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Visit-to-visit glucose variability is associated with echocardiographic variables in people with type 2 diabetes: epidemiological and mendelian randomization approaches

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Abstract

Background This study aimed to examine the associations between visit-to-visit variability in fasting plasma glucose (FPG) and HbA1c with echocardiographic variables in patients with type 2 diabetes using epidemiologic and Mendelian randomization (MR) methods.

Methods From January 2001 to December 2020, 2,326 (1,233 men and 1,093 women) subjects with type 2 diabetes who underwent echocardiography assessment were enrolled in the diabetes care management program of a medical center in Taiwan. The echocardiographic variables included those for cardiac structural, cardiac systolic, and diastolic function. Variability in FPG and HbA1c within one-year prior echocardiographic measurements was calculated using coefficient of variation (CV). A two-stage multivariable regression analysis was used to assess the causal relationship among FPG-CV, HbA1c-CV, and echocardiographic variables using 22 SNPs for FPG and 14 SNPs for HbA1c as instrumental variables.

Results A total of 2,326 participants were included, with a mean age of 64.5 years and 53.0% were men. Epidemiologic and MR analyses show the significant associations between left atrium diameter (LAD), left ventricular systolic diameter (LVSd), left ventricular mass (LVM), left ventricular ejection fraction (LVEF), E, and E/e' ratio with FPG variability. Significant associations between HbA1c variability and echocardiographic variables including LAD, E/e', and deceleration time identified in the epidemiologic approach became non-significant in the MR analysis when controlling for covariates.

Conclusions Our epidemiologic and MR studies demonstrated that visit-to-visit variability of FPG in patients with type 2 diabetes was independently associated with the left cardiac structure as well as systolic and diastolic function.

Keywords Type 2 diabetes, Echocardiography, Mendelian randomization, Glucose variability

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Background

The global pandemic of type 2 diabetes is driven by urbanization, aging populations, and rising obesity due to energy-rich diets and sedentary lifestyles, and it affects advanced and developing countries. The prevalence of type 2 diabetes surged from 151 million in 2000 to 537 million in 2021, which exceeded the projected 300 million for 2021 [1, 2]. This disease leads to serious complications, including macrovascular issues, such as stroke, coronary heart disease, and peripheral arterial disease, as well as microvascular conditions. These complications place a significant burden on healthcare systems [3]. Cardiovascular diseases, including coronary heart disease and stroke, were the leading cause of death globally, accounting for more than 30% of deaths in 2016 [4]. A meta-analysis of 102 studies found that adults with diabetes have two to four times the risk of coronary heart disease and ischemic stroke, and 1.5 to 3.6 times the risk of mortality compared with those without diabetes; the risk increases with poor glycemic control [5].

Glycemic control is crucial for managing diabetic complications, with glycosylated hemoglobin (HbA1c) often considered the "gold standard" marker. However, randomized control trials have shown that reducing blood glucose levels does not necessarily decrease the incidence of diabetic complications [6, 7]. These studies do not account for glucose variability, which refers to extreme fluctuations in glucose levels over time and could be linked to complications. Recent research has focused on "glucose variability" and its relationship to diabetes complications and mortality [8, 9]. Experimental evidence has not been established with regard to the detrimental effects of glucose variability. Therefore, further investigation is needed to establish a causal relationship between glucose variability and adverse outcomes through experimental methods. In the absence of randomized trials specifically addressing glucose variability and outcomes, Mendelian randomization (MR) offers an alternative approach to provide experimental evidence and assess causality.

Echocardiography is a rapid, non-invasive imaging technique used to assess cardiac function and detect ventricular wall motion abnormalities. It measures structural variables such as left ventricular diastolic diameter (LVDd) and left atrium diameter (LAD) as well as functional variables including left ventricular ejection fraction (LVEF) and E/A ratio. These echocardiographic variables are valuable for cardiac risk stratification and optimizing clinical outcomes [10]. High-risk echocardiographic features are linked to increased mortality risk [11]. Systolic and diastolic function markers from echocardiography are used to predict subclinical myocardial dysfunction and its progression to clinical heart failure [10].

A review of the literature revealed limited studies that used traditional epidemiologic designs to explore the associations between glucose variation and echocardiographic variables [12, 13]. One study was conducted in the general population [12], while another involved a small sample of individuals with type 2 diabetes [13]. Given the limited number of studies and small sample sizes, we investigated the associations between glucose variation and echocardiographic variables using observational epidemiologic and MR approaches.

Methods

Study design and study subjects

This cross-sectional study included participants enrolled between November 2001 and December 2020 in the Diabetes Care Managed Program (DCMP). Established in 2001, DCMP is a case management program designed to improve the quality of diabetes care and reduce the risk of complications through intensive monitoring, continuous care, and encouraging members to implement healthy lifestyle choices. The inclusion criteria were a diagnosis of diabetes (ICD-9-CM code 250 before 2016 or ICD-10-CM code E0800 after 2016) and age 30 years or older. Additionally, participants had to have undergone an echocardiographic examination. Initially, 6,960 individuals were enrolled in the DCMP at a medical center in Taiwan. The exclusion criteria included a diagnosis of type 1 diabetes (ICD-9-CM codes 250.x1/x3; ICD-10-CM code E10.9), gestational diabetes (ICD-9-CM code 648.83; ICD-10-CM code O24.419), and age under 30 years ($n = 44$). After applying these exclusions, 3,611 participants were retained in the dataset. Further exclusion for missing data on laboratory tests, anthropometric measurements, and comorbidities reduced the sample to 2,326 participants (Supplementary Fig. 1). The index date was defined as the date of the first echocardiographic assessment. If individuals had multiple echocardiographic examinations, then only the first was used. Measurements for other variables were taken from the closest date to the index date.

