Association of Pericardial Adipose Tissue With Left Ventricular Structure and Function: A Region-specific Effect?

Jin-Seok Kim
Korea University Ansan Hospital

Seon Won Kim
Korea University Ansan Hospital

Jong Seok Lee
Korea University Ansan Hospital

Seung Ku Lee
Korea University Ansan Hospital

Robert Abbott
Korea University Ansan Hospital

Ki Yeol Lee
Korea University Ansan Hospital

Hong Euy Lim
Hallym University Sacred Heart Hospital

Ki-Chul Sung
Kangbuk Samsung Hospital: Kangbuk Samsung Medical Center

Goo-Yeong Cho
Seoul National University Bundang Hospital

Kwang Kon Koh
Gachon University Gil Hospital

Sun H. Kim
Stanford University School of Medicine

Chol Shin
Korea University Ansan Hospital

Seong Hwan Kim (cardioguy@korea.ac.kr)
Division of Cardiology, 2Institute of Human Genomic Study, 3Division of Radiology, Korea University Ansan Hospital, Ansan, Korea

Original investigation
Keywords: Pericardium, adipose tissue, tissue Doppler echocardiography, left ventricular function, left ventricular hypertrophy

DOI: https://doi.org/10.21203/rs.3.rs-84379/v1

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Abstract

**Background:** The independent role of pericardial adipose tissue (PAT) as an ectopic fat associated with cardiovascular disease (CVD) remains controversial. This study aimed to determine whether PAT is associated with left ventricular (LV) structure and function independent of other markers of general obesity.

**Methods:** We studied 2,471 participants (50.9% women) without known CVD from the Korean Genome Epidemiology Study, who underwent 2D-echocardiography with tissue Doppler imaging (TDI) and computed tomography measurement for PAT.

**Results:** Study participants with more PAT were more likely to be men and had higher cardiometabolic indices, including blood pressure, glucose, and cholesterol levels (all $P<0.001$). Greater pericardial fat levels across quartiles of PAT were associated with increased LV mass index and left atrial volume index (all $P<0.001$) and decreased systolic ($P = 0.015$) and early diastolic ($P<0.001$) TDI velocities, except for LV ejection fraction. These associations remained after a multivariable-adjusted model for traditional CV risk factors and persisted after additional adjustment for general adiposity measures, such as waist circumference and body mass index. PAT was the only obesity index independently associated with systolic TDI velocity ($P<0.001$).

**Conclusions:** PAT was associated with subclinical LV structural and functional changes, and these associations were independent of and stronger than with general and abdominal obesity measures.

Background

Pericardial adipose tissue (PAT) may contribute to the development of cardiovascular disease (CVD) and events [1]. Increased PAT has been associated with coronary artery calcification [2], atrial fibrillation [3], and impaired left ventricular (LV) structure and function in various clinical settings [4, 5]. Because of its anatomic contiguity to the myocardium and the coronary arteries, PAT may mediate adverse cardiac effects by direct lipotoxicity, local compressive forces, and/or endocrine/paracrine effects [6]. However, because pericardial fat accumulation is among a variety of ectopic fat depots (e.g., in liver, pancreas, and muscle) associated with general obesity, there is controversy regarding its independent role in heart diseases beyond those associated with the standard indices of excess adiposity, such as body mass index (BMI) and waist circumference (WC). Indeed, the Framingham Heart Study has demonstrated an association between PAT and cardiac structure and function but the association did not persist after adjustment of body weight, suggesting that the systemic effects of obesity outweighs local effects of PAT [7]. On the other hand, other studies with small samples have shown independent associations between pericardial fat and LV mass, left atrial (LA) size, as well as LV systolic or diastolic function [8–10].

To address these unresolved issues, we investigated the relationship of PAT with LV structure and function using the tissue Doppler technique after accounting for clinical measures of general obesity in a
large community-based cohort study.

Methods

Study population

The study population was recruited from an ongoing population-based Ansan cohort embedded in the Korean Genome Epidemiology Study, which is described in detail elsewhere [11]. Briefly, the baseline cohort comprised of 5,020 participants and has been followed biennially from 2001. This eighth follow-up examination, including 3,083 participants, was conducted between March 2015 and December 2016. Among these individuals, a total of 2,524 completed conventional and tissue Doppler echocardiography and chest computed tomography (CT) for the measurement of PAT. From this sample, we excluded individuals who had incomplete echocardiography data (n = 7) or CT data (n = 2); known CVD, including a previous history of myocardial infarction, congestive heart failure, congenital heart disease, coronary revascularization, angina, stroke, cardiomyopathy, significant valvular heart disease, arrhythmia, and LV ejection fraction < 50% (n = 45); or a serum creatinine level ≥ 2.0 mg/dL (n = 7), leaving a total of 2,471 subjects for the analysis.

