International Journal of Cardiology 293 (2019) 153–158

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Visit-to-visit variability of metabolic parameters and risk of heart failure: A nationwide population-based study☆

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ARTICLE INFO

Article history:
Received 16 April 2019
Received in revised form 4 June 2019
Accepted 13 June 2019
Available online 20 June 2019

Keywords:
Blood glucose
Blood pressure
Body mass index
Cholesterol
Heart failure

ABSTRACT

Background: This study examined the effects of variability of four metabolic parameters, namely systolic blood pressure (BP), body mass index (BMI), fasting blood glucose (FBG), and total cholesterol level (TC) on the risk of HF. The effects of metabolic parameter variability on the risk of heart failure (HF) remain unclear.
Methods: We studied individuals aged ≥40 years who had undergone ≥3 health check-ups under the Korean National Health Insurance Corporation during 2009 and 2012, and those who did not have hypertension, diabetes, or dyslipidemia. BP, BMI, FBG, and TC were measured at every visit. We defined the variability of each parameter using the variability independent of the mean (VIM) method. VIMs were categorized into four groups according to quartiles. The metabolic variability (MV) score for each subject was defined as the number of VIMs in the highest quartile.
Results: Among the 3,820,191 subjects, 17,253 (0.45%) had incident HF during a mean 5.3 ± 1.1 years of follow-up. High variability of each parameter was associated with increased HF risk, which increased according to the MV score. After multivariable adjustment, compared to subjects with MV score = 0, subjects with MV score = 1–4 had an increased risk of HF (adjusted HR [95% CI], 1.15 [1.10–1.19] for MV score = 1, 1.33 [1.28–1.39] for MV score = 2, 1.48 [1.40–1.57] for MV score = 3, 1.74 [1.55–1.96] for MV score = 4 [p-for-trend ≪0.0001]).
Conclusions: High variability of BP, BMI, FBG, and TC was synergistically associated with a higher incidence of new-onset HF.

1. Introduction

Visit-to-visit variability has attracted attention as a new predictor of cardiovascular disease [1–9]. Blood pressure (BP) variability is one of the earliest studied parameters, and higher variability of BP was consistently associated with an increased risk of cardiovascular events [1–3]. It also has been known as a risk factor for poor cardiovascular outcome and cognitive deterioration [4,5]. High cholesterol variability was related to poor cardiovascular outcomes [6–8]. Not only the variability of low-density lipoprotein cholesterol but also that of high-density lipoprotein cholesterol was associated with a higher occurrence of major adverse cardiovascular events [7]. Similarly, variability in body weight and fasting blood glucose (FBG) has been reported as risk factors for cardiovascular mortality [9,10]. The mechanisms by which such variability affects adverse cardiovascular outcomes may vary between parameters.

Previous variability studies had focused on major adverse cardiovascular events such as myocardial infarct, ischemic stroke, and cardiovascular mortality, whereas few studies have reported on heart failure (HF). HF has now become a global public health concern owing to its high socioeconomic burden and the requirement of frequent hospitalization [11]. Therefore, it is essential to determine the impact of variability on the development of HF, especially among healthy individuals without previously well-known risk factors such as coronary heart disease, hypertension, diabetes, and dyslipidemia.

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; FBG, fasting blood glucose; HF, heart failure; HR, hazard ratio; MV score, metabolic variability score; NHIS, the National Health Insurance Service; TC, total cholesterol; VIM, variability independent of the mean.

☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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https://doi.org/10.1016/j.ijcard.2019.06.035
0167-5273/

In this study, we aimed to investigate the association between the variabilities of selected metabolic parameters (systolic BP, body mass index [BMI], FBG, and total cholesterol [TC]) and the risk of HF among the general Korean population using a nationwide population-based database from the National Health Insurance Service (NHIS). To evaluate the effect of variability itself on the risk of HF, we targeted individuals without known hypertension, diabetes, and dyslipidemia.

2. Methods

2.1. Data source

We utilized the claims database constructed by the National Health Insurance Service (NHIS) of Korea. The database is anonymized and comprises demographic information, prescription and procedural records, and codes of diagnoses; the diagnoses are coded in the International Classification of Disease, Tenth Revision, Clinical Modification. As the NHIS of Korea offers national health examination programs biennially, the database also includes body measurements; comorbidities; family history; laboratory results; and additional information on health behaviors such as physical activities, smoking status, and alcohol consumption, using standardized self-reporting questionnaires. It provides comprehensive coverage of medical care of almost the entire Korean population, and it is a mandatory health insurance service in Korea. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Seoul National University Hospital Institutional Review Board (IRB No. 1807-031-955). Informed consent was exempted because of anonymized and de-identified information.

