Circulation

ORIGINAL RESEARCH ARTICLE

Associations of Variability in Blood Pressure, Glucose and Cholesterol Concentrations, and Body Mass Index With Mortality and Cardiovascular Outcomes in the General Population

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BACKGROUND: Variability in metabolic parameters, such as fasting blood glucose and cholesterol concentrations, blood pressure, and body weight can affect health outcomes. We investigated whether variability in these metabolic parameters has additive effects on the risk of mortality and cardiovascular outcomes in the general population.

METHODS: Using nationally representative data from the Korean National Health Insurance System, 6 748 773 people who were free of diabetes mellitus, hypertension, and dyslipidemia and who underwent ≥3 health examinations from 2005 to 2012 were followed to the end of 2015. Variability in fasting blood glucose and total cholesterol concentrations, systolic blood pressure, and body mass index was measured using the coefficient of variation, SD, variability independent of the mean, and average real variability. High variability was defined as the highest quartile of variability. Participants were classified numerically according to the number of high-variability parameters (eg, a score of 4 indicated high variability in all 4 metabolic parameters). Cox proportional hazards models adjusting for age, sex, smoking, alcohol, regular exercise, income, and baseline levels of fasting blood glucose, systolic blood pressure, total cholesterol, and body mass index were used.

RESULTS: There were 54 785 deaths (0.8%), 22 498 cases of stroke (0.3%), and 21 452 myocardial infarctions (0.3%) during a median follow-up of 5.5 years. High variability in each metabolic parameter was associated with a higher risk for all-cause mortality, myocardial infarction, and stroke. Furthermore, the risk of outcomes increased significantly with the number of high-variability metabolic parameters. In the multivariable-adjusted model comparing a score of 0 versus 4, the hazard ratios (95% CIs) were 2.27 (2.13–2.42) for all-cause mortality, 1.43 (1.25–1.64) for myocardial infarction, and 1.41 (1.25–1.60) for stroke. Similar results were obtained when modeling the variability using the SD, variability independent of the mean, and average real variability, and in various sensitivity analyses.

CONCLUSIONS: High variability of fasting blood glucose and total cholesterol levels, systolic blood pressure, and body mass index was an independent predictor of mortality and cardiovascular events. There was a graded association between the number of high-variability parameters and cardiovascular outcomes.

Key Words: blood pressure ■ body mass index ■ cholesterol ■ glucose ■ mortality ■ myocardial infarction ■ stroke ■ variability

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Clinical Perspective

What Is New?

- High variability in fasting glucose and cholesterol levels, systolic blood pressure, and body mass index was associated with a higher risk for all-cause mortality, myocardial infarction, and stroke.
- Variabilities in several metabolic parameters had additive associations with the risk of mortality and cardiovascular outcomes in the general population.

What Are the Clinical Implications?

- Variability in metabolic parameters may have a role in predicting mortality and cardiovascular outcomes.
- Treatment strategies to reduce fluctuations in metabolic parameters should be another goal to prevent adverse health outcomes.

Dysregulation of homeostasis is a risk factor for several diseases and for cardiovascular events in particular.[1–7] For example, blood pressure (BP) variability is an independent cardiovascular risk factor regardless of average BP.[1–3] BP does not remain steady but instead fluctuates continually within a 24-hour period, from day to day, and from month to month.[8] These fluctuations are not random and tend to remain consistent for a given individual.[1–3] Increased BP variability increases the stress on blood vessels and leads to endothelial dysfunction, thereby promoting early target organ damage. Similarly, variability in fasting blood glucose (FBG) and cholesterol concentrations is associated with future cardiovascular events.[4–7] In a recent study, we provided evidence that variability in cholesterol concentration was an independent risk factor for all-cause mortality, myocardial infarction (MI), and stroke in the Korean population.[7] Although the mechanisms may differ between parameters, these fluctuations in physiological measures such as BP and glucose and lipid levels may contribute to, or be predictors of, adverse health outcomes.

Variability in BP and glucose and cholesterol concentrations may underlie variable compliance with a healthy diet or changes in dietary habits or body weight. Previous studies have reported that body weight variability is a risk factor for all-cause mortality and fatal cardiovascular events.[9,10] In the Framingham study, people with a highly variable body weight had higher total mortality and higher coronary heart disease-related mortality.[10] In the current study, we investigated whether the variabilities in several metabolic parameters are interrelated and whether they have additive associations with the risk of mortality and cardiovascular outcomes. We conducted a large population-based study involving >6.7 million Koreans who had ≥3 measurements to examine the prognostic significance of increased variability of metabolic parameters (glucose and cholesterol concentrations, BP, and body mass index [BMI]) on the rates of all-cause mortality, MI, and stroke.

METHODS

The authors declare that all supporting data are available within the article and its online-only Data Supplement.

