Journal of the American Heart Association

ORIGINAL RESEARCH

Effect of Variability in Blood Pressure, Glucose and Cholesterol Concentrations, and Body Weight on Emergency Hospitalization and 30-Day Mortality in the General Population

Seung-Hwan Lee, MD, PhD; Kyungdo Han, PhD; Hyuk-Sang Kwon, MD, PhD; Kun-Ho Yoon, MD, PhD; Mee Kyoung Kim, MD, PhD

BACKGROUND: Variability in blood pressure, glucose concentration, cholesterol concentration, or body weight is associated with a wide range of health outcomes. We hypothesized that high variability in metabolic parameters is associated with an increased risk of emergency hospitalization and mortality.

METHODS AND RESULTS: Using a nationally representative database from the Korean National Health Insurance System, 8 049 228 individuals who underwent 3 or more health examinations during 2005 to 2010 were followed up until the end of 2016. Variability in fasting blood glucose and total cholesterol concentrations, systolic blood pressure, and body weight was measured using the variability independent of the mean (VIM). High variability was defined as the highest quartile of variability. Subjects were classified according to the number of high variability parameters. The end points of the study were emergency hospitalization and 30-day mortality. There were 733 387 emergency hospitalizations (9.1%) during a median follow-up of 5.6±1.2 years. For each metabolic parameter, an incrementally higher risk of emergency hospitalization was observed for higher VIM quartile groups than for the lowest quartile group. Compared with the group with low variability for all 4 parameters, the group with high variability for all 4 parameters had a significantly higher risk for emergency hospitalization (hazard ratio [HR], 1.58; 95% CI, 1.54–1.61) and 30-day mortality (HR, 2.44; 95% CI, 1.62–3.69), after adjusting for possible confounding factors.

CONCLUSIONS: High variability in metabolic parameters was associated with increased risk of emergency hospitalization and short-term mortality.

Key Words: emergency ■ epidemiology ■ mortality ■ variation

In recent years, the visit-to-visit variability in various biological parameters has received increasing attention. High variability in blood pressure (BP), glucose concentration, cholesterol concentration, or body weight (BW) is associated with a wide range of health outcomes, such as cardiovascular events, diabetes mellitus (DM), end-stage renal disease, dementia, and all-cause mortality.[1–10] Moreover, high variability in BP, lipid concentration, or BW is also associated with the risk of new-onset atrial fibrillation.[11–13] Arrhythmia, cerebral infarction, heart failure, and emergency dialysis are major causes of emergency room (ER) visits and

Correspondence to Mee Kyoung Kim, MD, PhD, Division of Endocrinology and Metabolism, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, #10 63-ro, Yeongdeungpo-gu, Seoul 07345, Korea. E-mail: makung@catholic.ac.kr

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.017475

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The risk of emergency hospitalization increased by 58%, and short-term mortality increased by 140% for subjects with high variability of glucose, cholesterol, blood pressure, and body weight.

What Are the Clinical Implications?

- High variability in metabolic parameters could be used for detecting individuals at high risk.
- Stabilizing metabolic parameters may be important for reducing the emergency hospitalization and short-term mortality in the general population.

Nonstandard Abbreviations and Acronyms

ARV	average real variability
BW	body weight
CV	coefficient of variation
DM	diabetes mellitus
ER	emergency room
VIM	variability independent of the mean

unplanned hospitalization.[14] Previous studies have reported that visit-to-visit variability in BP or cholesterol concentration is associated with the development of dementia.[3,15] Older adults with dementia are frequent ER visitors who have greater comorbidity and higher mortality after an ER visit.[16] Variability in blood glucose concentration, BP, or other metabolic parameters might not be limited to an increased risk of developing certain diseases and could be related to an increased risk of ER visits and mortality.

An ER visit is an indicator that reflects acute disease flares or complications of underlying diseases and is associated with quality of life. There is an increasing focus on the importance of identifying and mitigating various patient risks as a cost-reduction strategy. Notably, it is important to identify and mitigate any potentially avoidable risks for emergency hospitalization. Recently, variability in hemoglobin A1c (HbA1c) level was found to be strongly associated with overall mortality and emergency hospitalization, which could not be explained by average HbA1c level or hypoglycemic episodes.[17] This finding suggested that for patients with type 2 DM that have a lower or moderately increased average HbA1c level, <9% in the studied cohort, the mortality risk could be reduced more by promoting stability in HbA1c levels than with reductions in chronic hyperglycemia, and even at higher average HbA1c levels, stability remains important.[17]

The effect of the variability in metabolic parameters on the risk of emergency hospitalization and short-term mortality has not been studied previously and remains to be better understood. We conducted a large population-based study involving >8 million Koreans who had received at least 3 health examinations to evaluate the prognostic effect of increased variability in metabolic parameters (fasting blood glucose [FBG] and total cholesterol [TC] concentrations, BP, and BW) on the risks of emergency hospitalization and mortality.

METHODS

All supporting data are available within the article and its online supplementary file.

Data Source and Study Population

We used the Korean National Health Insurance Service (NHIS) data sets of claims and health checkups from January 2005 to December 2016. The Korean NHIS is a single-payer insurance organization managed by the Korean government and covers all residents in Korea. The NHIS claims database includes a de-identified research data set of demographic information, primary and secondary diagnoses classified according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*), prescriptions, procedures, hospital arrival route, date of admission, and duration of hospitalization for all residents of Korea.[1–4,18–20] The NHIS consists of employee subscribers and regional insurance subscribers. All examinees are requested to have biannual health checkups, but employee subscribers are requested to have annual examinations. These health examination results are compiled into data sets of preventive health checkups, which constitute the largest-scale, nationwide cohort database with laboratory information in Korea. Details about this database were provided in previous reports.[1–4,18–20]

In this study, individuals aged ≥20 years who underwent national health checkups between January 2009 and December 2010 (index year) were selected. Of 17 539 886 individuals, 8 376 754 underwent 3 or more health examinations from 2005 to the index year. A total of 171 787 individuals with missing data for at least one variable were excluded. Analysis was performed after excluding subjects with end points occurring during the first year of follow-up (n=155 739) to account for the possibility of reverse causation (Figure S1). For example, among those who had undergone a health examination in 2009 (index year), we included those who had undergone

3 or more health examinations from January 2005 to December 2009; we excluded subjects who were hospitalized through the emergency department during the first year of follow-up (2010). Among those who had undergone a health examination in 2010 (index year), we included those who had undergone 3 or more health examinations from January 2006 to December 2010; we excluded subjects who were hospitalized through the emergency department during the first year of follow-up (2011) (Figure S2). Finally, 8 049 228 subjects were eligible for inclusion in the analysis. The study population was followed up from baseline to the date of end point event, or the date of the subject's disqualification from receiving health services caused by death or emigration, or until the end of the study period (December 31, 2016). This study was approved by the Institutional Review Board of the Catholic University of Korea (No. SC19ZESI0119). Deidentified information was used for analysis; therefore, informed consent was not required.

Health Examination

Hospitals in which health examinations were performed were certified by the NHIS and subjected to regular quality control. The general medical examination included surveys for past medical history, family history, and lifestyle factors along with BP measurements, blood sampling, and urinalysis. Blood samples for the measurement of serum glucose and lipid levels were obtained after an overnight fast. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Information on smoking and alcohol consumption (heavy alcohol consumption defined as ≥30 g/day) was obtained using a questionnaire. Regular exercise was defined as performing >30 minutes of moderate physical activity at least 5 times per week or >20 minutes of strenuous physical activity at least 3 times per week. Household income assessed by the national health insurance premium was classified into income quartiles from the lowest to the highest. Household income level was dichotomized at the lower 25%. The presence of DM was defined according to the presence of at least one claim per year under *ICD-10* codes E10–14 and at least one claim per year for the prescription of antidiabetic medication, or fasting glucose level ≥126 mg/dL.[20,21] The presence of hypertension was defined according to the presence of at least one claim per year under *ICD-10* codes I10 or I11 and at least one claim per year for the prescription of antihypertensive agents, or systolic/diastolic BP ≥140/90 mm Hg. The presence of dyslipidemia was defined according to the presence of at least one claim per year under *ICD-10* code E78 and at least one claim per year for the prescription of a lipid-lowering agent, or TC concentration ≥240 mg/dL.