2.2. Study population

The selection procedure of the study population is presented in Online Fig. 1. In total, 23,503,802 subjects aged 20 years or more underwent routine health check-ups provided by the NHIS during 2009–2012. Subjects with missing measurements of BP, BMI, FBG, or TC (n = 170,921); those who had undergone fewer than three check-ups during the 5 years preceding the study (n = 12,027,734); those with a previous diagnosis of hypertension, diabetes mellitus, or dyslipidemia (n = 4,466,601), or heart failure (n = 3474); and those aged ≪40 years (n = 3,014,881) were excluded. Finally, 3,820,191 subjects were included. The definitions of hypertension, diabetes, dyslipidemia, and other comorbidities are summarized in Online Table 1.

2.3. Definitions of measurements and variability

The BP, BMI, FBG, and TC were measured for each subject at each health checkup. We used the standardized questionnaire provided by the NHIS to evaluate obesity, smoking status, alcohol consumption, exercise, and income level. Detailed definitions for these parameters are summarized in Online Table 2.

We calculated the variability of the four metabolic parameters (BP, BMI, FBG, and TC) by using three different methods: variability independent of the mean (VIM), standard deviation, and coefficient of variation. VIM was defined as $100 \times \text{standard deviation}/\text{mean}^{\beta}$, where β is the coefficient derived from curve fitting using the PROC NLIN procedure of the SAS package [12,13]. We evaluated the effect of the three different variabilities and compared them to check whether the results were consistent. We defined metabolic variability score (MV score) as the total number of parameters having VIM values ≥75 percentile. Its value ranged from 0 to 4, and the study population was divided into five subgroups according to the MV score.

2.4. Study outcome

The primary outcome was incident HF. Newly diagnosed HF was defined when the subject had a diagnostic code of I50 during either outpatient clinic or hospitalization [14,15]. The follow-up period was set from the baseline to the time of incident HF or until December 31, 2015.

Initially, we compared the baseline characteristics between the HF and non-HF groups to check whether variabilities of BP, BMI, FBG, and TC were higher in subjects with HF. We then categorized the study population into five groups based on their MV scores. Each group was evaluated for incident HF, and the trend between MV score and incident HF was analyzed.

2.5. Statistical analysis

We performed the Kolmogorov-Smirnov test for evaluating normal distribution of continuous variables. We used one-way analysis of variance and chi-square test to compare the differences of clinical characteristics between the groups. The incidence rate of HF was measured as the number of events during the follow-up period divided by 1000 person-years. The Kaplan–Meier analysis and log-rank test were used to compare the survivals between the different groups. The hazard ratio (HR) and 95% confidence interval (CI) for HF were calculated by multivariate Cox proportional hazards regression analysis. To account possible covariates, we adjusted with age, sex, smoking status, alcohol consumption, exercise, and income (Model 1), or further by baseline BP, BMI, FBG, and TC (Model 2), or even further by history of ischemic heart disease, chronic kidney disease, and chronic obstructive pulmonary disease (Model 3). All data are presented as mean ± standard deviation for continuous variables or as numbers with percentages for categorical ones. All statistical analyses were two-sided, and p-value ≪.05 was considered statistically significant. Data were analyzed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Because of the national security policy on the health data of the NHIS, raw data are not available to other researchers for replication.

3. Results

3.1. Baseline characteristics of the study population

We stratified the study population into five groups according to the number of high-variability metabolic parameters. Table 1 summarizes the clinical characteristics of the subjects according to the MV score. The number and proportions of subjects according to MV scores of 0 to 4 were 1,284,988 (33.6%), 1,511,246 (39.6%), 787,662 (20.6%), 211,586 (5.5%), and 24,709 (0.7%) respectively. Subjects with higher MV score were older, more likely to be current smokers, less likely to exercise regularly, and less likely to have family history of coronary artery disease, stroke, hypertension, and diabetes. BP, FBG, and TC increased with increasing MV scores, whereas BMI decreased.

3.2. Variability of metabolic parameters and risk of HF

During a mean 5.3 ± 1.1 years of follow-up, HF occurred in 17,253 (0.45%) subjects (incident rate = 6.33 per 1000 person-years). Compared to subjects who did not experience HF, those who experienced HF were older, more likely to be male, current smokers, with heavy alcohol consumption and less regular exercise, along with lower baseline BMI, higher BP, higher FBG, and lower TC (Online Table 3). Compared to subjects without HF, those with HF showed more variability in metabolic parameters. Comparing the variability of the different parameters, we found that higher quartiles of VIM showed increasing trends of both incidence rates and the risk of HF, compared with the lowest quartile group (Table 2 and Fig. 1). For the highest quartile in BP, BMI, FBG, and TC variability compared with the lowest quartile, the risk of HF increased by 16% (HR, 1.16; 95% CI, 1.11–1.21), 28% (HR, 1.28; 95% CI, 1.23–1.34), 15% (HR, 1.15; 95% CI, 1.10–1.20), and 17% (HR, 1.17; 95% CI, 1.12–1.22), respectively.