Data Source and Study Population

The Korean National Health Insurance System (NHIS) comprises a complete set of health information pertaining to ≈50 million Koreans. The NHIS includes an eligibility database (eg, age, sex, socioeconomic variables, type of eligibility), a medical treatment database (based on the accounts submitted by medical service providers for medical expenses), a health examination database (results of general health examinations and questionnaires on lifestyle and behavior), a medical care institution database (types of medical care institutions, location, equipment, and number of physicians), and death information.[11–13] In Korea, the NHIS is the single insurer, is managed by the government, and includes all Koreans. Enrollees in the National Health Insurance Corporation are recommended to undergo standardized medical examinations every 2 years. In our study, we included those who had undergone a health examination between 2009 and 2012 (index year) and ≥2 health examinations between January 1, 2005, and December 31, 2008. Of 25 503,802 people ≥20 years of age with health examination data in the index year, 11 476 068 underwent ≥3 health examinations during this period. We excluded 170 921 people with missing data for ≥1 variable. A total of 4 466 601 people had diabetes mellitus, hypertension, or dyslipidemia (diagnostic criteria are listed later) and had already received medical treatment before the index year. Because these treatments can affect body weight and other measurements, and to exclude the possible effect of variable compliance with drug treatment, these people were excluded from the analysis. To avoid confounding by preexisting diseases and to minimize the possible effects of reverse causality, those with a history of MI (International Classification of Disease, 10th Revision [ICD-10] codes: I21, I22) or stroke (ICD-10 codes: I63, I64) before the index year were also excluded (n=89 773). Ultimately, the study population included 6 748 773 people (Figure I in the online-only Data Supplement). This study was approved by the Institutional Review Board of The Catholic University of Korea (No. KC17ZESI0505). Anonymous and deidentified information was used for analysis and, therefore, informed consent was not obtained.

Measurements and Definitions

The general medical examination included history taking, BP measurement, blood sampling, urinalysis, and chest x-ray results. According to the protocol, BP was measured by a trained clinician after the participant had been seated for 5 minutes with an arm in the appropriate position. Blood samples for the measurement of serum glucose and lipid levels were drawn after an overnight fast. Hospitals in which

these health examinations were performed were certified by the NHIS and subjected to regular quality control. The presence of diabetes mellitus was defined according to the presence of ≥1 claim per year under ICD-10 codes E10-14 and ≥1 claim per year for the prescription of antidiabetic medication or fasting glucose level ≥126 mg/dL. The presence of hypertension was defined according to the presence of ≥1 claim per year under ICD-10 codes I10 or I11 and ≥1 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 ≥1 claim per year under ICD-10 code E78 and ≥1claim per year for the prescription of a lipid-lowering agent or TC ≥240 mg/dL. BMI was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as BMI ≥25 kg/m^2.[14,15] Information on current smoking and alcohol consumption (heavy alcohol consumption defined as ≥30 g/day) was obtained by questionnaire. Regular exercise was defined as performing >30 minutes of moderate physical activity ≥5 times per week or >20 minutes of strenuous physical activity ≥3 times per week. Household income level was dichotomized at the lower 25%.

Definition of Parameter Variability and Scoring

Variability was defined as intraindividual variability in FBG, TC, systolic BP (SBP), or BMI values recorded in the health examinations. Four indices of variability were used: (1) coefficient of variation (CV), (2) SD, (3) variability independent of the mean, and (4) average real variability (ARV). Variability independent of the mean is SD divided by the mean to the power *x*. Power *x* is modeled as SD = $k \times \text{mean}^x$ and was derived from fitting curves by nonlinear regression analysis as implemented in the PROC NLIN procedure of the SAS package.[16,17] ARV is the average of the absolute differences between consecutive values and was calculated using the following formula, where N denotes the number of measurements of the metabolic parameters.[18]

$$ARV = \frac{1}{N-1}\sum_{k=1}^{N-1}\left|Value_{K+1} - Value_K\right|$$

The number of measurements per participant ranged as follows: 3 measurements (n=4 626 146 or 68%), four measurements (n=999 872 or 15%), and 5 measurements (n=1 122 755 or 17%). High variability was defined as the highest quartile (Q4) of variability, and low variability was defined as the lower 3 quartiles (Q1–Q3) of variability. The participants were classified further according to the number of high-variability metabolic parameters (FBG, TC, SBP, and BMI) using a score range from 0 to 4. 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 of the 4 total parameters (eg, a score of 3 indicated high variability in 3 of 4 parameters).

To consolidate our findings, we also used another scoring system of variability. We defined the variability score by assigning 0 points to Q1 (lowest quartile of variability), 1 point to Q2, 2 points to Q3, and 3 points to Q4 (highest quartile of variability) for each of the 4 parameters (FBG, TC, SBP, and BMI). We then summed these to give a variability score ranging from 0 to 12 points, in which a person with 12 points was in the Q4 group and a person with 0 points was in the Q1 group for all 4 parameters.

Study Outcomes and Follow-Up

The end points of the study were newly diagnosed MI, stroke, or death. MI was defined as the recording of ICD-10 codes I21 or I22 during hospitalization or these codes having been recorded ≥2 times. Stroke was defined as the recording of ICD-10 codes I63 or I64 during hospitalization with claims for brain MRI or brain computerized tomography. Participants without MI or stroke during their follow-up were considered to have completed the study at the date of their death or at the end of follow-up, whichever came first. The study population was followed from baseline to the date of death or cardiovascular events, or until December 31, 2015, whichever came first.