Variability Indices and Scoring

Three indices of variability were used: (1) variability independent of the mean (VIM), (2) coefficient of variation (CV), and (3) average real variability (ARV). VIM and ARV were calculated in the manner described previously.[1–4]

High variability was defined as the highest quartile (Q4) of variability and low variability as the lower 3 quartiles (Q1–Q3) of variability. The subjects were classified further according to the number of high variability metabolic parameters (FBG, TC, systolic BP [SBP], and BW) using a score range from 0 to 4.[2] In this classification, a score of 0 indicated no high variability parameter and the scores 1 to 4 indicated the number of high variability parameters among the 4 parameters (eg, a score of 3 indicated high variability in 3 of the 4 parameters).[2]

Study Outcomes

The NHIS database provides the number of hospital visits, length of hospital stays, and disease codes for ER visits. ER visits were defined using the emergency medical care charge code (AC101–AC105), which is required while making an insurance claim for emergency management. All-cause death was identified using the National Death Registry. The end points of this study were emergency hospitalization and 30-day mortality. Emergency hospitalization (for >1 day) was defined as being hospitalized through the emergency department. Cause of emergency hospitalization was defined using the principal or first additional diagnosis at the time of discharge among patients who were admitted through the emergency department. Among patients admitted to the hospital through the emergency department, 30-day mortality was assessed.

Statistical Analysis

Baseline characteristics of the subjects are presented as the mean±standard deviation or n (%). Subjects were classified into 5 groups according to the number of high variability metabolic parameters. The incidence rate of primary outcomes was calculated by dividing the number of incident cases by the total follow-up duration (person-years). The cumulative incidence of primary outcomes according to the number of parameters with high variability was presented using unadjusted Kaplan–Meier curves, and the log rank test was performed to analyze differences between groups. The hazard ratio (HR) and

95% CI for emergency hospitalization and 30-day mortality were analyzed using the Cox proportional hazards model. The proportional hazards assumption was evaluated using the Schoenfeld residuals test with the logarithm of the cumulative hazards function based on Kaplan–Meier estimates for quartile groups of variability or groups based on the number of parameters with high variability. There was no significant departure from proportionality in hazards over time. A multivariable-adjusted proportional hazards model was applied. Model 1 was adjusted for age, sex, smoking, alcohol consumption, regular exercise, and income status. Model 2 was adjusted further for baseline FBG, SBP, TC, BW, and a history of ER visits. The potential effect modification by age, sex, DM, hypertension, dyslipidemia, and chronic kidney disease (CKD; estimated glomerular filtration rate <60 mL/min per 1.73 m^2) was evaluated using stratified analysis and interaction testing using a likelihood ratio test. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA), and a $P<0.05$ was considered significant.

RESULTS

Baseline Characteristics of the Study Population

The characteristics of the subjects grouped according to the number of high variability metabolic parameters are listed in Table 1. Subjects with a greater number of high variability parameters were older, more likely to be female, less likely to exercise regularly, and had lower income. The highest prevalence of comorbidities, such as DM, hypertension, and dyslipidemia, were observed in subjects with 4 high variability parameters. Subjects with a greater number of high variability parameters had a higher rate of previous ER visits during the 5 years before the index year.

Risk of All-Cause Emergency Hospitalization According to the Variability of Each Metabolic Parameter

There were 733 387 emergency hospitalizations (9.1%) during a median follow-up of 5.6±1.2 years in the entire cohort. For each metabolic parameter, an incrementally higher risk of emergency hospitalization was observed for higher VIM quartile groups than for the lowest quartile group (Table 2, Figure 1). After adjusting for possible confounding factors, including previous history of ER visits, the highest quartile group of FBG, TC, SBP, and BW variability had 16%, 14%, 11%, and 24% increased risk of emergency hospitalization, respectively, compared with the lowest quartile group.

Risk of All-Cause Emergency Hospitalization According to the Number of High Variability Parameters

There was a dose-response relationship between the number of high variability parameters and the risk of emergency hospitalization (Table 3, Figure 1). Compared with the group with low variability for all 4 parameters (reference group), the group with high variability for all 4 parameters had a significantly higher risk of emergency hospitalization (HR, 1.58; 95% CI, 1.54–1.61). These associations were confirmed even after adjusting for baseline FBG, TC, SBP, BMI, and previous history of ER visits (Table 3). We further analyzed these associations according to the causes of emergency hospitalization (Table 4). Multivariable-adjusted HRs for emergency hospitalization increased continuously and linearly with an increasing number of high variability parameters, regardless of causes of hospitalization (P for trend <0.0001). The risk of emergency hospitalization due to endocrine, nutritional, and metabolic diseases (*ICD-10* E) increased more than 3-fold (HR, 3.66; 95% CI, 3.27–4.11), that due to respiratory system diseases (*ICD-10* J) increased by 83% (HR, 1.83; 95% CI, 1.71–1.96), and that due to genitourinary system diseases (*ICD-10* N) increased by 74% (HR, 1.74; 95% CI, 1.60–1.90) for the group with high variability for all 4 parameters.

Risk of 30-Day Mortality After Emergency Hospitalization According to the Number of High Variability Parameters

We analyzed the relationship between high variability in metabolic parameters and 30-day mortality associated with ER visit. There were 1029 deaths within 30 days of emergency hospitalization. The 30-day mortality increased progressively with an increasing number of high variability parameters (Figure 2). After adjusting for possible confounding factors, the HR values (95% CI) of 30-day mortality were 1.28 (1.08–1.51) in subjects with 1 parameter, 1.35 (1.13–1.62) in subjects with 2 parameters, 1.77 (1.41–2.22) in subjects with 3 parameters, and 2.44 (1.62–3.69) in subjects with 4 parameters of high variability compared with those of subjects with no high variability parameters, measured as VIM.

Subgroup and Sensitivity Analyses

We performed stratified analyses by age, sex, and the presence of DM, CKD, hypertension, and dyslipidemia. The risk of emergency hospitalization increased significantly in subjects with 4 parameters of high variability compared with subjects with no

Table 1. Baseline Characteristics of Subjects by the Number of High Variability Metabolic Parameters