3.3. Risk of HF according to the number of the high variability of metabolic parameters (MV score)

MV score represents the composite effect of the variabilities of all four parameters. There was an increasing tendency of incidence rates of HF according to higher MV score: 0.60, 0.80, 1.12, 1.55 and 2.27 per 1000 person-year for MV score from 0 to 4 respectively (log-rank p ≪ .0001). Kaplan–Meier survival analysis showed that MV score had graded association with the development of HF (Fig. 2). Compared with the group with MV score zero (low variability of all metabolic parameters), subjects with higher variability of all metabolic parameters showed a higher risk of HF: HR 1.15 (95% CI, 1.10–1.19) for MV score 1, HR 1.33 (95% CI 1.28–1.39) for MV score 2, HR 1.48 (95% CI 1.40–1.57) for MV score 3, and HR 1.74 (95% CI 1.55–1.96) for MV score 4 (p-for-trend ≪0.0001).

3.4. Sensitivity analysis

The risk of HF was similar for other definitions of variability such as standard deviation and coefficient of variation (Online Tables 4 and 5, and Fig. 1). For standard deviation, the highest quartile in BP, BMI, FBG, and TC variability showed an increased risk of HF by 17% (HR 1.17; 95% CI 1.12–1.22), 29% (HR 1.29; 95% CI 1.23–1.34), 13% (HR 1.13; 95% CI 1.08–1.18), and 18% (HR 1.18 95% CI 1.13–1.23), respectively, compared with the lowest quartile. Likewise, in the case of coefficient of variation, the highest quartile in BP, BMI, FBG, and TC variability showed an increased risk of HF

Table 1
Baseline characteristics according to metabolic variability score.