Statistical Analysis

Baseline characteristics are presented as the mean±SD or n (%). Participants 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 because of the large sample size and relatively balanced distribution of baseline covariates, and the log-rank test was performed to analyze differences between groups. The hazard ratio (HR) and 95% CI for all-cause mortality, MI, and stroke 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 high-variability parameters. 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, and BMI. To account for the possible changes in FBG, SBP, TC, and BMI levels before the index year, we also adjusted for the mean values instead of baseline values in model 2 of the Cox proportional-hazards model. A sensitivity analysis was performed to exclude participants with end points occurring in ≤3 years of the follow-up to account for the possibility of reverse causation. In addition, analysis using another criterion for high variability, being >1 SD of variability indices, was performed. To account for the possible influence of incident diabetes mellitus, hypertension, and dyslipidemia during follow-up on the outcomes, analysis censoring these subjects and time-dependent Cox regression analysis were performed. The potential effect modification by age, sex, BMI categories, and presence of malignancy was evaluated using stratified analysis and interaction testing using a likelihood ratio test. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc), and a *P* value <0.05 indicated significance.

RESULTS

Baseline Characteristics of the Study Population

The characteristics of the participants grouped according to the number of high-variability metabolic parameters are listed in Table 1. Participants with more high-variability parameters were older and more likely to be female. The highest baseline FBG, TC, SBP, and BMI values as well as the highest prevalence of metabolic syndrome were observed in participants with 4 high-variability parameters. The CV of each parameter increased gradually with the number of high-variability parameters. For trend values, $P<0.0001$ for all variables because of the large study population.

Correlations Between Variability in Metabolic Parameters

The correlations between FBG variability and TC variability (r=0.071), SBP variability (r=0.021), and BMI variability (r=0.036) were not robust (Table I in the online-only Data Supplement). The maximum correlation coefficient was observed between TC variability and BMI variability (r=0.105) but was not strong.

Risk of All-Cause Mortality, MI, and Stroke According to the Variability for Each Parameter

There were 84 625 deaths (2.3%) during a median (5% to 95%) follow-up of 5.5 (3.2–6.7) years in the entire cohort. For each metabolic parameter, an incrementally higher risk of all-cause mortality, MI, and stroke was observed for higher CV quartiles compared with the lowest quartile group (Table 2). The associations between variability for each parameter and outcomes were confirmed after adjusting for baseline FBG, TC, SBP, and BMI. For the highest quartile in FBG variability compared with the lowest quartile, the risk of all-cause mortality increased by 20% (HR, 1.20; 95% CI, 1.18–1.23), MI by 16% (HR, 1.16; 95% CI, 1.12–1.21), and stroke by 13% (HR, 1.13; 95% CI, 1.09–1.17). For the highest quartile in TC variability compared with the lowest quartile, the risk of all-cause mortality increased by 31% (HR, 1.31; 95% CI, 1.28–1.34), MI by 10% (HR, 1.10; 95% CI, 1.06–1.14), and stroke by 6% (HR, 1.06; 95% CI, 1.03–1.10). For the highest quartile in systolic BP variability compared with the lowest quartile, the risk of all-cause mortality increased by 19% (HR, 1.19; 95% CI, 1.16–1.22),

Table 1. Baseline Characteristics of Subjects by the Number of High Variability in the Metabolic Parameters (Fasting Blood Glucose, Total Cholesterol Levels, Systolic Blood Pressures, and Body Weight)

Variable	0	1	2	3	4
N	2 274 176	2 676 353	1 384 775	370 761	42 708
Age, y	42.7±11.5	42.7±12.1	42.8±12.7	43.1±13.5	43.8±14.3
Sex, m	1 365 674 (60.1)	1 529 956 (57.2)	759 710 (54.9)	195 571 (52.8)	22 066 (51.7)
Fasting blood glucose, mg/dL	92.6±9.8	93.8±12.4	95.0±14.4	96.3±16.1	97.9±18.0
TC, mg/dL	191.2±28.3	191.8±29.7	193.0±31.7	194.3±33.9	195.3±35.9
HDL cholesterol, mg/dL	55.6±17.4	55.9±18.2	56.0±18.5	56.1±19.3	56.1±20.2
LDL cholesterol, mg/dL	110.1±41.8	109.1±42.9	108.2±43.7	107.2±44.6	106.3±45.8
Triglyceride, mg/dL	101 (100.7, 100.8)	101 (101.3, 101.4)	102 (102.3, 102.4)	103 (103.2, 103.6)	104 (103.9, 105)
Systolic blood pressure, mm Hg	119.7±11.1	119.9±12.1	120.2±13.0	120.5±14.0	121.0±15.2
Diastolic blood pressure, mm Hg	75.4±8.3	75.4±8.6	75.4±8.9	75.4±9.2	75.5±9.7
Body mass index, kg/m^2	23.2±2.9	23.3±3.0	23.4±3.2	23.4±3.3	23.5±3.4
Waist circumferences, cm	78.4±8.6	78.3±8.7	78.3±8.8	78.3±8.9	78.3±9
Variability, coefficient of variation					
Fasting blood glucose, %	6.7±2.8	9.3±5.7	11.8±6.6	14.4±6.7	17.2±6.0
Total cholesterol, %	6.6±2.7	8.7±4.6	11.4±5.6	14.1±5.7	16.6±5.0
Systolic blood pressure, %	5.3±2.2	7.0±3.7	8.5±4.0	10.1±3.9	12.1±2.8
Diastolic blood pressure, %	7.3±3.9	8.2±4.4	9.1±4.7	10±4.9	11.2±4.9
Body mass index, %	2.2±0.9	3.1±2.0	4.1±2.6	5.3±2.8	6.4±2.8
Current smoker, yes	610 955 (26.9)	740 750 (27.7)	388 509 (28.1)	103 514 (27.9)	11 938 (28.0)
Heavy alcohol drinker, yes	157 794 (6.9)	190 713 (7.1)	101 722 (7.4)	28 247 (7.6)	3361 (7.9)
Regular exercise	426 009 (18.7)	487 705 (18.2)	244 861 (17.7)	63 552 (17.1)	7062 (16.5)
Household income, lower 25%	324 096 (14.3)	427 962 (16.0)	240 159(17.3)	68 193 (18.4)	8116 (19.0)
Metabolic syndrome, yes	268 513 (11.8)	335 318 (12.5)	185 409 (13.4)	53 118 (14.3)	6816 (16.0)

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.

