



Effect of polygenic risk for schizophrenia on cardiac structure and function: a UK Biobank observational study



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Summary

Background Cardiovascular disease is a major cause of excess mortality in people with schizophrenia. Several factors are responsible, including lifestyle and metabolic effects of antipsychotics. However, variations in cardiac structure and function are seen in people with schizophrenia in the absence of cardiovascular disease risk factors and after accounting for lifestyle and medication. Therefore, we aimed to explore whether shared genetic causes contribute to these cardiac variations.

Methods For this observational study, we used data from the UK Biobank and included White British or Irish individuals without diagnosed schizophrenia with variable polygenic risk scores for the condition. To test the association between polygenic risk score for schizophrenia and cardiac phenotype, we used principal component analysis and regression. Robust regression was then used to explore the association between the polygenic risk score for schizophrenia and individual cardiac phenotypes. We repeated analyses with fibro-inflammatory pathway-specific polygenic risk scores for schizophrenia. Last, we investigated genome-wide sharing of common variants between schizophrenia and cardiac phenotypes using linkage disequilibrium score regression. The primary outcome was principal component regression.

Findings Of 33 353 individuals recruited, 32 279 participants had complete cardiac MRI data and were included in the analysis, of whom 16 625 (51.5%) were female and 15 654 (48.5%) were male. 1074 participants were excluded on the basis of incomplete cardiac MRI data (for all phenotypes). A model regressing polygenic risk scores for schizophrenia onto the first five cardiac principal components of the principal components analysis was significant ($F=5.09$; $p=0.00012$). Principal component 1 captured a pattern of increased cardiac volumes, increased absolute peak diastolic strain rates, and reduced ejection fractions; polygenic risk scores for schizophrenia and principal component 1 were negatively associated ($\beta=-0.01$ [SE 0.003]; $p=0.017$). Similar to the principal component analysis results, for individual cardiac phenotypes, we observed negative associations between polygenic risk scores for schizophrenia and indexed right ventricular end-systolic volume ($\beta=-0.14$ [0.04]; $p=0.0013$, $p_{FDR}=0.015$), indexed right ventricular end-diastolic volume ($\beta=-0.17$ [0.08]; $p=0.025$; $p_{FDR}=0.082$), and absolute longitudinal peak diastolic strain rates ($\beta=-0.01$ [0.003]; $p=0.0024$, $p_{FDR}=0.015$), and a positive association between polygenic risk scores for schizophrenia and right ventricular ejection fraction ($\beta=0.09$ [0.03]; $p=0.0041$, $p_{FDR}=0.015$). Models examining the transforming growth factor- β (TGF- β)-specific and acute inflammation-specific polygenic risk scores for schizophrenia found significant associations with the first five principal components ($F=2.62$, $p=0.022$; $F=2.54$, $p=0.026$). Using linkage disequilibrium score regression, we observed genetic overlap with schizophrenia for right ventricular end-systolic volume and right ventricular ejection fraction ($p=0.0090$, $p=0.0077$).

Interpretation High polygenic risk scores for schizophrenia are associated with decreased cardiac volumes, increased ejection fractions, and decreased absolute peak diastolic strain rates. TGF- β and inflammatory pathways might be implicated, and there is evidence of genetic overlap for some cardiac phenotypes. Reduced absolute peak diastolic strain rates indicate increased myocardial stiffness and diastolic dysfunction, which increases risk of cardiac disease. Thus, genetic risk for schizophrenia is associated with cardiac structural changes that can worsen cardiac outcomes. Further work is required to determine whether these associations are specific to schizophrenia or are also seen in other psychiatric conditions.

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Introduction

People with schizophrenia die 15 years earlier than the general population, with cardiovascular disease being a major contributing factor.¹ There are several reasons for

increased burden of cardiovascular disease in schizophrenia, including unhealthy lifestyle, reduced access to physical health care, and the metabolic effect of antipsychotics.² However, studies using cardiac MRI

Research in context

Evidence before this study

Cardiac MRI studies found that physically healthy people with schizophrenia had concentric cardiac remodelling, smaller ventricular volumes, and slower myocardial relaxation than healthy people without schizophrenia. The cause of these phenotypic variations is unclear, although schizophrenia involves multiple organ systems from illness onset, including variations in fibro-inflammatory signalling pathways that could contribute. Genetic liability to schizophrenia increases risk of heart failure; however, it remains unclear whether structural and functional cardiac variations seen in people with schizophrenia are due to common causal genetic determinants. Furthermore, the role of fibro-inflammatory signalling pathways in any such genetic associations is not defined. To evaluate previous evidence, we searched PubMed using the search terms “schizophrenia”, “cardiac”, and “genetic”, or “polygenic” from inception to Nov 3, 2022, without language restrictions. Of 463 studies retrieved, no studies explored the association between genetic risk for schizophrenia and variations in cardiac structure and function.

Added value of this study

In the first study of its kind, using genetic and cardiac MRI data from a large population-based sample without schizophrenia, we found that increased genetic liability for schizophrenia is associated with variations in cardiac structure and function, specifically decreased cardiac volumes, increased ejection

fractions, and decreased absolute peak diastolic strain rates. Reduced absolute peak diastolic strain rates indicate increased myocardial stiffness, which accompanies diastolic dysfunction. Diastolic dysfunction increases risk of major adverse cardiovascular events and all-cause mortality. We identified a role for gene variants in transforming growth factor- β and inflammatory pathways. We also observed genetic overlap with schizophrenia for right-sided cardiac phenotypes, providing evidence that shared risk alleles might contribute to the observed association between genetic liability for schizophrenia and cardiac phenotypic variation.

