Journal of the American Heart Association

ORIGINAL RESEARCH

Genetic Determinants of Body Mass Index and Fasting Glucose Are Mediators of Grade 1 Diastolic Dysfunction

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BACKGROUND: Early (grade 1) cardiac left ventricular diastolic dysfunction (G1DD) increases the risk for heart failure with preserved ejection fraction and may improve with aggressive risk factor modification. Type 2 diabetes, obesity, hypertension, and coronary heart disease are associated with increased incidence of diastolic dysfunction. The genetic drivers of G1DD are not defined.

METHODS AND RESULTS: We curated genotyped European ancestry G1DD cases (n=668) and controls with normal diastolic function (n=1772) from Vanderbilt's biobank. G1DD status was explored through (1) an additive model genome-wide association study, (2) shared polygenic risk through logistic regression, and (3) instrumental variable analysis using 2-sample Mendelian randomization (the inverse-variance weighted method, Mendelian randomization-Egger, and median) to determine potential modifiable risk factors. There were no common single nucleotide polymorphisms significantly associated with G1DD status. A polygenic risk score for BMI was significantly associated with increased G1DD risk (odds ratio [OR], 1.20 for 1-SD increase in BMI [95% CI, 1.08–1.32]; *P*=0.0003). The association was confirmed by the inverse-variance weighted method (OR, 1.89 [95% CI, 1.37–2.61]). Among the candidate mediators for BMI, only fasting glucose was significantly associated with G1DD status by the inverse-variance weighted method (OR, 4.14 for 1-SD increase in fasting glucose [95% CI, 1.55–11.02]; *P*=0.005). Multivariable Mendelian randomization showed a modest attenuation of the BMI association (OR, 1.84 [95% CI, 1.35–2.52]) when adjusting for fasting glucose.

CONCLUSIONS: These data suggest that a genetic predisposition to elevated BMI increases the risk for G1DD. Part of this effect may be mediated through altered glucose homeostasis.

Key Words: body mass index ■ diastolic dysfunction ■ fasting glucose ■ genetic epidemiology ■ Mendelian randomization

Left ventricular diastolic dysfunction (DD) is a combination of 2 defects: (1) impaired myocardial relaxation ability and (2) reduced filling of the left ventricle in the absence of increased filling pressures.[1] Early-stage DD (grade 1 DD [G1DD]) is characterized by impaired relaxation, and even among young adults, early disease is associated with incident heart failure with preserved ejection fraction.[2–4] Important modifiable risk factors for G1DD include obesity, diabetes, hypertension, and coronary heart disease.[2–11] Heart failure with preserved ejection fraction lacks life-extending treatments, and delineating genetic drivers of diastolic dysfunction risk could help identify modifiable predisposing risk mechanisms to improve outcomes for patients.[1–4,12–15]

The genetics of diastolic function are not well characterized. The ECHOGEN consortium examined diastolic function parameters in a large population and

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Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.025578

For Sources of Funding and Disclosures, see page 8.

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CLINICAL PERSPECTIVE

What Is New?

- Grade 1 left ventricular diastolic dysfunction (G1DD) is a modifiable risk factor associated with incident heart failure with preserved ejection fraction risk, but its genetic drivers are not known.
- This study investigated the genetic drivers of G1DD measured by echocardiography in a European ancestry population aged <60 years.
- Polygenic risk associated with body mass index variation is also associated with G1DD prevalence and is mediated, in part, by altered glucose homeostasis.

What Are the Clinical Implications?

- Body mass index is an important modifiable risk factor for G1DD.
- Prevention efforts should be directed to mitigate weight gain in early life to prevent adverse cardiac modeling that predisposes to G1DD and subsequent heart failure with preserved ejection fraction.
- If G1DD is observed on echocardiogram, risk reduction strategies should include maintaining a healthy weight and controlling hyperglycemia.

Nonstandard Abbreviations and Acronyms

DD	diastolic dysfunction
FG	fasting glucose
G1DD	grade 1 diastolic dysfunction
MR	Mendelian randomization
MVMR	multivariable Mendelian randomization
PRS	polygenic risk score
T2D	type 2 diabetes

did not observe significant single nucleotide polymorphism (SNP) heritability estimates or SNPs associated with these parameters.[16] However, structural traits related to diastolic function, such as left ventricular mass and other functional left ventricular measures, have been demonstrated to have a significant heritable component based on common SNPs.[17,18] This could suggest that diastolic dysfunction is a genetically heterogeneous phenotype representing the accumulated contributions from many risk mechanisms.

We hypothesized that examining early diastolic dysfunction in a clinical population would identify genetic risk mechanisms associated with this potentially reversible stage of cardiac remodeling. To address this hypothesis, we developed a large, genotyped population of individuals aged <60 years who had undergone transthoracic echocardiography studies as part of routine clinical care. We identified a genetic predisposition to elevated body mass index (BMI) and glycemic dysregulation associated with diastolic dysfunction. Addressing these risk mechanisms, especially obesity, may prevent or reverse the pathological cardiac changes associated with diastolic dysfunction.

METHODS

An overview of the analytic approach to identify the underlying genetic risk mechanisms between genetically regulated comorbid traits and G1DD is presented in Figure 1. The genome-wide association study (GWAS) summary statistics generated in these analyses are available from the corresponding author upon request.

Study Population

BioVU is Vanderbilt University Medical Center's DNA biobank linked to a deidentified mirror of the electronic medical records of the Vanderbilt health system.[19] Individuals seeking health care at Vanderbilt University Medical Center are consented to participate and may opt out at any time. Sample collection began in 2007 and is ongoing. The biobank comprises ≈260 000 individuals of European, African, and Asian ancestries. Access to the data in the biobank is overseen by the Vanderbilt Institutional Review Board. All participants provided written consent.

Individual-level genotype data were obtained from BioVU.[19] Approval for the present study was obtained from the Vanderbilt University Medical Center Institutional Review Board.

G1DD cases and controls were identified from transthoracic echocardiogram reports generated during routine clinical care, as previously described.[2] Briefly, diastolic function stage was extracted from the first available transthoracic echocardiogram report and was assigned by a clinical echocardiographer at the time of collection of the transthoracic echocardiogram. Cases were individuals classified as impaired left ventricle relaxation (stage 1), whereas controls were individuals classified as having no dysfunction. Individuals with higher DD stages were excluded, as were individuals with a left ventricular ejection fraction <50%. Subjects who had echocardiograms collected during acute cardiac illnesses (eg, endocarditis), with exposure to chemotherapy, or with congenital diseases were also excluded. The analyses were restricted to individuals who had been previously genotyped on the Multi-Ethnic Genotyping Array platform (described below) as part of a broad-based institutional genotyping initiative. The analyses were further restricted to

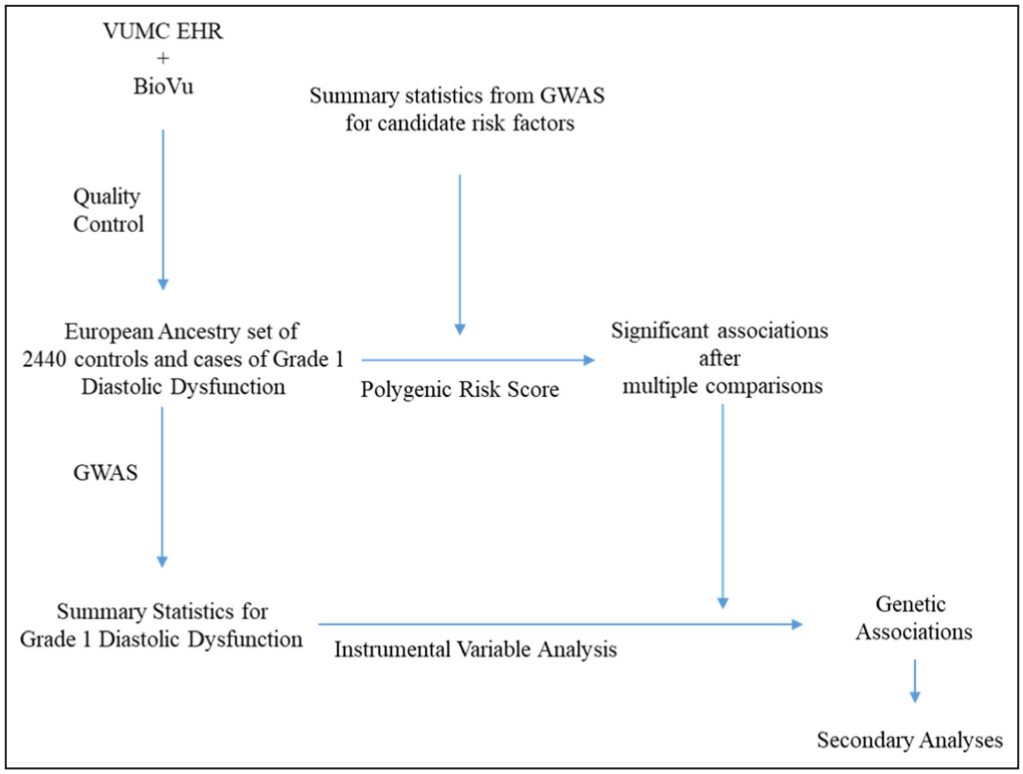

Figure 1. Overview of the study design.
Grade 1 diastolic dysfunction cases and controls were selected from BioVU, Vanderbilt University Medical Center's electronic health record (HER)–linked DNA biobank. A genome-wide association study (GWAS) was performed on 2440 individuals. A polygenic risk score screen identified traits that shared genetic risk with grade 1 diastolic dysfunction. Associated traits were further investigated under a 2-sample Mendelian randomization framework. Secondary analyses investigated for potential pleiotropic mediators.

subjects aged <60 years and of European ancestry, as determined using HAPMAP reference populations in conjunction with genetic principal components.