Table 2. Hazard Ratios and 95% Confidence Intervals of All-Cause Mortality, Myocardial Infarction, and Stroke, by Quartiles of Metabolic Parameters Variability

	All-Cause Mortality				Myocardial Infarction				Stroke			
	Events (n)	Follow-Up Duration (Person-Year)	Incidence Rate (per 1000)	Hazard Ratio (95% CI)	Events (n)	Follow-Up Duration (Person-Year)	Incidence Rate (per 1000)	Hazard Ratio (95% CI)	Events (n)	Follow-Up Duration (Person-Year)	Incidence Rate (per 1000)	Hazard Ratio (95% CI)
Glucose variability (coefficient of variation of fasting blood glucose)												
Q1	11798	8806171	1.34	1 (ref.)	4860	8794426	0.55	1 (ref.)	5161	8794570	0.59	1 (ref.)
Q2	12159	9050500	1.34	1.02 (1.00–1.05)	4880	9038635	0.54	1.00 (0.96–1.04)	5267	9038599	0.58	1.03 (1.00–1.07)
Q3	13270	9150610	1.45	1.07 (1.04–1.09)	5250	9137697	0.57	1.04 (1.01–1.08)	5504	9138182	0.60	1.06 (1.02–1.10)
Q4	17558	9160473	1.92	1.20 (1.18–1.23)	6462	9145139	0.71	1.16 (1.12–1.21)	6566	9145806	0.72	1.13 (1.09–1.17)
P for trend				<0.0001				<0.0001				<0.0001
Cholesterol variability (coefficient of variation of total cholesterol)												
Q1	11930	8916927	1.34	1 (ref.)	5045	8904617	0.57	1 (ref.)	5423	8904649	0.61	1 (ref.)
Q2	12034	9127654	1.32	1.03 (1.00–1.05)	5079	9115212	0.56	1.00 (0.96–1.04)	5251	9115814	0.58	0.98 (0.95–1.02)
Q3	13262	9135125	1.45	1.11 (1.08–1.13)	5328	9122124	0.58	1.03 (0.99–1.07)	5409	9122853	0.59	0.99 (0.95–1.03)
Q4	17559	8988047	1.95	1.31 (1.28–1.34)	6000	8973944	0.67	1.10 (1.06–1.14)	6415	8973841	0.71	1.06 (1.03–1.10)
P for trend				<0.0001				<0.0001				<0.0001
Blood pressure variability (coefficient of variation of systolic blood pressure)												
Q1	11552	8944443	1.29	1 (ref.)	5031	8932185	0.56	1 (ref.)	4962	8933234	0.56	1 (ref.)
Q2	11776	9042206	1.30	1.04 (1.01–1.06)	4762	9030495	0.53	0.97 (0.94–1.01)	4744	9031404	0.53	1.00 (0.96–1.04)
Q3	13320	9307861	1.43	1.06 (1.03–1.08)	5382	9294869	0.58	1.01 (0.96–1.04)	5522	9295488	0.59	1.04 (1.00–1.08)
Q4	18137	8873243	2.04	1.19 (1.16–1.22)	6277	8858350	0.71	1.07 (1.03–1.11)	7270	8857030	0.82	1.14 (1.10–1.18)
P for trend				<0.0001				<0.0001				<0.0001
Body mass index variability (coefficient of variation of body mass index)												
Q1	11931	8994236	1.32	1 (ref.)	5457	8981011	0.61	1 (ref.)	5614	8981449	0.63	1 (ref.)
Q2	12265	9147736	1.34	1.06 (1.03–1.08)	5413	9134474	0.59	1.02 (0.98–1.06)	5415	9135406	0.59	1.00 (0.96–1.04)
Q3	13371	9103773	1.47	1.17 (1.15–1.20)	5238	9090890	0.58	1.03 (0.99–1.07)	5622	9091145	0.62	1.07 (1.03–1.11)
Q4	17218	8922009	1.93	1.53 (1.50–1.57)	5344	8909522	0.60	1.14 (1.09–1.18)	5847	8909156	0.66	1.14 (1.10–1.18)
P for trend				<0.0001				<0.0001				<0.0001

Adjusted for age, sex, alcohol drinking, smoking, regular exercise, income status, baseline fasting glucose levels, total cholesterol, systolic blood pressure, and body mass index.

MI by 7% (HR, 1.07; 95% CI, 1.03–1.11), and stroke by 14% (HR, 1.14; 95% CI, 1.10–1.18). For the highest quartile in BMI variability compared with the lowest quartile, the risk of all-cause mortality increased by 53% (HR, 1.53; 95% CI, 1.50–1.57), MI by 14% (HR, 1.14; 95% CI, 1.09–1.18), and stroke by 14% (HR, 1.14; 95% CI, 1.10–1.18). When the variability index was used as a continuous variable, 5% increase in CV of each metabolic parameter was associated with significantly increased risk for outcomes after full multivariable adjustment (Table II in the online-only Data Supplement).