Implications of all the available evidence

Our results build on previous cardiac MRI findings of decreased cardiac volumes and slower myocardial relaxation in patients with schizophrenia, to show that genetic risk for schizophrenia is associated with these phenotypes. Furthermore, we have observed that genetic risk for schizophrenia is associated with cardiac structural changes that worsen cardiac outcomes. Our findings have implications for conceptualising schizophrenia as a single-organ disorder and future monitoring, and potentially treating cardiac disease in people with schizophrenia. The implication that genetic risk for schizophrenia is associated with cardiac structural changes that exacerbate cardiac outcomes supports the argument for regular cardiac screening in patients from schizophrenia onset.

have observed variations in cardiac structure and function in people with schizophrenia, even in the absence of established risk factors for cardiovascular disease and after accounting for lifestyle effects and medication.^{3,4} Studies comparing cardiac phenotypes in two physically healthy groups, one with schizophrenia and one without schizophrenia, found that the group with schizophrenia had smaller cardiac volumes, concentric cardiac remodelling (a key predictor of future cardiac disease), and evidence of cardiac fibro-inflammation.^{3,4} The cause of this cardiac phenotypic variation is unclear;⁵ schizophrenia involves multiple organ systems from illness onset that could affect cardiac structure and function.^{6,7} For example, elevated systemic concentrations of inflammatory cytokines and transforming growth factor- β (TGF- β), a key mediator of cardiac fibrogenesis,⁸ are observed in people naive to antipsychotics with first-episode psychosis.⁹

Schizophrenia is a polygenic condition, with multiple, common genetic variants increasing the risk of illness.¹⁰ A polygenic risk score for schizophrenia can be calculated on the basis of the number of genetic risk variants for schizophrenia carried and the strength of the association of each variant with schizophrenia.¹¹ In population samples, the polygenic risk score for schizophrenia is associated with individual differences

in brain structure¹² and increased risk for various physical health conditions.¹³ To date, studies that have explored shared genetic origins for schizophrenia and cardiac pathology have focused on the risk of developing various cardiac disease processes (eg, cardiovascular disease and heart failure). For example, in 2021, a Mendelian randomisation study showed that genetic liability to schizophrenia increases the risk of heart failure, independent of health behaviours, such as smoking or levels of physical activity.¹⁴ However, it is unknown whether a shared genetic cause exists between schizophrenia and cardiac structure and function. Therefore, we aimed to test the association between the polygenic risk score for schizophrenia and cardiac structure and function in the general population. Because of the evidence of cardiac fibro-inflammation and systemic inflammation in people with schizophrenia, we also aimed to examine the role of fibro-inflammatory gene pathways in the association between the polygenic risk score and cardiac phenotypes. Furthermore, since associations between the polygenic risk score for schizophrenia and cardiac phenotypes could reflect shared risk alleles or a causal effect, we investigated genome-wide sharing of common variants between schizophrenia and cardiac phenotypes using linkage disequilibrium score regression.

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Methods

Study design and participants

For this observational study, we used data from the UK Biobank and included individuals without diagnosed schizophrenia (application 65321). Such studies have been previously described,¹⁵ with participants randomly invited to take part in the imaging sub-study in 2014.¹⁶ Exclusion criteria were schizophrenia, identified by ICD-10 diagnosis (F20–F29: schizophrenia, schizotypal, and delusional disorders), and ethnicities other than White British or Irish. The latter exclusion criterion recognised alterations in cardiac structure and function across ethnic groups¹⁷ and was done according to previous UK Biobank studies on cardiac MRI.¹⁸ The UK Biobank acquires data on participant sex (male or female) from the central NHS registry at recruitment, but in some cases, this is updated by the participant. Participants provided written informed consent.

Cardiac MRI protocol and analysis

The protocol for standardised cardiac MRI acquisition has been detailed previously.¹⁹ Cardiac phenotypes were selected on the basis of those previously measured in studies examining cardiac structure and function in people with schizophrenia,^{3,4} complemented by measures of diastolic function. We used a validated deep-learning neural network algorithm for cardiac MRI segmentation and analysis to derive cardiac measures (appendix p 2). When appropriate, phenotypes were indexed to body surface area (appendix p 2). The cardiac phenotypes derived were left and right ventricular end-diastolic volumes, end-systolic volumes, stroke volumes, and ejection fractions with left ventricular mass, maximal end-diastolic septal wall thickness, concentricity, and longitudinal and radial peak diastolic strain rates.

Genotyping and imputation processing

Procedures for genotyping, imputation, and quality control for the UK Biobank have previously been reported²⁰ (appendix p 3). Quality control checks and filtering for single nucleotide polymorphisms (SNPs) in the 2022 Psychiatric Genomics Consortium genome-wide association studies (GWAS) of schizophrenia¹⁰ provided 410 319 individuals and 83 326 SNPs.

Derivation of polygenic risk score

Plink (version 1.9) was used to create an SNP set in approximate linkage equilibrium. Clump-based linkage disequilibrium pruning was performed with an r^2 less than 0.25 within a 200-kb window (appendix p 3). To account for population stratification, we calculated ten genetic principal components using Plink. Using PRSice-2, marker weights (logarithm of the association odds ratio) and p value association statistics for individual SNPs were derived from the 2022 Psychiatric Genomics Consortium GWAS of schizophrenia.¹⁰ As previously described, five polygenic risk scores for schizophrenia

were generated for each individual using SNPs selected according to the significance of their association with the phenotype in the discovery GWAS at nominal p value thresholds of 0.01 or less, $p=0.05$, $p=0.1$, $p=0.5$, and $p=1.00$.¹² Furthermore, a polygenic risk score of best-fit was generated by PRSice-2, although it was not our primary outcome owing to overfitting concerns.¹¹ For this study, the inclusion threshold of SNPs was set at $p=0.05$ or less as this threshold was shown to explain the most phenotypic variance in the discovery cohort,¹⁰ and contains an acceptable signal-to-noise ratio in polygenic prediction for associations with schizophrenia;¹⁰ 18918 SNPs were included at this threshold. The standardised polygenic risk scores for schizophrenia were used for analyses.