The protocol of the study was approved by the Human Subjects Review Committee at the Korea University Ansan Hospital, and all participants provided written informed consent at every site visit.

Echocardiography

Standard 2D echocardiography examinations were performed by an expert using the Vivid 7 system (GE Vingmed, Horton, Norway) with a 4-MHz transducer. Cardiac chamber diameters and wall thickness were measured according to the current recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [12]. The LA volume and LV mass were calculated using the area-length method and Devereux formula and were indexed to body surface area. LV ejection fraction measurement was conducted using the modified biplane Simpson's method. The peak transmitral E and A diastolic velocities and the deceleration time (DT) were recorded in the apical 4-chamber view at the tips of the mitral valve leaflets during diastole. The systolic tissue Doppler imaging (TDI) Sm and early diastolic Em velocities were measured at the septal side of the mitral annulus. Subsequently, the mitral E/Em ratio was calculated as an index of LV diastolic filling pressure. Echocardiographic LV hypertrophy was defined as an LV mass index > 95 g/m² for women and > 115 g/m² for men. Subclinical LV diastolic dysfunction was defined if at least two of the following conditions were met: (i) septal TDI Em velocity ≤ 7 cm/s; (ii) septal E/Em ratio > 15; (iii) LA volume index ≥ 34 mL/m² [13].

Pericardial fat volume quantification

Participants underwent chest CT scans by well-trained technicians using a commercial 64-multidetector CT (Brilliance 64, Philips Healthcare, Cleveland, OH, USA) according to a standardized protocol. CT
images were acquired in the supine position during end-inspiratory and end-expiratory breath holds. Scanning parameters were held constant at the 64 × 0.625 mm detector configuration, 120 kV (peak), 100 mAs, and a section thickness of 0.625 mm without intravenous contrast material. Pericardial fat measurements were performed three-dimensionally using Aquarius iNtuition Edition software version 4.4.11 (TeraRecon Headquarters, Foster City, CA, USA), which is an automated lung image analysis tool, with non-contrast chest CT images (Fig. 1). PAT was defined as epicardial adipose tissue (EAT, fat enclosed in the pericardium) plus paracardial adipose tissue (fat located external to the pericardium) [3]. Segmentation of the overall volume was automatically interpolated using manually defined tracings, and PAT volume was subsequently quantified by calculating the total volume of the tissue in which CT density ranged from −500 to 0 Hounsfield units within the thoracic cavity.

**Risk factor assessment**

Clinical information, CV risk factors, and medical history were obtained using interviewer-administered questionnaires. WC was measured at the level of umbilicus. BMI (kg/m²) was defined as body weight (kg) divided by the square of height (m). BMI ≥ 23 kg/m² was classified as overweight, and BMI ≥ 25 kg/m² was classified as obese. Blood pressure was measured according to a standardized protocol using a mercury sphygmomanometer. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg and/or the use of antihypertensive drugs. After an overnight fasting of at least 8 hours, blood samples were collected for serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), plasma glucose, HbA1c, and serum creatinine analysis. Type 2 diabetes (T2D) was defined as a fasting blood glucose ≥ 126 mg/dL or the use of either insulin or hypoglycemic agents.

**Statistical analyses**

Average (± standard deviation [SD]) and percent study characteristics are presented across quartiles of PAT. Quartiles included the following PAT ranges (cm³): Q1 (101–205); Q2 (206–245); Q3 (246–291); Q4 (292–565). We used χ² test for dichotomous variables and analysis of variance (ANOVA) for continuous variables to compare the four groups of PAT. Average (± SD) measures of LV structure and function were also summarized across the quartiles of PAT and were compared using ANOVA. Linear regression modeling was used to assess associations of the adiposity measures as the independent variable with LV structural and functional parameters as the dependent variables. The standardized β coefficient provides the change in measures of LV structure and function per 1 SD increase in the adiposity variable. In addition to age and sex (Model 1), adjustments (Model 2) were made for WC, BMI, and other characteristics including systolic blood pressure, heart rate, serum creatinine, fasting glucose, hypertension treatment, diabetes treatment, smoking, alcohol, and exercise. All reported p-values were based on two-sided tests of significance using the SPSS statistical software package (IBM SPSS statistic 18.0).