	0	1	2	3	4
N	2 728 426	3 158 473	1 647 015	458 505	56 809
Age, y	47.1±12.6	47.9±13.6	49.2±14.5	50.8±15.4	52.6±16.0
Sex (male)	1 713 232 (62.8)	1 839 314 (58.2)	901 717 (54.8)	238 358 (52.0)	28 259 (49.7)
Weight, kg	65.0±11.2	64.4±11.5	63.8±11.8	63.2±12.0	62.2±12.1
BMI, kg/m^2	23.7±3.0	23.8±3.1	23.8±3.2	23.8±3.4	23.7±3.5
Systolic BP, mm Hg	122.4±13.0	122.3±14.5	122.5±15.8	122.7±17.1	122.9±18.8
Diastolic BP, mm Hg	76.5±9.3	76.4±9.7	76.3±10.2	76.3±10.7	76.1±11.3
FBG, mg/dL	95.3±16.9	96.7±21.0	98.6±25.4	100.9±29.9	103.8±35.1
TC, mg/dL	196.3±33.2	195.6±35.8	195.2±38.9	194.9±42.3	193.7±45.3
HDL cholesterol, mg/dL	54.8±19.0	55.1±19.8	55.3±20.6	55.5±21.8	55.3±21.5
LDL cholesterol, mg/dL	116.6±44.4	115.2±46.1	114.1±47.9	112.8±48.8	111.1±49.3
Triglyceride, mg/dL*	113.5 (113.4–113.5)	114.5 (114.5–114.6)	116.5 (116.4–116.6)	119.1 (118.9–119.3)	121.1 (120.5–121.7)
eGFR, mL/min per 1.73 m^2	86.5±42.3	87.1±40.4	87.2±39.2	87.3±39.5	87.0±39.9
eGFR <60 mL/min per 1.73 m^2	163 984 (6.0)	196 946 (6.2)	116 682 (7.1)	38 448 (8.4)	5870 (10.3)
Variability					
VIM of FBG	7.11±3.07	9.85±5.71	12.50±6.59	15.34±6.57	18.52±5.43
VIM of TC	13.75±5.63	18.68±10.66	24.62±12.93	30.87±13.09	36.58±11.46
VIM of systolic BP	6.93±2.90	9.27±4.89	11.38±5.50	13.59±5.39	16.37±3.99
VIM of BW	1.32±0.57	1.88±1.28	2.52±1.65	3.23±1.84	3.98±1.87
CV of FBG, %	7.32±3.48	10.33±6.86	13.48±8.73	17.11±10.03	21.54±10.85
CV of TC, %	7.09±2.91	9.63±5.51	12.70±6.68	15.92±6.76	18.86±5.92
CV of systolic BP, %	5.63±2.38	7.52±3.98	9.27±4.55	11.11±4.54	13.45±3.56
CV of BW, %	2.05±0.90	2.93±2.00	3.94±2.58	5.07±2.89	6.26±2.94
Current smoker	700 264 (25.7)	802 866 (25.4)	406 567 (24.7)	108 708 (23.7)	12 908 (22.7)
Heavy alcohol drinker	211 645 (7.8)	239 365 (7.6)	123 279 (7.5)	34 005 (7.4)	4127 (7.3)
Regular exercise	558 755 (20.5)	625 576 (19.8)	314 295 (19.1)	83 379 (18.2)	9735 (17.1)
Income (lower 25%)	500 205 (18.3)	659 449 (20.9)	378 453 (23.0)	111 134 (24.2)	14 374 (25.3)
Diabetes mellitus	133 392 (4.9)	252 274 (8.0)	197 649 (12.0)	78 680 (17.2)	13 605 (24.0)
Hypertension	580 070 (21.3)	812 832 (25.7)	507 914 (30.8)	165 328 (36.1)	23 784 (41.9)
Dyslipidemia	307 518 (11.3)	489 680 (15.5)	332 466 (20.2)	113 098 (24.7)	16 303 (28.7)
Previous ED visit†	118 077 (4.3)	166 783 (5.3)	109 291 (6.6)	39 115 (8.5)	6361 (11.2)

Data are expressed as the means±SD, or n (%). *P* values for the trend were <0.0001 for all variables because of the large size of the study population. BMI indicates body mass index; BP, blood pressure; BW, body weight; CV, coefficient of variation; ED, emergency department; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; and VIM, variability independent of the means.

*Triglycerides are presented as median (Q1–Q3).

†History of ED visit during 5 years before the index year.

high variability parameters in all subgroups (Figure 3). Higher adjusted HRs for hospitalization were observed in the middle-aged (40–64 years), elderly (≥65 years), male, DM, and CKD subgroups. The highest HR for emergency hospitalization was observed in the CKD subgroup (HR 1.70, 95% CI 1.09–5.08).

The results were similar when the variability of parameters was determined using the CV and ARV (Tables S1 and S2). The number of high variability parameters, as measured using the CV or ARV, was also an independent predictor of emergency hospitalization after multivariable adjustment (Tables S1 and S2). Because comorbidities and/or treatments might modulate the changes in metabolic parameters during the follow-up, we performed a sensitivity analysis after excluding those with DM, hypertension, or dyslipidemia, which also revealed similar results. The number of high-variability parameters was also an independent predictor of emergency hospitalization after excluding subjects with DM, hypertension, and dyslipidemia (score 0 versus 4; HR, 1.49; 95% CI, 1.43–1.55).

Table 2. Hazard Ratios and 95% CIs of Emergency Hospitalization by Quartiles of Metabolic Parameter Variability

	Events (n)	Follow-Up Duration (Person-Year)	Incidence Rate (Per 1000 Person-Years)	Model 1	Model 2
Glucose variability (VIM of FBG)					
Q1	173 881	11 288 585	15.4	1 (ref.)	1 (ref.)
Q2	173 619	11 402 040	15.2	1.04 (1.03–1.05)	1.04 (1.03–1.04)
Q3	179 457	11 426 983	15.7	1.09 (1.08–1.09)	1.08 (1.07–1.09)
Q4	206 430	11 328 929	18.2	1.20 (1.19–1.20)	1.16 (1.16–1.17)
P for trend				<0.001	<0.001
Cholesterol variability (VIM of TC)					
Q1	166 079	11 371 977	14.6	1 (ref.)	1 (ref.)
Q2	165 894	11 485 533	14.4	1.03 (1.02–1.03)	1.02 (1.02–1.03)
Q3	177 620	11 432 471	15.5	1.07 (1.06–1.08)	1.06 (1.06–1.07)
Q4	223 794	11 156 555	20.1	1.19 (1.18–1.20)	1.14 (1.14–1.15)
P for trend				<0.001	<0.001
BP variability (VIM of systolic BP)					
Q1	174 946	11 531 883	15.2	1 (ref.)	1 (ref.)
Q2	162 624	11 282 797	14.4	1.01 (1.00–1.01)	1.01 (1.01–1.02)
Q3	179 676	11 404 823	15.8	1.04 (1.03–1.04)	1.03 (1.03–1.04)
Q4	216 141	11 227 032	19.3	1.12 (1.11–1.12)	1.11 (1.10–1.12)
P for trend				<0.001	<0.001
BW variability (VIM of BW)					
Q1	173 183	11 376 582	15.2	1 (ref.)	1 (ref.)
Q2	172 919	11 454 747	15.1	1.03 (1.03–1.04)	1.03 (1.02–1.04)
Q3	180 788	11 404 361	15.9	1.10 (1.09–1.11)	1.09 (1.08–1.09)
Q4	206 497	11 210 846	18.4	1.28 (1.27–1.28)	1.24 (1.23–1.25)
P for trend				<0.001	<0.001

Model 1: adjusted for age, sex, smoking, alcohol drinking, regular exercise, and income status. Model 2: adjusted for model 1 plus baseline fasting glucose levels, total cholesterol, systolic blood pressure, and body weight, and a history of emergency room visits. BP indicates blood pressure; BW, body weight; FBG, fasting blood glucose; TC, total cholesterol; and VIM, variability independent of the mean.

DISCUSSION

In this study, high variability in metabolic parameters was not only associated with increased risk of emergency hospitalization but also with 30-day mortality in the general population. Especially, the risk of emergency hospitalization due to endocrine, respiratory, or genitourinary diseases was strongly associated with high variability in metabolic parameters. Stronger associations were noted in patients with DM or CKD. High variability of each metabolic parameter on its own is significantly associated with both emergency hospitalization and short-term death (except TC variability). Further research is needed to determine whether variability in these biological parameters directly increases adverse outcomes.