Genetic Data

SNP genotyping of BioVU subjects was measured using the Illumina Infinium Multi-Ethnic Genotyping Array platform.[19] Quality control analyses used PLINK version 1.90β3 software.[20] Before imputation, genetic data were filtered and standardized through the HRC-1000G-check tool version 4.2.5 (http://www.well.ox.ac.uk/~wrayner/tools/) and prephased using Eagle version 2.4.1.[21] Principal components were calculated using the SNPRelate package.[22] Data were imputed using the Michigan Imputation Server in conjunction with the 10/2014 release of the 1000 Genomes cosmopolitan reference haplotypes.[23] Imputed data were filtered for a sample missingness rate <2%, a SNP missingness rate <4%, and SNP deviation from Hardy-Weinberg $P<10^{-06}$. After quality control, 7 585 258 SNPs were available for analysis. Genome-wide study and polygenic risk scores were calculated using PLINK version 2.[24]

Clinical Phenotypes

Age was defined as the age at the time of cardiac echocardiogram. Clinical diagnoses for the G1DD risk factors of obesity (278.10), type 2 diabetes (T2D) (250.20), ischemic heart disease (401.00), and hypertension (411.00) were defined using PheCodes, which are derived from *International Classification of Diseases, Ninth and Tenth Revision* (*ICD-9* and *ICD-10*) codes.[25]

Statistical Analysis

GWAS Summary Statistics

Summary statistics for BMI,[26] systolic blood pressure,[27] diastolic blood pressure,[27] T2D,[28] coronary artery disease,[29] fasting glucose (FG),[30] hemoglobin A1C (HbA1C),[31] high-density lipoprotein cholesterol,[32] low-density lipoprotein cholesterol,[32] and triglycerides [32] obtained from the publicly available large-scale GWAS performed among individuals of European ancestry.

Baseline Characteristics

Mean age and the prevalence of comorbidities were calculated and stratified by G1DD case status.

Differences in mean age and number of each sex, by G1DD status, was computed as a test of proportions between cases and controls using a Pearson χ^2 test statistic. Significant differences in prevalence rates of comorbidities, by G1DD status, were assessed using logistic regression, adjusting for age and sex.

Genome-Wide Association Study

The GWAS was used to identify SNPs associated with G1DD case-control status (Data S1). The analyses used a logistic regression, assuming an additive genetic model, and was adjusted for age, sex and 5 principal components of ancestry using PLINK version 2.[24] SNPs with an association of $P<5\times10^{-08}$ were deemed to be significant. We performed a power calculation based on our sample size and distribution of cases and controls (https://zzz.bwh.harvard.edu/gpc/cc2.html). We had >80% power to detect an association at genome-wide significance for a SNP with an odds ratio (OR) >1.6, assuming a disease prevalence of 5% and a minor allele frequency >20%. Annotations for SNPs with an association of $P<5\times10^{-06}$ of GWAS results are presented in Data S2.

Polygenic Risk Score

To identify traits that share genetic risk with G1DD, polygenic risk scores (PRSs) for each trait were computed and then tested for an association with DD case-control status, using PLINK version 2.[24] An independent set of SNPs significantly associated with the respective trait ($P<5\times10^{-08}$) was selected using a pruning-and-thresholding algorithm that selected an Linkage Disequilibrium-reduced ($r^2<0.05$) set of common SNPs with a minor allele frequency >5%. A genetically predicted trait score was then calculated for each individual in the G1DD cohort by summing the product of each SNP effect size and the SNP dosage (a value ranging from 0 to 2). The association with the polygenic risk score and DD status was tested using a logistic regression model that adjusted for sex, age, and 5 principal components as covariates. A Bonferroni-adjusted $P<0.01$ (=0.05/5 phenotypes) was considered significant.

Mendelian Randomization

Mendelian randomization (MR) was used to further probe traits significantly associated with G1DD by PRS analysis. MR is an instrumental variable approach used to define causal relationships between exposures and outcomes.[33] It uses SNPs associated with a chosen exposure as instrumental variables that define the direction and magnitude of associations between the exposure/risk factor and the chosen outcome, G1DD. To create genetic instruments for each risk factor, we used a pruning-and-thresholding algorithm that selected an Linkage Disequilibrium-reduced set of SNPs with a minor allele frequency >5%. All MRs conducted were 2-sample average inverse-variance weighted method (IVWM) analyses, using the Mendelian Randomization R package.[33] An association was considered significant for a $P<0.05$. Association measures represent the change in risk factor level versus the log odds of G1DD status. To ensure that significant associations were not caused by pleiotropy, sensitivity analyses were conducted using the pleiotropy-robust MR-Egger and weighted median methods to confirm the magnitude and direction of associations. IVWM results were considered reliable if they had a similar direction and magnitude of association as the other 2 methods.

In secondary analyses, we sought to identify candidate mediators of an observed genetic association between G1DD and BMI. MR association analyses were performed for FG, HbA1C, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides using the same methods as described above.

Multivariable Mendelian Randomization

Multivariable MR (MVMR)[34] was used to determine whether an observed association between G1DD and BMI was independent of other modifiable risk factors. MVMR estimates the effects of multiple exposures on an outcome. MVMR[34] analysis was performed that included BMI and each candidate mediator that significantly associated with G1DD by MR in the analyses described above. We identified those risk factors that decreased the primary mediator's coefficient by >1.96 standard errors ($P<0.05$), as compared with the original coefficient after adjustment, and in the process, estimated the magnitude of the direct effect of the exposure and the indirect effect ascribed to the mediator.[35]

Phenotypic Association of Genetic Risk Score

We examined if the PRS for BMI also associated with prevalent T2D, ischemic heart disease, and hypertension within this cohort. We ran a logistic regression for the outcome status in a model of the BMI PRS adjusted for age, sex, top 5 principal components, and G1DD status. We established a multiple comparisons threshold of <0.05/3 for significance.

Sensitivity Analyses to Examine Treatment Effects

Therapeutic interventions could lead to misclassification of case-control status. Specifically, treatment of diabetes and hypertension by therapeutic agents could have prevented or reversed G1DD, resulting in misclassification of controls. To explore this possibility, we conducted sensitivity analyses by removing either

controls treated for hypertension or for diabetes before the date of the echocardiogram. All primary analyses were repeated using these new control groups.

RESULTS

The final study population comprised 2440 individuals, with 668 G1DD cases and 1772 controls (Table). There were 1457 (≈60%) women, and the mean age was 47.2 (SD, 10) years. Cases had significantly higher prevalence of diagnoses for ischemic heart disease (OR, 1.40 [95% CI, 1.15–1.71]; P=0.001), obesity (OR, 1.57 [95% CI, 1.28–1.92]; P=1.5×10^{-05}), hypertension (OR, 2.14 [95% CI, 1.72–2.66]; P=2.61×10^{-11}), and diabetes (OR, 1.88 [95% CI, 1.51–2.34]; P=2.4×10^{-09}).

There were no common SNPs associated with G1DD case status at genome-wide significance by the GWAS (Figure S1A). Though there were no genome-wide significant SNPs, annotations from SNPs with an association P<5×10^{-06} indicated that these SNPs were associated with cardiometabolic phenotypes (Figure S1B, Tables S1A and S1B), and with the left ventricle in HiC chromatin interaction. We tested for associations between G1DD status and PRS for systolic blood pressure, diastolic blood pressure, BMI, T2D, and coronary artery disease to determine whether genetic variation underlying any of these risk factors also associated with G1DD prevalence. Only BMI was significantly associated (OR, 1.20 for 1-SD increase in BMI [95% CI, 1.08–1.32]; P=0.0004) (Figure 2, Table S1C). Given that BMI demonstrated shared genetics with G1DD, we asked if the relationship held under an instrumental variable framework. Genetically predicted BMI was significantly associated with G1DD by IVWM (OR, 1.84 for 1-SD increase in BMI [95% CI, 1.35–2.52]; P=0.0002). Similar results were seen across other MR methods (Table S2, Figure S2).

To determine whether the BMI association may be mediated through lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides) or glycemic factors (FG, HbA1C), we first ascertained whether genetic instruments for these factors were associated with G1DD by MR analyses. There was only a significant association with FG (OR, 4.14 for 1-SD increase in FG [95% CI, 1.55–11.02]; P=0.005) (Figure 3, Table S3), but not HbA1C (OR, 2.23 for 1-SD increase in FG [95% CI, 0.59–8.44]; P=0.24). A BMI predictor was associated with FG by IVWM, but an FG predictor did not associate with BMI, suggesting that FG may be a downstream effector of BMI (Table S4, Table S5).

