



# Association between metabolic syndrome and left ventricular geometric change including diastolic dysfunction

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## Abstract

**Background:** We investigated the association between individual components of metabolic syndrome (MetS) and left ventricular (LV) geometric changes, including diastolic dysfunction, in a large cohort of healthy individuals.

**Methods:** Overall, 148 461 adults who underwent echocardiography during a health-screening program were enrolled. Geographic characteristics on echocardiography and several markers of LV relaxation function were identified according to individual MetS components. Univariate linear regression analysis and a multivariate regression model adjusted for factors known to influence LV relaxation function were conducted.

**Results:** The prevalence of LV diastolic dysfunction (LVDD) was higher in the MetS group than in the non-MetS group (0.56% vs. 0.27%,  $p < .001$ ). In univariate and multivariate analyses, E/A ratio,  $e'$  velocity, and left atrial volume index were significantly associated with each component of MetS and covariates (all  $p \leq .001$ ). In the age- and sex-adjusted model, MetS was significantly associated with LVDD (odds ratio [95% confidence interval], 1.350 [1.103, 1.652]). However, subjects with more MetS components did not have a significantly higher risk of LVDD. As the analysis was stratified by sex, the multivariate regression model showed that MetS was significantly associated with LVDD only in men (1.3 [1.00, 1.68]) with higher risk in more MetS component ( $p$  for trend  $< .001$ ). In particular, triglyceride (TG) and waist circumference (WC) among MetS components were significantly associated with LVDD in men.

**Conclusions:** MetS was associated with the risk of LVDD, especially in men, with a dose-dependent association between an increasing number of components of MetS and LVDD. TG and WC were independent risk factors for LVDD in men.

## KEYWORDS

diastolic dysfunction, echocardiography, heart failure, left ventricle, metabolic syndrome, relaxation function, sex difference

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## 1 | INTRODUCTION

Metabolic syndrome (MetS), once referred to as “Syndrome X” or “insulin resistance,” is a set of risk factors that are correlated with each other and occur together, increasing the incidence of atherosclerotic cardiovascular disease diseases such as coronary artery disease, stroke, diabetes, chronic kidney disease, and several cancers.<sup>1-4</sup> There are various diagnostic criteria in the definition of MetS by different organizations, but they generally include abdominal obesity, hypertension, hyperglycemia, hypertriglyceridaemia, and low high-density lipoprotein cholesterol (HDL-C).<sup>5</sup> Left ventricular diastolic dysfunction (LVDD) refers to a condition in which the cardiac filling pressure increases due to impaired LV relaxation and abnormal stiffening of the LV chamber.<sup>6</sup> Since LVDD is considered a pathophysiological abnormality in the development of heart failure with preserved ejection fraction (HFpEF), the presence of LVDD is also necessary for diagnosing HFpEF.<sup>7,8</sup> Therefore, LVDD is considered an important tool in clinical practice.

Although the pathophysiological mechanisms related to LVDD and MetS have not yet been clearly established, many epidemiological studies have reported a positive association between the two.<sup>9-13</sup> However, most studies have a small sample size, which is likely to result in a bias or decrease in the representativeness of the entire population. Therefore, the purpose of this study was to evaluate whether MetS can affect LV geometric changes and relaxation function in relatively healthy young adults.

## 2 | METHODS

### 2.1 | Study population

The study population consisted of individuals aged 18 years or older registered in the Kangbuk Samsung Health Study (KSHS). The KSHS is a cohort study of subjects who had a comprehensive health screening program at the Total Healthcare Center of the Kangbuk Samsung Hospital in Seoul and Suwon, Korea. The purpose of the comprehensive health screening program was to improve health status through the early detection of chronic diseases and associated risk factors. In Korea, the Industrial Safety and Health Law requires employees to undergo annual or biennial health examinations. Approximately 80% of the examinees are employees of various organizations and companies, and the rest are voluntarily registered in health screening programs. This study analyzed individuals who underwent echocardiography as a part of comprehensive health examination between January 2011 and December 2018 (Figure 1). To the 158 422 individuals for whom echocardiography and associated data were initially available, we applied the following exclusion criteria: history of malignancy ( $n = 4674$ ), history of heart surgery ( $n = 7$ ), history of heart disease ( $n = 1651$ ), history of coronary disease ( $n = 1641$ ), and history of stroke ( $n = 830$ ). Finally, a total of 148 461 participants were eligible for inclusion in our study (102 416 men and 46 045 women; mean age,  $40.3 \pm 8.8$  years). This study was

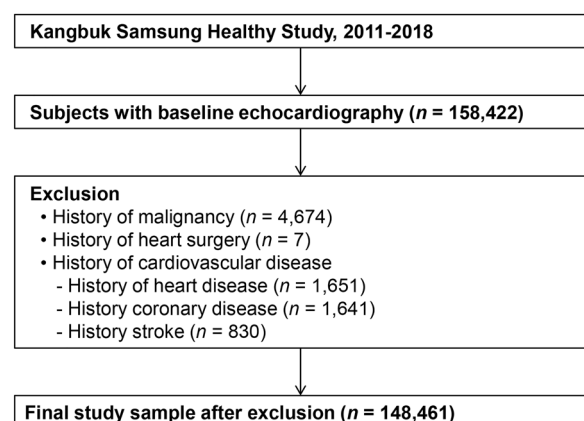
approved by the Institutional Review Board of Kangbuk Samsung Hospital (IRB No: 2020-03-049). As anonymized and deidentified data were used for analysis, the need for informed consent was waived. Data supporting the findings of this study are available from the corresponding author upon request.