Data source

Data were obtained from the computerized database of the DCMP of China Medical University Hospital (CMUH) in Taichung, Taiwan. DCMP comprises patients with type 2 diabetes diagnosed based on the American Diabetes Association guideline. In DCMP, health care providers should participate in clinical education and training programs. The health care team consists of physicians of various specialties, including endocrinology, family medicine, internal medicine, cardiology, nephrology, and others. The continuing education and training programs in DCMP promote the standardization of clinical practices, such as assessment, monitoring glucose

control, and diagnosis of diabetic complications. Coordinated care is provided by physician-led multidisciplinary teams, including physicians and their care managers who worked in adherence to the established clinical guidelines for diabetes care. The DCMP database provides information on diabetes care, including annual self-care education and assessments, annual eye tests, and quarterly screening tests for blood sugar, cholesterol, and kidney function.

Measurements

Before joining the DCMP, participants underwent a series of tests, including blood and urine analyses. They were also interviewed by a case manager using a standardized computerized questionnaire to collect data on their dietary habits, lifestyle, and medical history, including previous or current disease status. These tests and interviews were conducted annually or quarterly. Sociodemographic factors included age at entry to DCMP, sex, and family history of diabetes, hypertension, hyperlipidemia, and obesity. Lifestyle behaviors assessed in this study included smoking status, alcohol consumption, and exercise habits. These variables were dichotomized (yes vs. no) based on participants' self-reported information. Individuals were classified as nonsmokers if they reported never having smoked or had not smoked continuously for at least six months. Alcohol consumption was defined as affirmative if participants reported drinking at least 150 cc of alcohol per week on a continuous basis for six months. Physical activity was categorized as "yes" if participants reported engaging in exercise at least three times per week, with each session lasting more than 30 min; otherwise, it was classified as "no."

Anthropometric measurements included height, weight, body mass index (BMI), and blood pressure (BP). Weight and height were recorded using an auto-anthropometer (Super-view HW-666). An auto-anthropometer is a device designed to automatically measure various anthropometric parameters, such as height, weight, and systolic and diastolic blood pressure, with minimal manual intervention. Its key features include automated operation to reduce human error and operator bias, the ability to measure multiple body dimensions in a single session, and applicability in both research and clinical settings. The participants removed their shoes and wore light clothing. BMI was calculated using the formula: weight (kg) / (height (m)) ^{2}. BP was measured in the right arm with an electronic sphygmomanometer (OMRON HEM-770 A, Japan) using an appropriately sized cuff, while the participant was seated in a quiet environment. The device's accuracy was validated against the European Society of Hypertension International Protocol Revision 2010 [14]. If multiple BP readings were taken in a single day, the average value was used.

Baseline comorbidities included obesity, hypertension, and hyperlipidemia. Diabetic complications at baseline were classified into acute and chronic categories. Acute complications encompassed severe hypoglycemia, hyperglycemic hyperosmolar nonketotic coma, and diabetic ketoacidosis. Chronic complications included neuropathy, peripheral vascular disease, nephropathy, stroke, diabetic foot, amputation, and diabetic retinopathy. All comorbidities and complications were categorized into two groups: yes or no.

Diabetes-related variables included duration of the disease. Anti-diabetes treatments were categorized into oral medications and insulin injections. Oral medications were further divided into seven categories: meglitinides, sulfonylureas, α-glucosidase inhibitors, biguanides, dipeptidyl peptidase 4 inhibitors, insulin sensitizers, and other compounds. Medication-related variables also included treatments for hypertension (e.g., calcium channel blockers), hyperlipidemia (e.g., statins [HMG-CoA reductase inhibitors]), and nephropathy. Participants were classified into two groups based on their use of other medications, as recorded in their electronic medical records (yes vs. no).

Blood samples were drawn from the antecubital vein in the morning following a 12-hour overnight fast and analyzed within 4 h of collection. Laboratory tests included HbA1c, fasting plasma glucose (FPG), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), serum creatinine, uric acid (UA), and protein levels from urinalysis. These biochemical markers were analyzed using a biochemical auto-analyzer (Beckman Coulter Synchron system, Lx-20, Fullerton, CA, USA) in the Clinical Laboratory Department of CMUH. The urine albumin-to-creatinine ratio (uACR) from the morning urine sample was used to determine albumin excretion rate. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Glucose variability measures were calculated based on data collected during the year preceding the index date, defined as the date of the first echocardiographic assessment. For each patient, the coefficients of variation (CV) for FPG (FPG-CV) and HbA1c (HbA1c-CV) were derived using outpatient measurements obtained within the first year from the index date. These measures were calculated only for individuals with more than two FPG and HbA_{1c} measurements during that period. To account for variability in the number of visits across individuals, the CV value were adjusted by dividing by the square root of the ratio of total visits to total visits minus 1 [15].