Assessments of cardiac data distribution, collinearity, clustering, and confounding

All analyses were conducted using R (version 3.6.1). Significance for individual analyses was set at p less than 0.05; for false discovery rate (FDR) adjusted p values (p_{FDR}), significance was set at p_{FDR} less than 0.10. Density plots of cardiac phenotype data were visually inspected to assess normality of distribution. Heteroscedasticity of linear regression models was assessed using the Breusch-Pagan test. To assess collinearity, we calculated the variance inflation factor for each cardiac phenotype; a variance inflation factor of more than ten represented excessive or serious multi-collinearity. Pearson correlation coefficients between cardiac phenotypes were calculated and presented as a heatmap, complete-linkage hierarchical agglomerative clustering was used to identify related groups of cardiac phenotypes, and the average silhouette method determined the optimum number of clusters (appendix p 3). These clusters were used to colour-code loading plots for the subsequent principal components analysis. To assess confounding, linear and robust regression were used to determine if age and BMI were associated with the polygenic risk score for schizophrenia.

Principal component analysis

Due to expected collinearity between cardiac phenotypes, a principal component analysis was performed to derive orthogonal principal axes of variation in cardiac phenotypes, whereby each principal axis is a linear combination of the original cardiac phenotypes. Before principal component analysis, nuisance covariates were regressed out from each cardiac phenotype, which were: age, age-squared, sex, genotype array, and the first ten genetic principal components (to account for the effects attributable to the primary genotypic axes of variance). The resultant cardiac phenotype residuals were Z scored before the principal component analysis (appendix p 2). Stroke volume is expressed as a weighted sum of the difference between end-systolic and end-diastolic volumes so that left and right stroke volumes were excluded leaving 11 phenotypes in the principal

See Online for appendix

component analysis. This technique enabled the projection of the original data onto the identified principal axes. The first principal components (ie, columns) that cumulatively explained at least 90% of the cardiac data variance were selected for principal component regression (five components).²¹ To help with the interpretation of the principal components, we displayed the contributed direction and strength of each cardiac phenotype to a given principal axis included in the regression model; the additive inverse of radial peak diastolic strain rate was used for these plots so that longitudinal and radial strain measures were of the same sign. Linear regression was used to explore the association between the polygenic risk score for schizophrenia and selected principal components as a group (appendix p 3). Correlation coefficients for the polygenic risk score for schizophrenia and each principal component contributing to this multivariate model were examined. Since antipsychotic treatment might alter cardiac structure and function,^{3,4} we performed a sensitivity analysis and excluded people prescribed antipsychotics (appendix p 3).

Robust regression analysis of individual cardiac phenotypes

In anticipation of outlying and heteroscedastic cardiac phenotype data, robust regression was used to determine whether the polygenic risk score for schizophrenia was associated with individual cardiac phenotypes. Robust regression mitigates the effect of extreme observations in an otherwise normally distributed dataset by iterated reweighted least squares.²² Huber-weighted robust analyses were done using the MASS package (version 7.3.55); age, age-squared, sex, genotype array, and the first ten genetic principal components were included as covariates. Standardised regression coefficients were calculated, and for each regression model, a robust *F*-test was done to determine significance. p_{FDR} values were calculated, correcting for 13 cardiac phenotypes.

Derivation of pathway-based polygenic risk scores and signalling-pathway-specific analyses

To explore the fibro-inflammatory mechanisms underlying the association between the polygenic risk score for schizophrenia and cardiac alterations, genetic pathways related to acute inflammation, TGF- β signalling,²³ and myocardial fibrosis were selected from the Molecular Signatures Database (version 7.4)²⁴ to help calculate the pathway-based polygenic risk score (appendix p 5). PRSet implemented in PRSice-2 was used to calculate gene-set-based polygenic risk scores for schizophrenia for genetic pathways associated with acute inflammation, TGF- β signalling,²³ and myocardial fibrosis. A *p* value threshold of 1.00 for PRSet was used because gene-set polygenic risk scores contain a small proportion of SNPs, which might be unrepresentative of

whole gene sets. Linear regression was used to explore the association between a given pathway-based polygenic risk score for schizophrenia and the group of cardiac principal components identified in the principal component analysis, followed by an examination of correlation coefficients for the polygenic risk score for schizophrenia and each principal component contributing to the model. Robust regression was then used to determine whether a pathway-based polygenic risk score for schizophrenia was significantly associated with individual cardiac phenotypes, with age, age-squared, sex, genotype array, and the first ten genetic principal components as covariates. For each regression model, self-contained and competitive *p* values were provided. Self-contained *p* values tested the association with the target cardiac phenotype whereas competitive *p* values tested the signal enrichment of the specific gene set (appendix p 4). The competitive *p* value was obtained by comparing the observed association of the gene-set polygenic risk score with the 10 000 permuted null *p* value distribution of random gene-set polygenic risk scores. p_{FDR} was calculated correcting for 13 cardiac phenotypes.

Linkage disequilibrium score regression

To evaluate sharing of risk alleles, we used the LDSC package (version 1.0.1) to estimate pairwise genome-wide genetic correlations between schizophrenia (Psychiatric Genomics Consortium GWAS of schizophrenia) and cardiac phenotypes.²⁵ In addition to the ten cardiac phenotypes with available results from GWAS, we included bipolar disorder as a positive control and height as a negative control (appendix p 4). p_{FDR} values were calculated, correcting for ten analyses.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 33 353 individuals recruited with available genetic and cardiac data, 32 279 (96.8%) with all 13 cardiac phenotypes were included in the principal component analysis, of whom 16 625 were female participants and 15 654 were male participants ($p < 0.0001$; table). 1074 individuals were excluded on the basis of incomplete cardiac imaging (for all phenotypes). Sex was included as a covariate in analyses, and where appropriate, cardiac phenotypes were indexed to body surface area. BMI and polygenic risk score for schizophrenia were significantly negatively associated ($\beta = -0.06$, $p = 0.0061$; robust regression $\beta = -0.05$, $p = 0.018$).