### 2.2 | Clinical and laboratory measurements

All examinations were conducted at the Total Healthcare Center of the Kangbuk Samsung Hospital in Seoul and Suwon, according to a standardized protocol. Blood was drawn from participants after a fast of at least 10 h and analyzed at the Laboratory Medicine Department at Kangbuk Samsung Hospital, accredited by the Korean Society of Laboratory Medicine and the Korean Association of Quality Assurance for Clinical Laboratories.

Height, weight, waist circumference (WC), and body composition were measured by well-trained nurses with participants wearing lightweight gowns. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The WC was measured in the standing position, at the midpoint between the top of the anterior iliac crest and the lower border of the last palpable rib margin. Blood pressure and heart rate were measured using an automated oscillometric device (53000, Welch Allyn) by trained nurses while participants were in a sitting position with their arm supported at heart level after a 5-min rest. Blood pressure and heart rate were measured three times in a row, and we used the average of the second and third readings for our analysis. The fat mass was measured using a multifrequency bioimpedance analyzer (Inbody 3.0, Inbody 720, Biospace Co.). As a marker of insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using equation<sup>14</sup>:  $\text{HOMA-IR} = [\text{fasting insulin (IU/ml)} \times \text{fasting glucose (mmol/L)}] / 22.5$ .

Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, self-reported history of hypertension, or current use of antihypertensive medications.<sup>15</sup> Diabetes mellitus was defined based on the diagnostic



**FIGURE 1** Flowchart summarizing the study population.

criteria of the American Diabetes Association, a self-reported history of diabetes, or current use of antidiabetic medications.<sup>16</sup> Dyslipidaemia was defined as a low-density lipoprotein cholesterol (LDL-C) level  $\geq 160$  mg/dl, HDL-C level  $< 40$  mg/dl, or triglyceride (TG) level  $\geq 200$  mg/dl, self-reported history of dyslipidaemia, or history of medications for dyslipidaemia.<sup>17</sup> Obesity was defined as a BMI  $\geq 25$  kg/m<sup>2</sup> according to the Asia-Pacific Region definition and the Korean Society for the Study of Obesity obesity guidelines.<sup>17,18</sup>

### 2.3 | Definition of MetS

MetS was defined according to the Joint Interim Statement of 2009.<sup>19</sup> MetS was defined as the presence of any three or more of the following five criteria: (a) WC  $\geq 90$  cm in men or  $\geq 80$  cm in women; (b) TG level  $\geq 150$  mg/dl or drug treatment; (c) HDL-C  $< 40$  mg/dl in men or  $< 50$  mg/dl in women or drug treatment; (d) blood pressure  $\geq 130/85$  mmHg or antihypertensive medication; and (e) fasting glucose level  $\geq 100$  mg/dl or antidiabetic medication.

### 2.4 | Echocardiographic data

Transthoracic echocardiography with a 4 MHz, sector-type transducer probe (Vivid 7 and E9, General Electric) was performed by a trained sonographer following the guidelines.<sup>6,20</sup> Linear internal measurements of left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum thickness (IVST), and posterior LV wall thickness (PWT) were acquired from the parasternal long-axis view. LV mass was calculated through the linear method using the following cube formula: LV mass =  $0.8 \times [1.04 \times (\text{LVEDD} + \text{IVST} + \text{PWT})^3 - \text{LVEDD}^3] + 0.6$  g. Left ventricular mass index (LVMI) was determined as LV mass/body surface area (g/m<sup>2</sup>). The left atrial (LA) size was obtained through the linear dimension method measuring the anteroposterior diameter of the LA. LV diastolic function was evaluated in the apical four-chamber view using pulse-wave Doppler with blood flow. Peak velocities of the early (E) and late (A) phases of mitral inflow and deceleration time of the E velocity were also measured. Peak early velocities of the early diastolic (e) and late diastolic (a') phases were measured at the level of the septal mitral valve annulus using tissue Doppler imaging. We used the following four variables and abnormal cut-off values to identify the LVDD: (a) septal e'  $< 7$  cm/s; (b) average E/e' ratio  $> 14$ ; (c) LA volume index  $> 34$  ml/m<sup>2</sup>; (d) peak TR velocity  $> 2.8$  m/s.<sup>6,20</sup> LVDD was defined if more than half of the available parameters met these cut-off values.

### 2.5 | Statistical analyses

Categorical variables are expressed as numbers (%) and compared using the  $\chi^2$  test. Continuous variables were expressed as mean (standard deviation) or median (interquartile range) according to their

distribution. We used Student's *t*-test or Mann–Whitney test to compare the two groups according to the presence/absence of MetS and LVDD, and analysis of variance (ANOVA) or Kruskal–Wallis tests to compare the four groups according to MetS and LV diastolic dysfunction. Linear regression and stepwise multiple regression analyses were performed to determine the association between diastolic measurement (E/A ratio, e' velocity, and LA volume index) and potential variables, including clinical parameters, other echocardiographic parameters, and components of MetS. Odds ratios (ORs) and 95% confidence intervals (CIs) for LVDD according to MetS risk were estimated using multivariable logistic regression analysis. In our analyses, we used three models to adjust for confounding factors: model 1 was adjusted for age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, glucose, WC, BMI, HDL-C, LDL-C, and LVMI; model 2 was adjusted for age, sex, BMI, LDL, and LVMI; and model 3 was further adjusted by adding regular exercise, alcohol intake, and smoking status to the covariates of model 2. Associations between the number of MetS components and LVDD risk were evaluated using the same regression analyses. All *p* values were two-tailed, and *p*  $< .05$  was considered statically significant. All statistical analyses were conducted using STATA version 17.0 (StataCorp LP).