Recently, it was reported that systolic BP variability exceeding 10 to 12 mm Hg or diastolic BP variability exceeding 8 mm Hg significantly increased the risk of hospitalization and all-cause mortality.[22] High BP variability enhances periodic pressure loading and shear stress on the cardiovascular system, and the progression of atherosclerosis.[9] Multiple adverse pathological processes, including cardiac diastolic dysfunction, endothelial dysfunction, increased intima-media thickness, and arterial stiffness, have been proposed as potential mechanisms to explain the association between the visit-to-visit BP variability and cardiovascular outcomes.[9] Among the patients receiving antihypertensive medications, visit-to-visit BP variability independently predicted adverse events, including acute kidney injury, hypotension, and syncope. The exaggerated BP variability could be explained by sympathetic nervous system activation.[23] Chronic hypoxia in obstructive sleep apnea or chronic lung disease may lead to exaggerated BP variability associated with sympathetic nervous system activation. Although their BP levels are not particularly high, patients with lung diseases may show large fluctuations of BP, which could be associated with a future development of cardiovascular disease (CVD).[23] Therefore, high BP variability could increase

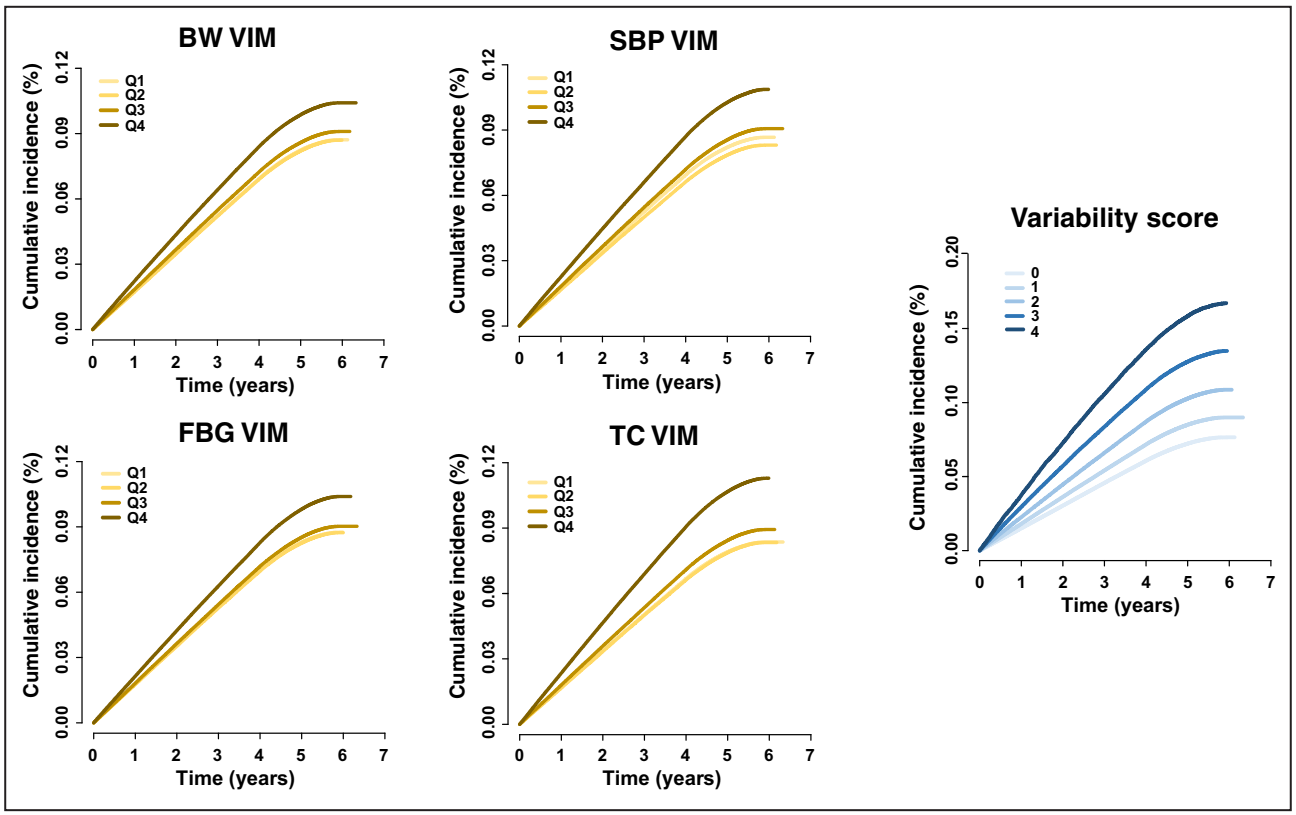

Figure 1. Kaplan–Meier estimates of cumulative incidence of emergency hospitalization according to the variability (Q1–Q4) of each metabolic parameter and the number of high variability parameters.
High variability was defined as the highest quartile (Q4) of variability independent of the mean (VIM). BW indicates body weight; FBG, fasting blood glucose; SBP, systolic blood pressure; and TC, total cholesterol.

emergency hospitalizations and mortality associated with conditions such as acute kidney injury, hypotension, syncope, falls, and hypoxia.

High glucose variability was associated with longer hospitalization and increased mortality in hospitalized patients, regardless of the presence of DM.[24] Glucose variability could potentially constitute a risk factor for falls and injuries. We found that high variability in metabolic parameters was an independent predictor of emergency hospitalization due to injury (*ICD-10* S codes). Moreover, high glucose variability is an independent risk factor of severe hypoglycemia and subsequent hospitalization in patients with DM.[25,26] The incidence and duration of hypoglycemia are associated with glucose variability.[25,26] There was a J-shaped association between HbA1c levels and the incidence rate of hypoglycemia.[27] Therefore, high glucose variability, independent of mean glucose levels, is associated with hypoglycemic events in patients with varying levels of glycemia.

Table 3. Hazard Ratios and 95% CIs of Emergency Hospitalizations by the Number of High Variability Metabolic Parameters

	Events (n)	Follow-Up Duration (Person-Years)	Incidence Rate (Per 1000 Person-Years)	Model 1	Model 2
Variability score					
0	206 407	15 608 093	13.2	1 (ref.)	1 (ref.)
1	280 489	17 858 477	15.7	1.12 (1.11–1.13)	1.10 (1.10–1.11)
2	176 398	9 176 413	19.2	1.28 (1.27–1.28)	1.23 (1.22–1.24)
3	60 795	2 502 156	24.3	1.49 (1.47–1.50)	1.40 (1.38–1.41)
4	9298	301 397	30.8	1.73 (1.69–1.77)	1.58 (1.54–1.61)
P for trend				<0.0001	<0.0001

Model 1: adjusted for age, sex, smoking, alcohol drinking, regular exercise, and income status. Model 2: adjusted for model 1 plus baseline fasting glucose levels, total cholesterol, systolic blood pressure, and body weight, and a history of emergency room visits.

Table 4. Hazard Ratios and 95% CIs of Cause-Specific Emergency Hospitalizations by the Number of High Variability Metabolic Parameters