Instrumental variables

SNPs genotyping in MR analysis

In MR analysis, single nucleotide polymorphism (SNP) data served as instrumental variables and were obtained from iHi Genomics, CMUH [16]. These data originated from DNA samples genotyped with TPM array and processed on Axiom genome-wide array plate system (Affymetrix, Santa Clara, CA, USA). PLINK (v2.0) was employed to evaluate Hardy–Weinberg equilibrium for all selected SNPs. IMPUTE2 was utilized for data imputation using 1000 Genomes Project as a reference. The selection of genetic variants was based on existing literature employing candidate genes and genome-wide association study (GWAS) approaches for HbA1c [17–19] and FPG [20, 21]. A comprehensive list of selected genetic variants for FPG and HbA1c was compiled. Our literature review found hundreds of loci associated with HbA1c through glycemic pathways, including CDKAL, MTAP, DGKB, SLC30A8, GCK, and KL, as well as loci associated with nonglycemic pathways such as TRAM2-AS1, SPATS2L, SPATS2L, KCNKS, RPA2P2, and ARAP3 [17–19]. Additionally, dozens of loci were found to be associated with FPG, including ANK1, HFE, HK1, MYB, and PHB2 [20, 21]. We further explored SNPs in MR literature [22–29], particularly those linked to possible biological mechanisms of glucose variation. A total of 536 SNPs found in the GWAS data of iHi Genomics were pooled, with SNPs not found in iHi genomics dataset or with minor allele frequencies < 5% were excluded. After removing SNPs that did not meet MR assumptions 1 and 3 (SNP = 498) and those in high-linkage disequilibrium (SNP = 5), we included 33 SNPs in the analysis (22 for HbA1c-CV and 14 for FPG-CV, with 3 SNPs overlapping between the two traits). This study was approved by the Human Research Committee of China Medical University Hospital (CMUH112-REC1-007) and conducted in accordance with relevant regulations and guidelines.

Outcome measures: echocardiographic examinations

Echocardiographic examinations were conducted by an experienced cardiologist using a transthoracic echocardiography machine (Vivid 7, GE Medical Systems, Horten, Norway) with a 3.5-MHz transducer, following a standardized protocol. Parameters were assessed according to the American Society of Echocardiography (ASE) guidelines [30, 31]. Patients were positioned in the left lateral decubitus position and were instructed to breathe quietly. In brief, 2D-guided M-mode images were captured from a standardized view. For measuring left ventricular inflow waveforms, the Doppler sample volume was positioned at the tip of the mitral leaflets from the apical four-chamber view. Sample volumes were aligned with the ultrasonic beam to the direction of flow. Tissue Doppler imaging was performed by placing the sample volume at the lateral corner of the mitral annulus from the apical four-chamber view. Wall filter settings were adjusted to exclude high-frequency signals, and the gain was minimized to the lowest possible level.

Cardiac structural parameters assessed included LAD, LVDd, left ventricular mass (LVM), and left ventricular systolic diameter (LVSd). Cardiac systolic function was evaluated using the LVEF, which was measured visually using Quinones method. Indicators of cardiac diastolic function included peak spectral transmittal flow velocities such as atrial diastolic velocity (A), mitral early diastolic velocity (E), E/A ratio, and deceleration time of the E wave.

Statistical analysis

Descriptive statistics, including mean and standard deviation, were used to summarize continuous variables, while frequency and proportion were reported for categorical variables. For bivariate analysis, a two-sample t-test was conducted for continuous variables, and Chi-square tests were used for categorical variables.

To develop multiple linear regression models, we followed these steps. First, univariate models were created for key independent variables (glucose variation in FPG and HbA1c) and all covariates, selecting variables with p-values < 0.25 for the next step [21]. Second, glucose variation in FPG and HbA1c were individually added to multivariate models along with the candidate covariates identified in the first step to determine their statistical significance (p-value < 0.05). Multiple linear regression models were then used to estimate regression coefficients. All analyses were conducted using SAS version 9.4 (SAS, Cary, NC). P-values were two-tailed, with significance set at $p < 0.05$.

MR analysis

First, quality control (QC) procedures were performed. This included excluding individuals with a high missing genotyping rate, those with extreme heterozygosity rate, and duplicated or related individuals. Additionally, SNPs with a high missing genotyping rate, low frequency, or deviation from Hardy-Weinberg equilibrium were removed. Hardy-Weinberg equilibrium was assessed in control participants using Chi-square test.

The assumptions of MR analysis were evaluated through the following steps. First, we analyzed the relationships between glucose variability and glucose-related SNPs, assessing SNP-level MR assumption 1 using ANOVA. For SNP-level MR assumption 3, we examined the relationships between echocardiographic variables and glucose-related genotypes using Chi-square tests to determine whether the selected SNPs could serve as instrumental variables for MR analysis. Only SNPs that satisfied MR assumptions 1 and 3 were retained for

deriving weighted and unweighted genetic risk score (GRS). Assumption 1 indicates that genetic variants are associated with glucose variability while assumption 3 indicates that there is no association between genetic variants and echocardiographic variables. The associations of selected SNPs with glucose variability were quantified by linear regression. Each SNP was coded as 0, 1, or 2 according to the number of minor alleles, following an additive model.