## 3 | RESULTS

### 3.1 | Baseline characteristics of the study population

In this study, 148 461 participants were included; 69% were male with a mean age of  $40.3 \pm 8.8$  years. The prevalence of MetS was 16.8%. Table 1 shows the clinical, anthropometric, and echocardiographic characteristics of the study population, divided by comparing those with and without MetS. Participants with MetS were older ( $43.9 \pm 9.5$  vs.  $39.6 \pm 8.5$  years), more obese (BMI,  $27.3 \pm 3.2$  vs.  $23.3 \pm 3.4$  kg/m<sup>2</sup>; WC,  $93.1 \pm 7.7$  vs.  $81.5 \pm 8.5$  cm) and more likely to be men (85.1% vs. 65.8%). They were more likely to be current or former smokers, more likely to drink, and less likely to exercise regularly. All metabolic values were significantly higher in the MetS group than in the MetS group. In addition, the proportions of current and former smokers and alcohol consumption were higher in the MetS group, and the proportion of those who exercised regularly was lower. Regarding echocardiographic parameters that reflect the cardiac structure, people with MetS showed statistically significant differences compared to those without MetS. In the MetS group, the ratio of LVDD was higher than in the group without MetS (0.56% vs. 0.27%, *p*  $< .001$ ), and in detail, larger LA diameter ( $36.56 \pm 4.13$  mm vs.  $32.79 \pm 4.34$  mm, *p*  $< .001$ ), lower E/A ratio ( $1.18 \pm 0.36$  vs.  $1.47 \pm 0.43$ , *p*  $< .001$ ), longer deceleration time (DecT) ( $191.23 \pm 40.88$  ms vs.  $184.74 \pm 36.88$  ms, *p*  $< .001$ ), and higher E/e' ratio ( $8.05 \pm 2.01$  vs.  $7.15 \pm 1.62$ , *p*  $< .001$ ) were found.

Furthermore, when the entire population was divided according to the presence or absence of LVDD, the demographic and clinical characteristics showed significant differences (Table S1). The subjects with LVDD were older than the subjects without LVDD ( $46.55 \pm 8.08$

**TABLE 1** Baseline characteristics of variables between individuals with and without MetS

|  | Total<br>(n = 148,461) | MetS                   |                       | p-value |
|--|------------------------|------------------------|-----------------------|---------|
|  |                        | MetS (-) (n = 123,578) | MetS (+) (n = 24,883) |         |
| Age (years)                            | 40.34 ± 8.84           | 39.61 ± 8.51           | 43.92 ± 9.54          | <.001   |
| Sex (male)                             | 102 416 (68.99)        | 81 252 (65.75)         | 21 164 (85.05)        | <.001   |
| Hypertension                           | 12 889 (8.68)          | 5923 (4.79)            | 6966 (28.00)          | <.001   |
| Diabetes                               | 7068 (4.76)            | 2610 (2.11)            | 4458 (17.92)          | <.001   |
| Dyslipidaemia                          | 45 939 (30.94)         | 27 494 (22.27)         | 18 445 (74.13)        | <.001   |
| Obesity                                | 51 588 (34.75)         | 32 169 (26.03)         | 19 419 (78.04)        | <.001   |
| Systolic BP (mmHg)                     | 111.07 ± 12.62         | 109.03 ± 11.61         | 121.17 ± 12.59        | <.001   |
| Diastolic BP (mmHg)                    | 71.71 ± 9.9            | 70.14 ± 9.1            | 79.46 ± 10.07         | <.001   |
| Heart rate (bpm)                       | 64.84 ± 9.1            | 64.23 ± 8.85           | 67.89 ± 9.69          | <.001   |
| BMI (kg/m <sup>2</sup> )               | 23.97 ± 3.35           | 23.29 ± 2.95           | 27.32 ± 3.17          | <.001   |
| Waist circumference (cm)               | 83.47 ± 9.44           | 81.49 ± 8.50           | 93.10 ± 7.70          | <.001   |
| Blood urea nitrogen (mg/dl)            | 12.75 ± 3.26           | 12.64 ± 3.20           | 13.29 ± 3.48          | <.001   |
| Creatinine (mg/dl)                     | 0.86 ± 0.21            | 0.85 ± 0.20            | 0.91 ± 0.25           | <.001   |
| Total cholesterol (mg/dl)              | 194.68 ± 34.07         | 193.06 ± 32.94         | 202.73 ± 38.20        | <.001   |
| Triglyceride (mg/dl)                   | 123.79 ± 85.20         | 106.84 ± 61.87         | 207.98 ± 125.62       | <.001   |
| HDL-C (mg/dl)                          | 57.1 ± 15.26           | 59.43 ± 14.82          | 45.51 ± 11.66         | <.001   |
| LDL-C (mg/dl)                          | 125.13 ± 32.05         | 123.40 ± 31.19         | 133.75 ± 34.75        | <.001   |
| Glucose (mg/dl)                        | 96.19 ± 14.8           | 93.74 ± 10.95          | 108.32 ± 23.12        | <.001   |
| hsCRP (mg/dl)                          | 0.11 ± 0.33            | 0.10 ± 0.33            | 0.15 ± 0.33           | <.001   |
| Insulin (μU/ml)                        | 6.86 ± 4.52            | 6.07 ± 3.58            | 10.78 ± 6.32          | <.001   |
| Fat mass (kg)                          | 17.76 ± 6.09           | 16.63 ± 5.30           | 23.32 ± 6.64          | <.001   |
| HOMA-IR                                | 1.67 ± 1.31            | 1.42 ± 0.91            | 2.92 ± 2.05           | <.001   |
| Antihypertensive therapy               | 9593 (6.47)            | 3716 (3.01)            | 5877 (23.62)          | <.001   |
| Anti-lipaeamic therapy                 | 5703 (3.85)            | 2587 (2.1)             | 3116 (12.52)          | <.001   |
| Diabetes mellitus therapy              | 3282 (2.21)            | 1222 (0.99)            | 2060 (8.28)           | <.001   |
| Smoking status                         |                        |                        |                       |         |
| Current smoker                         | 28 284 (19.93)         | 21,334 (18.08)         | 6950 (29.11)          | <.001   |
| Former smoker                          | 46 082 (32.48)         | 36 592 (31.01)         | 9490 (39.74)          | <.001   |
| Alcohol (g/day)                        | 14.46 ± 21.70          | 13.14 ± 19.93          | 20.94 ± 28.00         | <.001   |
| Regular exercise<br>(≥1 time per week) | 58 737 (39.6)          | 49 129 (39.8)          | 9608 (38.6)           | <.001   |
| LVDD                                   | 471 (0.32)             | 332 (0.27)             | 139 (0.56)            | <.001   |
| Echocardiographic parameters           |                        |                        |                       |         |
| IVSd (mm)                              | 8.10 ± 1.28            | 7.95 ± 1.23            | 8.86 ± 1.22           | <.001   |
| LVPWd (mm)                             | 8.00 ± 1.21            | 7.85 ± 1.17            | 8.74 ± 1.14           | <.001   |
| LVIDd (mm)                             | 48.11 ± 4.07           | 47.96 ± 4.02           | 48.86 ± 4.24          | <.001   |
| LVIDs (mm)                             | 30.28 ± 3.42           | 30.23 ± 3.39           | 30.53 ± 3.55          | <.001   |
| LA diameter (mm)                       | 33.42 ± 4.53           | 32.79 ± 4.34           | 36.56 ± 4.13          | <.001   |