MVMR was used to ascertain independent associations between BMI and FG using the IVWM. After adjustment, BMI was still significantly associated with G1DD, but not FG. For BMI, there was a modest attenuation of the OR from 1.89 (95% CI, 1.37–2.61) to 1.84 (95% CI, 1.35–2.52) (Table S6, Table S7, Figure S3). This suggests that 5.5% for the BMI effect is attributable to FG (Table S8). In sum, these data suggest that genetic factors that predispose to elevated BMI may impact the development of G1DD directly and may mediate a modest fraction of their effects by modulating glucose homeostasis (Figure 4).

Finally, we tested the association between PRS for BMI and G1DD-associated comorbidities. Among the G1DD-associated comorbidities, only T2D was significantly associated with a BMI PRS (OR, 1.23 for 1-SD change in BMI PRS [95% CI, 1.12–1.36]; P=1.4×10^{-05}) (Table S9, Figure S4).

The sensitivity analyses were conducted after removing controls receiving either hypertension medications or diabetes medications before the date of the echocardiogram. The exclusion of these individuals did not alter the overall findings for either the controls receiving antihypertensive medications (Figures S5 and S6, Tables S10 through S17) or glucose-lowering medications (Figures S7 and S8, Tables S18 and S25). Similar results were seen across the other MR methods (Tables S5, S12, S13, S20 and S21, Figures S6 and S8). In addition, no new associations were observed in the post-GWAS or MR analyses with these exclusions.

The precision and variance estimate from MR is strongly influenced by the number of SNPs used as genetic instruments. The larger variance estimates associated with the instrumental variables for glycemic traits (HbA1C, FG) reflect the smaller number of

Table. Demographic Profile of the Study Population

Characteristic*	All participants, n=2440	Cases, n=668	Controls, n=1772	P value
Age, y, mean (SD)	47.2 (10.0)	52.9 (5.9)	45.1 (10.3)	<2.2×10^{-16}†
Women	1457 (59.7%)	365 (54.6%)	1092 (61.6%)	0.002†
Obesity	716 (29.3%)	248 (37.1%)	468 (26.4%)	1.5×10^{13}‡
Ischemic heart disease	728 (29.8%)	286 (42.8%)	442 (24.9%)	0.001‡
Hypertension	1472 (60.3%)	527 (78.9%)	945 (53.3%)	2.6×10^{-11}‡
Diabetes	654 (26.8%)	263 (39.4%)	391 (22.1%)	2.4×10^{-9}‡

*Values in the table represent counts and column percentages, except for age.
†P value for the difference in proportions between cases and controls is based on the value of Pearson χ^2 test statistic.
‡Association P value for the risk factor from a logistic regression model adjusting for age and sex.

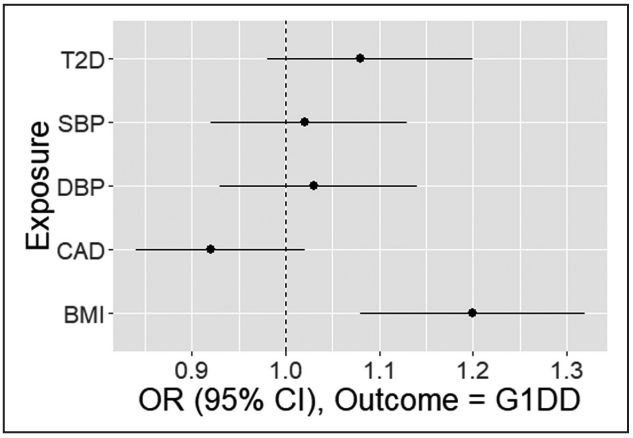

Figure 2. Genetic determinants of body mass index (BMI) share a genetic risk with grade 1 diastolic dysfunction (G1DD).
Forest plot summarizing associations between polygenic risk score (PRS) for diastolic blood pressure (DBP), systolic blood pressure (SBP), ischemic heart disease (IHD)/coronary artery disease (CAD) , type 2 diabetes (T2D), and BMI and G1DD. Odds ratio (OR) represents the change in risk for G1DD per standard deviation increase in the PRS.

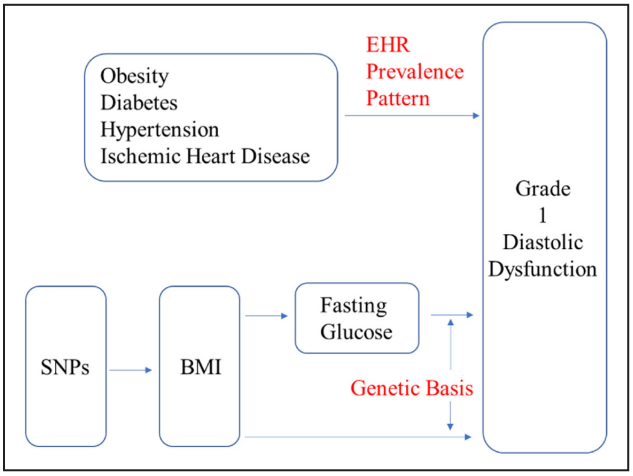

Figure 4. Genetic determinants of body mass index (BMI) associated with grade 1 diastolic dysfunction (G1DD).
Higher prevalence of comorbid phenotypic associations with G1DD are observed in the electronic health record (EHR). The underlying genetic basis is driven, in part, by a genetic predisposition to elevated BMI directly and mediated through fasting glucose. SNPs indicate single nucleotide polymorphisms.

SNPs significantly associated with these variables, as compared with the other instruments. Exclusion of the treated controls did not substantially change these estimates. For the cohort where controls receiving hypertension medication were removed from the analyses (Table S13), there was only a significant association with FG (OR, 9.70 for 1-SD increase in FG [95% CI, 2.71–34.71]; *P*=0.0005), but not HbA1C (OR, 4.01 for 1-SD increase in FG [95% CI, 0.72–22.39]; *P*=0.11). For the cohort where controls receiving diabetes medication were removed from the analyses (Table S21), there was only a significant association with FG (OR, 5.76 for 1-SD increase in FG [95% CI, 2.03–16.33]; $P=9.93\times10^{-04}$), but not HbA1C (OR, 2.48 for 1-SD increase in FG [95% CI, 0.61–10.14]; *P*=0.21). The distributions of PRS for BMI and FG by G1DD case-control status and concordance statistics for models with and without these PRSs are presented in Figure S9 and Table S26.

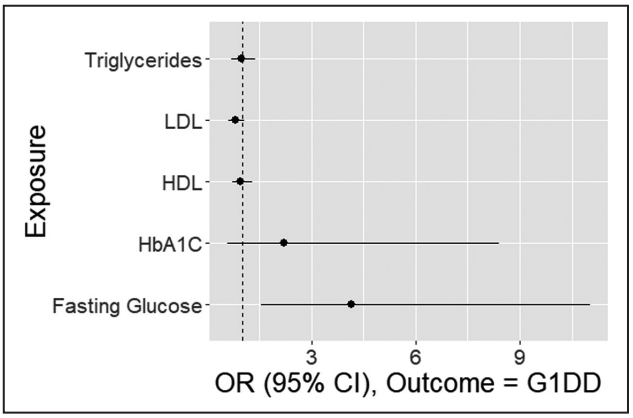

Figure 3. Genetic determinants of fasting glucose are associated with grade 1 diastolic dysfunction (G1DD) in 2-sample Mendelian randomization analysis.
Forest plot of inverse variance instrumental variable estimates for glucose, hemoglobin A1C (HbA1C), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides levels and G1DD status. Odds ratio (OR) represents the change in risk for G1DD per standard deviation increase in the respective mediator.

DISCUSSION

This study examined genetic determinants of early diastolic dysfunction in a clinical population. A GWAS did not identify common SNPs significantly associated with G1DD status, consistent with prior studies examining diastolic function phenotypes.[16,17] However, several of the top SNPs had appeared to have relevance to cardiometabolic phenotypes and the left ventricle. Thus, we examined associations with genetic predictors of established risk factors, which is a more powered approach to detect weak associations. Although diagnoses of obesity, ischemic heart disease, hypertension, and T2D were more prevalent among cases, only a genetic predictor for BMI positively associated with G1DD risk. MVMR models suggested that a small portion of this risk may be mediated by glycemic dysregulation, as measured by FG levels. In sum, these results suggest that a genetic predisposition to elevated BMI contributes to G1DD risk, acting directly and through a mediated fraction impacting glycemic regulation.