**Results**
The baseline demographic, clinical, and biochemical measurements stratified by PAT quartiles are shown in Table 1. The mean age of study population was 62 ± 7 years, and 1,214 (49.1%) were male. Compared with the participants in the lowest quartile, those with more PAT were older, heavier, and more likely to be men; drink alcohol and smoke; and have comorbidity diseases, including hypertension, T2D, or dyslipidemia.
| Variable                               | Q1 (n = 617) | Q2 (n = 622) | Q3 (n = 615) | Q4 (n = 617) | P value |
|----------------------------------------|--------------|--------------|--------------|--------------|---------|
| Age (years)                            | 59.9 ± 5.6   | 61.2 ± 6.2   | 61.7 ± 6.5   | 63.34 ± 7.6  | < 0.001 |
| Male, n (%)                            | 222 (36)     | 283 (46)     | 332 (54)     | 377 (61)     | < 0.001 |
| Waist circumference (cm)               | 76.2 ± 6.2   | 82.2 ± 6.1   | 85.4 ± 6.4   | 91.3 ± 7.7   | < 0.001 |
| Body mass index (kg/m^2)               | 22.2 ± 2.2   | 24.1 ± 2.2   | 25.2 ± 2.4   | 26.9 ± 2.9   | < 0.001 |
| Systolic blood pressure (mmHg)         | 112 ± 14     | 115 ± 14     | 117 ± 14     | 120 ± 13     | < 0.001 |
| Diastolic blood pressure (mmHg)        | 72 ± 8       | 74 ± 9       | 75 ± 9       | 76 ± 9       | < 0.001 |
| Heart rate (bpm)                       | 62 ± 7       | 63 ± 7       | 62 ± 9       | 62 ± 7       | 0.691   |
| Hypertension (%)                       | 20           | 33           | 41           | 53           | < 0.001 |
| Hypertension treatment (%)             | 16           | 27           | 34           | 45           | < 0.001 |
| Diabetes (%)                           | 9            | 12           | 13           | 22           | < 0.001 |
| Diabetes treatment (%)                 | 8            | 10           | 13           | 21           | < 0.001 |
| Fasting glucose (mg/dL)                | 94 ± 17      | 99 ± 26      | 100 ± 24     | 104 ± 25     | < 0.001 |
| HbA1c (%)                              | 5.7 ± 0.7    | 5.9 ± 1.0    | 5.9 ± 0.7    | 6.1 ± 1.0    | < 0.001 |
| Total cholesterol (mg/dL)              | 196 ± 36     | 191 ± 34     | 190 ± 38     | 186 ± 36     | < 0.001 |
| HDL-cholesterol (mg/dL)                | 51 ± 13      | 47 ± 12      | 45 ± 11      | 43 ± 10      | < 0.001 |
| Triglycerides (mg/dL)                  | 115 ± 64     | 128 ± 78     | 142 ± 79     | 153 ± 87     | < 0.001 |
| Creatinine (mg/dL)                     | 0.92 ± 0.16  | 0.96 ± 0.18  | 0.99 ± 0.19  | 1.02 ± 0.19  | < 0.001 |

HDL indicates high-density lipoprotein.
| Variable                        | Q1 (n = 617) | Q2 (n = 622) | Q3 (n = 615) | Q4 (n = 617) | P value |
|--------------------------------|--------------|--------------|--------------|--------------|---------|
| Current smoker (%)             | 7            | 8            | 12           | 14           | < 0.001 |
| Current alcohol drinker (%)    | 36           | 42           | 47           | 51           | < 0.001 |
| Pericardial adipose tissue (cm³) | 176 ± 22     | 226 ± 12     | 267 ± 13     | 342 ± 45     | < 0.001 |

HDL indicates high-density lipoprotein.

The mean PAT was 253 ± 66 cm³. There are consistent increases in WC and BMI with rising PAT (all P < 0.001). For those in the top PAT quartile, the mean WC is more than 15 cm higher than that of participants in the bottom quartile. The mean BMI is nearly 5 kg/m² higher.