TABLE 1 (Continued)

|                                   | Total<br>(n = 148,461) | MetS                   |                       | p-value |
|-----------------------------------|------------------------|------------------------|-----------------------|---------|
|                                   |                        | MetS (-) (n = 123,578) | MetS (+) (n = 24,883) |         |
| E (m/s)                           | 0.69 ± 0.15            | 0.70 ± 0.15            | 0.65 ± 0.14           | <.001   |
| A (m/s)                           | 0.52 ± 0.13            | 0.50 ± 0.12            | 0.58 ± 0.14           | <.001   |
| E/A                               | 1.42 ± 0.43            | 1.47 ± 0.43            | 1.18 ± 0.36           | <.001   |
| DecT (ms)                         | 185.83 ± 37.66         | 184.74 ± 36.88         | 191.23 ± 40.88        | <.001   |
| e' (m/s)                          | 0.10 ± 0.02            | 0.10 ± 0.02            | 0.08 ± 0.02           | <.001   |
| E/e'                              | 7.30 ± 1.73            | 7.15 ± 1.62            | 8.05 ± 2.01           | <.001   |
| LV mass index (g/m <sup>2</sup> ) | 129.54 ± 33.00         | 125.66 ± 31.70         | 148.39 ± 32.68        | <.001   |
| Ejection fraction (%)             | 66.63 ± 5.57           | 66.53 ± 5.52           | 67.13 ± 5.78          | <.001   |

Note: Data are presented as n (%) or mean ± standard deviation. The blank fields were not significant.

Abbreviations: A, peak late diastolic transmitral flow; BMI, body mass index; BP, blood pressure; DecT, deceleration time; E, peak early diastolic transmitral flow; e', early diastolic mitral annulus velocity; EF, ejection fraction; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; LA, left atrial; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVDD, left ventricular diastolic dysfunction; LVIDD, end-diastolic left ventricular internal diameter; LVIDs, end-systolic left ventricular internal diameter; LVPWd, end-diastolic left ventricular posterior wall; MetS, metabolic syndrome.

vs. 40.32 ± 8.84 years,  $p < .001$ ), and had a higher proportion of each component of MetS. The echocardiographic parameters measured to evaluate diastolic dysfunction also showed significant differences between groups, excluding end-diastolic left ventricular internal diameter, peak late diastolic transmitral flow (A), and left atrial volume index (LAVI). Table S2 shows the results of analyzing the total study population in more detail by dividing it into four groups according to the presence or absence of MetS and LVDD, and all variables showed significant differences. Table S3 shows the results of analysis of the entire population stratified by sex, and there were significant differences in demographic and clinical characteristics, except for age.

### 3.2 | Univariate and multivariate regression analysis of LVDD

We used univariate and multivariate regression models to determine how each component of MetS, age, sex, and other factors affected the LVDD measures (Table 2). Univariate analysis demonstrated that all variables were statistically significantly related to E/A ratio, e' velocity, and LAVI ( $p \leq .007$  for all). Similarly, the multivariate regression analysis demonstrated that all variables were independently related to the E/A ratio ( $r^2 = .375$ ), e' velocity ( $r^2 = .439$ ), and LAVI ( $r^2 = .385$ ) ( $p \leq .005$  for all).