	Events (n)	Incidence Rate (Per 1000 Person-Years)	HR (95% CI)
Diseases of circulatory system (*ICD-10 I*)			
0	31 667	2.03	1 (ref.)
1	45 061	2.52	1.10 (1.09–1.12)
2	29 592	3.22	1.22 (1.20–1.24)
3	10 618	4.24	1.37 (1.34–1.40)
4	1670	5.54	1.52 (1.45–1.60)
Injury & poisoning (*ICD-10* S)			
0	41 694	2.67	1 (ref.)
1	54 975	3.08	1.09 (1.08–1.11)
2	33 192	3.62	1.19 (1.18–1.21)
3	11 205	4.48	1.36 (1.33–1.39)
4	1530	5.08	1.40 (1.33–1.48)
Disease of digestive system (*ICD-10* K)			
0	29 470	1.89	1 (ref.)
1	38 440	2.15	1.09 (1.07–1.10)
2	23 451	2.56	1.20 (1.18–1.22)
3	7879	3.15	1.36 (1.33–1.39)
4	1215	4.03	1.58 (1.49–1.67)
Disease of respiratory system (*ICD-10* J)			
0	14 170	0.91	1 (ref.)
1	20 818	1.17	1.16 (1.13–1.18)
2	14 510	1.58	1.37 (1.34–1.40)
3	5398	2.16	1.59 (1.54–1.64)
4	888	2.95	1.83 (1.71–1.96)
Neoplasm (*ICD-10* C)			
0	13 809	0.88	1 (ref.)
1	19 363	1.08	1.08 (1.06–1.11)
2	12 562	1.37	1.17 (1.14–1.20)
3	4371	1.75	1.27 (1.22–1.31)
4	641	2.13	1.30 (1.20–1.41)
Infectious diseases (*ICD-10* A)			
0	11 109	0.71	1 (ref.)
1	15 358	0.86	1.13 (1.10–1.16)
2	9490	1.03	1.25 (1.22–1.29)
3	3210	1.28	1.42 (1.37–1.48)
4	487	1.62	1.62 (1.48–1.77)
Diseases of genitourinary system (*ICD-10* N)			
0	12 073	0.77	1 (ref.)
1	16 011	0.90	1.08 (1.05–1.10)
2	10 068	1.10	1.21 (1.18–1.25)
3	3574	1.43	1.44 (1.39–1.50)
4	576	1.91	1.74 (1.60–1.90)
Endocrine, nutritional & metabolic diseases (*ICD-10* E)			
0	1782	0.11	1 (ref.)
1	3525	0.20	1.37 (1.30–1.45)
2	3421	0.37	1.98 (1.87–2.10)
3	1616	0.65	2.61 (2.44–2.80)
4	368	1.22	3.66 (3.27–4.11)

Adjusted for age, sex, smoking, alcohol drinking, regular exercise, income status, baseline fasting glucose levels, total cholesterol, systolic blood pressure, and body weight, and a history of emergency room visits. *ICD-10* indicates *International Classification of Diseases, Tenth Revision. ICD-10 A,* infectious diseases; *ICD-10 C,* neoplasm; *ICD-10 E,* endocrine, nutritional & metabolic diseases; *ICD-10 I,* diseases of circulatory system; *ICD-10 J,* disease of respiratory system; *ICD-10 K*, disease of digestive system; *ICD-10 N*, diseases of genitourinary system; *ICD-10 S*, injury & poisoning.

High visit-to-visit cholesterol variability was also associated with increased CVD in both patients with coronary artery disease and in the general population.[1,5,10] A recent study showed that cholesterol variability was significantly associated with coronary atheroma progression and clinical outcomes, providing a plausible mechanism for association between cholesterol variability and cardiovascular events,[10] although the association between achieved cholesterol levels and atheroma progression was stronger. It is reported that cholesterol variability is a risk factor for atrial fibrillation development. Cholesterol is a main component of the cell membrane and changes in cholesterol levels can cause changes in membrane properties through effects on membrane permeability and membrane proteins, such as ion channels, pumps, and receptors.[11–13] This may affect electrical gradient and resting potential across the membranes and potentiate the development of arrhythmias. Lipoproteins may also affect the course of sepsis by binding to bacterial endotoxins and attenuating the harmful excessive inflammatory responses.[28] Both low-density lipoprotein

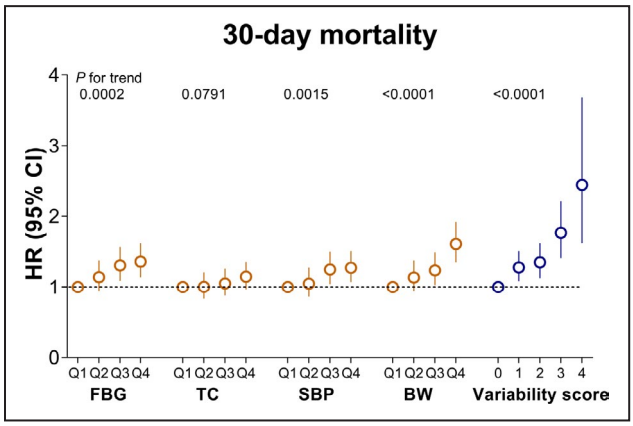

Figure 2. Hazard ratios and 95% CIs of 30-day mortality according to the variability (Q1–Q4) of each metabolic parameter and the number of high variability parameters. High variability was defined as the highest quartile (Q4) of variability independent of the mean (VIM). BW indicates body weight; FBG, fasting blood glucose; SBP, systolic blood pressure; and TC, total cholesterol.

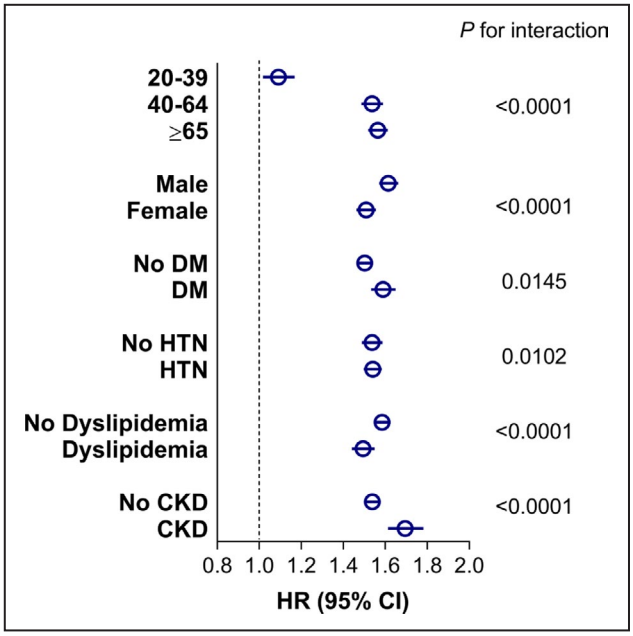

Figure 3. Subgroup analyses of the association between the number of high variability parameters (4 versus 0) and emergency hospitalization stratified by age, sex, diabetes mellitus (DM), hypertension (HTN), dyslipidemia, and chronic kidney disease (CKD).
Hazard ratios and 95% CIs of emergency hospitalization in subjects with 4 parameters of high variability (variability score 4) compared with subjects with no high variability parameters (variability score 0). CI indicates confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; HR, hazard ratio; and HTN, hypertension.

(LDL) and high-density lipoprotein (HDL) cholesterol play a proven role in the clearance of bacterial toxins, lipopolysaccharide from Gram-negative bacteria, and lipoteichoic acid from Gram-positive bacteria.[28] The alterations in lipids correlate with the severity of the underlying infection. Moreover, epidemiologic studies have suggested that low cholesterol levels increase the chance of developing an infection.

Individuals with weight fluctuation showed ≈24% higher emergency hospitalization and 61% higher 30-day mortality than those maintaining a stable weight over time (highest quartile group versus lowest quartile group); this observation is in line with the hypothesis that sarcopenia and intercurrent protein energy wasting may underlie the increased risk for hospitalization.[29] High variation in BW negatively impacts lipid metabolism by lowering HDL cholesterol and increasing the abdominal fat proportion. In an analysis from the Framingham Heart Study involving patients without known CVD, highly variable BWs were associated with higher mortality and morbidity related to coronary heart disease.[30] Among subjects with coronary artery disease, fluctuation in BW was associated with higher mortality independent of traditional cardiovascular risk factors.[6]

Another factor that may increase variability in metabolic parameters could be poor social support. It was recently reported that income variability and decreases during a 15-year period of formative earning years were associated with a nearly 2-fold risk of CVD and all-cause mortality.[31] Unpredictable and episodic low income was associated with an array of unhealthy behaviors, such as alcohol use, smoking, and inadequate physical activity. Stress was another mediating factor implicated in the relationship between income variability and adverse health outcomes.[31] Income variability has been shown to be associated with increases in BP, which can also be induced by stress and are associated with CVD and mortality.[31]