Table 2 depicts the association of PAT with various echocardiographic parameters. The highest PAT quartile was associated with a higher LA volume index, LV mass index, mitral inflow A velocity, DT, and E/Em ratio. Conversely, the highest PAT quartile was associated with lower mitral inflow E/A ratio, systolic TDI velocity, and early diastolic TDI velocity, compared with the lowest PAT quartile. The prevalence of LV hypertrophy and LV diastolic dysfunction increased with rising PAT (Fig. 2). There was no significant difference in LV ejection fraction among quartiles of PAT. These strong associations were also observed between other adiposity measures (WC and BMI) and LV structural and functional measures in both unadjusted and multivariable (Model 1) adjusted models (Table 3). Interestingly, in a fully adjusted model (Model 2) including all of adiposity measures (WC, BMI, and PAT), BMI and PAT showed significant associations with LV structural (LV mass and LA volume) and functional variables (early diastolic TDI velocity), but not WC. The magnitude of the associations was higher with PAT than with BMI. Also, a statistical significance between systolic TDI velocity and adiposity was only observed in association with PAT.
Table 2
Measurements of left ventricular structure and function using 2D-echocardiography in the pericardial adipose tissue quartiles

| Variable                        | Q1 (n = 617) | Q2 (n = 622) | Q3 (n = 615) | Q4 (n = 617) | P value |
|---------------------------------|-------------|-------------|-------------|-------------|---------|
| LA volume (mL)                  | 26.5 ± 4.7  | 27.7 ± 5.4  | 28.6 ± 6.1  | 29.1 ± 6.2  | < 0.001 |
| LA volume index (mL/m^2)        | 26.5 ± 4.7  | 27.7 ± 5.4  | 28.6 ± 6.0  | 29.1 ± 6.2  | < 0.001 |
| Relative wall thickness (cm)    | 0.42 ± 0.07 | 0.44 ± 0.07 | 0.45 ± 0.07 | 0.46 ± 0.07 | < 0.001 |
| LV mass (g)                     | 137 ± 27    | 157 ± 30    | 169 ± 31    | 192 ± 36    | < 0.001 |
| LV mass index (g/m^2)           | 87 ± 14     | 95 ± 15     | 99 ± 15     | 107 ± 17    | < 0.001 |
| LV ejection fraction (%)        | 64 ± 5      | 64 ± 4      | 64 ± 5      | 65 ± 5      | 0.326   |
| Mitral inflow velocity          |             |             |             |             |         |
| E, cm/s                         | 0.65 ± 0.13 | 0.62 ± 0.13 | 0.61 ± 0.14 | 0.60 ± 0.14 | < 0.001 |
| A, cm/s                         | 0.65 ± 0.14 | 0.68 ± 0.14 | 0.70 ± 0.16 | 0.73 ± 0.16 | < 0.001 |
| E/A ratio                       | 1.05 ± 0.29 | 0.95 ± 0.26 | 0.90 ± 0.23 | 0.86 ± 0.24 | < 0.001 |
| DT, ms                          | 178 ± 34    | 184 ± 37    | 187 ± 40    | 189 ± 41    | < 0.001 |
| Tissue Doppler imaging (TDI)    |             |             |             |             |         |
| TDI Sm velocity (cm/sec)        | 7.43 ± 1.03 | 7.34 ± 1.06 | 7.32 ± 1.13 | 7.23 ± 1.08 | 0.015   |
| TDI Em velocity (cm/sec)        | 7.32 ± 1.48 | 6.73 ± 1.41 | 6.46 ± 1.26 | 6.04 ± 1.27 | < 0.001 |
| E/Em ratio                      | 9.1 ± 2.0   | 9.5 ± 2.4   | 9.7 ± 2.6   | 10.2 ± 2.6  | < 0.001 |

DT, deceleration time; LA, left atrium; LV, left ventricle; TDI, tissue Doppler imaging.
Table 3
Multivariable-adjusted linear regression models of association of adiposity measures with LV structure and function

| LV structure and function | LV mass | LA volume | TDI Sa | TDI Ea |
|---------------------------|---------|-----------|--------|--------|
|                           | β       | P value   | β      | P value | β      | P value |
| Waist circumference       |         |           |        |        |        |         |
| Unadjusted                | 0.568   | < 0.001   | 0.348  | < 0.001| 0.025  | 0.205   | -0.285  | < 0.001|
| Model 1                   | 0.398   | < 0.001   | 0.297  | < 0.001| -0.0373| 0.121   | -0.215  | < 0.001|
| Model 2                   | 0.042   | 0.127     | -0.047 | 0.202  | -0.012 | 0.765   | -0.047  | 0.181  |
| Body mass index           |         |           |        |        |        |         |         |         |
| Unadjusted                | 0.437   | < 0.001   | 0.340  | < 0.001| -0.018 | 0.367   | -0.261  | < 0.001|
| Model 1                   | 0.390   | < 0.001   | 0.318  | < 0.001| -0.020 | 0.319   | -0.206  | < 0.001|
| Model 2                   | 0.179   | < 0.001   | 0.225  | < 0.001| 0.051  | 0.179   | -0.085  | 0.009  |
| Pericardial adipose tissue|         |           |        |        |        |         |         |         |
| Unadjusted                | 0.577   | < 0.001   | 0.396  | < 0.001| -0.061 | 0.002   | -0.332  | < 0.001|
| Model 1                   | 0.444   | < 0.001   | 0.337  | < 0.001| -0.082 | < 0.001 | -0.226  | < 0.001|
| Model 2                   | 0.310   | < 0.001   | 0.226  | < 0.001| -0.106 | < 0.001 | -0.146  | < 0.001|