### 3.3 | Risk of LVDD according to MetS status

Table 3 shows the association between MetS and the risk of LVDD. In the univariate analysis, people with MetS had an increased risk of

LVDD compared to those without MetS (OR, 2.085; 95% CI, 1.710–2.543;  $p < .001$ ). Among those with MetS, the risk of LVDD increased with MetS components (3, 4, and 5 MetS risk factors vs. no MetS; OR, 1.790, 1.987, and 2.481;  $p \leq .003$  for all). In the analysis adjusting for age and sex, people with MetS remained a significant risk factor for LVDD (OR, 1.350; 95% CI, 1.103–1.652,  $p = .004$ ). However, when analyzed by dividing people with MetS according to the number of components of MetS, the risk of LVDD seemed to increase as the number of components increased, but this was not statistically meaningful (3, 4, 5 and MetS risk factors vs. No MetS; OR, 1.216, 1.323 and 1.709;  $p \geq .081$  for all). In the multivariate analysis adjusted for age, sex, systolic BP, diastolic BP, TG, glucose, WC, BMI, HDL-C, LDL-C, and LVMI (model 1), people with MetS had a lower risk of LVDD than those without MetS, but there was no statistical significance, and the sub-analysis showed similar results. Further analyses of model 2 (adjusted for age, sex, BMI, LDL, LVMI) and model 3 (adjusted for age, sex, BMI, LDL, LVMI, regular exercise, alcohol amount in grams, and current/former smoker) also showed that the risk of LVDD in the MetS group was not significant (models 2 and 3 vs. no MetS; OR, 1.081 and 1.094;  $p \geq .495$  for all). In addition, there was no statistical significance when analyzed according to the number of MetS components.

On the other hand, when people with LVDD were stratified by sex, it was confirmed that the risk of LVDD according to MetS was significantly associated, especially in men (OR [95% CI], 1.3 [1.00, 1.68] for men; 1.03 [0.39, 2.76] for women) (Table 4). In addition, there was a dose-response relationship in the risk of LVDD according to the number of MetS components in men (3, 4, and 5 MetS risk factors vs. no MetS; OR [95% CI], 1.2 [0.89, 1.63], 1.5 [1.00, 2.24], and 2.1 [1.01, 4.38], respectively). As a result of analyzing the effect of each of the MetS criteria on the risk of LVDD, TG and WC had

**TABLE 2** Correlation coefficients of univariate and multiple variable regression analyses of E/A ratio, e' velocity and LA volume index for each component of the metabolic syndrome and covariates

| Variable                      | E/A ratio            |         |                             | e' velocity          |         |                             | LA volume index      |         |                             |
|-------------------------------|----------------------|---------|-----------------------------|----------------------|---------|-----------------------------|----------------------|---------|-----------------------------|
|                               | Univariate<br>B (se) | p-value | Multiple variable<br>B (se) | Univariate<br>B (se) | p-value | Multiple variable<br>B (se) | Univariate<br>B (se) | p-value | Multiple variable<br>B (se) |
| Systolic BP                   | -0.010 (0.000)       | <.001   | 0.002 (0.000)               | -0.001 (0.000)       | <.001   | 0.0001 (0.000)              | 0.200 (0.013)        | <.001   | 0.136 (0.022)               |
| Diastolic BP                  | -0.016 (0.000)       | <.001   | -0.011 (0.000)              | -0.001 (0.000)       | <.001   | -0.001 (0.000)              | 0.165 (0.019)        | <.001   | -0.128 (0.028)              |
| Triglyceride                  | -0.001 (0.000)       | <.001   | -0.00008 (0.000)            | -0.00006 (0.000)     | <.001   | -0.00001 (0.000)            | 0.014 (0.002)        | <.001   |                             |
| Glucose                       | -0.006 (0.000)       | <.001   | -0.001 (0.000)              | -0.0004 (0.000)      | <.001   | -0.00003 (0.000)            | 16.600 (1.238)       | <.001   |                             |
| Waist circumference           | -0.014 (0.000)       | <.001   | -0.006 (0.000)              | -0.001 (0.000)       | <.001   | -0.0002 (0.000)             | 0.294 (0.019)        | <.001   |                             |
| BMI                           | -0.036 (0.000)       | <.001   | -0.007 (0.001)              | -0.002 (0.000)       | <.001   | -0.0004 (0.000)             | 0.840 (0.052)        | <.001   | 0.492 (0.057)               |
| HDL-C                         | 0.005 (0.000)        | <.001   | 0.001 (0.000)               | 0.0003 (0.000)       | <.001   | 0.00004 (0.000)             | -0.063 (0.014)       | <.001   |                             |
| LDL-C                         | -0.003 (0.000)       | <.001   | -0.001 (0.000)              | -0.0001 (0.000)      | <.001   | -0.00004 (0.000)            | 0.018 (0.007)        | <.007   | -0.015 (0.005)              |
| MetS (+) Group                | -0.288 (0.003)       | <.001   |                             | -0.017 (0.000)       | <.001   | -0.001 (0.000)              | 5.041 (0.465)        | <.001   |                             |
| Age                           | -0.025 (0.000)       | <.001   | -0.022 (0.000)              | -0.001 (0.000)       | <.001   | -0.001 (0.000)              | 0.306 (0.02)         | <.001   | 0.222 (0.019)               |
| Sex                           | -0.132 (0.002)       | <.001   | 0.034 (0.003)               | -0.008 (0.000)       | <.001   | 0.001 (0.000)               | 2.394 (0.447)        | <.001   |                             |
| LVMl                          | -0.01 (0.000)        | <.001   | 0.001 (0.000)               | -0.001 (0.000)       | <.001   | -0.000 (0.000)              | 0.302 (0.014)        | <.001   | 0.141 (0.017)               |
| Model adjusted r <sup>2</sup> |                      |         | .375                        |                      |         | .439                        |                      |         | .385                        |

Note: The blank fields were not significant. The  $\beta$  estimate represents the change in echocardiographic measures in patients with and without MetS.