Before estimating GRS, we analyzed the linkage disequilibrium (LD) between SNPs that satisfied MR assumptions 1 and 3. Pairwise LD among the selected SNPs was estimated by correlation coefficient r^2 in Haploview (v4.2). If two SNPs have $r^2 > 0.8$, then we selected one of them based on which SNP was the most common associated with glucose-related genes in literature. Only SNPs with a low LD were retained for deriving GRS. We constructed the weighted GRS by multiplying the estimated coefficients of the regression model of each genotype by the number of minor alleles for each retained SNP, and then summing the products across all retained SNPs. Weighted GRSs were further categorized into quartiles for data analyses to assess the assumption of linearity for linear regression. We also assessed the linear trend for weighted GRSs by treating them as continuous variables.

Linear regression models were employed to explore the associations between GRSs and glucose variability variables to verify the GRS-level MR assumption (1) Next, we assessed MR assumption (2) Multinomial logistic regression models were used to determine whether the selected covariates could serve as confounders for MR analysis by exploring the associations between the GRSs and the covariates. As for the GRS-level MR assumption 3, linear regression models were applied to investigate the associations between the GRSs and echocardiographic variables.

For MR analyses, the causal association of glucose variability on echocardiographic variables were quantified using instrumental variable analyses with two-stage regression and multivariate adjustment. The first stage involved linear regression, with glucose variability as the dependent variables and weighted GRSs as the independent variables, to determine whether GRSs could predict glucose variation. The predicted glucose variability derived from the linear regression was referred to as the genetic predicted-glucose variability. The second stage consisted of using the predicted glucose variability estimated from the first stage as the independent variable, while the echocardiographic variables were treated as the dependent variable in linear regression analyses. The analyses were conducted with adjustments for covariates. The covariates in this stage included residuals estimated from the first stage, covariates of demographic factors, and lifestyle behavior that did not satisfy MR assumption 2 and the top 10 principal components from principal component analysis (PCA) of all SNPs in the GWAS data. In addition, all SNPs that met the MR assumptions were assessed for potential horizontal pleiotropy using MR-Egger regression. All reported p-values were two-sided, and the level of significance was set at 0.05.

Results

Baseline characteristics of study subjects

Among the 2,326 individuals with type 2 diabetes included in this study, 1,233 (53.0%) were men. Table 1 indicates that men were significantly younger ($P < 0.001$) and had a higher prevalence of smoking, alcohol consumption, and physical activity ($P < 0.001$, $P < 0.001$, and $P = 0.03$, respectively). Men also had a higher prevalence of no medication use, oral anti-diabetic drug use, or insulin injection alone, but a lower prevalence of combined oral anti-diabetic drug and insulin injection use ($P = 0.03$). Additionally, men were more commonly diagnosed with coronary artery disease ($P < 0.001$), neuropathy ($P = 0.02$), and nephropathy ($P = 0.01$) and were more likely to be on cardiovascular medication ($P < 0.001$).

The association between glucose variability and echocardiographic variables using epidemiologic approach

Table 2 shows the association between glucose variability and echocardiographic variables. In the age- and sex-adjusted models, all echocardiographic variables were significantly associated with variability in FPG, except for LADd, s', and E/A ratio. After adjusting for lifestyle behavior and baseline blood glucose, the significant associations remained the same, with the exception that LVDd became significant. Further adjustment for comorbidities and medication did not change the significant associations, with the exception that LVDd and e' became insignificant. Among these significant associations, LVEF (β=-0.74, $p < 0.001$) and deceleration time (β=-4.41, $p < 0.01$) showed a negative association, that is, high values of LVEF and deceleration time were associated with low glucose variability. By contrast, the other parameters exhibited positive associations (β = 0.42 for LAD, $p < 0.01$; β = 0.39 for LVSd, $p < 0.01$; β = 4.02 for LVM, $p < 0.001$; β = 0.02 for E, $p < 0.001$; and β = 0.39 for E/e', $p < 0.001$). The values of R-squared in the final models ranged from 0.06 (LVEF and E) to 0.22 (e').

In the age- and sex-adjusted models, all echocardiographic variables were significantly associated with variability in HbA1c, except for LAD, LVDd, LVM, E, s', and E/A ratio. After adjusting for lifestyle behavior and baseline blood glucose, the significant associations for E/e' and deceleration time remained the same, while LAD became significant and LVSd, LVEF, and e' became insignificant. Further adjustment for comorbidities and

Table 1 Comparisons of sociodemographic factors, lifestyle behaviors, diabetes-related variables, glucose variation and comorbidities according to sex