	0	1	2	3	4	p-Value	p-for-trend
MV score[a]							
N	1,284,988 (33.6)	1,511,246 (39.6)	787,662 (20.6)	211,586 (5.5)	24,709 (0.7)		
Age (years)	51 ± 8.2	51.6 ± 8.7	52.4 ± 9.4	53.5 ± 10.1	54.7 ± 10.8	≪0.0001	≪0.0001
Male	725,394 (56.5)	789,482 (52.2)	390,874 (49.6)	102,878 (48.6)	12,073 (48.9)	≪0.0001	≪0.0001
Height (cm)	163.9 ± 8.5	162.9 ± 8.6	162.1 ± 8.6	161.4 ± 8.7	160.9 ± 8.8	≪0.0001	≪0.0001
Weight (kg)	63.2 ± 10.2	62.1 ± 10.2	61.1 ± 10.2	60.1 ± 10.2	59.1 ± 10.3	≪0.0001	≪0.0001
Waist circumference (cm)	79.6 ± 8.0	79.1 ± 8.1	78.7 ± 8.1	78.4 ± 8.1	78.1 ± 8.0	≪0.0001	≪0.0001
Waist circumference (more than those of metabolic syndrome definition) (cm)	267,118 (20.8)	321,058 (21.3)	168,947 (21.5)	45,341 (21.4)	5168 (20.9)	≪0.0001	≪0.0001
BMI ≪25 (kg/m^2)	942,791 (73.4)	1,128,087 (74.7)	596,931 (75.8)	162,959 (77.0)	19,362 (78.4)	≪0.0001	≪0.0001
Smoking						≪0.0001	≪0.0001
Never-smoker	778,411 (60.6)	945,896 (62.6)	501,658 (63.7)	134,841 (63.7)	15,596 (63.1)	≪0.0001	≪0.0001
Ex-smoker	232,969 (18.1)	240,630 (15.9)	115,092 (14.6)	29,593 (14.0)	3344 (13.5)	≪0.0001	≪0.0001
Current smoker	273,608 (21.3)	324,720 (21.5)	170,912 (21.7)	47,152 (22.3)	5769 (23.4)	≪0.0001	≪0.0001
Alcohol						≪0.0001	≪0.0001
None	675,640 (52.6)	842,189 (55.7)	457,831 (58.1)	126,466 (59.8)	15,197 (61.5)	≪0.0001	≪0.0001
Mild	526,525 (41.0)	574,737 (38.0)	281,292 (35.7)	71,365 (33.7)	7810 (31.6)	≪0.0001	≪0.0001
Heavy	82,823 (6.5)	94,320 (6.2)	48,539 (6.2)	13,755 (6.5)	1702 (6.9)	≪0.0001	≪0.0001
Regular exercise	278,915 (21.7)	316,021 (20.9)	158,584 (20.1)	40,960 (19.4)	4548 (18.4)	≪0.0001	≪0.0001
Comorbidity							
Metabolic syndrome	199,165 (15.5)	231,124 (15.3)	120,533 (15.3)	32,743 (15.5)	3991 (16.2)	≪0.0001	≪0.0001
IHD	175,796 (13.7)	218,591 (14.5)	122,511 (15.6)	35,640 (16.8)	4704 (18.6)	≪0.0001	≪0.0001
PAD	17,432 (1.4)	25,182 (1.7)	16,070 (2.0)	5405 (2.6)	764 (3.1)	≪0.0001	≪0.0001
AF	1369 (0.1)	1765 (0.1)	1075 (0.1)	380 (0.2)	54 (0.2)	≪0.0001	≪0.0001
CKD	61,833 (4.8)	68,309 (4.5)	35,868 (4.6)	9821 (4.6)	1245 (5.0)	≪0.0001	≪0.0001
COPD	59,846 (4.7)	78,963 (5.2)	46,310 (5.9)	14,203 (6.7)	1871 (7.6)	≪0.0001	≪0.0001
Familial history							
CAD	54,351 (5.9)	53,275 (5.1)	24,666 (4.8)	5940 (4.4)	602 (4.0)	≪0.0001	≪0.0001
Stroke	97,279 (10.6)	101,713 (9.8)	48,760 (9.4)	12,004 (8.9)	1339 (8.9)	≪0.0001	≪0.0001
DM	114,825 (12.5)	122,691 (11.8)	59,262 (11.4)	14,994 (11.1)	1633 (10.9)	≪0.0001	≪0.0001
HTN	127,300 (13.8)	136,590 (13.1)	65,976 (12.6)	16,907 (12.5)	1819 (12.1)	≪0.0001	≪0.0001