Abbreviations: A, peak late diastolic transmitral flow; BMI, body mass index; BP, blood pressure; E, peak early diastolic transmitral flow; HDL-C, high-density lipoprotein cholesterol; LA, left atrial; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVMl, left ventricular mass index; MetS, metabolic syndrome.

**TABLE 3** Crude and adjusted odds ratios for the presence of any grade of diastolic dysfunction according to metabolic syndrome status

|   | Prevalence<br>of LVDD | ORs (95% CIs)       |           |                       |           |                     |           |                     |           |                     |           |
|---|-----------------------|---------------------|-----------|-----------------------|-----------|---------------------|-----------|---------------------|-----------|---------------------|-----------|
|   |                       | Crude               |           | Age- and sex-adjusted |           | Model 1             |           | Model 2             |           | Model 3             |           |
|   |                       | OR (95% CI)         | p-value   | OR (95% CI)           | p-value   | OR (95% CI)         | p-value   | OR (95% CI)         | p-value   | OR (95% CI)         | p-value   |
| No MetS (n = 123 578)                   | 332 (0.30)            | Reference           | Reference | Reference             | Reference | Reference           | Reference | Reference           | Reference | Reference           | Reference |
| Metabolic Syndrome<br>(n = 24 883)      | 139 (0.60)            | 2.085 (1.710–2.543) | <.001     | 1.350 (1.103–1.652)   | .004      | 0.888 (0.669–1.178) | .409      | 1.081 (0.843–1.386) | .541      | 1.094 (0.846–1.415) | .495      |
| Three MetS risk factors<br>(n = 16 293) | 85 (0.50)             | 1.790 (1.415–2.266) | <.001     | 1.216 (0.959–1.543)   | .106      | 0.913 (0.692–1.203) | .516      | 1.011 (0.771–1.326) | .935      | 1.012 (0.765–1.339) | .932      |
| Four MetS risk factors<br>(n = 71 666)  | 43 (0.60)             | 1.987 (1.451–2.721) | <.001     | 1.323 (0.964–1.815)   | .084      | 0.942 (0.645–1.376) | .758      | 1.107 (0.770–1.592) | .583      | 1.115 (0.767–1.621) | .570      |
| Five MetS risk factors<br>(n = 14 244)  | 11 (0.80)             | 2.481 (1.361–4.521) | <.003     | 1.709 (0.935–3.123)   | .081      | 1.084 (0.519–2.264) | .831      | 1.212 (0.591–2.486) | .600      | 1.287 (0.626–2.645) | .493      |

Note: Model 1 was adjusted for age, sex, systolic BP, diastolic BP, triglyceride, glucose, waist circumference, BMI, HDL-C, LDL-C, and LVMI. Model 2 was adjusted for age, sex, BMI, LDL-C level, and LVMI. Model 3 was adjusted for age, sex, BMI, LDL-C, LVMI, regular exercise, alcohol amount grams, current/former smoker.

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVDD, left ventricular diastolic dysfunction; LVMI, left ventricular mass index; MetS, metabolic syndrome; OR, odds ratio.



significantly increased the risk of LVDD after multivariate adjustment (OR, 1.3; 95% CI, 1.03–1.64 and 1.38; 1.02–1.85, respectively).

## 4 | DISCUSSION

In this cross-sectional cohort study, we showed that MetS was associated with LV geometric changes and diastolic dysfunction using echocardiographic measurements. The data were obtained from large samples of relatively young and healthy individuals. The main findings of the present study showed that (i) MetS increased the prevalence of LVDD; (ii) in age- and sex-adjusted analysis, the risk of LVDD increased in the MetS group compared with the no MetS group, but the risk of LVDD did not tend to increase as the number of MetS components increased; (iii) after adjustment for multiple confounders, MetS showed a significant relationship with diastolic parameters, but it was difficult to find a significant association with the development of LVDD; and (iv) the correlation between MetS and LVDD was stronger in men than in women, and WC and TG were independent risk factors for LVDD. These findings suggest that MetS and each risk factor of MetS may cause a change in LV geometry as well as the diastolic parameters of the echocardiogram. In addition, it was suggested that not only does MetS have a sex difference in influencing diastolic dysfunction, but also that the components of MetS may not be affected with the same weight.

The exact pathophysiological mechanisms by which MetS induces the development of LVDD are unknown, but it is generally known that MetS is significantly associated with LVDD in several studies.<sup>9,10,12,21</sup> In two studies of subjects with normal LV function, MetS was associated with diastolic dysfunction regardless of LV hypertrophy,<sup>9,21</sup> and diastolic dysfunction occurred even in the pre-MetS state.<sup>9</sup> A Multi-Ethnic Study of Atherosclerosis study using cardiac MRI for 1582 subjects showed that insulin resistance was associated with diastolic function, but MetS without type 2 DM could also develop diastolic dysfunction.<sup>10</sup> A study of 684 Portuguese people showed a stepwise association between an increasing number of components of MetS and diastolic dysfunction.<sup>12</sup> The mechanism by which the components of MetS induce LVDD is multifactorial and does not induce LVDD via different mechanisms. As a result, MetS is known to be a risk factor in the development of LVDD, but also to develop synergistically through the interaction of each component of MetS.<sup>11</sup> Our results seem to be consistent with those of previous studies but showed some differences. The strength of our study and the distinction from other studies is that, through a large number of participants, MetS increased the risk of LVDD, especially in men, and that WC and TG could play an important role.