	Total	Sex, *N* (%)		
Variables	**(*n* = 2,326)**	**Men (*n* = 1,233)**	**Women (*n* = 1,093)**	***P* value**
Sociodemographic factors				
Age, years†	64.54 ± 11.21	62.9 ± 11.13	66.4 ± 11.02	< 0.001
Lifestyle behaviors				
Smoking				< 0.001
No	2003 (86.11)	932 (75.59)	1071 (97.99)	
Yes	323 (13.89)	301 (24.41)	22 (2.01)	
Alcohol drinking				< 0.001
No	2176 (93.55)	1088 (88.24)	1088 (99.54)	
Yes	150 (6.45)	145 (11.76)	5 (0.46)	
Physical activity				0.03
No	1226 (52.71)	624 (50.61)	602 (55.08)	
Yes	1100 (47.29)	609 (49.39)	491 (44.92)	
BMI, kg/m^2†	26.53 ± 4.35	26.54 ± 4.06	26.52 ± 4.65	0.89
Diabetes-related variables				
Duration of diabetes, years†	6.85 ± 7.42	6.58 ± 7.29	7.16 ± 7.56	0.06
Type of hypoglycemic drug use				0.03
No	75 (3.22)	41 (3.33)	34 (3.11)	
OAD	1870 (80.4)	1005 (81.51)	865 (79.14)	
Inject insulin	40 (1.72)	27 (2.19)	13 (1.19)	
Both	341 (14.66)	160 (12.98)	181 (16.56)	
Comorbidity				
Hypertension	978 (42.05)	507 (41.12)	471 (43.09)	0.36
Hyperlipidemia	624 (26.83)	320 (25.95)	304 (27.81)	0.34
Obesity	583 (25.06)	297 (24.09)	286 (26.17)	0.27
Coronary artery disease	153 (6.58)	110 (8.92)	43 (3.93)	< 0.001
Stroke	95 (4.08)	52 (4.22)	43 (3.93)	0.81
Peripheral neuropathy	175 (7.52)	90 (7.3)	85 (7.78)	0.72
Neuropathy	29 (1.25)	22 (1.78)	7 (0.64)	0.02
Nephropathy	140 (6.02)	89 (7.22)	51 (4.67)	0.01
Drug-related variables				
Hypertension medications	875 (37.62)	474 (38.44)	401 (36.69)	0.41
Hyperlipidemia medications	442 (19.00)	222 (18.00)	220 (20.13)	0.21
Cardiovascular medications	666 (28.63)	401 (32.52)	265 (24.25)	< 0.001
Biomarker†				
FPG (mg/dl)	140.01 ± 49.58	141.25 ± 51.82	138.62 ± 46.9	0.20
HbA1c (%)	7.61 ± 1.36	7.60 ± 1.34	7.62 ± 1.39	0.70

Differences in continue variables were tested using the Student's t test. Differences in categorical variables were tested using the chi-square test

FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c

†: data are presented as mean ± standard deviation (SD)

medication did not change the significant associations. Among these significant associations, deceleration time (β=-3.04, $p < 0.05$) showed a negative association, indicating that high values of deceleration time were associated with low glucose variability. By contrast, the other parameters exhibited positive associations (β = 0.32 for LAD, $p < 0.05$; and β = 0.21 for E/e', $p < 0.001$). The values of R-squared in the final models ranged from 0.05 (LVEF and E) to 0.22 (e').

Assessment of MR assumptions 1 and 3 in SNP level

The assessment of whether glucose-related SNPs satisfy SNP-level MR assumptions 1 and 3 was conducted using an additive model. Supplementary Table 1 displays the regression coefficients of significant SNPs that met MR assumptions 1 and 3 for glucose variation measures and echocardiographic variables (all $p < 0.05$ for glucose variables, and all $p > 0.05$ for echocardiographic variables). Considering that SNPs satisfied MR assumptions 1 and 3, the LD of these SNPs were examined (Supplementary Fig. 2). The number of SNPs of echocardiographic

Table 2 Association of echocardiographic variables for various glucose variation measures in patients with type 2 diabetes using observational epidemiologic approach ($n = 2326$)

	FPG-CV per 1 SD						HbA1c-CV per 1 SD					
	Model 1		Mode 2		Model 3		Model 1		Mode 2		Model 3	
Echocardiographic variables	**β (SE)**	**R^2**	**β (SE)**	**R^2**	**β (SE)**	**R^2**	**β (SE)**	**R^2**	**β (SE)**	**R^2**	**β (SE)**	**R^2**
Cardiac structural parameters												
LAD (mm)	0.36 (0.12)**	0.02	0.52 (0.13)***	0.13	0.42 (0.13)**	0.14	0.16 (0.12)	0.01	0.35 (0.13)**	0.12	0.32 (0.13)*	0.14
LVDd (mm)	0.11 (0.12)	0.07	0.26 (0.13)*	0.10	0.18 (0.13)	0.12	-0.01 (0.12)	0.07	0.12 (0.13)	0.10	0.10 (0.13)	0.12
LVSd (mm)	0.44 (0.11)***	0.06	0.45 (0.13)***	0.08	0.39 (0.13)**	0.09	0.23 (0.11)*	0.06	0.21 (0.13)	0.07	0.20 (0.13)	0.09
LVM (g)	3.52 (0.81)***	0.09	4.69 (0.87)***	0.16	4.02 (0.87)***	0.19	0.54 (0.82)	0.09	1.33 (0.88)	0.15	1.17 (0.87)	0.19
Cardiac systolic function												
LVEF (%)	-0.98 (0.17)***	0.03	-0.79 (0.18)***	0.04	-0.74 (0.19)***	0.06	-0.61 (0.17)***	0.02	-0.34 (0.19)	0.04	-0.36 (0.19)	0.05
Cardiac diastolic function												
E	0.02 (0.004)***	0.03	0.02 (0.004)***	0.05	0.02 (0.004)***	0.06	0.00 (0.004)	0.02	0.01 (0.004)	0.04	0.01 (0.004)	0.05
e′	-0.16 (0.04)***	0.18	-0.08 (0.04)*	0.20	-0.06 (0.04)	0.22	-0.12 (0.04)***	0.17	-0.05 (0.04)	0.20	-0.05 (0.04)	0.22
s′	-0.05 (0.03)	0.11	0.01 (0.04)	0.12	0.02 (0.04)	0.13	-0.01 (0.03)	0.10	0.03 (0.04)	0.12	0.03 (0.04)	0.13
E/A ratio	0.00 (0.01)	0.08	0.00 (0.01)	0.09	0.00 (0.01)	0.10	0.00 (0.01)	0.08	0.01 (0.01)	0.09	0.01 (0.01)	0.10
E/e′ ratio	0.63 (0.09)***	0.14	0.48 (0.09)***	0.18	0.39 (0.09)***	0.20	0.33 (0.09)***	0.13	0.23 (0.09)*	0.17	0.21 (0.09)*	0.20
Deceleration time (msec)	-4.33 (1.20)***	0.05	-4.16 (1.34)**	0.06	-4.41 (1.36)**	0.07	-3.19 (1.21)**	0.05	-2.93 (1.35)*	0.06	-3.04 (1.36)*	0.06