Visual inspection of density plots suggested that cardiac phenotype data were broadly normally distributed; however, most parameters were slightly skewed (appendix p 6). Furthermore, there was heteroscedasticity in linear regression models examining an association between the polygenic risk score for

	Total participants (n=33 353)	Participants included in the analysis (n=32 279)	Test statistic; p value
Male	16 238 (48.7%)	15 654 (48.5%)	$\chi^2=29.2$; $p<0.0001$
Female	17 115 (51.3%)	16 625 (51.5%)	..
Age, years	55.1 (7.4)	55.0 (7.4)	$\beta=-0.02$; $p=0.61$
BMI, kg/m ²	26.6 (4.2)	26.6 (4.2)	$\beta=-0.06$; $p=0.0061$

Data are n (%) or mean (SD). β values denote the linear association between age or BMI and the polygenic risk score for schizophrenia.

Table: Baseline characteristics

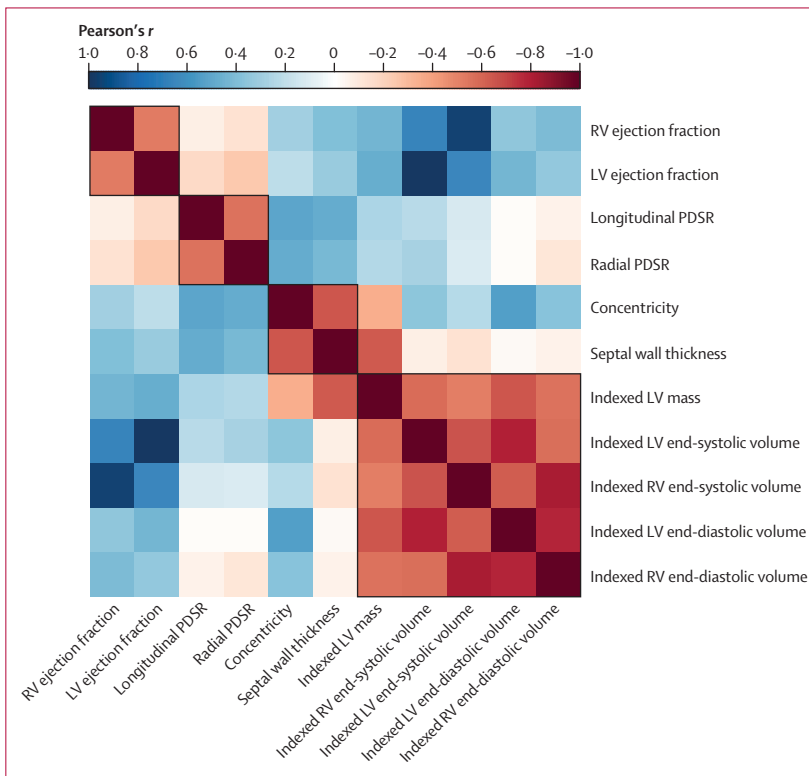


Figure 1: Collinearity assessment and cluster analysis
 Heatmap demonstrating degree of association between cardiac parameters using *r*. There was a significant ($p<0.05$) association between all cardiac parameters except between septal wall thickness and left ventricular (LV) ejection fraction, and indexed LV end-diastolic volume, and indexed LV end-systolic volume. The black rectangles show cardiac phenotypes divided into four clusters: an ejection fraction cluster, including LV ejection fraction and right ventricular (RV) ejection fraction; a peak diastolic strain rate (PDSR) cluster, including longitudinal PDSR and radial PDSR (the additive inverse of radial PDSR is used so longitudinal and radial strain measures are the same sign); a concentricity and septal wall thickness cluster; and a ventricular mass and volume cluster, including indexed LV mass, indexed LV end-diastolic volume, indexed LV end-systolic volume, indexed RV end-diastolic volume, and indexed RV end-systolic volume.

schizophrenia and cardiac phenotypes (all Breusch-Pagan tests $p<0.001$), and evidence of collinearity with a variance inflation factor of more than 10 for ten cardiac phenotypes (appendix p 7). Correlations for 96% cardiac phenotype comparisons were significant, with *r* values up to 0.83 (figure 1, appendix p 8). Complete linkage hierarchical clustering visualised grouping of the cardiac phenotypes based on correlation coefficients. Four

clusters optimally grouped the data into ejection fractions, ventricular mass or volumes, peak diastolic strain rates, and septal wall thickness or concentricity (figure 1, appendix p 9).

The first five principal components explained 90.60% of the data variance (figure 2). A multiple regression model regressing polygenic risk score for schizophrenia onto these principal components was significant ($F=5.09$; $p=0.00012$). Correlation coefficients for each principal component contributing to this multivariate model were examined. We observed a negative association between polygenic risk score for schizophrenia and principal component 1 ($\beta=-0.01$ [SE 0.003]); $p=0.017$; figure 3A). Principal component 1 explained 36.2% of cardiac data variance and captured a pattern of variation characterised by increased ventricular end-diastolic and end-systolic volumes, increased rates of absolute peak diastolic strain (ie, reduced myocardial stiffness), and reduced ejection fractions. We also observed a positive association between the polygenic risk score for schizophrenia and principal component 4 ($\beta=0.02$ [SE 0.01]; $p<0.0001$). Principal component 4 captured a pattern of variation characterised by increased ejection fractions, decreased absolute peak diastolic strain rates (ie, increased myocardial stiffness), and increased ventricular end-diastolic and end-systolic volumes. Associations between polygenic risk score for schizophrenia and principal components 2, 3, and 5 were not significant (appendix p 11). Associations between polygenic risk score for schizophrenia at all nominal *p* value thresholds and the first five principal components as a group are provided in the appendix (p 10). A sensitivity analysis excluding data from people prescribed an antipsychotic (339 participants excluded, 31941 participants remaining) did not materially change the multiple regression result ($F=4.95$; $p=0.00016$). Thus, we observed a significant association between polygenic risk for schizophrenia and cardiac variations, as people with increased polygenic risk score for schizophrenia have decreased cardiac volumes, increased myocardial stiffness, and increased ejection fractions.