Risk of All-Cause Mortality, MI, and Stroke According to the Number of High-Variability Parameters

The number of high-variability parameters was linearly related to the outcome measures (Figure 1 and Table 3). 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 for all-cause mortality (HR, 2.27; 95% CI, 2.13–2.42), MI (HR, 1.43; 95% CI, 1.25–1.64), and stroke

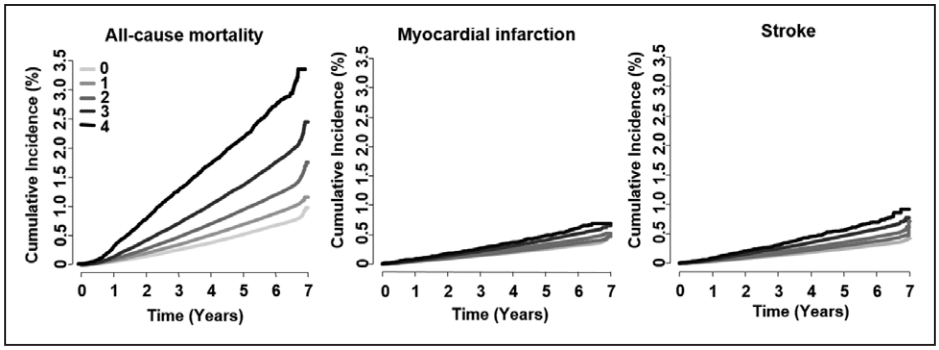

Figure 1. Kaplan–Meier estimates of cumulative incidence of all-cause mortality, myocardial infarction, and stroke by the number of high variability in the metabolic parameters.

High variability was defined as the highest quartile (Q4) of coefficient of variation. Unadjusted Kaplan–Meier curves are presented because of the large sample size and relatively balanced distribution of baseline covariates.

(HR, 1.41; 95%, CI 1.25–1.60). Given a variability score from 0 to 12 points, multivariable-adjusted HRs for all-cause mortality, MI, and stroke increased continuously and linearly with increasing variability score (Figure 2).

Sensitivity Analysis

The results were similar when the variability of parameters was determined using the SD, variability independent of the mean, and ARV. The number of high-variability parameters as measured by the SD, variability independent of the mean, or ARV was also an independent predictor of all-cause mortality, MI, and stroke after multivariable adjustment (Table III through V in the online-only Data Supplement). Excluding participants with end points that occurred in ≤3 years of the follow-up produced incrementally higher incidence rates and HRs (95% CI) for all-cause mortality, MI, and stroke

Table 3. Hazard Ratios and 95% CIs of All-Cause Mortality, Myocardial Infarction, and Stroke by the Number of High Variability in the Metabolic Parameters

	Variable	No. of Events	Follow-Up Duration (Person-Years)	Incidence Rate (per 1000 Person-Years)	Model 1	Model 2
All-cause mortality						
	0	13192	12238820	1.08	1 (ref.)	1 (ref.)
	1	20429	14338740	1.42	1.23 (1.20–1.25)	1.21 (1.18–1.23)
	2	14458	7391614	1.96	1.51 (1.47–1.54)	1.45 (1.42–1.49)
	3	5697	1972516	2.89	1.93 (1.87–1.99)	1.81 (1.76–1.87)
	4	1009	226063	4.46	2.48 (2.33–2.65)	2.27 (2.13–2.42)
	P for trend				<0.0001	<0.0001
Myocardial infarction						
	0	6316	12223050	0.52	1 (ref.)	1 (ref.)
	1	8272	14318717	0.58	1.07 (1.04–1.11)	1.07 (1.04–1.11)
	2	5004	7379724	0.68	1.18 (1.14–1.23)	1.19 (1.14–1.23)
	3	1637	1968835	0.83	1.33 (1.26–1.41)	1.34 (1.27–1.42)
	4	223	225570	0.99	1.41 (1.23–1.61)	1.43 (1.25–1.64)
	P for trend				<0.0001	<0.0001
Stroke						
	0	6292	12224423	0.51	1 (ref.)	1 (ref.)
	1	8710	14319108	0.61	1.09 (1.08–1.13)	1.09 (1.06–1.13)
	2	5366	7379664	0.73	1.17 (1.13–1.21)	1.17 (1.13–1.22)
	3	1864	1968450	0.95	1.33 (1.26–1.40)	1.34 (1.27–1.41)
	4	266	225511	1.18	1.40 (1.24–1.58)	1.41 (1.25–1.60)
	P for trend				<0.0001	<0.0001

Model 1 was adjusted for age, sex, alcohol drinking, smoking, regular exercise. and income status.
Model 2 was adjusted for model 1 plus baseline fasting glucose levels, total cholesterol, systolic blood pressure, and body mass index.
Ref. indicates reference.