Multivariate model 1 adjusted for age and sex

Multivariate model 2 adjusted for life style behaviors, diabetes-related variables, HbA1c and FPG in addition to age and sex in multivariate model 1

Multivariate model 3 adjusted for baseline status of complications and medicines use in addition to the variables in the multivariate model 2

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$

Table 3 Association of echocardiographic variables for predictive FPG-CV and HbA1c-CV derived from unweighted and weighted GRS using MR approach

	wGRS $_{FPG-CV}$ per 1 SD			wGRS $_{HbA1c-CV}$ per 1 SD		
Echocardiographic variables	**Model 1**	**Mode 2**	**Model 3**	**Model 1**	**Mode 2**	**Model 3**
	β (SE)	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**
Cardiac structural parameters						
LAD (mm)	0.33 (0.12)**	0.34 (0.12)**	0.38 (0.12)**	0.14 (0.12)	0.14 (0.12)	0.20 (0.13)
LVDd (mm)	0.17 (0.12)	0.17 (0.12)	0.25 (0.12)*	0.21 (0.12)	0.20 (0.12)	0.20 (0.13)
LVSd (mm)	0.29 (0.12)*	0.28 (0.12)*	0.30 (0.12)*	0.32 (0.12)**	0.31 (0.12)**	0.24 (0.13)
LVM (g)	2.05 (0.84)*	2.07 (0.84)*	2.49 (0.86)**	1.34 (0.84)	1.35 (0.84)	0.81 (0.90)
Cardiac systolic function						
LVEF (%)	-0.50 (0.17)**	-0.49 (0.17)**	-0.41 (0.18)*	-0.48 (0.17)**	-0.47 (0.17)**	-0.32 (0.18)
Cardiac diastolic function						
E	0.01 (0.004)**	0.01 (0.004)**	0.01 (0.004)**	0.00 (0.004)	0.00 (0.004)	0.00 (0.004)
e'	-0.15 (0.04)***	-0.15 (0.04)***	-0.10 (0.04)*	0.15 (0.04)***	0.15 (0.04)***	0.03 (0.04)
s'	-0.05 (0.03)	-0.05 (0.03)	0.00 (0.04)	0.12 (0.03)***	0.12 (0.03)***	0.06 (0.03)
E/A ratio	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	-0.01 (0.01)
E/e' ratio	0.55 (0.09)***	0.56 (0.09)***	0.42 (0.09)***	-0.20 (0.09)*	-0.19 (0.09)*	-0.03 (0.09)
Deceleration time (msec)	0.05 (1.23)	0.07 (1.23)	0.10 (1.30)	-3.99 (1.23)**	-4.01 (1.23)**	-1.03 (1.31)

Model 1 adjusted for residuals

Model 2 adjusting for residuals and PCA

Model 3 adjusting for residuals, PCA and confounding variables

*: $P<0.05$; **: $P<0.01$; ***: $P<0.001$; OR: odds ratio; CI: Confidence interval

variables retained included 22 SNPs for FPG-CV and 14 for HbA1c-CV. The weighted genetic risk scores were derived using these glucose variation-associated SNPs.

Assessment of MR assumptions 1, 2 and 3 in genetic risk score level

We then examined the genetic risk score-level MR assumption 1, that is, the associations between weighted genetic risk scores and glucose variability measures (Supplementary Table 2). The results revealed that weighted genetic risk scores were significantly positively associated with glucose variability measures with and without adjustment, that is, satisfying assumption (1) As the weighted genetic risk scores increase, the scores of glucose variability measures increase. We then examined the MR genetic risk score-level MR assumption 3 (Supplementary Table 3). Supplementary Table 4 lists the covariates that did not meet MR assumption (2) To test the horizontal pleiotropy, MR-Egger regression was performed. The absolute values of the intercepts for echocardiographic variables range from 0.0004 to 0.83 (Supplementary Table 5). All intercepts were not significantly different from zero (all $p>0.05$), suggesting no apparent horizontal pleiotropy. The exception was LVM, for which the MR-Egger intercept suggested potential pleiotropy.