We examined if the pattern of cardiac alterations associated with polygenic risk score for schizophrenia in the principal component analysis was maintained in individual regression analyses using the original cardiac phenotypes. Four associations were unaffected by correction of false discovery rate, with significant negative associations observed between polygenic risk score for schizophrenia and indexed right ventricular end-systolic volume ($\beta=-0.14$ [SE 0.04]; $p=0.0013$, $p_{FDR}=0.015$), indexed right ventricular end-diastolic volume ($\beta=-0.17$ [0.08]; $p=0.025$, $p_{FDR}=0.082$), and rate of longitudinal peak diastolic strain ($\beta=-0.01$ [0.003]; $p=0.0024$, $p_{FDR}=0.015$; figure 3B). We observed a significant positive association between polygenic risk score for schizophrenia and right ventricular ejection fraction ($\beta=0.09$ [0.03]; $p=0.0041$, $p_{FDR}=0.018$; figure 3B). These associations are consistent with the principal

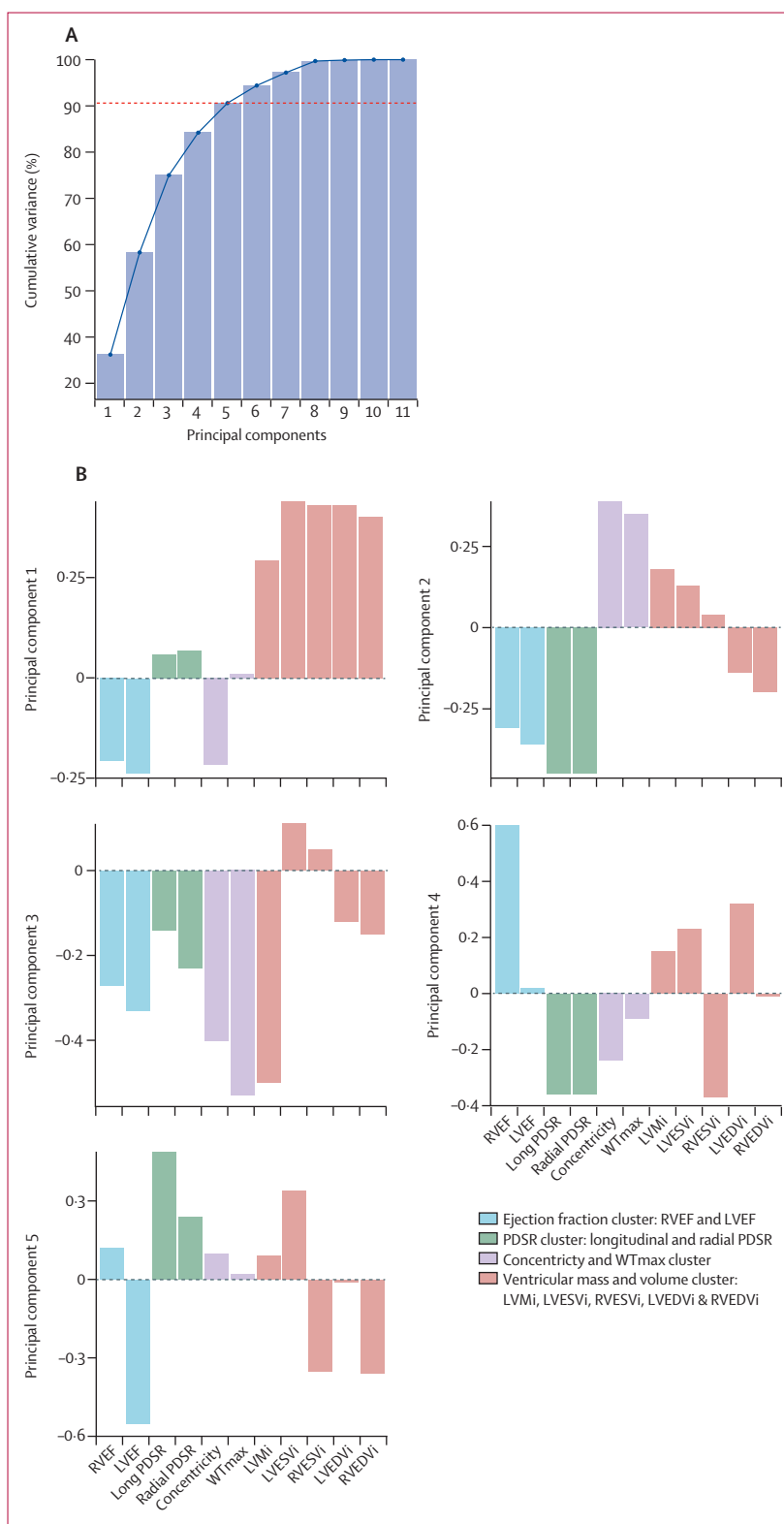
component regression of a negative relationship between the polygenic risk score for schizophrenia and principal component 1 (ie, an increased polygenic risk score for schizophrenia associated with small ventricular end-diastolic and end-systolic volumes, reduced absolute peak diastolic strain rates, and increased ejection fractions). We did not observe a significant association between polygenic risk score for schizophrenia and other cardiac phenotypes; regression results for polygenic risk score for schizophrenia at all nominal p value thresholds are provided in the appendix (p 12).

