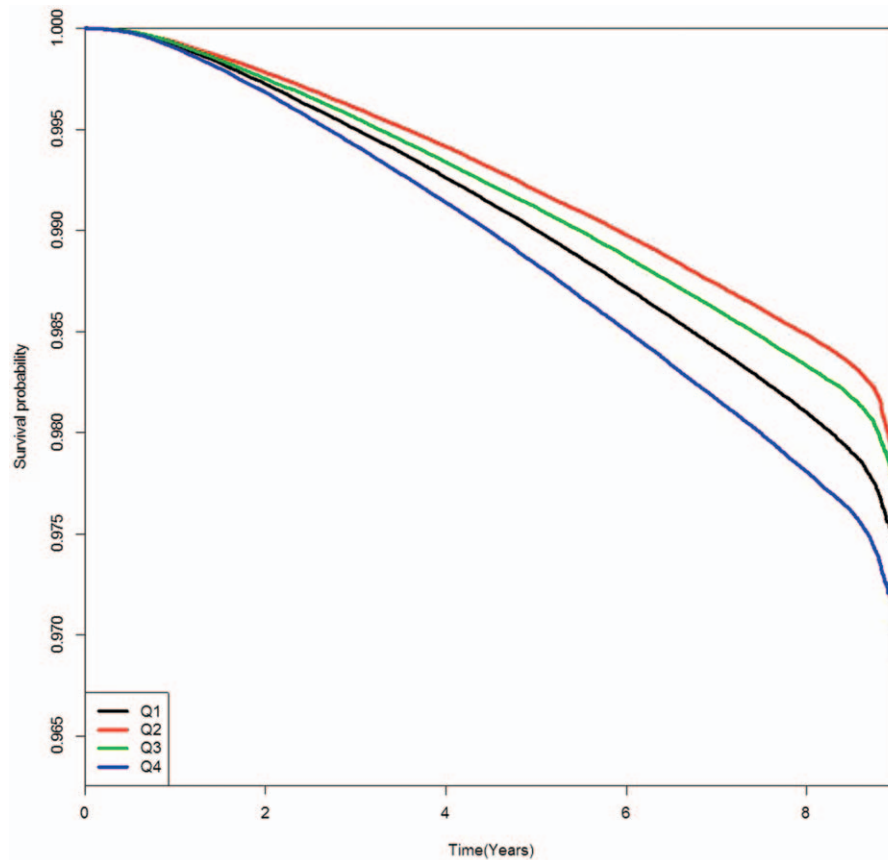
Figure 3. Kaplan–Meier event-free survival curves for all-cause death according to glycemic variability quartile.

diabetes.[13] This finding suggests that GV is more strongly associated with atherogenic factors compared to sustained hyperglycemia represented by HbA1c and FPG. Endothelial

dysfunction is generated by glucose oscillations in people with and without type 2 diabetes. Use of an antioxidant prevents this effect.[26] Second, repeated glycemic fluctuation increases inflammatory cytokines and macrophage adhesion to endothelial cells,[26,27] which are involved in atherosclerosis progression. However, whether these mechanisms should be interpreted in ways similar to their interpretation for people without diabetes is doubtful, because most studies have investigated patients with

Table 3

Hazard ratios for death, myocardial infarction, and stroke according to quartiles of standard deviation of fasting plasma glucose and glucose tolerance status.

	NGT		IFG	
	Q1–3	Q4	Q1–3	Q4
MI				
Model 1	1.00	1.22 (1.18–1.26)	1.44 (1.39–1.49)	1.59 (1.52–1.67)
Model 2	1.00	1.11 (1.08–1.15)	1.07 (1.03–1.11)	1.16 (1.11–1.22)
Model 3	1.00	1.08 (1.05–1.12)	1.02 (0.99–1.06)	1.09 (1.04–1.15)
Stroke				
Model 1	1.00	1.22 (1.18–1.26)	1.44 (1.40–1.49)	1.59 (1.52–1.66)
Model 2	1.00	1.10 (1.07–1.14)	1.04 (1.00–1.07)	1.12 (1.08–1.18)
Model 3	1.00	1.07 (1.04–1.11)	0.99 (0.96–1.02)	1.05 (1.01–1.10)
Death				
Model 1	1.00	1.29 (1.27–1.32)	1.56 (1.53–1.60)	1.87 (1.82–1.92)
Model 2	1.00	1.14 (1.12–1.17)	1.07 (1.05–1.10)	1.25 (1.22–1.29)
Model 3	1.00	1.12 (1.09–1.14)	1.10 (1.08–1.12)	1.24 (1.21–1.28)

Data are HR (95% CI).
Model 1: Adjusted for FPG.
Model 2: Adjusted for FPG, age, and sex.
Model 3: Adjusted for FPG, age, sex, smoking, alcohol, exercise, HTN, and dyslipidemia.
CI = confidence interval, FPG = fasting plasma glucose, HTN = hypertension, IFG = impaired fasting glucose, MI = myocardial infarction, NGT = normal glucose tolerance.