The association between increased variability and emergency hospitalization was more prominent in men, individuals without dyslipidemia, and those with CKD, as shown in the subgroup analysis (*P* for interaction <0.001). This finding suggests that utility of high variability in metabolic parameters as a predictor of emergency hospitalization may be more valid in these subpopulations. The reasons why men are more vulnerable to high variability are not known. Previous studies showed that the association between high variability in metabolic parameters and adverse health outcomes was also more significant in men rather than in women.[1–3,15] This sex disparity might be due to differences in estradiol, which is thought to a have protective role in vascular disease, or from differences in social stress or health behaviors. The association between high variability and emergency hospitalization was attenuated in subjects with dyslipidemia. We previously reported the association between cholesterol variability and cardiovascular outcomes.[1] In that study, the association between high TC variability and the risk of CVD was weakened in the subjects using lipid-lowering agents compared with subjects not using lipid-lowering agents.[1] New use of lipid-lowering agents in patients with dyslipidemia might be related to high TC variability, but it is likely that the beneficial effects of the use of lipid-lowering agents mitigated the impact of high TC variability on adverse health outcomes.[1] Increased BP variability is more common in patients with CKD and worsens with advancing CKD stages.[32] BP variability has been reported to independently predict cardiovascular outcomes as well as hypotension, syncope, and acute kidney injury in patients with CKD.[32] High variability in metabolic parameters might be closely related to emergency hospitalization in patients with CKD.

This study did have some limitations. First, this was an observational study and, therefore, the association found between variability and end points may not be causal. To minimize the possible effects of reverse causality, we excluded those with emergency hospitalization during the first year of

follow-up. In our study, high variability in metabolic parameters was associated with emergency hospitalization due to injury and poisoning. This finding for injury and poisoning may also suggest that variability is not a causal relationship, but an indicator of the unstable health status of these patients. High variability in metabolic parameters may reflect something else about a patient's interactions with the healthcare system or about other health conditions. Therefore, this study did not reveal a direct causal relationship between high variability and emergency hospitalization. Second, excluding participants with fewer than 3 health examinations might have been a source of selection bias. Third, although the NHIS contains information on a wide range of confounding factors, residual confounding cannot be completely excluded. Variability in metabolic parameters may be affected by time-varying behavioral variables, changes in diagnosis, and treatments during follow-up. Fourth, variables for health behavior are limited since those data were obtained from self-reporting in nationwide health screenings. However, considering the large number of participants, we believe that misclassification of alcohol, smoking, or physical activity had only a limited influence on the results obtained. Lastly, because the optimal method of calculating variability is unknown, the results might differ according to the definition of variability. There is a lack of consensus about the appropriate metrics to define high variability. In our study, high variability was defined as the highest quartile of variability, based on the distribution of variability in the cohort. It is unknown whether these findings would be replicated in populations with different distributions and underlying causes of variability.

One major strength of this study is its population-based design. Thus, it includes all patients visiting the ER and being hospitalized in this region, which minimizes selection bias and allows for a complete follow-up. Second, the cause of emergency hospitalization could be analyzed. The association of high metabolic parameter variability with the risk of emergency hospitalization due to malignancy was relatively weak; however, the association with the risk of emergency hospitalization due to endocrine, respiratory, or genitourinary diseases was strong. Variability in metabolic parameters may possibly be a marker of poor health status, with variations in blood glucose or BP levels reflecting changes in renal, adrenal, or liver dysfunction. This also has important implications in that high variability in metabolic parameters could be used for detecting individuals at high risk of emergency hospitalization and short-term mortality. Variability is a calculated variable not intuitively obvious to the clinician. With the use of electronic medical records, a variability index can be calculated and presented to the clinician relatively easily. Our findings suggest alerting clinicians about variability in metabolic parameters, which is an important but largely ignored risk factor.

CONCLUSIONS

The impact of variability in metabolic parameters is not limited to certain diseases. Our study indicates that variability in metabolic parameters was not only associated with emergency hospitalization but also with 30-day mortality, regardless of the causes of hospitalization. ER visits serve as the source for most of the unscheduled hospitalizations. ER visits and hospitalizations are often considered to be costly. Stabilizing metabolic parameters may be important for reducing ER visits, emergency hospitalization, and short-term mortality. Before reaching this conclusion, further research identifying the underlying causes of high variability are warranted. More research is needed to see if reducing variability in metabolic parameters can improve long-term health outcomes.

ARTICLE INFORMATION

Received June 12, 2020; accepted September 24, 2020.

Affiliations

From the Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine (S.-H.L., K.-H.Y.) and Department of Medical Informatics, College of Medicine (S.-H.L., K.-H.Y.), The Catholic University of Korea, Seoul, Korea; Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea (K.H.); and Division of Endocrinology and Metabolism, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea (H.-S.K., M.K.K.).

Sources of Funding

This work was supported in part by the National Research Foundation of Korea Grant funded by the Korean Government (NRF-2019R1H1A1100951). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Disclosures

None.

Supplementary Material

Tables S1–S2
Figures S1–S2

REFERENCES

1. Kim MK, Han K, Kim HS, Park YM, Kwon HS, Yoon KH, Lee SH. Cholesterol variability and the risk of mortality, myocardial infarction, and stroke: a nationwide population-based study. *Eur Heart J*. 2017;38:3560–3566.
2. Kim MK, Han K, Park YM, Kwon HS, Kang G, Yoon KH, Lee SH. Associations of variability in blood pressure, glucose and