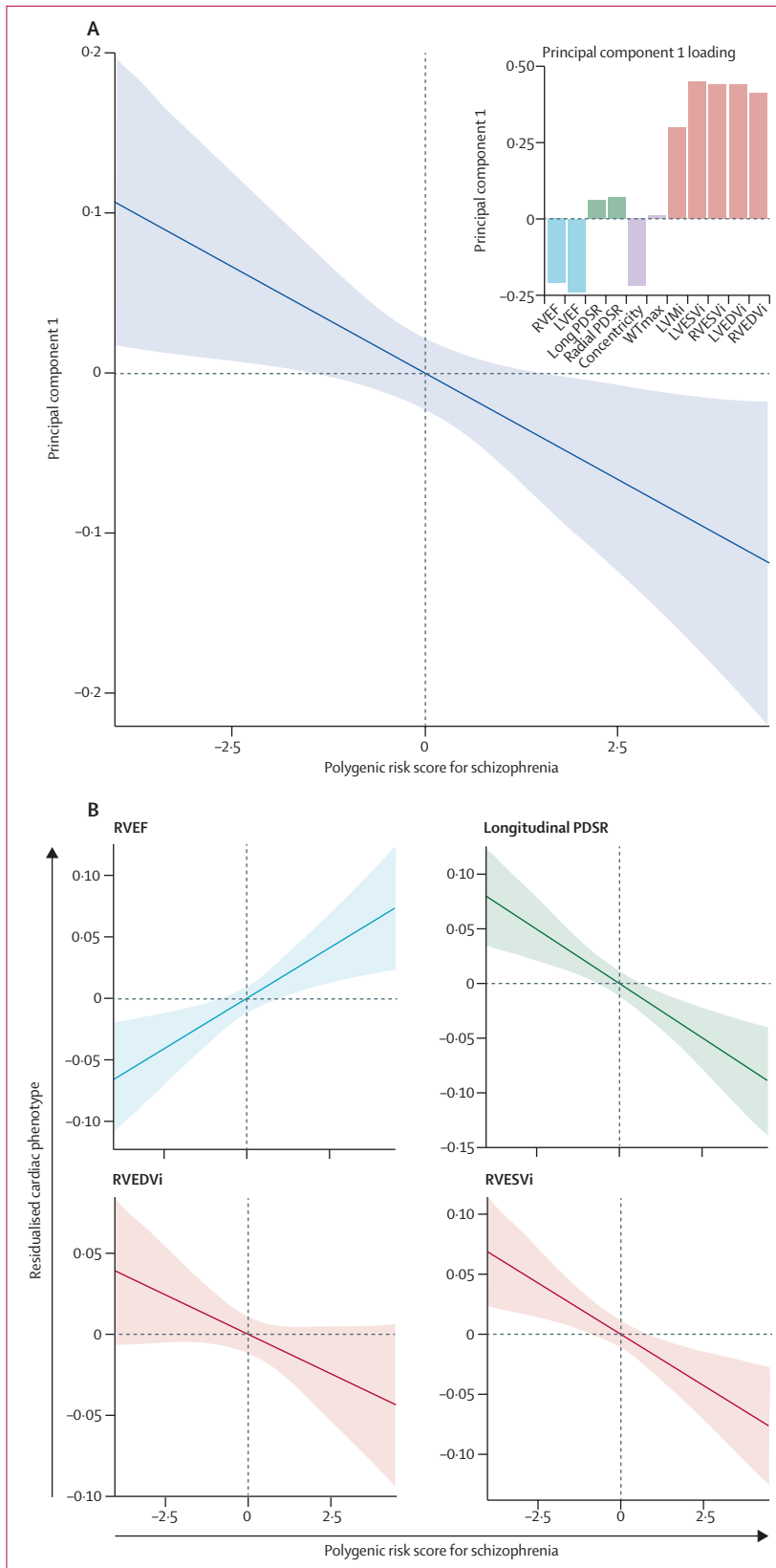
For principal component regression analyses (appendix p 14), a model regressing the TGF- β -specific polygenic risk score for schizophrenia onto the first five principal components was significant ($F=2.62$; $p=0.022$). When bivariate correlations between each principal component and TGF- β -specific polygenic risk scores for schizophrenia were examined, we observed a significant positive association between the TGF- β -specific polygenic risk score for schizophrenia and principal component 1 ($\beta=0.01$ [SE 0.003]; $p=0.024$); associations with remaining principal components were not significant (appendix p 15). Furthermore, a model regressing the acute inflammation-specific polygenic risk score for schizophrenia onto the first five principal components was significant ($F=2.54$; $p=0.026$). When bivariate correlations between each principal component and acute inflammation-specific polygenic risk score for schizophrenia were examined, we found a negative association between the acute inflammation-specific polygenic risk score for schizophrenia and principal component 4 ($\beta=-0.02$ [SE 0.01]; $p=0.0020$); associations with the remaining principal components were not significant. The model regressing myocardial fibrosis-specific polygenic risk scores for schizophrenia onto the first five principal components was not significant.

When examining cardiac phenotypes in isolation (appendix p 16), we observed a positive association between the TGF- β -specific polygenic risk score for schizophrenia and indexed left ventricular end-systolic volume ($\beta=0.12$ [SE 0.04]; self-contained $p=0.0022$, $p_{FDR}=0.029$), and a negative association between the TGF- β -specific polygenic risk score for schizophrenia and left ventricular ejection fraction ($\beta=-0.08$ [0.03]; self-contained $p=0.013$, $p_{FDR}=0.085$). Competitive p values

Figure 2: Principal component analysis

(A) Plot demonstrating cumulative percentage variance provided by principal components; the first five principal components explained more than 90% variance (indicated by the horizontal dotted red line at 90.6%) and were included in subsequent regression models. (B) Cardiac phenotype loadings for the first five principal components. RVEF=right ventricular ejection fraction. LVEF=left ventricular ejection fraction. Long PDSR=longitudinal peak diastolic strain rate. Radial PDSR=radial peak diastolic strain rate. WTmax=maximal end-diastolic septal wall thickness. LVMI=indexed left ventricular mass. LVESVi=indexed left ventricular end-systolic volume. RVESVi=indexed left ventricular end-systolic volume. LVEDVi=indexed left ventricular end-diastolic volume. RVEDVi=indexed right ventricular end-diastolic volume.





were also significant. These associations are broadly consistent with the principal regression finding of a positive association between the TGF- β -specific polygenic risk score for schizophrenia and principal component 1. There was evidence that increased acute inflammation-specific polygenic risk score for schizophrenia was associated with reduced longitudinal peak diastolic strain rates, however, adjustment of the false discovery rate affected this outcome. No further significant associations were observed.