Obesity-driven remodeling and expansion of adipose tissue, in addition to systemic inflammation from obesity, is increasingly recognized as a key driver of

dysfunction in the left ventricle.[36] Excess body mass is associated with several adverse physiologic alterations and cardiac structure changes that adversely affect the heart. These include concentric left ventricular remodeling, right ventricular dilatation, increased epicardial fat thickness, and elevated left ventricular filling pressures.[37] The adverse effect of obesity on cardiac diastolic function are recapitulated in genetic animal models. For instance, leptin-deficient (ob/ob) or leptin receptor-deficient (db/db) mice, both isolated models of obesity, develop cardiac diastolic dysfunction.[38]

In these analyses, we observed that a polygenic predisposition toward elevated BMI was associated with an increased risk for early clinical diastolic dysfunction. A polygenic association between an exposure and a phenotype could be caused by either shared genetic mechanisms that affect both phenotypes or a direct mediating effect of the exposure on the outcome. MR analyses confirmed the BMI-G1DD association and did not demonstrate heterogeneity in the association among the underlying SNP instruments. These results suggest that BMI is a mediator of disease, and all underlying genetic mechanisms that increase BMI also drive disease risk. The implications of these findings are that avoiding or possibly reversing obesity through any mechanism could decrease the risk of early diastolic dysfunction. Furthermore, because G1DD is often reversible with attenuation of risk factors, weight loss could improve function.[2]

The prevalence of established risk factors in addition to obesity was higher among the G1DD cases than controls in this study population. However, we did not observe significant associations between genetic predictors of coronary heart disease, hypertension, and T2D. Hypertension and insulin resistance are well-established downstream risk factors of obesity.[39] Thus, it is possible that the higher prevalence of these risk factors among G1DD cases is because of the other secondary factors of metabolic syndrome.

Although we did not see an association with a genetic predictor of T2D, there was a positive association with a predictor of FG and G1DD. Of note, the genetic architectures of these phenotypes differ.[30,31] In multivariable analyses, the association with FG was no longer significant, and there was a modest attenuation of the association statistics associated with BMI, suggesting altered FG levels may be secondary to the effects of elevated BMI, and may mediate some of the risk associated with BMI. Elevated FG levels have been observed to be associated with diastolic dysfunction, though the associations have not been consistent.[40–43] Higher fasting plasma glucose levels among individuals without diabetes was also found to be an independent risk factor for heart failure hospitalization.[44] Furthermore, SGLT2 (Sodium-glucose Cotransporter-2) inhibitor use has been shown to reverse diastolic dysfunction among individuals with diabetes.[45] Perhaps these findings align the development of G1DD as an antecedent to the current paradigm of the diabesity phenotype, the combined burden of obesity and diabetes on heart disease.[46]

The current study has limitations. The outcome studied was a binary outcome based on an echocardiographer's clinical assessment, which can result in loss of power caused by binning and misclassification. There was limited power to detect SNP associations with a magnitude of effect usually observed for common SNPs (ie, an OR of <1.3) associated with a complex phenotype, which can lead to false-negative findings by the GWAS. The study was done in a European ancestry population; this limits insights into other ancestries. The study cohort was curated from electronic health records in a health system, and controls are not necessarily healthy. The modest number of SNPs available for use in constructing the genetic instruments for the glycemic predictors likely contributed to the low precision in effect size estimates associated with these instruments.

Future studies to dissect out the impact of genetic determinants on the development of G1DD could include looking at more continuous measures of diastolic function, taking multitrait GWAS/polygenic risk approaches, and recruiting more subjects representing non-European ancestries. The genetic underpinnings of later stages of diastolic dysfunction should be studied to identify genetic drivers of risk of late-stage cardiac diastolic remodeling.

In conclusion, among multiple risk factors epidemiologically associated with diastolic dysfunction, only a polygenic predictor of BMI was associated with G1DD, suggesting a predisposition to elevated BMI could be an important driver of risk and may also underlie the development of other risk factors, such as impaired glucose homeostasis. Obesity is driven by gene-x-environment interactions, and thus a genetic predisposition is not deterministic of an individual's fate.[47] Treatment and prevention strategies that reduce BMI are apt to mitigate an important genetic driver of early diastolic dysfunction. Based on these results, there might be a role for preventive echocardiograms to detect early G1DD and mitigate downstream complications, including heart failure, among subjects seen to be increasing BMI, of high BMI, or showing altered glycemic homeostasis.

ARTICLE INFORMATION

Received January 28, 2022; accepted March 31, 2022.

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Acknowledgments

Data on coronary artery disease/myocardial infarction have been contributed by the CARDIoGRAMplusC4D investigators and have been downloaded from www.CARDIOGRAMPLUSC4D.ORG. Data on glycemic traits were contributed by the MAGIC investigators and have been downloaded from www.magicinvestigators.org.

Sources of Funding

American Heart Association 16FTF30130005 (J.D.M.) and National Institutes of Health/National Heart, Lung, and Blood Institute R01-HL142856 (J.D.M.). Vanderbilt University Medical Center's BioVU is supported by institutional funding, private agencies, and federal grants. These include the National Institutes of Health–funded Shared Instrumentation Grant S10RR025141; and Clinical and Translational Science Awards grants UL1TR002243, UL1TR000445, and UL1RR024975. Genomic data are also supported by investigator-led projects that include U01HG004798, R01NS032830, RC2GM092618, P50GM115305, U01HG006378, U19HL065962, R01HD074711; and additional funding sources listed at https://victr.vumc.org/biovu-funding/.

Disclosures

None.

Supplemental Material

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SUPPLEMENTAL MATERIAL

Data S1 - GWAS

Genome-wide association studies to identify SNPs associated with G1DD status among a European ancestry population were conducted. Logistic regression, assuming an additive genetic model and adjusted for age and sex, was used to test for SNP associations. Summary statistics generated from the GWAS were used for downstream analyses.

Data S2 - Annotation of top GWAS associations

There were 8 independent loci with associations at *P* value threshold $<5x10^{-06}$. For each lead SNP, we identified the nearest gene and examined the GWAS catalog for reported associations, using FUMA (https://fuma.ctglab.nl/).[48-52] We annotated the clinical significance of these genes (see **Table S1a**). We also looked up tissue associations, as provided through FUMA, by chromatin interaction using HiC for these SNPs, repository at the Gene expression omnibus, Series GSE87112 (**Table S1a**). Interestingly, the major tissue association was the Left Ventricle. Next, we examined the MAGMA based gene annotation of these SNPs, as provided through FUMA. Input SNPs were mapped to 7 protein coding genes (**Figure S1b, Table S1b**). The **Figure S1b** is the Manhattan plot of the gene-based test, negative log of *P* value is from the respective SNPs.

Table S1a

Annotation of top GWAS associations ($P<5x10^{-6}$)

SNP id	chr	pos	*P* value	Nearest Gene	Distance in kb	Positional Significance	Clinical significance of gene	Tissue with chromatin interaction by Hi-C
rs1850497:118956998:G:T	2	118956998	$8.55x10^{-07}$	AC093901.1	13036	Intergenic	Obstructive sleep apnea associated gene, PMID:26977737	Left Ventricle
rs1850497:118956998:G:T	2	118956998	$8.55x10^{-07}$	RP11-19E11.1	634278	Intergenic	lncRNA associated with cell proliferation and cell death, PMID: 31934613; variant at position 118579583 (rs115387174) associated with waist circumference	Left Ventricle
rs75587283:3907109:G:A	8	3907109	$4.76x10^{-06}$	CSMD1	0	Intronic	Associated with poor response to metformin in Type 2 diabetics, PMID: 27415606; Associated with Metabolic Syndrome in FHS, PMID: 20018043	Left Ventricle
rs12546520:103832256:G:A	8	103832256	$1.48x10^{-06}$	AZIN1	6328	Intergenic	Downregulation associated with myocardial fibrosis post-MI, PMID: 33568517 This SNP is also close to rs12541595, associated with left ventricular end diastolic dimension, PMID: 28394258	Left Ventricle
rs11142595:73406226:A:T	9	73406226	$4.60x10^{-06}$	TRPM3	0	Intronic	This ion channel levels are reduced in human failing left ventricular samples, PMID: 27614169; Associated with glucose homeostasis and metabolic syndrome, this ion channel is inhibited by pioglitazone and rosiglitazone, PMID: 21406603; Expressed by human pancreatic beta cells, PMID: 29356488	Left Ventricle
rs75964618:84506342:T:C	11	84506342	$4.25x10^{-06}$	DLG2:CTD-2537O9.1	0	ncRNA_intronic	Associated with hyperglycemia, PMID: 32356104; Hypermethylation of DLG2 associated with heart disease and atherosclerosis, PMID: 28577936	Left Ventricle
rs10773594:129559557:C:T	12	129559557	$3.47x10^{-06}$	TMEM132D		Exonic	Associated with panic and anxiety disorders, PMID: 27318301 This SNP is also close to rs10774625, associated with left ventricular end diastolic dimension, PMID: 28394258	
rs12933847:77964270:A:C	16	77964270	$2.80x10^{-06}$	VAT1L	0	Intronic	Associated with glucose homeostasis and type 2 diabetes, PMID: 32500584	Left Ventricle

Table S1b

Protein coding annotations of top SNPs

ensg	symbol	chr	type	Clinical Significance of gene
ENSG00000183117	CSMD1	8	protein_coding	Associated with poor response to metformin in Type 2 diabetics, PMID: 27415606; Associated with Metabolic Syndrome in Framingham Heart Study, PMID: 20018043
ENSG00000155096	AZIN1	8	protein_coding	Downregulation associated with myocardial fibrosis post-MI, PMID: 33568517
ENSG00000253320	KB-1507C5.2	8	protein_coding	The SNP rs2513877 at position 103883630 (our related top variant is at position 103832256), located in this gene, is a diastolic blood pressure associated variant at genome-wide significance, PMID: 30224653
ENSG00000083067	TRPM3	9	protein_coding	This ion channel levels are reduced in human failing left ventricular samples, PMID: 27614169; Associated with glucose homeostasis and metabolic syndrome, this ion channel is inhibited by pioglitazone and rosiglitazone, PMID: 21406603; Expressed by human pancreatic beta cells, PMID: 29356488
ENSG00000150672	DLG2	11	protein_coding	Associated with hyperglycemia, PMID: 32356104; Hypermethylation of DLG2 associated with heart disease and atherosclerosis, PMID: 28577936
ENSG00000151952	TMEM132D	12	protein_coding	Associated with panic and anxiety disorders, PMID: 27318301
ENSG00000171724	VAT1L	16	protein_coding	Associated with glucose homeostasis and type 2 diabetes, PMID: 32500584