Models constructed with cardiovascular measures as dependent variables and obesity parameters as independent variables. β coefficient is per 1 SD of the obesity parameter. Model 1 is adjusted for age, sex, systolic blood pressure, heart rate, serum creatinine, fasting glucose, hypertension treatment, diabetes treatment, smoking, alcohol, and exercise. Model 2 is adjusted for Model 2 plus waist circumference, body mass index, and pericardial adipose tissue. LV, left ventricle; TDI, tissue Doppler imaging.

Discussion
In this large population-based cohort of community-dwelling adults, we found strong associations among pericardial fat, cardiometabolic risk factors, and LV structure and function. Although these relationships with LV structure and function were also observed with general adiposity measures, such as WC and BMI, the magnitude of the associations was highest with PAT than with WC or BMI. Interestingly, only pericardial fat was associated with subclinical LV systolic function, and the association persisted in a multivariate-adjusted model including WC and BMI. The present findings strongly support the importance of a local pathogenic effect of pericardial fat on the structure and function of the heart.

Because of the lack of a universal definition of a fat depot around the heart, heterogeneous and inconsistent terminology has been used in clinical research. In the present study, we used the term PAT because PAT refers to all EAT within pericardium in addition to paracardial fat surrounding pericardium [3]. Pericardial fat, among the ectopic visceral adipose tissues, is considered a potential contributor to CVD pathogenesis via local mechanical forces or paracrine effects due to its direct anatomical proximity to the myocardium without fascial interruption [14]. Indeed, there is mounting evidence that pericardial fat increases risk for atrial fibrillation (AF) [15–17], coronary artery calcification [2, 18], and vascular calcification [19], independent of general adiposity measures, such as BMI and WC [20]. Although mechanisms remain unclear, a study by Batal et al. [21] has shown that peri-atrial fat thickness at the mid-left atrium was closely associated with AF burden, independent of age, BMI, and LA size, which again highlights a potential local pathogenic effect of PAT. In contrast to AF, controversy remains regarding the regional effects of PAT on LV structure and function, particularly on LV systolic function.

In the current study, we found that the amount of PAT was strongly associated with both increased LV mass and LA volume, in line with previous findings from autopsy and experimental studies [22, 23]. Previous studies, however, have only shown significant associations in univariate analysis [24], or shown inconsistent associations depending on CVD status [25], obesity, and gender. A study by Bakkum et al. [9] demonstrated that the independent association between EAT and LV mass was limited to nonobese people, and the Jackson Heart Study [26] reported that LV mass and LA size were independent predictors of PAT only among women. As opposed to these previous studies, our study represents a large sample, and we show a consistent association between PAT with LV mass and LA volume, regardless of the BMI and gender (data not shown). In addition, the magnitude of association between PAT and LV structure was stronger than with measures of generalized adiposity. Thus, the current findings support local pathogenic role of PAT in the alterations of LV structure.

To evaluate the association between pericardial fat and LV systolic and diastolic function, we measured TDI systolic and diastolic velocities, in addition to LV ejection fraction and conventional Doppler measurements for diastolic function. Previous studies have shown a consistent association between PAT and LV diastolic variables/grades, even after adjustment for other markers of adiposity [5]. Although definitions of LV diastolic dysfunction have varied, increasing pericardial or epicardial fat depots appear to be an independent predictor of altered diastolic function, especially when TDI measurements were performed for assessing LV diastolic function, which is in line with the present findings. In contrast, the impact of PAT on LV systolic function has been controversial [5]. A series of recent studies using TDI or
2D/3D speckle tracking strain techniques for measuring LV systolic function in lieu of LV ejection fraction, although limited by small sample size, has indicated that epicardial fat is associated with subclinical deterioration of systolic myocardial function, independent of general measures of obesity, such as BMI and waist/hip ratio [7, 27]. The present study results, generated from a large sample, also strongly support the regional effects of PAT on LV systolic function, independent of general obesity measures and gender (data not shown). However, one study found that the association of EAT with impaired LV systolic function assessed by strain and TDI techniques was observed only in men [28]. There is a myriad of possible pathophysiological mechanisms potentially explaining the role of pericardial fat on LV function, including sympathetic activation, the release of hormones (cytokines and adipokines), and mechanical restriction. A recent study proposed that LV contractile dysfunction is likely to be modulated by a burden of interstitial myocardial fibrosis and increased intramyocardial TG content measured by proton magnetic resonance spectroscopy [27].