Highest quartile							
SBP	0 (0)	390,048 (25.8)	385,838 (49.0)	154,453 (73.0)	24,709 (100)	≪0.0001	≪0.0001
BMI	0 (0)	368,788 (24.4)	399,634 (50.7)	161,917 (76.5)	24,709 (100)	≪0.0001	≪0.0001
FBG	0 (0)	384,837 (25.5)	389,802 (49.5)	155,688 (73.6)	24,709 (100)	≪0.0001	≪0.0001
TC	0 (0)	367,573 (24.3)	400,050 (50.8)	162,700 (76.9)	24,709 (100)	≪0.0001	≪0.0001
Baseline							
SBP (mmHg)	120.4 ± 11.2	120.7 ± 12.4	121 ± 13.3	121.4 ± 14.3	122.1 ± 15.5	≪0.0001	≪0.0001
DBP (mmHg)	75.8 ± 8.4	75.8 ± 8.7	75.8 ± 9	75.9 ± 9.3	76.1 ± 9.8	≪0.0001	≪0.0001
BMI (kg/m^2)	23.6 ± 2.7	23.5 ± 2.8	23.4 ± 2.9	23.3 ± 3.0	23.1 ± 3.1	≪0.0001	≪0.0001
FBG (mg/dL)	95.2 ± 10.8	95.2 ± 12.7	95.4 ± 14.4	95.7 ± 16.1	96.4 ± 18.2	≪0.0001	≪0.0001
TC (mg/dL)	195.8 ± 27.6	196.3 ± 29.3	196.8 ± 31.1	197.2 ± 33.2	196.8 ± 35.2	≪0.0001	≪0.0001
TG (mg/dL)	105.5 (105.4–105.6)	104.5 (104.5–104.6)	104.1 (104–104.2)	104 (103.8–104.3)	104.3 (103.6–105)	≪0.0001	≪0.0001
HDL (mg/dL)	54.9 ± 17.8	55.4 ± 18.7	55.6 ± 19.2	55.9 ± 20.6	55.8 ± 21.4	≪0.0001	≪0.0001
LDL (mg/dL)	114.1 ± 35.5	112.9 ± 36.9	111.8 ± 38.3	110.3 ± 38.6	108.7 ± 42.8	≪0.0001	≪0.0001
Non-HDL (mg/dL)	141.2 ± 28.9	141.4 ± 30.4	141.6 ± 32.0	141.9 ± 33.8	141.7 ± 35.3	≪0.0001	≪0.0001
Cholesterol ratio[b]	3.8 ± 1.1	3.8 ± 1.1	3.8 ± 1.1	3.8 ± 1.2	3.8 ± 1.1	≪0.0001	≪0.0001
VIM							
SBP (%)	6.4 ± 2.7	8.4 ± 4.4	10.4 ± 5.0	12.4 ± 4.8	14.8 ± 3.6	≪0.0001	≪0.0001
DBP (%)	5.4 ± 2.9	6.1 ± 3.3	6.8 ± 3.6	7.6 ± 3.7	8.5 ± 3.8	≪0.0001	≪0.0001
BMI (%)	0.5 ± 0.2	0.7 ± 0.4	0.9 ± 0.6	1.1 ± 0.6	1.3 ± 0.6	≪0.0001	≪0.0001
FBG (%)	5.8 ± 2.6	8.2 ± 4.8	10.4 ± 5.5	12.7 ± 5.3	15.1 ± 4.0	≪0.0001	≪0.0001
TC (%)	12.4 ± 5.1	16.4 ± 8.8	21.1 ± 10.4	25.9 ± 10.3	30.4 ± 8.4	≪0.0001	≪0.0001
SD							
SBP (mmHg)	6.4 ± 2.7	8.5 ± 4.5	10.4 ± 5.1	12.5 ± 5.0	15 ± 3.9	≪0.0001	≪0.0001
DBP (mmHg)	5.4 ± 2.9	6.1 ± 3.3	6.8 ± 3.6	7.6 ± 3.8	8.6 ± 3.8	≪0.0001	≪0.0001
BMI (kg/m^2)	0.5 ± 0.2	0.7 ± 0.5	0.9 ± 0.6	1.1 ± 0.6	1.3 ± 0.6	≪0.0001	≪0.0001
FBG (mg/dL)	6.3 ± 3.3	8.6 ± 6.0	10.9 ± 7.4	13.3 ± 8.3	16.1 ± 9.0	≪0.0001	≪0.0001
TC (mg/dL)	12.7 ± 5.4	16.8 ± 9.2	21.4 ± 10.8	26.2 ± 10.9	30.6 ± 9.2	≪0.0001	≪0.0001
CV							
SBP (%)	5.4 ± 2.3	7.2 ± 3.7	8.8 ± 4.2	10.5 ± 4.1	12.5 ± 3.0	≪0.0001	≪0.0001
DBP (%)	7.3 ± 3.9	8.3 ± 4.5	9.2 ± 4.8	10.3 ± 5.0	11.5 ± 5.0	≪0.0001	≪0.0001
BMI (%)	2.0 ± 0.9	2.9 ± 1.9	3.8 ± 2.4	4.8 ± 2.7	5.8 ± 2.7	≪0.0001	≪0.0001
FBG (%)	6.7 ± 3.1	9.2 ± 5.7	11.7 ± 6.8	14.2 ± 7.0	17.1 ± 6.7	≪0.0001	≪0.0001
TC (%)	6.6 ± 2.7	8.8 ± 4.7	11.3 ± 5.6	13.9 ± 5.5	16.4 ± 4.5	≪0.0001	≪0.0001