The association between glucose variability and echocardiographic variables using MR approach

Table 3 presents the regression coefficients of echocardiographic variables for genetic-related glucose variability that were derived from the weighted GRS with adjustment. After adjusting for residuals, LAD, LVSd, LVM, E, and E/e' ratio were positively associated with weighted genetic-related FPG-CV while LVEF and e' were negatively associated. After additionally adjusting for PCA, these significant associations remained the same. After further adjustment for covariates that did not satisfy MR assumption 2, the significant associations persisted, except that LVDd became significant. Among these significant associations, LVEF (β=-0.41, $p<0.05$) and e' (β=-0.1, $p<0.05$) showed negative associations, indicating that high values of LVEF and e' were linked to low glucose variability. By contrast, the other parameters exhibited positive associations (β = 0.38 for LAD, $p<0.01$; β = 0.25 for LVDd, $p<0.05$; β = 0.30 for LVSd, $p<0.05$; β = 2.49 for LVM, $p<0.01$; β = 0.01 for E; and β = 0.42 for E/e' ratio).

After adjusting for residuals, LVSd, e', and s' were positively associated with weighted genetic-related HbA1c-CV, while LVEF, E/e', and deceleration time were negatively associated. After additionally adjusting for PCA, these significant associations remained unchanged. However, upon further adjustment for covariates that did not satisfy MR assumption 2, all significant associations became non-significant.

Discussion

This study comprehensively examined the independent associations between glucose variability with various echocardiographic variables using epidemiologic and MR approaches. All tested echocardiographic variables

were significantly associated with glucose variability in FPG, except for LVDd, e', s', and E/A. Only LAD, E/e', and deceleration time were associated with HbA1c variability using epidemiologic approach. Additionally, the regression coefficients indicated that FPG variability had a greater association on echocardiographic variables compared with HbA1c variability. The MR analysis confirmed the significant associations between LAD, LVSd, LVEF, E, and E/e' ratio with FPG variability. The significant associations between HbA1c variability and echocardiographic variables, including LAD, E/e', and deceleration time identified in epidemiologic approach became non-significant in the MR analysis when controlling for covariates.

Our study findings, based on an epidemiological approach, highlight the importance of stabilizing glucose levels, not merely focusing on cutoff point targets. The findings that most echocardiographic variables (with a few exceptions) are associated with FPG variability suggests that FPG variability may have a broader implication for cardiac structure and function than HbA1c variability. In contrast, HbA1c variability is linked specifically to diastolic function and left atrial size. LAD, E/e', and DT are markers of diastolic dysfunction or increased filling pressure—often early signs of diabetic cardiomyopathy or heart failure with preserved ejection fraction. However, these associations were not confirmed by MR analysis. Instead, the MR study provides genetic evidence supporting a potential causal role of FPG variability in adverse changes in cardiac structure (e.g., LV hypertrophy, atrial enlargement) and function (both systolic and diastolic). These findings highlight that even in the absence of sustained hyperglycemia, unstable fasting glucose levels may independently contribute to the early heart disease processes in individuals with diabetes.

Diabetes is associated with an increased risk of heart failure, with LVDd being one of early cardiac changes in people with diabetic cardiomyopathy [32, 33]. Insulin resistance and metabolic syndrome are potential underlying mechanisms that lead to diabetic cardiomyopathy [33]. Substantial evidence indicates that echocardiographic variables can help stratify the risk of mortality in patients with type 2 diabetes [34, 35]. Therefore, identifying risk factors associated with these echocardiographic variables is clinically important.

Few studies have explored the association between visit-to-visit variability in blood glucose with echocardiographic variables [12, 13]. One study assessed the risk of LVDd using a composite measure of echocardiographic variables, including LEVF, E/e' ratio, LVMI, and LAVI. This study found an association between visit-to-visit variability of FPG and LVDd but not with visit-to-visit variability of HbA1c in adults aged 20 years and over who underwent two or more serial screening echocardiograms during annual or biennial health evaluations from January 2006 to July 2016 [12]. Although the interval for measuring FPG was longer in that study (annual vs. our 4-month period), our findings are consistent with this prior study because the components of LVDd were significantly associated with FPG variability but not with HbA1c variability.

Another study by Tang X et al. explored the association between visit-to-visit FPG variability and changes in the left cardiac structure and function in 455 patients with type 2 diabetes over a follow-up period of 4.7 years using an epidemiologic approach [13]. Their findings showed that annual changes in LVMI and LVEF are associated with FPG variability. These results found in the study of Tang X et al. are consistent with our findings, which demonstrate that one-year FPG variability was linked to subsequent measures of left cardiac structure (including LAD, LVDd, and LVSd) and function (LVEF). Additionally, our study is the first to investigate the causal relationship between genetically predicted glycemic variability traits and echocardiographic variables using MR approach and a robust set of >500 SNPs as instrumental variables for glycemic trait and data from a large cohort of individuals with type 2 diabetes.