Table 4

Hazard ratios for death within 1 month or 1 year after cardiovascular disease event according to quartiles of fasting plasma glucose standard deviation.

	N	Death	Person-years	MR	HR (95% CI)
Within 1 month					
Q1	5996	133	486.5	273.4	1
Q2	6030	114	491.9	231.7	0.84 (0.66–1.09)
Q3	5995	157	487.8	321.9	1.15 (0.91–1.45)
Q4	6010	137	489.9	279.7	0.95 (0.75–1.21)
Within 1 year					
Q1	5996	284	5212.4	54.5	1
Q2	6030	270	5289.2	51	0.95 (0.80–1.12)
Q3	5995	322	5293.9	60.8	1.09 (0.93–1.29)
Q4	6010	377	5299.9	71.1	1.21 (1.03–1.41)

Model adjusted for age, sex, BMI, smoking, alcohol, exercise, HTN, dyslipidemia, and FPG.
BMI = body mass index, FPG = fasting plasma glucose, HR = hazard ratio, HTN = hypertension, MR = mortality rate.

diabetes. Meugnier et al[28] showed that genes involved in free radical detoxification are downregulated during phases of acute hyperglycemia in normal participants. Insights from cultured vascular cells also identify the importance of posttranslational modification of histone tails in the persistent inflammatory response to glycemic variation.[29] Further studies are warranted to elucidate the associations between GV and outcomes in normoglycemic people.

As shown in Figures 1–3 in this study, the Kaplan–Meier cumulative risks for MI, stroke, and all-cause death were higher in the Q1 group than in the Q2 or Q3 group. The point that the Q1 group is older than the Q2 or Q3 group might be considered the main cause of higher incidence of events in the Q1 group. This trend disappeared when age and sex were adjusted in model 2 to 5 of Table 2. Although the interaction between the FPG and each outcome may be an important because the average FPG level has increased significantly from Q1 to Q4 group, there has been no significant interaction between the FPG and each outcome after adjustment for age and gender (data not shown).

Increasing GV is clearly related to higher mortality in critically ill patients, both with and without diabetes, independent of illness severity.[30–32] Results from a large multicenter study concluded that GV is a stronger predictor of intensive care unit mortality than mean glucose concentrations.[33] Even in noncritically ill patients, increased GV during hospitalization is independently associated with increased mortality.[32] These studies showed the prognostic impact of short-term GV during hospitalization. However, our study used relatively long-term GV in a stable state and demonstrated that the highest GV quartile was associated with 12% increased risk for death in a general population and 21% higher risk for 1-year death after CVD. When we did not consider FPG categories, the highest GV quartile conferred 12% increased risk of death; it escalated to 24% in the highest quartile for GV and IFG. This finding suggests that the impact of higher GV is stronger in people with prediabetes. Therefore, targeting these high-risk populations even though they do not have diabetes would be reasonable to reduce future CVD events and death.

We used SD among other GV indices to assess FPG variation. No gold standard exists for determining glucose variability. SD is most widely used to assess GV. MAGE,[34] M value,[35] continuous overlapping net glycemic action,[36] and mean of daily differences[37] are also frequently used as GV indices. Although these indices reflect different aspects of GV and largely correlate with each other, SD seemed like the best way to quantify GV.[38,39] Since SD is positively associated with mean value, the coefficient of variance (CV) has also been suggested as a strong independent index for measuring GV because it corrects for mean glucose level.[40] When we conducted our analysis using CV instead of SD, the results of our study did not differ (data not shown).

This study has some limitations. First, our findings were limited by potential residual and unrecognized confounding variables because this was an observational study. Second, we could not determine a causal relationship between elevated GV and CVD outcomes. GV might reflect the effects of coexisting illness or comorbidity that heighten the risk of CVD rather than directly cause it. Strengths of our study include a comparatively large nationwide population and a sufficiently long follow-up. Focusing on individuals without diabetes rather than patients with diabetes is another strong point of this study. We believe our study provides a novel perspective of the implications that GV might have in a general population without diabetes.

In conclusion, long-term FPG variation was positively associated with CVD and mortality in a general population without diabetes. The risk of death associated with higher GV increased even in those who developed CVD or who had IFG. Our findings imply that minimizing glucose fluctuations is important not only for patients with diabetes, but also healthy individuals without diabetes. Prospective studies will be needed to investigate the influence of lowering GV on cardiovascular outcomes in both populations.

Author contributions

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Funding acquisition: Nan Hee Kim.
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Writing – original draft: Ji Hee Yu.
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