Data are presented as mean ± SD or N (%). For TG, the data are presented as geometric mean with interquartile range.
Abbreviations: AF = Atrial fibrillation; BMI = Body-mass index; CAD = Coronary artery disease; CKD = Chronic kidney disease; COPD = Chronic obstructive pulmonary disease; CV = Coefficient of variation; DBP = Diastolic blood pressure; DM = Diabetes mellitus; FBG = Fasting serum glucose; HDL = High-density lipoprotein cholesterol; HTN = Hypertension; IHD = Ischemic heart disease; LDL = Low-density lipoprotein cholesterol; MV score = Metabolic variability score; PAD = Peripheral artery disease; SBP = Systolic blood pressure; SD = Standard deviation; TC = Total cholesterol; TG = Triglyceride; VIM = Variability independent of the mean.

[a] MV score is defined to be the total number of parameters (SBP, BMI, FBG and TC) having VIM values of ≥75 percentile.

[b] Cholesterol ratio is calculated by dividing total cholesterol by HDL.

Table 2
Incidences and risks of heart failure by the variability of metabolic parameters calculated by the VIM method.

	N	Event	Follow-up duration (PY)	Incidence rate (per 1000 PY)	Model 1 Adjusted HR (95% CI)	Model 2 Adjusted HR (95% CI)	Model 3 Adjusted HR (95% CI)	p-Value
BP								
Q1	952,443	3716	5,031,978	0.74	1	1	1	
Q2	957,682	3740	5,125,177	0.73	0.994 (0.950–1.040)	1.004 (0.959–1.050)	1.006 (0.961–1.053)	≪0.0001
Q3	955,090	4087	5,158,972	0.79	1.030 (0.985–1.076)	1.032 (0.987–1.079)	1.033 (0.988–1.080)	≪0.0001
Q4	954,976	5710	5,063,311	1.13	1.170 (1.122–1.219)	1.177 (1.129–1.227)	1.161 (1.114–1.210)	≪0.0001
BMI								
Q1	954,985	3609	5,068,428	0.71	1	1	1	
Q2	955,108	3673	5,151,720	0.71	1.015 (0.970–1.063)	1.017 (0.971–1.065)	1.016 (0.970–1.064)	≪0.0001
Q3	955,042	4120	5,126,361	0.80	1.090 (1.042–1.140)	1.093 (1.046–1.143)	1.092 (1.044–1.142)	≪0.0001
Q4	955,056	5851	5,032,929	1.16	1.303 (1.250–1.359)	1.311 (1.258–1.368)	1.283 (1.230–1.338)	≪0.0001
FBG								
Q1	955,361	3797	4,978,854	0.76	1	1	1	
Q2	954,665	3875	5,092,886	0.76	1.018 (0.973–1.064)	1.017 (0.972–1.063)	1.009 (0.964–1.055)	≪0.0001
Q3	955,122	4243	5,147,161	0.82	1.064 (1.018–1.112)	1.060 (1.014–1.108)	1.049 (1.004–1.096)	≪0.0001
Q4	955,043	5338	5,160,538	1.03	1.190 (1.141–1.241)	1.178 (1.129–1.229)	1.150 (1.102–1.200)	≪0.0001
TC								
Q1	955,028	3932	5,047,511	0.78	1	1	1	
Q2	955,060	3843	5,142,682	0.75	1.004 (0.961–1.050)	1.005 (0.961–1.051)	1.004 (0.960–1.049)	≪0.0001
Q3	955,056	4181	5,136,367	0.81	1.069 (1.024–1.117)	1.071 (1.025–1.118)	1.055 (1.010–1.102)	≪0.0001
Q4	955,047	5297	5,052,878	1.05	1.218 (1.169–1.269)	1.218 (1.169–1.269)	1.166 (1.118–1.215)	≪0.0001
MV score[a]								
0	1,286,755	4127	6,893,864	0.60	1	1	1	
1	1,509,787	6405	8,051,809	0.80	1.165 (1.120–1.211)	1.164 (1.120–1.211)	1.147 (1.103–1.193)	≪0.0001
2	785,914	4674	4,176,607	1.12	1.385 (1.327–1.445)	1.384 (1.327–1.444)	1.332 (1.277–1.390)	≪0.0001
3	212,433	1745	1,124,003	1.55	1.578 (1.491–1.670)	1.578 (1.491–1.671)	1.479 (1.397–1.566)	≪0.0001
4	25,302	302	133,156	2.27	1.883 (1.675–2.118)	1.882 (1.673–2.117)	1.738 (1.545–1.955)	≪0.0001

The statistical model was adjusted the data by age, sex, smoking status, alcohol consumption, exercise and income (Model 1), or further by baseline systolic blood pressure, body-mass index, fasting serum glucose and total cholesterol (Model 2), or even more by history of ischemic heart disease, chronic kidney disease, and chronic obstructive pulmonary disease (Model 3).
Abbreviations: BMI = Body-mass index; BP = Systolic blood pressure; CI = Confidence interval; FBG = Fasting serum glucose; HR = Hazard ratio; MV score = Metabolic variability score; PY = Person-year; TC = Total cholesterol; VIM = Variability independent of the mean.
[a] MV score is defined to be the total number of parameters (SBP, BMI, FBG, and TC) having VIM values of ≥75 percentile.

by 18% (HR 1.18, 95% CI 1.14–1.24), 29% (HR 1.29, 95% CI 1.23–1.34), 14% (HR 1.14, 95% CI 1.09–1.19), and 17% (HR 1.17, 95% CI 1.13–1.22), respectively, compared with the lowest quartile. In line with the VIM method, both standard deviation and coefficient of variation methods showed incrementally higher risks of HF according to the number of metabolic parameters: HR 1.17 (95% CI 1.12–1.21) and HR 1.16 (95% CI 1.11–1.21) for MV score 1, HR 1.34 (95% CI 1.28–1.39) and HR 1.33 (95% CI 1.28–1.39) for MV score 2, HR 1.47 (95% CI 1.39–1.56), and HR 1.47 (95% CI 1.39–1.56) for MV score 3, and HR 1.74 (95% CI 1.54–1.96) and HR 1.64 (95% CI 1.46–1.85) for MV score 4, respectively (all p-for-trends ≪0.0001).

To confirm the association between the variability of metabolic parameters and the risk of HF in finer subgroups, we investigated the incidence rates and risks of HF by subgroups according to the 12 scoring system. In this scoring system, the score was calculated by summing $(n-1)$'s of n^{th} quartiles of all four variables for each subject. From the subgroup with score 0 to 12 points, there was a monotonically increasing tendency of the incidence rate and risk of HF for the subgroup with higher scores (Online Table 6 and Online Fig. 2).