Glucose variability is an important indicator of glycemic status in addition to blood glucose control. However, the preferred method for measuring glucose variability has not reached consensus. This study adopted a relative long-term visit-to-visit variation, rather than focusing on hypoglycemic or hyperglycemic episodes, or within-day glucose variability. The significance of daily blood glucose variability differs from that observed during outpatient visits. Daily variability is influenced by the short-term effects of daily diet and medication, while outpatient variability relates to the long-term maintenance of medication and lifestyle choices. The advantage of the latter approach is that, under managed care, routine outpatient visits facilitate consistent measurement of blood glucose levels. Wide variation in outpatient variability may indicate suboptimal medication management and a complicated clinical course. Visit-to-visit variation is consistently associated with diabetes-related complications and mortality in patients with type 2 diabetes [34, 36]. In the present study, the CV of FPG and HbA1c was used as a statistical measure to indicate relative variability compared with the mean; hence, it can be used to determine the degree of variation between FPG and HbA1c. In addition, the CV and standard deviation are the most commonly used measures in the literature.

Possible biological mechanisms involved in the pathophysiological processes linking glucose variability to cardiovascular consequences include inflammatory cytokines [37], oxidative stress [38], and epigenetic changes [39]. Inflammatory cytokines [37] and platelet activation [37, 38] are implicated in the effects of hypoglycemia.

These adverse molecular and systemic changes lead to endothelial damage and dysfunction [40], which subsequently contribute to cardiovascular issues, as measured by cardiac function via echocardiography [41].

We found the inconsistency between the observational and MR findings regarding the association between HbA1c variability and the outcome. While the observational analysis suggested a significant association, the MR estimates did not reach statistical significance after adjustment. There are several plausible explanations for this discrepancy. First, observational studies are inherently susceptible to residual confounding, even after adjustment for known covariates. Unmeasured factors such as lifestyle behaviors, medication adherence, or healthcare access may partially explain the observed associations. It is also possible that the observational association reflects a correlation rather than a true causal relationship — a possibility that MR is specifically designed to address.

Although the R^2 values for some of our models were relatively low (e.g., $R^2 = 0.06$ for LVEF), this is not uncommon in clinical studies where complex physiological outcomes are influenced by a wide array of factors, many of which may not be fully captured in the available data. These low R^2 values indicate that the model explains only a small proportion of the variability in the outcome, suggesting limited predictive power. However, the observed associations remain statistically significant and may still offer meaningful insights into potential relationships. It is also important to acknowledge that unmeasured confounders—such as genetic variability, detailed medication adherence, socioeconomic factors, or undetected comorbidities—may contribute to residual variance. Future studies with more data with broader variable inclusion may help improve model performance and better capture the multifactorial nature of these outcomes.

Several limitations of this study should be noted. First, the glucose variables of FPG and HbA1c measurements were obtained from clinical monitoring, and participants had a varied number of FPG and HbA1c measurements. To minimize the variability, we adjusted for the number of FPG and HbA1c measurements on deriving variability measures. Additionally, the FPG or HbA1c measurements were taken prior to echocardiography screening, which might not have been long enough to fully assess the association of glucose variability with echocardiographic variables. Second, participants may have undergone echocardiography due to specific clinical indications, meaning that they might not be representative of the population with type 2 diabetes. Specifically, echocardiography in clinical practice is typically performed when there are suspected or known cardiovascular issues. As a result, individuals who underwent echocardiographic assessment may have had underlying cardiac symptoms or risk factors that prompted the examination. Therefore, these participants may not represent the broader population of individuals with type 2 diabetes, particularly those without overt cardiovascular concerns. This limitation may affect external generalizability of our findings. Finally, this observational cohort study can only demonstrate associations rather than casualty.

Conclusions

In summary, our epidemiologic and MR studies demonstrated that visit-to-visit variability of FPG in patients with type 2 diabetes was independently associated with the left cardiac structure as well as systolic and diastolic function. Identifying associations between visit-to-visit variability of FPG and these echocardiographic variables may aid in risk stratification for diabetes care in clinical settings.

Abbreviations

HbA1c	glycosylated hemoglobin
MR	Mendelian randomization
LVDd	left ventricular diastolic diameter
LAD	left atrium diameter
LVEF	left ventricular ejection fraction
DCMP	Diabetes Care Managed Program
CMUH	China Medical University Hospital
BMI	body mass index
BP	blood pressure
FPG	fasting plasma glucose
TG	triglycerides
LDL-C	low-density lipoprotein cholesterol
HDL-C	high-density lipoprotein cholesterol
TC	total cholesterol
UA	uric acid
uACR	urine albumin-to-creatinine ratio
eGFR	estimated glomerular filtration rate
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CV	coefficients of variation
FPG-CV	CV for FPG
HbA1c-CV	CV for HbA1c
SNP	single nucleotide polymorphism
GWAS	genome-wide association study
ASE	American Society of Echocardiography
LVM	left ventricular mass
LVSd	left ventricular systolic diameter
QC	quality control
GRS	genetic risk score
LD	linkage disequilibrium
PCA	principal components analysis

Supplementary Information

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Supplementary Material 1

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Author contributions

T.C.L., and C.C.L. developed the study design, obtained funding and drafted manuscript. C.I L. and S.Y.Y acquired data, carried out the statistical analysis,

analyzed and interpreted data, and critically revised the manuscript. C.S.L., C.H.L., T.C.L., and C.C.L. contributed to discussion, and reviewed and edited this manuscript. All authors read and approved the final manuscript. T.C.L. and C.C.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data availability
The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethical Review Board of China Medical University Hospital (CMUH112-REC1-007). Informed consent of the study participants was not required because the dataset used in this study consists of de-identified secondary data released for research purposes.

Competing interests
The authors declare no competing interests.

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