Table S1c

Estimate of shared genetics between G1DD and candidate risk factors

G1DD Status (Outcome) = PRS +Age+Sex+PC1to5, logistic regression model				
Polygenic risk score	**Beta (95% CI)**	**SE**	***P* value**	**OR (95% CI)**
Diastolic Blood Pressure	0.02 (-0.08, 0.12)	0.05	0.66	1.02 (0.93, 1.13)
Systolic Blood Pressure	0.02 (-0.08, 0.12)	0.05	0.66	1.02 (0.93, 1.13)
Coronary Artery Disease	-0.05 (-0.15, 0.05)	0.05	0.31	0.95 (0.86, 1.05)
Type 2 Diabetes	0.08 (-0.02, 0.18)	0.05	0.10	1.08 (0.98, 1.20)
Body Mass Index	0.18 (0.08, 0.28)	0.05	0.0004	1.20 (1.08, 1.32)

G1DD – Grade 1 Diastolic dysfunction, PRS – Polygenic Risk Score, PC- Principal Components

CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio

Table S2

Instrumental variable analyses of BMI vs G1DD (Two sample mendelian randomization)

Exposure	**Outcome**	**Method**	**SNPs**	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**	
BMI	**G1DD**	**IVW**	1132	0.61 (0.30, 0.92)	0.16	0.0002	1.84 (1.35, 2.52)	0.54 **(H)**
		Egger	1132	0.95 (-0.03, 1.93)	0.50	0.06	2.59 (0.97, 6.89)	0.47 **(I)**
		Median	1132	0.59 (0.05, 1.13)	0.28	0.03	1.80 (1.04, 3.12)	

BMI – Body Mass Index, G1DD – Grade 1 Diastolic dysfunction, IVW – Inverse Variance Weighted, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H – Heterogeneity *P* value, I – Intercept *P* value

Table S3

Instrumental variable analyses of candidate mediators for BMI (Two sample mendelian randomization)

Exposure	Method	SNPs	Estimate (95% CI)	SE	OR (95% CI)	*P* value	
FG	**IVW**	15	1.42 (0.44, 2.40)	0.50	4.14 (1.55, 1.02)	0.005	0.65 (**H)**
	Egger	15	0.27 (-1.94, 2.49)	1.13	1.31 (0.14, 12.00)	0.81	0.26 **(I)**
	Median	15	1.01 (-0.39, 2.40)	0.71	2.75 (0.68, 11.04)	0.16	
HbA1C	**IVW**	44	0.80 (-0.52, 2.13)	0.68	2.23 (0.59, 8.44)	0.24	0.87 (**H)**
	Egger	44	2.50 (-0.04, 5.04)	1.29	12.18 (0.97, 152.69)	0.05	0.12 **(I)**
	Median	44	1.06 (-1.07, 3.18)	1.08	2.89 (0.35, 23.97)	0.33	
HDL	**IVW**	150	-0.03 (-0.33, 0.26)	0.15	0.97 (0.72, 1.30)	0.82	0.63 (**H)**
	Egger	150	0.02 (-0.52, 0.56)	0.28	1.02 (0.59, 1.77)	0.95	0.83 **(I)**
	Median	150	0.09 (-0.39, 0.57)	0.25	1.09 (0.67, 1.79)	0.71	
LDL	**IVW**	120	-0.22 (-0.51, 0.08)	0.15	0.80 (0.60, 1.08)	0.15	0.35 (**H)**
	Egger	120	-0.52 (-1.08, 0.03)	0.28	0.59 (0.34, 1.03)	0.07	0.20 **(I)**
	Median	120	-0.21 (-0.67, 0.24)	0.23	0.81 (0.52, 1.27)	0.36	
TGL	**IVW**	100	-0.02 (-0.37, 0.33)	0.18	0.98 (0.69, 1.39)	0.90	0.47 (**H)**
	Egger	100	-0.44 (-1.02, 0.15)	0.30	0.64 (0.36, 1.16)	0.15	0.09 **(I)**
	Median	100	-0.06 (-0.63, 0.51)	0.29	0.94 (0.53, 1.66)	0.84	

BMI – Body Mass Index, FG – Fasting Glucose, HbA1C – Acetylated hemoglobin, HDL – high Density Lipoprotein, LDL – Low Density Lipoprotein, TGL – Triglycerides, IVW – Inverse Variance Weighted, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H – Heterogeneity *P* value, I – Intercept *P* value

Table S4

Instrumental variable analyses of BMI vs significant candidate mediator from Table S3 (Two sample mendelian randomization)

Exposure	**Outcome**	**Method**	**SNPs**	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**	
BMI	**Fasting glucose**	**IVW**	1132	0.08 (0.06, 0.10)	0.01	3.28×10^{-14}	1.08 (1.06, 1.10)	3.21×10^{-11} **(H)**
		Egger	1132	0.09 (0.03, 0.15)	0.03	0.002	1.09 (1.03, 1.16)	0.55 **(I)**
		Median	1132	0.07 (0.04, 0.10)	0.02	3.25×10^{-06}	1.07 (1.03, 1.12)	

IVW – Inverse Variance Weighted, H – Heterogeneity *P* value, I – Intercept *P* value

Table S5

Instrumental variable analyses of significant candidate mediator from Table S3 vs BMI (Two sample mendelian randomization)

Exposure	**Outcome**	**Method**	**SNPs**	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**	
Fasting glucose	**BMI**	**IVW**	15	0.00 (-0.09, 0.09)	0.05	0.99	1.00 (0.91, 1.10)	6.41×10^{-40} **(H)**
		Egger	15	0.07 (-0.14, 0.29)	0.11	0.50	1.08 (0.87, 1.33)	0.46 **(I)**
		Median	15	-0.01 (-0.05, 0.03)	0.02	0.61	0.99 (0.95, 1.03)	

IVW – Inverse Variance Weighted, H – Heterogeneity *P* value, I – Intercept *P* value

Multivariable Mendelian Randomization analysis of BMI and fasting glucose (FG) vs G1DD (Two sample mendelian randomization) (Tables S6-8)

Table S6

Exposure	**SNPs**	**Estimate (95% CI)**	**SE**	***P* value**	**H pval**	**OR (95% CI)**
BMI	1116	0.64 (0.31, 0.96)	0.16	0.0001	0.69	1.89 (1.37, 2.61)
FG	1116	0.61 (-0.10,1.32)	0.36	0.09	0.60	1.84 (0.90, 3.75)

BMI – Body Mass Index, FG – Fasting Glucose, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H pval – Heterogeneity *P* value

Table S7

Multivariable inverse-variance weighted method (variants uncorrelated, random-effect model)

Number of Variants 1116

Exposure	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**
Exposure 1 - BMI	0.61 (0.28, 0.94)	0.17	0.000	1.84 (1.35, 2.52)
Exposure 2 - FG	0.39 (-0.33, 1.11)	0.37	0.29	1.48 (0.72, 3.05)

Residual standard error 0.99
Residual standard error is set to 1 in calculation of confidence interval when its estimate is less than 1
Heterogeneity test statistic = 1089 on 1114 degrees of freedom, (p-value = 0.69)

BMI – Body Mass Index, FG – Fasting Glucose, CI – Confidence Interval, SE – Standard Error,

OR – Odds Ratio

Table S8

Exposure - BMI	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**
IVWM	0.64 (0.31, 0.96)	0.16	0.0001	1.89 (1.37, 2.61)
MVMR	0.61 (0.28, 0.94)	0.17	0.000	1.84 (1.32, 2.57)
Proportion Mediated, attributable to fasting glucose	4.7%			2.6%

BMI – Body Mass Index, IVWM – Inverse variance weighted method (Univariate), MVMR – Multivariate Mendelian Randomization, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio

Phenotypic association of BMI PRS on risk factors for G1DD

Table S9

Outcome=BMI PRS+DD_Status+Age+Sex+PC1to5 on G1DD cohort, logistic regression model					
Outcome	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**	**#Cases**
IHD	0.06 (-0.04, 0.16)	0.05	0.23	1.06 (0.96, 1.17)	728
HTN	0.04 (-0.04, 0.12)	0.04	0.32	1.05 (0.96, 1.13)	1472
T2D	0.21 (0.11, 0.31)	0.05	$1.44x10^{-05}$	1.23 (1.12, 1.36)	654

BMI – Body Mass Index, PRS – Polygenic Risk Score, G1DD – Grade 1 Diastolic Dysfunction, DD_Status – Grade 1 Diastolic Dysfunction status, IHD – Ischemic Heart Disease, HTN – Hypertension, T2D – Type 2 Diabetes, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, PC – Principal Components