4. Discussion

To the best of our knowledge, this is the largest study reporting the impact of metabolic variability on the risk of HF in subjects without prevalent hypertension, diabetes, or dyslipidemia, by using a population-based cohort. This study demonstrated the following: (1) higher variability of BP, BMI, FBG, and TC was associated with an increased risk of HF; (2) the results were consistent among the different definitions of variability (VIM, standard deviation, and coefficient of variation); and (3) the MV score, comprising all the effects of

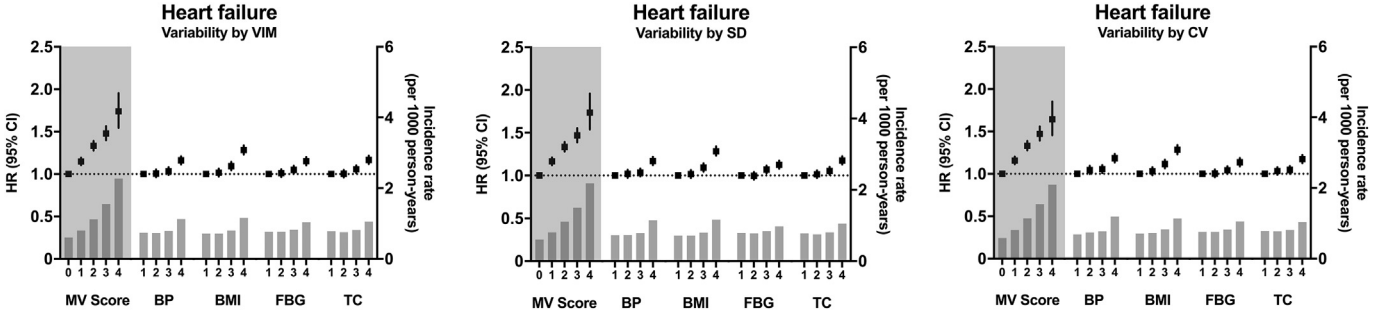

Fig. 1. Incidence rates and hazard ratios with 95% confidence intervals of heart failure according to the variability of metabolic parameters and MV score. The number n for each parameter stands for the n^{th} quartile of its variability. Adjusted by age, sex, smoking status, alcohol consumption, exercise and income, baseline systolic blood pressure, body-mass index, fasting serum glucose and total cholesterol, and any history of myocardial infarct or ischemic heart disease. Abbreviations: BMI = Body-mass index; BP = Systolic blood pressure; CI = Confidence interval; CV = Coefficient of variation; FBG = Fasting blood glucose; HR = Hazard ratio; MV score = Metabolic variability score; SD = Standard deviation; TC = Total cholesterol; VIM = Variability independent of mean.

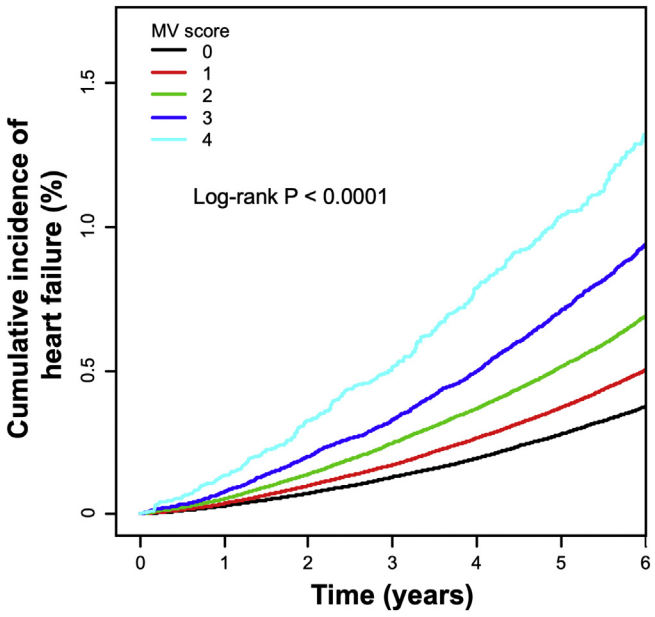

Fig. 2. Kaplan-Meier analysis of the crude cumulative incidence of heart failure by MV score. Abbreviations: MV score = Metabolic variability score.

variabilities from different parameters, made a good distinction between the groups of varying MV scores with regard to the risk of HF.

Variability in clinical parameters representing any biological status is recently attracting attention as a novel predictor. One of the earliest studies has reported that variability of biological parameters about cardiovascular outcomes depended on the visit-to-visit blood pressure variability [3]. Other recent studies of variability focused on body weight and cholesterol; however, most of them were not conducted in healthy individuals by excluding those with previous hypertension, diabetes, and dyslipidemia [2,6,7]. Another limitation of previous studies is that they were mostly focused on cardiovascular outcomes such as cardiovascular mortality, ischemic stroke, and myocardial infarction, and less on HF. Compared to previous studies reporting the variability of metabolic parameters and cardiovascular diseases, this study focused on the risk of HF and the variability of metabolic parameters [1–3,6–9]. Secondly, we evaluated the impact of metabolic variability on individuals without prevalent hypertension, diabetes, or dyslipidemia. Lastly, we examined not only the effect of each metabolic parameter but also a composite effect of variabilities of different metabolic parameters.