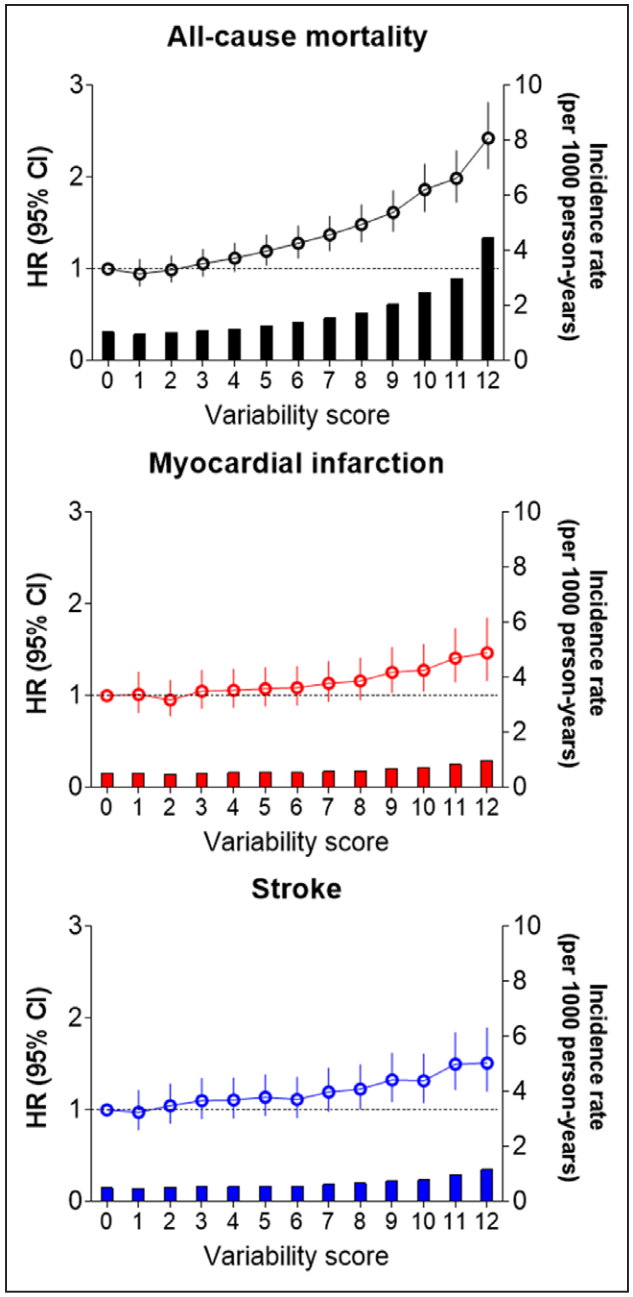

Figure 2. Incidence rate, hazard ratios, and 95% CIs of all-cause mortality, myocardial infarction, and stroke according to the variability score.

0 points were assigned for lowest quartile of variability (Q1), 1 point for Q2, 2 points for Q3, and 3 points for highest quartile of variability (Q4) for each of the 4 parameters (FBG, TC, systolic BP, and BMI). These points were summed to calculate the variability score, which ranged from 0 to 12. Adjusted for age, sex, alcohol drinking, smoking, regular exercise, income status, baseline FBG, TC, systolic BP, and BMI. BMI indicates body mass index; BP, blood pressure; FBG, fasting blood glucose; and TC, total cholesterol.

with an increasing number of high-variability parameters (Table VI in the online-only Data Supplement). Applying a different criterion for defining high variability, being >1 SD, produced similar results (Table VII in the online-only Data Supplement). The results were nearly identical when the mean levels of metabolic parameters were adjusted instead of the baseline levels in the Cox proportional-hazards model (Table VIII in the online-only Data Supplement). During follow-up, 1 905 262 subjects (28% of the study population) developed diabetes mellitus (n=240 816), hypertension (n=1 506 974), or dyslipidemia (n=1 195 030). Analyses censoring these subjects and incorporating incident metabolic diseases as time-varying covariates showed similar results (Table IX and X in the online-only Data Supplement).

Subgroup Analyses

We performed stratified analyses by age, sex, and BMI category (Figure 3). The risks of all-cause mortality, MI, and stroke increased significantly with the number of high-variability metabolic parameters in all study subgroups. Higher adjusted HRs for all-cause mortality were observed in the middle-aged (40–64 years), elderly (≥65 years), and male subgroups. The number of high-variability parameters was significantly associated with the incidence of MI and stroke in various subgroups. The highest HR for MI was observed in the underweight group (HR, 1.91; 95% CI, 1.24–2.94). The highest HR for stroke was observed in the severe obesity group (BMI >30 kg/m^2; HR, 2.35; 95% CI, 1.09–5.08). To account for a possible influence of survival, we performed another subgroup analysis according to the history of malignancy (Table XI in the online-only Data Supplement). The associations between the number of high-variability parameters and all-cause mortality were similar in participants with or without malignancy.

Next, we calculated the percentage of changes between the first and last values of each metabolic parameter. Subjects with >5% of improvement or worsening were designated as improved group and worsened group, respectively. Changes <5% were classified as unchanged. Individuals with high variability for each metabolic parameter showed a significantly higher HR (95% CI) for all-cause mortality compared with those with low variability, in both the improved group and in the worsened group (Table XII in the online-only Data Supplement).

DISCUSSION

In this nationwide population-based cohort study, we found that high variability in FBG and TC concentrations, SBP, and BMI was associated with a higher risk for mortality, MI, and stroke development during a 5.5-year follow-up period. We also found a graded association between the number of high-variability parameters and the primary outcomes. These associations persisted after multivariable adjustment, including baseline FBG and TC concentrations, SBP, and BMI.