Analyses after removal of controls receiving hypertension medications before the date of echocardiogram

Table S10

Demographic profile of study population Controls receiving hypertension medications before the date of echocardiogram have been removed

Characteristic*	**All participants**	**Cases**	**Controls**	***P* value**
	n=1419	n=668	n=751	
Age in years – mean (sd)	47.3(10.3)	52.9 (5.9)	42.2(10.7)	$<2x10^{-16}$†
Females	884 (62.3%)	365 (54.6%)	519 (68.6%)	0.0005†
Obesity	363 (24.7%)	248 (37.1%)	115 (15.3%)	$1.2x10^{-13}$‡
Ischemic Heart Disease	376 (26.5%)	286 (42.8%)	90 (12%)	$1.7x10^{-13}$‡
Hypertension	715 (50.4%)	527 (78.9%)	188 (25%)	$<2x10^{-16}$‡
Diabetes	334 (23.5%)	263 (39.4%)	71 (9.5%)	$<2x10^{-16}$‡

Footnotes:

* Values in the table represent counts and column percentages, except for age

† *P* value for the difference in proportions between cases and controls based on value of Pearson's chi-squared test statistic

‡ Association *P* value for the risk factor from a logistic regression model adjusting for age and sex

Table S11

Estimate of shared genetics between G1DD and candidate risk factors Controls receiving hypertension medications before the date of echocardiogram have been removed

G1DD Status (Outcome) = PRS +Age+Sex+PC1to5, logistic regression model				
Polygenic risk score	**Beta (95% CI)**	**SE**	***P* value**	**OR (95% CI)**
Diastolic Blood Pressure	0.09 (-0.04, 0.21)	0.06	0.19	1.09 (096, 1.24)
Systolic Blood Pressure	0.13 (0.00, 0.26)	0.06	0.04	1.14 (1.00, 1.30)
Coronary Artery Disease	-0.02 (-0.14, 0.11)	0.06	0.79	0.98 (0.87, 1.11)
Type 2 Diabetes	0.11 (-0.02, 0.23)	0.06	0.10	1.11 (0.98, 1.26)
Body Mass Index	0.20 (0.08, 0.33)	0.06	0.002	1.23 (1.08, 1.39)

G1DD – Grade 1 Diastolic dysfunction, PRS – Polygenic Risk Score, PC- Principal Components

CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio

Table S12

Instrumental variable analysis - BMI vs G1DD Controls receiving hypertension medications before the date of echocardiogram have been removed

Exposure	**Outcome**	**Method**	**SNPs**	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**	
BMI	**G1DD**	**IVW**	1132	0.69 (0.27, 1.11)	0.21	0.001	2.00 (1.32, 3.03)	0.96 **(H)**
		Egger	1132	1.77 (0.49, 3.04)	0.65	0.006	5.85 (1.64, 20.88)	0.08 **(I)**
		Median	1132	1.13 (0.44, 1.81)	0.35	0.001	3.09 (1.55, 6.14)	

BMI – Body Mass Index, G1DD – Grade 1 Diastolic dysfunction, IVW – Inverse Variance Weighted, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H – Heterogeneity *P* value, I – Intercept *P* value

Table S13

Instrumental variable analyses of candidate mediators for BMI (Two sample mendelian randomization) Controls receiving hypertension medications before the date of echocardiogram have been removed

Exposure	Method	SNPs	Estimate (95% CI)	SE	OR (95% CI)	*P* value	
FG	**IVW**	15	2.27 (1.00, 3.55)	0.65	9.70 (2.71, 34.71)	0.0005	0.50 (**H)**
	Egger	15	1.28 (-1.59, 4.15)	1.46	3.58 (0.20, 63.29)	0.38	0.45 **(I)**
	Median	15	1.60 (-0.21, 3.40)	0.92	4.95 (0.81, 30.06)	0.082	
HbA1C	**IVW**	44	1.39 (-0.33, 3.11)	0.88	4.01 (0.72, 22.39)	0.11	0.94 (**H)**
	Egger	44	3.02 (-0.23, 6.27)	1.66	20.52 (0.80, 528.07)	0.07	0.25 **(I)**
	Median	44	1.29 (-1.48, 4.07)	1.42	3.64 (0.23, 58.56)	0.36	
HDL	**IVW**	150	-0.12 (-0.50, 0.26)	0.20	0.89 (0.60, 1.30)	0.54	0.40 (**H)**
	Egger	150	0.15 (-0.56, 0.86)	0.36	1.16 (0.57, 2.37)	0.68	0.38 **(I)**
	Median	150	-0.41 (-1.02, 0.20)	0.31	0.66 (0.36, 1.22)	0.18	
LDL	**IVW**	121	-0.13 (-0.52, 0.25)	0.20	0.88 (0.60, 1.29)	0.50	0.24 (**H)**
	Egger	121	-0.26 (-0.99, 0.46)	0.37	0.77 (0.37, 1.58)	0.48	0.67 **(I)**
	Median	121	-0.11 (-0.71, 0.49)	0.30	0.90 (0.49, 1.63)	0.72	
TGL	**IVW**	100	0.01 (-0.47, 0.50)	0.25	1.01 (0.62, 1.64)	0.96	0.17 (**H)**
	Egger	100	-0.97 (-1.75, -0.19)	0.40	0.38 (0.17, 0.83)	0.02	0.002 **(I)**
	Median	100	0.29 (-0.45, 1.03)	0.38	1.34 (0.64, 2.81)	0.44	

BMI – Body Mass Index, FG – Fasting Glucose, HbA1C – Acetylated hemoglobin, HDL – high Density Lipoprotein, LDL – Low Density Lipoprotein, TGL – Triglycerides, IVW – Inverse Variance Weighted, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H – Heterogeneity *P* value, I – Intercept *P* value

Multivariable Mendelian Randomization analysis of BMI and fasting glucose (FG) vs G1DD (Two sample mendelian randomization) Controls receiving hypertension medications before the date of echocardiogram have been removed (Tables S14-16)

Table S14

Exposure	SNPs	Estimate (95% CI)	SE	*P* value	H pval	OR (95% CI)
BMI	1116	0.72 (0.30, 1.14)	0.21	0.0008	0.85	2.05 (1.35, 3.12)
FG	1116	0.99 (0.06, 1.91)	0.47	0.04	0.81	2.69 (1.06, 6.78)

BMI – Body Mass Index, FG – Fasting Glucose, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H pval – Heterogeneity *P* value

Table S15

Multivariable inverse-variance weighted method (variants uncorrelated, random-effect model) Number of Variants 1116

Exposure	Estimate (95% CI)	SE	*P* value	OR (95% CI)
Exposure 1 - BMI	0.66 (0.24,1.09)	0.22	0.002	1.94 (1.27, 2.97)
Exposure 2 - FG	0.75 (-0.19, 1.69)	0.48	0.12	2.11 (0.83, 5.40)

Residual standard error 0.977
Residual standard error is set to 1 in calculation of confidence interval when its estimate is less than 1
Heterogeneity test statistic = 1063.9803 on 1114 degrees of freedom, (*P* value = 0.8558)

BMI – Body Mass Index, FG – Fasting Glucose, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H pval – Heterogeneity *P* value

Table S16

Exposure - BMI	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**
IVWM	0.72 (0.30, 1.14)	0.21	0.0008	2.05 (1.35, 3.12)
MVMR	0.66 (0.24,1.09)	0.22	0.002	1.94 (1.27, 2.97)
Proportion Mediated, attributable to fasting glucose	8.3%			5.4%

BMI – Body Mass Index, IVWM – Inverse variance weighted method (Univariate), MVMR – Multivariate Mendelian Randomization, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H pval – Heterogeneity *P* value

Table S17

Phenotypic association of BMI PRS on risk factors for G1DD Controls receiving hypertension medications before the date of echocardiogram have been removed

Outcome=BMI PRS+DD_Status+Age+Sex+PC1to5 on G1DD cohort, logistic regression model					
Outcome	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**	**#Cases**
IHD	0.05 (-0.09, 0.19)	0.07	0.48	1.05 (0.92, 1.21)	376
HTN	0.11 (-0.01, 0.23)	0.06	0.08	1.12 (0.99, 1.26)	715
T2D	0.25 (0.11, 0.39)	0.07	0.0003	1.28 (1.12, 1.48)	334

BMI – Body Mass Index, PRS – Polygenic Risk Score, G1DD – Grade 1 Diastolic Dysfunction, DD_Status – Grade 1 Diastolic Dysfunction status, IHD – Ischemic Heart Disease, HTN – Hypertension, T2D – Type 2 Diabetes, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H pval – Heterogeneity *P* value, PC – Principal Components

Table S18

Demographic profile of study population Controls receiving diabetes medications before the date of echocardiogram have been removed

Characteristic *	**All participants**	**Cases**	**Controls**	***P* value**
	n=2061	n=668	n=1393	
Age in years – mean (sd)	47.3 (9.9)	52.9 (5.9)	44.6 (10.3)	$<2x10^{-16}$ †
Females	1257 (61.0%)	365 (54.6%)	892 (64.0%)	0.06 †
Obesity	551 (26.7%)	248 (37.1%)	303 (21.8%)	$6.17x10^{-10}$ ‡
Ischemic Heart Disease	571 (27.7%)	286 (42.8%)	285 (20.5%)	$6.51x10^{-08}$ ‡
Hypertension	1186 (57.5%)	527 (78.9%)	659 (47.3%)	$<2x10^{-16}$ ‡
Diabetes	506 (24.5%)	263 (39.4%)	143 (10.2%)	$<2x10^{-16}$ ‡

Footnotes:

* Values in the table represent counts and column percentages, except for age.