Waist circumference (abdominal obesity) is a well-known cause of LVDD among the components of MetS, which can affect multiple metabolic and neurohormonal pathways due to accumulation of adipose tissue, causing abnormalities in the renin-angiotensin system and myocardial oxidative stress.<sup>22</sup> In addition, obesity causes cardiomyocyte apoptosis and cardiac structural remodeling due to an increase in lipotoxicity resulting from an increase in free fatty acid

use, which can lead to diastolic dysfunction.<sup>23–25</sup> Hyperglycemia causes an increase in oxidative stress by increasing fatty acid metabolism and reducing glucose metabolism,<sup>26</sup> leading to contractile dysfunction,<sup>27</sup> mitochondrial dysfunction,<sup>28</sup> and endothelial dysfunction of cardiomyocytes.<sup>29</sup> As TG levels increase, myocellular lipid accumulation increases, which is known to trigger lipoapoptosis and cause diastolic dysfunction.<sup>30</sup> The combination of TG-rich lipoprotein secretion and clearance impairment leads to abdominal obesity,<sup>31</sup> and changes in TG levels could affect diastolic dysfunction by increasing the risk of diabetes.<sup>32</sup> Low HDL levels not only do not sufficiently remove cellular lipids, but also cause arterial stiffness by not properly inducing NO synthesis, preventing apoptosis, and inducing angiogenesis, increasing myocardial cell hypertrophy and myocardial collagen, and eventually inducing diastolic dysfunction.<sup>33,34</sup> HTN increases LV after-load and peripheral vascular resistance, causing LV structural remodeling.<sup>35,36</sup> This leads to myocardial fibrosis and LV hypertrophy, which increase the filling pressure, resulting in diastolic dysfunction.<sup>37</sup>

Unlike in other previous studies, it was difficult to conclude that the relationship between MetS and LVDD showed a significant trend after multivariate adjustment in this study. However, our study also confirmed that the MetS-related variables were significantly associated with the diastolic parameters, as in other studies. Based on the consistent epidemiologic data that there was a sex difference in the prevalence of HFpEF,<sup>38</sup> we were able to derive meaningful results by stratifying subjects with LVDD by sex. In addition, we divided the patients into four groups according to the presence or absence of MetS and LVDD, and further checked for regular exercise (Table S2). A recent study of 57 449 subjects suggested that physical activity may reduce the risk of impaired LV relaxation.<sup>39</sup> Since the limitation of cross-sectional studies is that the effects of differences in morbidity of each disease, changes in the condition of the disease due to drug use, and the causal relationship of exercise to the disease are difficult to elucidate, it is necessary to clarify our results through additional research.

## 5 | STUDY LIMITATIONS

The results of this study should be interpreted in the context of several limitations. The main limitation of this study was that it was cross-sectional and observational. Thus, our results might not only make it difficult to reach a conclusion about the causal relationship between MetS and LVDD, but might also be subject to unrecognized confounding factors or bias. Future research with a longitudinal design would provide better insights into the impact of the relationship between MetS and LVDD. Second, the majority of the study population was middle-aged and living in urban areas, so selection bias may have arisen. It may be unreasonable to generalize our results to the entire population. On the other hand, since we conducted studies on young people who do not have multiple diseases that could act as a confounding factor, the effect of underlying diseases apart from MetS in this study would have been relatively small. Nevertheless, further studies are needed to confirm our



TABLE 4 Crude and adjusted odds ratios for the presence of any grade of diastolic dysfunction according to metabolic syndrome status