Variability in BMI was an independent predictor of the outcomes studied. In a previous study, women reporting ever having lost >10 pounds (4.5 kg) of weight

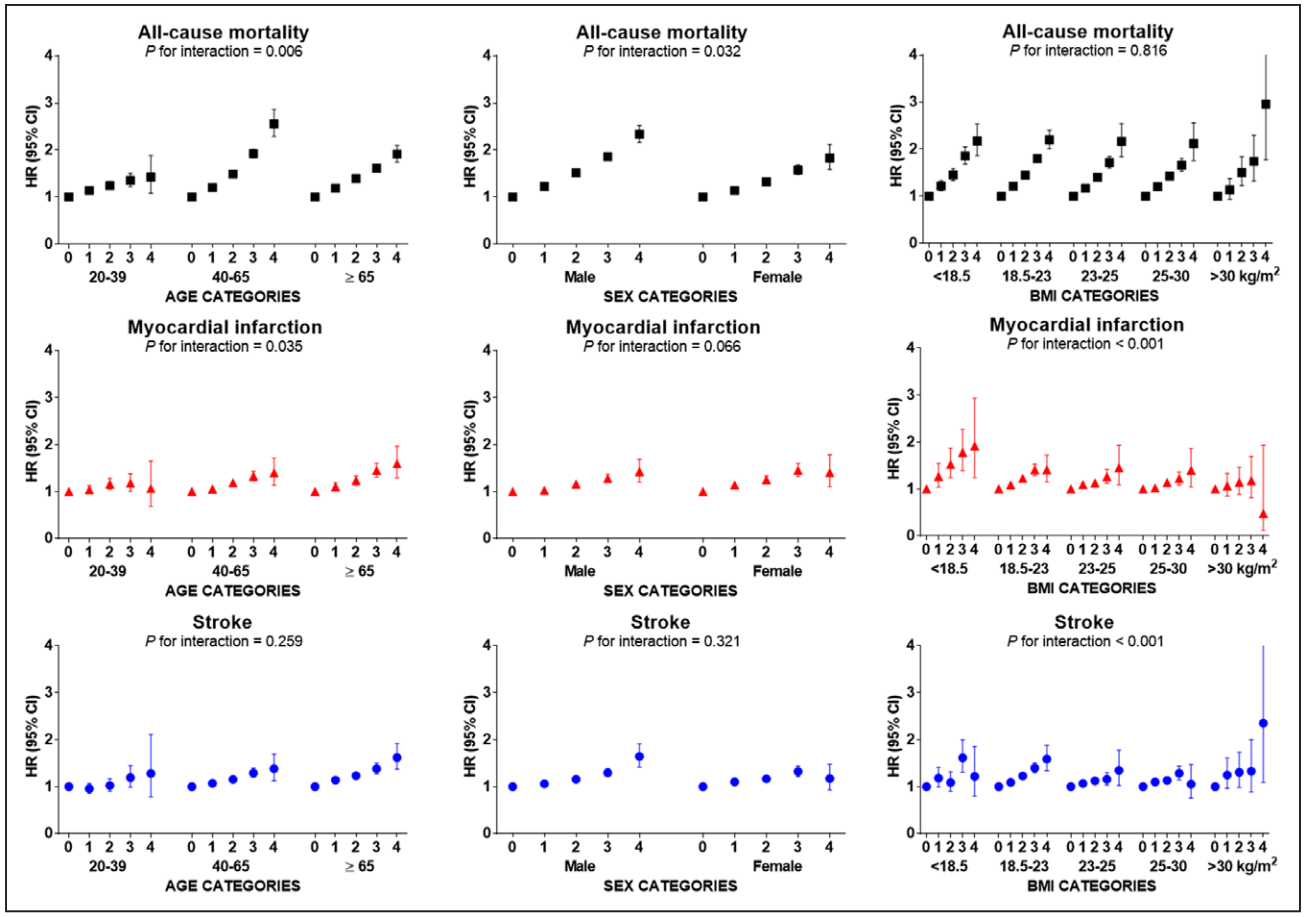

Figure 3. Subgroup analyses of association between the number of high variability parameters and all-cause mortality, myocardial infarction, and stroke stratified by age, sex, and BMI category.

Hazard ratios and 95% CIs of all-cause mortality, myocardial infarction, and stroke by the number of high variability parameters. Adjusted for age, sex, alcohol drinking, smoking, regular exercise, income status, baseline FBG, TC, systolic BP, and BMI. BMI indicates body mass index; BP, blood pressure; FBG, fasting blood glucose; and TC, total cholesterol.

had lower natural killer cell cytotoxicity,[19] and the magnitude of the effect on immune function was increased by increased frequency of intentional weight loss.[19] Weight fluctuation is also associated with lower high-density lipoprotein cholesterol concentration in women.[20] Unfavorable health effects of weight fluctuation have been attributed to an increase in body fat mass, a decrease in resting energy expenditure, and an increase in abdominal fat.[21] In contrast, some researchers have argued that the negative effects of weight fluctuation can be overcome by the positive effects of weight reduction.[22] However, a reverse J-shaped curve between the change in body weight over a 4-year period and all-cause mortality, independent of BMI status, was reported recently.[21] Both weight loss and weight gain were associated with increased mortality, and weight loss was associated with a higher risk of mortality.[21]