cholesterol concentrations, and body mass index with mortality and cardiovascular outcomes in the general population. *Circulation*. 2018;138:2627–2637.
3. Lee SH, Han K, Cho H, Park YM, Kwon HS, Kang G, Yoon KH, Kim MK. Variability in metabolic parameters and risk of dementia: a nationwide population-based study. *Alzheimers Res Ther*. 2018;10:110.
4. Lee SH, Kim HS, Park YM, Kwon HS, Yoon KH, Han K, Kim MK. HDL-cholesterol, its variability, and the risk of diabetes: a nationwide population-based study. *J Clin Endocrinol Metab*. 2019;104:5633–5641.
5. Bangalore S, Breazna A, DeMicco DA, Wun CC, Messerli FH. Visit-to-visit low-density lipoprotein cholesterol variability and risk of cardiovascular outcomes: insights from the TNT trial. *J Am Coll Cardiol*. 2015;65:1539–1548.
6. Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD. Body-weight fluctuations and outcomes in coronary disease. *N Engl J Med*. 2017;376:1332–1340.
7. Vidal-Petiot E, Stebbins A, Chiswell K, Ardissino D, Aylward PE, Cannon CP, Ramos Corrales MA, Held C, López-Sendón JL, Stewart RAH, et al. Visit-to-visit variability of blood pressure and cardiovascular outcomes in patients with stable coronary heart disease. Insights from the STABILITY trial. *Eur Heart J*. 2017;38:2813–2822.
8. Wang A, Liu X, Xu J, Han X, Su Z, Chen S, Zhang N, Wu S, Wang Y, Wang Y. Visit-to-visit variability of fasting plasma glucose and the risk of cardiovascular disease and all-cause mortality in the general population. *J Am Heart Assoc*. 2017;6:e006757. DOI: 10.1161/JAHA.117.006757.
9. Seo SM, Chung WB, Choi IJ, Koh YS, Ihm SH, Kim PJ, Chung WS, Seung KB. Visit-to-visit variability of systolic blood pressure predicts all-cause mortality in patients received percutaneous coronary intervention with drug-eluting stents. *Heart Vessels*. 2018;33:489–497.
10. Clark D III, Nicholls SJ, St John J, Elshazly MB, Kapadia SR, Tuzcu EM, Nissen SE, Puri R. Visit-to-visit cholesterol variability correlates with coronary atheroma progression and clinical outcomes. *Eur Heart J*. 2018;39:2551–2558.
11. Lee SR, Choi YJ, Choi EK, Han KD, Lee E, Cha MJ, Oh S, Lip GYH. Blood pressure variability and incidence of new-onset atrial fibrillation: a nationwide population-based study. *Hypertension*. 2020;75:309–315.
12. Lee HJ, Lee SR, Choi EK, Han KD, Oh S. Low lipid levels and high variability are associated with the risk of new-onset atrial fibrillation. *J Am Heart Assoc*. 2019;8:e012771. DOI: 10.1161/JAHA.119.012771.
13. Lee SR, Choi EK, Han KD, Lee SH, Oh S. Effect of the variability of blood pressure, glucose level, total cholesterol level, and body mass index on the risk of atrial fibrillation in a healthy population. *Heart Rhythm*. 2020;17:12–19.
14. Elixhauser A, Owens P. *Reasons for Being Admitted to the Hospital through the Emergency Department, 2003: Statistical Brief #2. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet].* Rockville, MD: Agency for Healthcare Research and Quality (US); 2006.
15. Yoo JE, Shin DW, Han K, Kim D, Lee SP, Jeong SM, Lee J, Kim S. Blood pressure variability and the risk of dementia: a nationwide cohort study. *Hypertension*. 2020;75:982–990.
16. LaMantia MA, Stump TE, Messina FC, Miller DK, Callahan CM. Emergency department use among older adults with dementia. *Alzheimer Dis Assoc Disord*. 2016;30:35–40.
17. Critchley JA, Carey IM, Harris T, DeWilde S, Cook DG. Variability in glycated hemoglobin and risk of poor outcomes among people with type 2 diabetes in a large primary care cohort study. *Diabetes Care*. 2019;42:2237–2246.
18. Kim MK, Han K, Koh ES, Kim ES, Lee MK, Nam GE, Kwon HS. Blood pressure and development of cardiovascular disease in Koreans with type 2 diabetes mellitus. *Hypertension*. 2019;73:319–326.
19. Ko SH, Han K, Lee YH, Noh J, Park CY, Kim DJ, Jung CH, Lee KU, Ko KS; TaskForce Team for the Diabetes Fact Sheet of the Korean Diabetes Association. Past and current status of adult type 2 diabetes mellitus management in korea: a national health insurance service database analysis. *Diabetes Metab J*. 2018;42:93–100.
20. Lee YH, Han K, Ko SH, Ko KS, Lee KU. Data analytic process of a nationwide population-based study using national health information database established by National Health Insurance Service. *Diabetes Metab J*. 2016;40:79–82.
21. Kim MK, Ko SH, Kim BY, Kang ES, Noh J, Kim SK, Park SO, Hur KY, Chon S, Moon MK, et al. 2019 clinical practice guidelines for type 2 diabetes mellitus in Korea. *Diabetes Metab J*. 2019;43:398–406.
22. Basson MD, Klug MG, Hostetter JE, Wynne J. Visit-to visit variability of blood pressure is associated with hospitalization and mortality in an unselected adult population. *Am J Hypertens*. 2018;31:1113–1119.
23. Imaizumi Y, Eguchi K, Taketomi A, Tsuchihashi T, Kario K. Exaggerated blood pressure variability in patients with pneumoconiosis: a pilot study. *Am J Hypertens*. 2014;27:1456–1463.
24. Akirov A, Diker-Cohen T, Masri-Iraqi H, Shimon I. High glucose variability increases mortality risk in hospitalized patients. *J Clin Endocrinol Metab*. 2017;102:2230–2241.
25. Peled S, Pollack R, Elishoov O, Haze A, Cahn A. Association of inpatient glucose measurements with amputations in patients hospitalized with acute diabetic foot. *J Clin Endocrinol Metab*. 2019;104:5445–5452.
26. Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? *Diabetes Metab J*. 2015;39:273–282.
27. Lipska KJ, Warton EM, Huang ES, Moffet HH, Inzucchi SE, Krumholz HM, Karter AJ. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. *Diabetes Care*. 2013;36:3535–3542.
28. van Leeuwen HJ, Heezius EC, Dallinga GM, van Strijp JA, Verhoef J, van Kessel KP. Lipoprotein metabolism in patients with severe sepsis. *Crit Care Med*. 2003;31:1359–1366.
29. Carrero JJ, Cabezas-Rodríguez I, Qureshi AR, Floege J, Ketteler M, London G, Locatelli F, Memmos D, Goldsmith D, Ferreira A, et al. Risk of hospitalization associated with body mass index and weight changes among prevalent haemodialysis patients. *Nefrologia*. 2018;38:520–527.
30. Lissner L, Odell PM, D'Agostino RB, Stokes J III, Kreger BE, Belanger AJ, Brownell KD. Variability of body weight and health outcomes in the Framingham population. *N Engl J Med*. 1991;324:1839–1844.
31. Elfassy T, Swift SL, Glymour MM, Calonico S, Jacobs DR Jr, Mayeda ER, Kershaw KN, Kiefe C, Zeki A, Hazzouri A. Associations of income volatility with incident cardiovascular disease and all-cause mortality in a US cohort. *Circulation*. 2019;139:850–859.
32. Mezue K, Goyal A, Pressman GS, Horrow JC, Rangaswami J. Blood pressure variability predicts adverse events and cardiovascular outcomes in chronic kidney disease: a post-hoc analysis of the SPRINT trial. *Am J Hypertens*. 2017;31:48–52.

SUPPLEMENTAL MATERIAL

Table S1. Hazard ratios and 95% confidence intervals of emergency hospitalization by quartiles of metabolic parameter variability and by the number of high variability metabolic parameters (measured by CV).

	Events (n)	Follow-up duration (person-year)	Incidence rate (per 1000 person-years)	Model 1	Model 2
Glucose variability (CV of FBG)					
Q1	165311	11331010	14.6	1 (ref.)	1 (ref.)
Q2	167062	11438539	14.6	1.04 (1.03,1.05)	1.04 (1.03,1.04)
Q3	176452	11434182	15.4	1.08 (1.07,1.09)	1.07 (1.06,1.08)
Q4	224562	11242806	20.0	1.24 (1.23,1.25)	1.18 (1.17,1.18)
P for trend				<0.001	<0.001
Cholesterol variability (CV of TC)					
Q1	165863	11372388	14.6	1 (ref.)	1 (ref.)
Q2	165891	11486503	14.4	1.02 (1.02,1.03)	1.02 (1.02,1.03)
Q3	177601	11432002	15.5	1.07 (1.06,1.08)	1.06 (1.05,1.07)
Q4	224032	11155643	20.1	1.18 (1.18,1.19)	1.14 (1.13,1.15)
P for trend				<0.001	<0.001
BP variability (CV of systolic BP)					
Q1	167607	11363470	14.7	1 (ref.)	1 (ref.)
Q2	161254	11503374	14.0	1.01 (1.00,1.01)	1.01 (1.00,1.01)
Q3	178199	11416928	15.6	1.04 (1.03,1.04)	1.03 (1.03,1.04)
Q4	226327	11162763	20.3	1.13 (1.12,1.13)	1.11 (1.10,1.12)
P for trend				<0.001	<0.001
BW variability (CV of BW)					
Q1	172894	11377934	15.2	1 (ref.)	1 (ref.)
Q2	172913	11476766	15.1	1.03 (1.02,1.04)	1.03 (1.02,1.03)
Q3	180249	11403330	15.8	1.10 (1.09,1.10)	1.09 (1.08,1.09)
Q4	207331	11188507	18.5	1.28 (1.27,1.28)	1.24 (1.23,1.25)
P for trend				<0.001	<0.001
Variability Score					
0	199956	15846215	12.6	1 (ref.)	1 (ref.)
1	274232	17636851	15.5	1.13 (1.12,1.13)	1.10 (1.10,1.11)
2	180936	9098436	19.9	1.29 (1.28,1.30)	1.24 (1.23,1.24)
3	66904	2544143	26.3	1.52 (1.51,1.53)	1.41 (1.39,1.42)
4	11359	320891	35.4	1.81 (1.78,1.84)	1.61 (1.58,1.64)
P for trend				<0.001	<0.001

Model 1: adjusted for age, sex, smoking, alcohol drinking, regular exercise, and income status

Model 2: adjusted for model 1 plus baseline fasting glucose levels, total cholesterol, systolic blood pressure and body weight and a history of emergency room visits

BP, blood pressure; BW, body weight; CV, coefficient of variation; FBG, fasting blood glucose; TC, total cholesterol

Table S2. Hazard ratios and 95% confidence intervals of emergency hospitalization by quartiles of metabolic parameter variability and by the number of high variability metabolic parameters (measured by ARV).