|                         | Men                       |                   | Women                     |                  |
|-------------------------|---------------------------|-------------------|---------------------------|------------------|
|                         | Prevalence of LVDD, n (%) | Model 1           | Prevalence of LVDD, n (%) | Model 1          |
| No MetS                 | 300 (69.44)/81 252        | 1 (reference)     | 32 (82.05)/42 326         | 1 (reference)    |
| Total MetS              | 132 (30.56)/21 164        | 1.43 (1.14–1.79)  | 7 (17.95)/3719            | 0.88 (0.35–2.21) |
| Three MetS risk factors | 80 (21.05)/13 852         | 1.31 (1.01–1.71)  | 5 (13.51)/2441            | 0.97 (0.35–2.68) |
| Four MetS risk factors  | 41 (12.02)/6140           | 1.6 (1.12–2.29)   | 2 (5.88)/1026             | 0.81 (0.18–3.71) |
| Five MetS risk factors  | 11 (3.54)/1172            | 2.37 (1.26–4.46)  | 0 (0)/252                 | N/A              |
| MetS components         |                           |                   |                           |                  |
| None                    | 85 (19.68)/30 357         | 1 (reference)     | 19 (48.72)/26 573         | 1 (reference)    |
| 1 risk                  | 116 (26.85)/28 797        | 1.2 (0.9–1.6)     | 7 (17.95)/10 834          | 0.45 (0.18–1.12) |
| 2 risks                 | 99 (22.92)/22 098         | 1.22 (0.9–1.66)   | 6 (15.38)/4919            | 0.46 (0.16–1.3)  |
| 3 risks                 | 80 (18.52)/13 852         | 1.54 (1.1–2.16)   | 5 (12.82)/2441            | 0.54 (0.17–1.76) |
| 4 risks                 | 41 (9.49)/6140            | 1.8 (1.19–2.73)   | 2 (5.13)/1026             | 0.47 (0.09–2.41) |
| 5 risks                 | 11 (2.55)/1172            | 2.67 (1.38–5.17)  | 0 (0)/252                 | N/A              |
| p for trend             |                           | <.001             |                           | .158             |
| MetS criteria           |                           |                   |                           |                  |
| Waist circumference     | 154 (35.65)/30 873        | 1.3 (0.999–1.69)  | 10 (25.64)/6984           | 1.34 (0.51–3.53) |
| Triglyceride            | 233 (53.94)/43 083        | 1.32 (1.07–1.62)  | 12 (30.77)/8200           | 0.98 (0.47–2.05) |
| HDL-C                   | 63 (14.58)/13 685         | 0.97 (0.73–1.28)  | 5 (12.82)/6664            | 0.59 (0.22–1.54) |
| Blood pressure          | 148 (34.26)/24 868        | 1.15 (0.93–1.43)  | 7 (17.95)/4604            | 0.53 (0.21–1.33) |
| Glucose                 | 175 (40.51)/32 460        | 1.06 (0.87–1.3)   | 8 (20.51)/6907            | 0.77 (0.34–1.74) |
| Model 2                 |                           |                   |                           |                  |
| No MetS                 |                           | 1 (reference)     |                           | 1 (reference)    |
| Total MetS              |                           | 1.3 (1.0003–1.68) |                           | 0.88 (0.35–2.21) |
| Three MetS risk factors |                           | 1.2 (0.89–1.63)   |                           | 0.97 (0.35–2.68) |
| Four MetS risk factors  |                           | 1.5 (1.002–2.24)  |                           | 0.81 (0.18–3.71) |
| Five MetS risk factors  |                           | 2.1 (1.01–4.38)   |                           | N/A              |
| MetS components         |                           |                   |                           |                  |
| None                    |                           | 1 (reference)     |                           | 1 (reference)    |
| 1 risk                  |                           | 1.15 (0.84–1.58)  |                           | 0.45 (0.18–1.12) |
| 2 risks                 |                           | 1.23 (0.87–1.72)  |                           | 0.46 (0.16–1.3)  |
| 3 risks                 |                           | 1.38 (0.94–2.02)  |                           | 0.54 (0.17–1.76) |
| 4 risks                 |                           | 1.66 (1.04–2.65)  |                           | 0.47 (0.09–2.41) |
| 5 risks                 |                           | 2.26 (1.05–4.88)  |                           | N/A              |
| p for trend             |                           | <.001             |                           | .310             |
| MetS criteria           |                           |                   |                           |                  |
| Waist circumference     |                           | 1.38 (1.02–1.85)* |                           | 1.69 (0.58–4.9)  |
| Triglyceride            |                           | 1.3 (1.03–1.64)*  |                           | 1.25 (0.55–2.82) |
| HDL-C                   |                           | 0.96 (0.7–1.32)   |                           | 0.4 (0.12–1.37)  |
| Blood pressure          |                           | 1.05 (0.82–1.34)  |                           | 0.66 (0.25–1.77) |
| Glucose                 |                           | 1.02 (0.81–1.28)  |                           | 0.64 (0.25–1.64) |

Note: Model 1 was adjusted for age, obesity (BMI  $\geq 25$  kg/m<sup>2</sup>), and LDL-C. Model 2 was adjusted for age, obesity (BMI  $\geq 25$  kg/m<sup>2</sup>), LDL-C, LVMI, regular exercise, alcohol amount grams, current/former smoker. Abbreviations: BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LV mass index, left ventricular mass index; LVDD, left ventricular diastolic dysfunction; MetS, metabolic syndrome.

\* $p < .001$ .

findings among people of different age groups or other races/ethnicities. Third, we used a uniform cut-off value without considering age as a criterion for diagnosing LVDD. In a study conducted with 2008 subjects, Miyoshi et al. suggested that as the diastolic parameters change with age in healthy people, the age-specific criteria should be changed for an appropriate assessment of LV relaxation function.<sup>40</sup> However, we targeted relatively young people with an average age of 40 years, so the elderly population is not large. Therefore, except for changes in LV diastolic parameters due to healthy aging, it is unlikely that the elderly participants who could be classified as normal belonged to the LVDD group and affected the study results.

## 6 | CONCLUSIONS

In this study, we have shown that MetS is associated with the risk of LVDD in a dose-dependent manner in the components of MetS, and there was a stronger association in men than in women. TG and WC were independent risk factors for LVDD in men. However, further studies are needed to clarify the specific mechanism and causal relationships between the components of MetS, sex differences, and LVDD.

### AUTHOR CONTRIBUTIONS

Jong-Young Lee contributed to the conception and design of the study. Seung-Jae Lee drafted the manuscript and edited the manuscript. Mi Yeon Lee contributed to the acquisition, analysis, and interpretation of data. Hyunah Kim, Byeong Kil Oh, Hyo-In Choi, Jeonggyu Kang, and Ki-Chul Sung contributed to the discussion. Jong-Young Lee is the guarantor for this article. All the authors have read the manuscript and agree with the findings.

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### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon request.

### ETHICS STATEMENT

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (IRB No. 2019-05-053).

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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