Increased glucose variability is related to increased mortality in people with and without diabetes mellitus.[23–26] Studies of critically ill patients have demonstrated consistently that increased glucose variability is independently associated with higher mortality.[23] This association was particularly strong among patients in the euglycemic range (mean glucose concentration of 70–99 mg/dL), as shown by the 5-fold mortality difference comparing patients between the lowest and highest quartiles of glucose variability.[23] Increasing glucose variability is independently associated with >90-day mortality in noncritically ill hospitalized patients.[24] It is evident that the effects on endothelial function and oxidation stress are greater in the presence of an oscillation of glucose levels compared with a stable high glucose level.[27] FBG variability, as assessed by the CV of FBG over a period of several years, was also an independent predictor of all-cause mortality in patients with type 2 diabetes mellitus.[4] Another possible mechanism is that glycemic variability might be an indicator of the development of poor health, morbidity, or complications.[23,24] Although low FBG concentration may indicate poor general health, we found that even after excluding individuals with end points occurring within the first 3 years of follow-up (ie, those who may have been ill at the baseline), individuals with high FBG variability were still at risk of death from all causes. Our findings

suggest that careful consideration of the variability in metabolic parameters is important when characterizing the population at risk of death, even among individuals without diagnosed comorbidities.

In our study, the risk of cardiovascular outcomes and particularly stroke was increased with greater variability in SBP. High variability of BP is a marker for the percentage of time that BP is not within the target range, which can contribute to a higher incidence of stroke and other cardiovascular outcomes.[28] Greater BP variability leads to greater cardiac and vascular damage as well as progression of the left ventricular mass index.[29] In patients with a history of MI, those with high variability for both low-density lipoprotein cholesterol and SBP had a significantly higher risk of any cardiovascular events, including death, compared with patients with low variability for both measures.[28] Higher visit-to-visit variability in low-density lipoprotein cholesterol concentration and BP may be an epiphenomenon of other systemic conditions, such as frailty. However, in that report, not all patients with greater variability in low-density lipoprotein cholesterol also had greater variability in BP, and the correlation between low-density lipoprotein cholesterol variability and BP variability was low.[28] In our study, the correlations between the variability of metabolic parameters were also low. The risks of all-cause mortality, MI, and stroke increased with an increasing number of high-variability parameters, which suggests that the associations of variability of each parameter with the cardiovascular outcomes were additive.

It is important to note that the relationship between the number of high-variability parameters and all-cause mortality was greater than the relationship for MI or stroke. This finding implies that both cardiovascular and noncardiovascular causes of death might be affected by variability in metabolic parameters. Although the specific cause of death could not be assessed with this database, cardiac disease, cerebrovascular disease, diabetes mellitus, and hypertensive disease were ranked as the 2nd, 3rd, 6th, and 10th causes of death, respectively, according to the Cause of Death Statistics 2015 released by the Korean government.[30] Furthermore, metabolic abnormality and its fluctuation are implicated in the progression of liver, kidney, and infectious diseases or associated mortality.[6,31–33] This finding suggests that a large proportion of death might have possible links with metabolic parameter variability in their underlying pathophysiology. Another interesting point is the directionality of changes, which causes increased variability. The effect of improvement or worsening of risk variables might be different, although both will result in increased variability. Our data, however, suggest that high variability is an independent predictor of all-cause mortality regardless of the directionality.

The current study has several strengths. First, this is the first study to examine the variability of various metabolic parameters and cardiovascular outcomes in a large general population using a well-established and validated longitudinal national database over 5 years. Second, we excluded those with diabetes mellitus, hypertension, or dyslipidemia because these conditions and treatments might affect body weight and changes in metabolic parameters during the follow-up. We also performed a time-dependent Cox regression analysis to account for incident metabolic diseases during the follow-up period. Third, most studies of the association between longitudinal weight changes and outcomes have used questionnaires to identify self-reported body weight or past weight loss episodes and were not free from information bias. Our study used actual measurements of weight variables because these data were based on the physical examination in the health checkups of study participants. Fourth, we conducted a number of sensitivity analyses. Consistency between the results of the original analyses and the sensitivity analyses strengthens the conclusions and credibility of our findings.

We also acknowledge several limitations of our study. First, we did not know whether body weight changes were intentional or unintentional. Intentional weight loss in people with obesity is associated with lower mortality.[22] Weight loss in elderly people mainly results from preexisting or new onset of disease, and weight gain may cause few adverse effects on mortality in elderly people. Therefore, we performed stratified analyses according to BMI and age categories, and we found that the association between greater variability and mortality was consistent regardless of the BMI and age categories. Second, this study was observational 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 previous MI or stroke. The sensitivity analysis that excluded people with outcomes occurring in the first 3 years of follow-up also revealed similar results. Third, selection of study subjects based on the number of health examinations might be a source of bias because men, and employee subscribers were more likely to participate in the regular health checkup.[11] Last, variability in cardiovascular risk factors may be affected by time-varying factors such as diet and physical activity during follow-up.

In previous studies, most variability measures were obtained from randomized controlled trials and cohort studies of populations with hypertension or diabetes mellitus or high-risk patients. By contrast, our data were extracted from a database of healthy people without heart disease, cerebrovascular disease, diabetes mellitus, hypertension, or dyslipidemia, and they showed that greater variability in various physiological parameters was associated with an increased risk of future cardiovascular outcomes and mortality

in this low-risk population. Our results add evidence that high variability in metabolic parameters is associated with adverse health outcomes not only in diseased populations but also in relatively healthy populations, although the mechanism could be somewhat different. These findings suggest that variability in metabolic parameters may be a prognostic surrogate marker for predicting mortality and cardiovascular outcomes.

ARTICLE INFORMATION

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Disclosures

None.

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