† *P* value for the difference in proportions between cases and controls based on value of Pearson's chi-squared test statistic

‡ Association *P* value for the risk factor from a logistic regression model adjusting for age and sex

Table S19

Estimate of shared genetics between G1DD and candidate risk factors Controls receiving diabetes medications before the date of echocardiogram have been removed

G1DD Status (Outcome) = PRS +Age+Sex+PC1to5, logistic regression model				
Polygenic risk score	**Beta (95% CI)**	**SE**	***P* value**	**OR (95% CI)**
Diastolic Blood Pressure	0.02 (-0.08, 0.12)	0.05	0.68	1.02 (0.92, 1.13)
Systolic Blood Pressure	0.02 (-0.08, 0.13)	0.05	0.65	1.02 (0.92, 1.13)
Coronary Artery Disease	-0.04 (-0.14, 0.06)	0.05	0.48	0.96 (0.87, 1.07)
Type 2 Diabetes	0.13 (0.03, 0.24)	0.05	0.012	1.14 (1.03, 1.27)
Body Mass Index	0.21 (0.10, 0.31)	0.05	9.47×10^{-05}	1.23 (1.11, 1.37)

G1DD – Grade 1 Diastolic dysfunction, PRS – Polygenic Risk Score, PC- Principal Components

CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio

Table S20

Instrumental variable analysis - BMI vs G1DD Controls receiving diabetes medications before the date of echocardiogram have been removed

Exposure	**Outcome**	**Method**	**SNPs**	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**	
BMI	**G1DD**	**IVW**	1132	0.68 (0.34,1.02)	0.17	$8.83x10^{-05}$	1.97 (1.40, 2.77)	0.52 **(H)**
		Egger	1132	1.15 (0.12,2.19)	0.53	0.03	3.17 (1.12, 8.93)	0.34 **(I)**
		Median	1132	0.82 (0.25,1.39)	0.29	0.004	2.27 (1.29, 4.00)	

BMI – Body Mass Index, G1DD – Grade 1 Diastolic dysfunction, IVW – Inverse Variance Weighted, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H – Heterogeneity *P* value, I – Intercept *P* value

Table S21

Instrumental variable analyses of candidate mediators for BMI (Two sample mendelian randomization) Controls receiving diabetes medications before the date of echocardiogram have been removed

Exposure	Method	SNPs	Estimate (95% CI)	SE	OR (95% CI)	*P* value	
FG	**IVW**	15	1.75 (0.71, 2.79)	0.53	5.76 (2.03, 16.33)	$9.93x10^{-04}$	0.67 **(H)**
	Egger	15	0.10 (-2.25, 2.45)	1.20	1.11 (0.11, 11.62)	0.93	0.13 **(I)**
	Median	15	1.30 (-0.18, 2.78)	0.76	3.68 (0.84, 16.18)	0.084	
HbA1C	**IVW**	44	0.91 (0.72, -0.50)	0.72	2.48 (0.61, 10.14)	$2.05x10^{-01}$	0.92 **(H)**
	Egger	44	2.01 (1.37, -0.68)	1.37	7.45 (0.51, 109.61)	0.14	0.35 **(I)**
	Median	44	0.65 (1.11, -1.52)	1.11	1.92 (0.22, 16.77)	0.557	
HDL	**IVW**	150	-0.10 (-0.41, 0.21)	0.16	0.90 (0.66, 1.23)	$5.18x10^{-01}$	0.66 **(H)**
	Egger	150	0.02 (-0.56, 0.59)	0.29	1.02 (0.57, 1.80)	0.96	0.64 **(I)**
	Median	150	-0.30 (-0.81, 0.22)	0.26	0.74 (0.44, 1.24)	0.259	
LDL	**IVW**	121	-0.13 (-0.44, 0.17)	0.15	0.87 (0.65, 1.18)	$3.84x10^{-01}$	0.48 **(H)**
	Egger	121	-0.24 (-0.81, 0.32)	0.29	0.79 (0.45, 1.38)	0.40	0.66 **(I)**
	Median	121	-0.03 (-0.51, 0.46)	0.25	0.97 (0.60, 1.58)	0.914	
TGL	**IVW**	100	-0.02 (-0.40, 0.35)	0.19	0.98 (0.67, 1.42)	$8.99x10^{-01}$	0.51 **(H)**
	Egger	100	-0.56 (-1.18, 0.06)	0.32	0.57 (0.31, 1.07)	0.08	0.04 **(I)**
	Median	100	0.02 (-0.56, 0.60)	0.30	1.02 (0.57, 1.83)	0.944	

BMI – Body Mass Index, FG – Fasting Glucose, HbA1C – Acetylated hemoglobin, HDL – high Density Lipoprotein, LDL – Low Density Lipoprotein, TGL – Triglycerides, IVW – Inverse Variance Weighted, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H – Heterogeneity *P* value, I – Intercept *P* value

Multivariable Mendelian Randomization analysis of BMI and fasting glucose (FG) vs G1DD (Two sample mendelian randomization) Controls receiving diabetes medications before the date of echocardiogram have been removed (Tables S22-24)

Table S22

Exposure	**SNPs**	**Estimate (95% CI)**	**SE**	***P* value**	**H pval**	**OR (95% CI)**
BMI	1116	0.73 (0.39, 1.07)	0.17	$3.12x10^{-05}$	0.46	2.07 (1.47, 2.92)
FG	1116	0.86 (0.10, 1.62)	0.39	0.03	0.36	2.37 (1.11, 5.06)

BMI – Body Mass Index, FG – Fasting Glucose, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H pval – Heterogeneity *P* value

Table S23

Multivariable inverse-variance weighted method (variants uncorrelated, random-effect model) Number of Variants 1116

Exposure	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**
Exposure 1 - BMI	0.68 (0.34, 1.03)	0.18	0.000	1.98 (1.40, 2.80)
Exposure 2 - FG	0.61 (-0.15, 1.38)	0.39	0.12	1.84 (0.86, 3.97)

Residual standard error 1.001
Residual standard error is set to 1 in calculation of confidence interval when its estimate is less than 1
Heterogeneity test statistic = 1116.7974 on 1114 degrees of freedom, (*P* value = 0.47)

BMI – Body Mass Index, FG – Fasting Glucose, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H pval – Heterogeneity *P* value

Table S24

Exposure - BMI	**Estimate (95% CI)**	**SE**	***P* value**	**OR (95% CI)**
IVWM	0.73 (0.39, 1.07)	0.17	$3.12x10^{-05}$	2.07 (1.47, 2.92)
MVMR	0.68 (0.34, 1.03)	0.18	0.68 (0.34, 1.03)	1.98 (1.40, 2.80)
Proportion Mediated, attributable to fasting glucose	6.8%			4.3%

BMI – Body Mass Index, FG – Fasting Glucose, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H pval – Heterogeneity *P* value

Table S25

Phenotypic association of BMI PRS on risk factors for G1DD Controls receiving diabetes medications before the date of echocardiogram have been removed

Outcome=BMI PRS+DD_Status+Age+Sex+PC1to5 on G1DD cohort, logistic regression model					
Outcome	**Estimate (95% CI)**	**SE**	**P-value**	**OR (95% CI)**	**#Cases**
IHD	0.09 (-0.008, 0.19)	0.05	0.08	1.09 (0.99, 1.21)	571
HTN	0.05 (-0.05, 0.15)	0.05	0.33	1.05 (0.95, 1.16)	1186
T2D	0.24 (0.12,0.36)	0.06	$4.52x10^{-05}$	1.27 (1.13, 1.43)	506

BMI – Body Mass Index, PRS – Polygenic Risk Score, G1DD – Grade 1 Diastolic Dysfunction, DD_Status – Grade 1 Diastolic Dysfunction status, PC – Principal Components, IHD – Ischemic Heart Disease, HTN – Hypertension, T2D – Type 2 Diabetes, CI – Confidence Interval, SE – Standard Error, OR – Odds Ratio, H pval – Heterogeneity *P* value

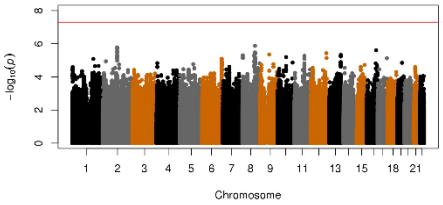
Table S26

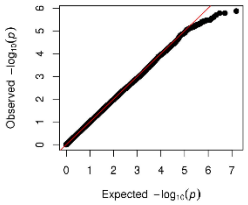
Predictive performance of BMI and FG genetic instruments

Model	AUC
Age+Sex+PC	0.7438
Age+Sex+PC+BMI PRS	0.7489
Age+Sex+PC+FG PRS	0.745

BMI – Body Mass Index, FG – Fasting Glucose, PC – Principal Components, AUC – Area Under the Curve