**Strengths And Limitations**

The major strengths of our study include the relatively large sample size from a population-based cohort, which reduced the potential for referral bias, and the use of a highly reproducible CT method for assessing PAT, which is the gold standard for fat quantification. Also, we assessed LV systolic and diastolic function using TDI measures, which can detect early subclinical deterioration in LV function. However, we did have limitations including use of a cross-sectional study design and evaluation of a single racial group. We also did not evaluate other fat depots such as visceral fat. Thus, our findings may not be generalizable, and we cannot conclude causality. It should be mentioned that our study results may not be directly comparable with prior studies that measured only epicardial fat between the myocardium and visceral pericardium because EAT is different from paracardial fat embryologically, and epicardial fat may serve protective functions under physiologic conditions [29]. A series of study results from the Framingham Heart Study pointed out differences between EAT and paracardial fat (also known as intrathoracic fat) and their association with metabolic risk factors and CVD prevalence [30, 31]. However, given potential opposing roles on LV structure and function between EAT and paracardial fat, our definition of PAT may have underestimated our results. Finally, because the results of the present study were obtained from relatively healthy individuals free from CVD, further studies are needed to elucidate the role of PAT in patients with coronary artery disease or congestive heart failure, as obesity may confer mortality benefits in these subgroups [6].

**Conclusions**

PAT accumulation is significantly associated with myocardial remodeling and subclinical impairment of LV systolic and diastolic function. Associations between PAT and cardiac structure and function are stronger than with other measures of general adiposity and thus represent a useful marker for obesity-associated cardiac changes.
Abbreviations

AF  
Atrial fibrillation; ANOVA:Analysis of variance; BMI:Body mass index; CT:Computed tomography; CVD:Cardiovascular disease; DT:Deceleration time; EAT:Epicardial adipose tissue; HDL:High-density lipoprotein; LA:Left atrium; LV:Left ventricle; PAT:Pericardial adipose tissue; SD:Standard deviation; TDI:Tissue Doppler imaging; TG:Triglycerides; T2D:Type 2 diabetes; WC:Waist circumference.

Declarations

Acknowledgements

Not applicable.

Authors’ contribution

JSK and SWK contributed to design and conception, acquisition of data, interpretation of data and writing of the first and final drafts of the manuscript. CS is the principal investigator of the Ansan cohort study. JSL, KYL, and SK interpreted the results and edited the manuscript. SKL and RA contributed to data management and statistical analyses. HEL, KCS, and GYC critically reviewed and edited the manuscript. All authors approved the paper for publication. SHK and CS are responsible for the integrity of the work as a whole.

Funding

This study was supported by grants (2015-P71001-00 and 2016-E71003-00) from the Korean Centers for Disease Control and Prevention.

Availability of data and materials

The data of this study are available from the corresponding authors on reasonable request and with permission of the Korean Centers for Disease Control and Prevention.

Ethics approval and consent to participate

The protocol of the study was reviewed and approved by the Human Subjects Review Committee at the Korea University Ansan Hospital, and all participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declared no potential conflicts of interest with respect to the research.
Author details

1Division of Cardiology, 2Institute of Human Genomic Study, 3Division of Radiology, Korea University Ansan Hospital, 123, Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do 15355, Korea. 4Division of Cardiology, Hallym University Sacred Heart Hospital, Anyang, Korea. 5Division of Cardiology, Kangbuk Samsung Medical Center, Seoul, Korea. 6Division of Cardiology, Seoul National University Bundang Hospital, Seongnam, Korea. 7Division of Cardiology, Gachon University Gil Medical Center, Incheon, Korea. 8Division of Endocrinology, Gerontology and Metabolism, Stanford Diabetes Research Center, Stanford University School of Medicine, Stanford, CA, USA.

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