Although the detailed mechanism linking the risk of HF to fluctuations of biological parameters remains unclear, several plausible explanations could be suggested, as follows. First, cholesterol variability may increase the risk of HF by aggravating subclinical coronary artery disease. It has been suggested that the cholesterol crystals may induce mechanical damage to plaque membrane [16–18]. The volume expansion of cholesterol during the crystallization within the confined space of the plaque leads to its rupture [17]. As a result, repetitive membranous insults due to crystallization and dissolution of cholesterol owing to the variability of its blood concentration may exacerbate underlying subclinical coronary artery disease, which could induce the progression of HF. Second, the variability of BMI may affect the risk of HF by developing relevant unfavorable conditions. The negative association between the degree of weight fluctuation and atrial-fibrillation-free survival was observed [19]. The impact of weight fluctuation on arrhythmia-free survival was still significant even after adjusting for baseline BMI. Thus, we may postulate that high variability of BMI may foster HF by developing atrial fibrillation. However, the impact of variability in weight is limited not only to arrhythmias. The study reported that weight fluctuation was not only associated with arrhythmia-free survival but also with increased left atrium volume indexed for body surface area and lateral E/E' ratio. Therefore, greater weight fluctuation is related to structural heart remodeling and poorer heart function. In this regard, the high variability of BMI may consequently be associated with HF. Also, the variability of BMI is possibly inter-related with the variability of cholesterol. Recently, significant fluctuation in BMI was shown to be related to the risk of HF in young individuals [20]. It has been suggested that high variation in body weight negatively impacts lipid metabolism by lowering high-density lipoprotein cholesterol and increasing the abdominal fat proportion [21,22]. Therefore, we postulate that high fluctuation in BMI is mostly associated with fluctuation in the amount of visceral fat, which has been suggested to be correlated with ventricular remodeling and blood pressure level, finally leading to HF [23,24]. Third, previous literature pointed out that poor compliance with antihypertensive or antidiabetic medication might have an adverse effect on patients with hypertension or diabetes [25–28]. However, our study excluded subjects with comorbidities, which was confirmed by the results of blood pressure and fasting serum glucose measurements (Table 1). Therefore, the high variability of BP itself may have an intrinsic impact on the risk of HF by damaging the vascular system and the heart [29]. Lastly, the variability of glucose level is related to an increase in the risk of cardiovascular mortality in subjects with diabetes mellitus [10]. However, this effect was also observed in those within the euglycemic range [30]. This could be explained by a possibility that highly fluctuating glucose level generates greater oxidative stress in endothelial cells, leading to the development of cardiovascular disease [31]. Meanwhile, the high variability of glucose is the result of poor health. In either way, we hypothesize that high glucose variability would affect the risk of HF.

4.1. Limitations

This study has several limitations. First, there is a possibility of selection bias. Although the health checkup provided by the NHIS is recommended to those aged 40 years or more, individuals with more health concerns might undergo more frequent health checkups, resulting possible selection bias to the results. Also, those who were unable to undergo health checkup owing to disability might be excluded. Second, a causal relationship could not be evaluated in this study using claims data. We found that there was a strong association between metabolic variability and the risk of HF. Third, it is unknown whether the variabilities of different biological parameters are inter-related or independent of each other. However, we found the additive impact of variabilities of BP, BMI, FBG, and TC on the risk of HF. This observation might be useful to discriminate a group of subjects at risk of HF from other subjects.

4.2. Future directions

A future risk model of HF might be developed combining metabolic variability and previously known predictors. Also, a new paradigm of the high-risk population for HF development would be defined using a concept of the high variability of metabolic parameters. However, future studies are warranted to elucidate the detailed mechanism linking the risk of HF and variabilities of metabolic parameters and to determine whether the variability is itself a direct risk factor or an indirect, representative risk factor arising from other hidden fundamental causes.

5. Conclusions

In conclusion, using a nationwide population-based database of the NHIS of Korea, higher metabolic variability (systolic BP, BMI, FBG, and TC) was associated with an increased incidence of new-onset HF. Also, the combination of metabolic variability showed an additive effect on the incidence of HF. Also, MV score showed a graded response with the risk of HF. These findings suggest that metabolic variability could be used as a surrogate marker for prediction of future development of HF.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.035.

Declaration of Competing Interest

None.

Acknowledgement of grant support

This study was supported by Grant no. 062018245 from Seoul National University Hospital Research Fund, and by the Technology Innovation Program or Industrial Strategic Technology Development Program (10052668, development of wearable self-powered energy source and low-power wireless communication system for a pacemaker) funded by the Ministry of Trade, Industry and Energy (MOTIE, Sejong, Korea).

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