Figure S1





Manhattan Plot **QQ Plot**

Figure S1a GWAS of Grade 1 Diastolic Dysfunction

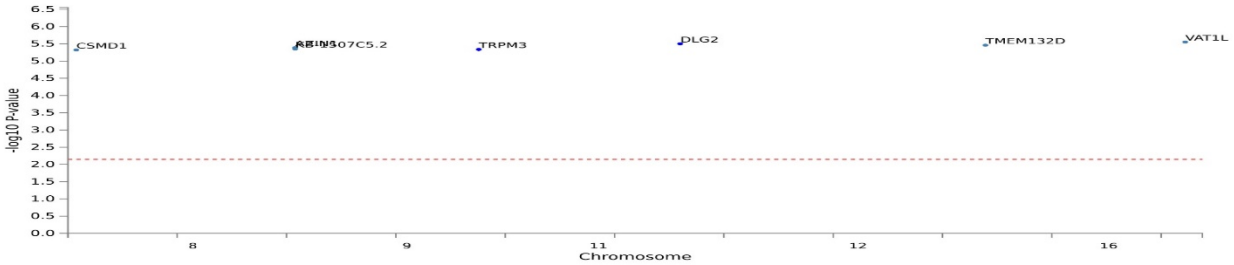


Figure S1b MAGMA based gene association of top SNPs.

Figure S2

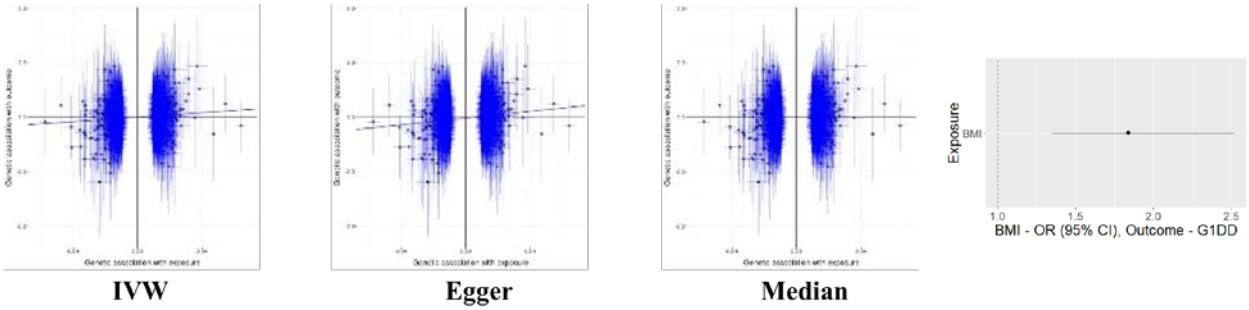

IVW
Egger
Median
Exposure
BMI
1.0
1.5
2.0
2.5
BMI - OR (95% CI), Outcome - G1DD

Figure S3

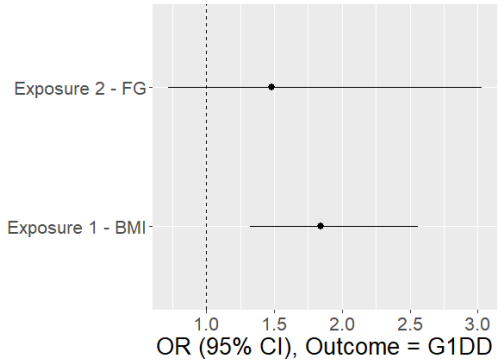

Exposure 2 - FG
Exposure 1 - BMI
1.0
1.5
2.0
2.5
3.0
OR (95% CI), Outcome = G1DD

Figure S4

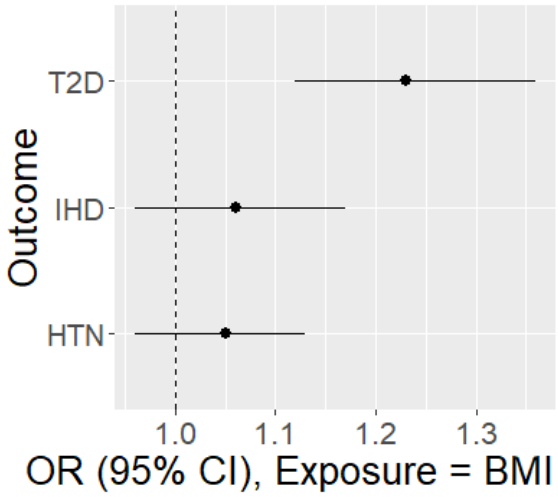
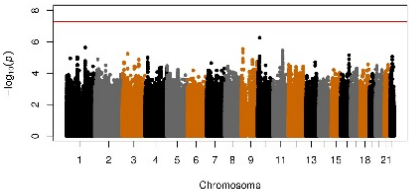
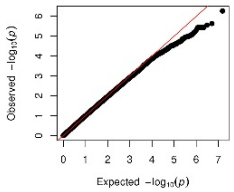


Figure S5



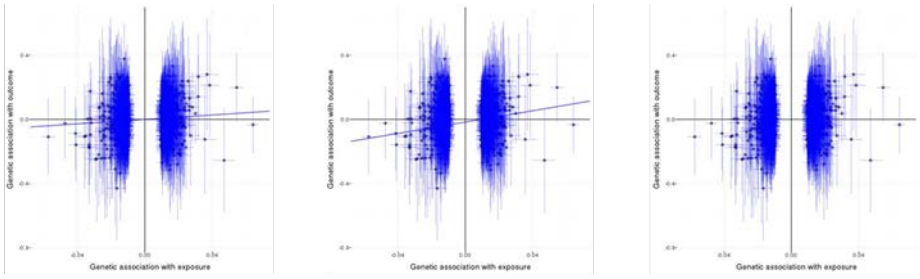


Manhattan Plot **QQ-Plot**

GWAS of Grade 1 Diastolic Dysfunction

Cases and controls differ by G1DD status on echo + controls on HTN drugs before echo removed

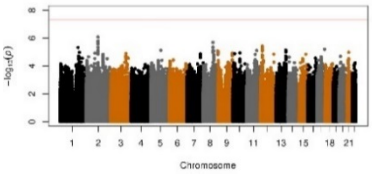
Figure S6

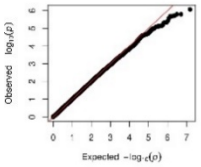


IVW **Egger** **Median**

Instrumental variable analysis - BMI vs G1DD - Controls receiving hypertension medications before the date of echocardiogram have been removed

Figure S7



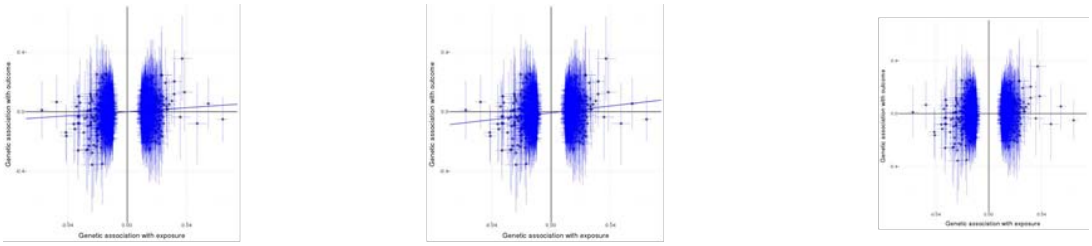


Manhattan Plot **QQ Plot**

GWAS of Grade 1 Diastolic Dysfunction

Cases and controls differ by G1DD status on echo + no controls on Diabetes drugs before echo removed

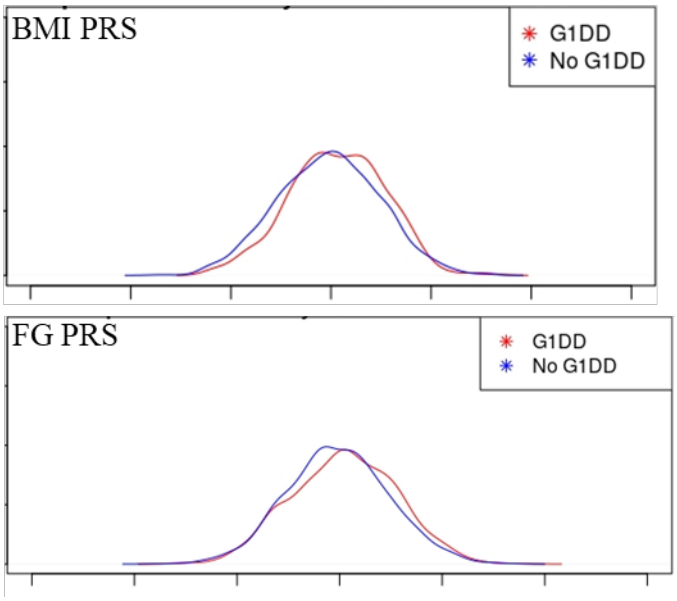
Figure S8



IVW Egger Median

Instrumental variable analysis - BMI vs G1DD - Controls receiving diabetes medications before the date of echocardiogram have been removed

Figure S9



Distribution of scaled PRS for BMI and FG genetic instruments