For linkage disequilibrium score regression, as previously reported,²⁵ bipolar disorder (positive control) had a significant genetic overlap with schizophrenia whereas height (negative control) did not (appendix p 18). We observed genetic overlap with schizophrenia for right ventricular end-systolic volume and right ventricular ejection fraction ($r_g = -0.08$ [SE 0.03], $p = 0.0090$, $p_{FDR} = 0.045$; $r_g = 0.09$ [SE 0.04], $p = 0.0077$, $p_{FDR} = 0.045$). Results for all cardiac phenotypes are shown in the appendix (p 18).

Discussion

In this observational study, we found that increased genetic liability for schizophrenia is associated with decreased cardiac volumes, increased ejection fractions, and reduced absolute peak diastolic strain rates (ie, increased myocardial stiffness). We also found a potential role for gene variants in TGF- β and inflammatory pathways in cardiac phenotype variations. Linkage disequilibrium score regression showed genetic correlation between schizophrenia and some right-sided cardiac phenotypes.

To our knowledge, this is the first study to explore the association between genetic risk for schizophrenia and anatomical and functional cardiac variation within a single large population-based sample, complemented by analyses of genome-wide summary statistics. Our results extend previous cardiac MRI findings of smaller cardiac volumes in patients with schizophrenia than in healthy volunteers,^{3,4} showing that genetic risk for schizophrenia is associated with these phenotypes. Our findings

Figure 3: Association between polygenic risk score for schizophrenia and alterations in cardiac phenotypes

(A) The relative loadings of cardiac phenotypes for principal component 1 are shown in the inset bar chart. Those phenotypes significantly associated with polygenic risk score for schizophrenia at an individual level are highlighted in the colours in which they are represented in figure 2B. (B) For all plots, solid lines correspond to regression estimates and complementary shaded areas correspond to 95% CIs. The cardiac values are residuals derived from linear regression models where the cardiac parameter was regressed against age, age-squared, sex, genotype array, and first ten genetic principal components. Polygenic risk score for schizophrenia and cardiac values are Z-scored. Long PDSR=longitudinal peak diastolic strain rate. RVEDVi=indexed right ventricular end-diastolic volume. LVEF=left ventricular ejection fraction. LVESVi=indexed left ventricular end-systolic volume. LVMi=indexed left ventricular mass. Radial PDSR=radial peak diastolic strain rate. RVEDVi=indexed right ventricular end-diastolic volume. RVEF=right ventricular ejection fraction. RVESVi=indexed right ventricular end-systolic volume. WTI_{max}=maximal end-diastolic septal wall thickness.

similarly build on previous evidence that genetic liability to schizophrenia causally increases risk of heart failure¹⁴ by indicating that genetic risk for schizophrenia is associated with structural changes (eg, reduced absolute peak diastolic strain rates) that increase the risk of major adverse cardiovascular events, including heart failure.^{26,27} Declining diastolic function is also a hallmark of cardiac aging, involving fibrosis.²⁸ TGF- β is a profibrotic mediator²⁹ and variants in the TGF- β gene, *TGFBI*, affect the susceptibility to schizophrenia.³⁰ Furthermore, increased concentrations of systemic TGF- β are seen in patients with schizophrenia from illness onset.⁹ This study is the first to identify TGF- β and inflammatory signalling as potential contributors to cardiac variations associated with genetic risk for schizophrenia. By contrast, our study did not provide strong evidence that cardiac remodelling in people with schizophrenia is genetically associated, suggesting that this cardiac variation is not mediated by genetic liability for the disorder. Overall, this finding indicates that cardiac differences are a consequence of genetic and environmental factors.

Cardiac MRI is the gold standard for assessing cardiac function and mass quantification,³¹ therefore, we have confidence in the accuracy and precision of measurements and the validity of results. Moreover, since the UK Biobank is a population-based sample and people with schizophrenia were excluded, we were able to test for associations while avoiding confounds, such as secondary effects of psychotic illness or antipsychotic use. Future studies should test our findings in people with schizophrenia. Another strength is derived from the use of robust statistical analyses that mitigate the effect of heteroscedastic and skewed data, as well as complementary statistical techniques and sensitivity analyses that produced consistent results. Although we used a polygenic risk score calculated at the SNP inclusion threshold of $p=0.05$ or less for primary outcomes, results were similar across multiple inclusion thresholds. The PRSice derived threshold of best-fit for the polygenic risk score was not chosen as our primary outcome because of overfitting concerns.¹¹ However, when using the best fit polygenic risk score we observed significant associations between polygenic risk score for schizophrenia and left-sided and right-sided individual cardiac phenotypes, consistent with our principal component analysis results. A further strength is our use of linkage disequilibrium score regression, which provided insight into the shared genetic cause potentially underlying some of the associations observed between polygenic risk score for schizophrenia and cardiac phenotypes.

A limitation is that the UK Biobank is recognised for not representing the UK population, with evidence of a so-called healthy volunteer selection bias, which could affect generalisability. We focused on White British or Irish participants to achieve homogeneous samples of

cardiac phenotypes, which limits the application of findings to people of other ethnicities: this should be addressed in future studies. Another limitation of the study, and studies in general that use polygenic risk scores, is that the variance of schizophrenia explained by the polygenic risk score is modest;¹⁰ thus, small effects could have been missed. However, despite this limitation, we were able to identify significant associations across several analyses; as discovery genome-wide association studies expand, more subtle associations between polygenic risk scores for schizophrenia and cardiac phenotypes might be determined.

There is already evidence that psychosis involves multiple organs from illness onset.⁶ Although several mechanisms are involved by which multi-system alterations might occur, shared genetic risk has been proposed,⁶ and our results suggest that cardiac, and potentially also BMI, alterations might be similarly associated. A negative association between genetic risk for schizophrenia and BMI has previously been reported, suggesting that increased rates of obesity in people with schizophrenia are largely influenced by environmental factors;³² however, studies comparing BMIs of individuals naïve to antipsychotics with first-episode psychosis and healthy controls have provided conflicting results. To date, no studies have used cardiac MRI to examine cardiac structure and function in people naïve to antipsychotics with first-episode psychosis, and this aspect should be a focus of future research.