	Events (n)	Follow-up duration (person-year)	Incidence rate (per 1000 person-years)	Model 1	Model 2
Glucose variability (ARV of FBG)					
Q1	151312	10840196	13.9	1 (ref.)	1 (ref.)
Q2	178504	12377238	14.4	1.03 (1.03,1.04	1.03 (1.02,1.03)
Q3	167041	10855156	15.4	1.07 (1.06,1.07)	1.05 (1.05,1.06)
Q4	236530	11373947	20.8	1.23 (1.23,1.24)	1.17 (1.16,1.17)
P for trend				<0.001	<0.001
Cholesterol variability (ARV of TC)					
Q1	159706	11264359	14.2	1 (ref.)	1 (ref.)
Q2	173365	11842992	14.6	1.02 (1.01,1.03)	1.03 (1.02,1.03)
Q3	178455	11209048	15.9	1.05 (1.04,1.05)	1.06 (1.05,1.06)
Q4	221861	11130136	19.9	1.12 (1.11,1.13)	1.12 (1.11,1.13)
P for trend				<0.001	<0.001
BP variability (ARV of systolic BP)					
Q1	167390	11887899	14.1	1 (ref.)	1 (ref.)
Q2	131347	9615158	13.7	0.98 (0.97,0.99)	0.98 (0.97,0.99)
Q3	192216	12451943	15.4	1.03 (1.02,1.03)	1.02 (1.01,1.03)
Q4	242434	11491537	21.1	1.13 (1.12,1.13)	1.10 (1.09,1.11)
P for trend				<0.001	<0.001
BW variability (ARV of BW)					
Q1	196243	12816378	15.3	1 (ref.)	1 (ref.)
Q2	146813	10007554	14.7	1.03 (1.03,1.04)	1.03 (1.03,1.04)
Q3	186857	11507643	16.2	1.09 (1.08,1.10)	1.08 (1.07,1.09)
Q4	203474	11114961	18.3	1.26 (1.25,1.26)	1.23 (1.22,1.23)
P for trend				<0.001	<0.001
Variability Score					
0	194589	15894636	12.2	1 (ref.)	1 (ref.)
1	269667	17377650	15.5	1.11 (1.10,1.11)	1.09 (1.09,1.10)
2	185277	9147086	20.3	1.26 (1.25,1.27)	1.22 (1.21,1.23)
3	71338	2669896	26.7	1.46 (1.45,1.47)	1.37 (1.36,1.38)
4	12516	357267	35.0	1.72 (1.69,1.75)	1.56 (1.53,1.59)
P for trend				<0.001	<0.001

Model 1: adjusted for age, sex, smoking, alcohol drinking, regular exercise, and income status

Model 2: adjusted for model 1 plus baseline fasting glucose levels, total cholesterol, systolic blood pressure and body weight and a history of emergency room visits

ARV, average real variability; BP, blood pressure; BW, body weight; FBG, fasting blood glucose; TC, total cholesterol

Figure S1. Flowchart of the study population.

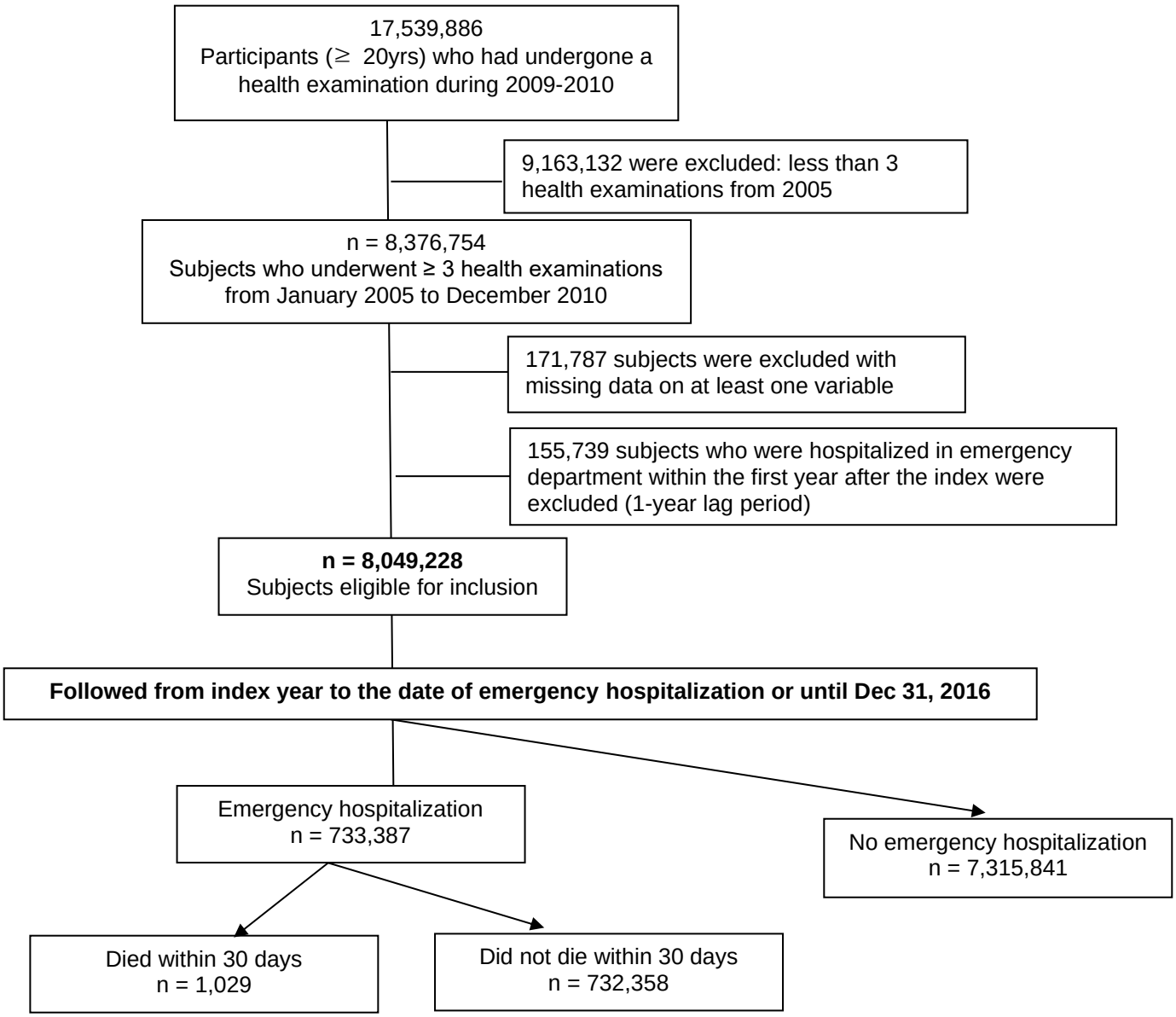

Figure S2. Study design.