Although we provided evidence of a genetic link between polygenic risk score for schizophrenia and cardiac variation, the precise mechanisms by which these cardiac alterations develop remain unclear. For some right-sided cardiac phenotypes, we provide evidence, through genetic (GWAS) correlations, of shared genetic causes. For other cardiac phenotypes, we observed a significant association with polygenic risk score for schizophrenia, but without accompanying genetic correlations; for these phenotypes, associations with polygenic risk scores for schizophrenia might be due to genetically moderated mediators, such as smoking propensity³³ or immune dysregulation.³⁴ Our signalling pathway-specific analyses identified potential roles for TGF- β signalling and inflammation in observed cardiac variations. There is biological plausibility for the role of TGF- β in cardiac changes, as the cytokine is a regulator of cardiac muscle turnover, promoting cardiomyocyte apoptosis and hypertrophy.³⁵ Furthermore, TGF- β signalling contributes to the development of cardiac disease.⁸ However, an interesting outcome of this study is that the direction of association between polygenic risk score for schizophrenia and cardiac phenotype alteration was reversed when the polygenic risk score was enriched for TGF- β signalling. This finding suggests an opposing role for the cytokine in the overarching cardiac changes observed, which should be explored in future research. A hereditary

component that involves immune signalling has been documented in certain cardiac disease states,³⁶ consistent with our finding of an association between polygenic risk score for schizophrenia enriched for acute inflammation and cardiac variation. However, we were unable to clearly define specific cardiac phenotypes involved in this association, with only weak evidence suggesting an association with diastolic dysfunction. Future studies should aim to clarify the role of inflammatory pathways in cardiac alterations associated with polygenic risk score for schizophrenia. Further work is also required to explain the pattern of cardiac phenotypic variation associated with increased polygenic risk score for schizophrenia, especially reduced cardiac volumes with increased ejection fractions. Increased sympathetic drive in schizophrenia has long been documented;³⁷ increased sympathetic drive is associated with positive inotropy resulting in reduced ejection systolic volumes and increased ejection fractions, describing a proportion of the overarching cardiac phenotype associated with increased polygenic risk score for schizophrenia. Although speculative, alterations in autonomic signalling pathways might explain this association and should be a focus for future research. Evidence that schizophrenia is a pathway disease is emerging,³⁸ and other gene pathways implicated in cardiac disease and schizophrenia should be explored (eg, those relating to sodium and calcium signalling).¹⁰ It is also unclear if our findings are specific to schizophrenia or are present in other psychiatric conditions.

An important finding from this study is the association between polygenic risk score for schizophrenia and reduced absolute peak diastolic strain rates, indicating increased myocardial stiffness and diastolic dysfunction. Diastolic dysfunction predicts major cardiovascular events and increases all-cause mortality.^{26,27} Excess cardiac mortality is well documented in people with schizophrenia, and with the mortality gap growing between individuals with schizophrenia and the general population, novel approaches are required to address cardiac disease in this cohort.¹ Further work is required to determine if the association between genetic risk for schizophrenia and cardiac alterations represents novel therapeutic targets for people with schizophrenia. Screening for cardiac disease is already poor in people with schizophrenia and gold-standard treatments are often delayed;³⁹ the implication that genetic risk for schizophrenia affects cardiac structure and function in a manner associated with increased cardiac disease risk supports the argument for regular cardiac screening in patients from illness onset, and initiatives to facilitate this process are encouraged.⁴⁰

Individuals with increased genetic risk for schizophrenia have variations in cardiac structure and function, characterised by decreased cardiac volumes, decreased absolute peak diastolic strain rates, and increased ejection fractions. Genetic overlap with

schizophrenia exists for some right-sided cardiac phenotypes. TGF- β and inflammatory pathways are implicated in the observed alterations. Some cardiac variations associated with genetic risk for schizophrenia increase the risk of major adverse cardiovascular events. Further work is required to determine how these associations relate to cardiac disease risk in people with schizophrenia, and whether they represent novel therapeutic targets.

Contributors

TP conceptualised the study, curated the data, contributed to the formal analysis and writing of the study, and had direct access to the data reported in the manuscript. TP and EFO verified the underlying data reported in the manuscript. EFO curated the data and contributed to the formal analysis and writing of the study. AdM, MS, JH, ED'A, MMN, RAM, and AFP contributed to the formal analysis and writing of the study. CF contributed to the formal analysis. JF conceptualised the study and contributed to the writing of the study. PMM, DPO'R, and ODH contributed to the writing of the study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. The views expressed are those of the authors and not necessarily those of H Lundbeck A/S, the NHS, the National Institute for Health Research, or the Department of Health.

Declaration of interests

TP has participated in speaker meetings organised by Lundbeck, Otsuka, Sunovion, CNX Therapeutics, Schwabe Pharma, Janssen, and Recordati. RAM has participated in speaker meetings organised by Otsuka and Janssen. DPO'R has received grant funding and honoraria from Bayer AG. JF has received honoraria or consultancy fees from Atheneum, Informa, Nutritional Medicine Institute, ParachuteBH, Richmond Foundation, and Nirakara. PMM has received consultancy fees from Roche and Biogen, honoraria or speakers' fees from Novartis and Biogen, and research or educational funds from Biogen and Novartis. ODH is a part-time employee and stockholder of H Lundbeck A/S and has received investigator-initiated research funding from or participated in advisory or speaker meetings organised by Angellini, Autifony, Biogen, Boehringer-Ingelheim, Eli Lilly, Heptares, Global Medical Education, Invicro, Janssen, Lundbeck, Neurocrine, Otsuka, Sunovion, Rand, Recordati, Roche, and Viatrix/Mylan. All other authors declare no competing interests.

Data sharing

All raw and derived data in this study are available from the UK Biobank (<http://www.ukbiobank.ac.uk/>).

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