

Exploring the Relationship Between Schizophrenia and Cardiovascular Disease: A Genetic Correlation and Multivariable Mendelian Randomization Study

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Individuals with schizophrenia have a reduced life-expectancy compared to the general population, largely due to an increased risk of cardiovascular disease (CVD). Clinical and epidemiological studies have been unable to unravel the nature of this relationship. We obtained summary-data of genome-wide-association studies of schizophrenia ($N = 130\,644$), heart failure ($N = 977\,323$), coronary artery disease ($N = 332\,477$), systolic and diastolic blood pressure ($N = 757\,601$), heart rate variability ($N = 46\,952$), QT interval ($N = 103\,331$), early repolarization and dilated cardiomyopathy ECG patterns ($N = 63\,700$). We computed genetic correlations and conducted bi-directional Mendelian randomization (MR) to assess causality. With multivariable MR, we investigated whether causal effects were mediated by smoking, body mass index, physical activity, lipid levels, or type 2 diabetes. Genetic correlations between schizophrenia and CVD were close to zero (-0.02 – 0.04). There was evidence that liability to schizophrenia causally increases heart failure risk. This effect remained consistent with multivariable MR. There was also evidence that liability to schizophrenia increases early repolarization pattern, largely mediated by BMI and lipids. Finally, there was evidence that liability to schizophrenia increases heart rate variability, a direction of effect contrasting clinical studies. There was weak evidence that higher systolic blood pressure increases schizophrenia risk. Our finding that liability to schizophrenia increases heart failure is consistent with the notion that schizophrenia involves a systemic dysregulation of the body with detrimental effects on the heart. To decrease cardiovascular mortality among individuals with schizophrenia, priority should lie with optimal treatment in early stages of psychosis.

Key words: coronary artery disease/heart rate variability/QT interval/early repolarization/dilated cardiomyopathy/causality

Introduction

Schizophrenia is a serious mental disorder affecting up to 1% of the population.¹ The life-expectancy of individuals diagnosed with schizophrenia is approximately 15–20 years shorter than that of the general population²—a major contributor being cardiovascular mortality.³ Both cardiovascular diseases (CVD), including coronary artery disease and heart failure, and CVD risk factors, including high blood pressure and abnormal electro-cardiogram (ECG) patterns, are prevalent amongst individuals with schizophrenia.^{4–8}

There are broadly 2, not mutually exclusive, explanations for this co-morbidity. First, there may be a shared etiology. Low birth weight, pre-term birth and maternal malnutrition during pregnancy are associated with an increased risk of both schizophrenia and CVD in offspring.^{9,10} There is also evidence for shared genetic influences, but only for a limited number of cardio-metabolic traits and using considerably smaller samples than currently available.¹¹ Second, there may be causal effects. The predominant hypothesis is that schizophrenia increases the risk of CVD. Schizophrenia is characterized by elevated cortisol levels, dysfunction of the autonomic nervous system, inflammation, lipid abnormalities, oxidative stress and increased platelet reactivity,^{4,9,10} all of which contribute to the development and progression of CVD.¹² Reverse causal effects have also been proposed,

with markers of CVD preceding and potentially inducing psychosis.^{10,13}

While systemic characteristics of schizophrenia may directly induce CVD, there are also potential mediators. Anti-psychotic medication use, which can cause central obesity, hypertension, and abnormal lipid patterns,¹⁴ may consequently increase CVD risk.¹⁵ This does not explain all excess cardiovascular mortality though, as patients who do not use anti-psychotics are also at increased risk of CVD.^{5,14} Other potential mediators are smoking, poor diet and lack of physical activity, all common in individuals with schizophrenia.^{16,17} While conducting a randomized controlled trial (RCT) to determine causal factors is not feasible, a powerful alternative is Mendelian Randomization (MR).¹⁸ MR mimics an RCT by using genetic variants as proxies, or “instrumental variables,” for the proposed risk factor.¹⁹ Because genetic variants are randomly passed on from parents to offspring, bias from confounders can be circumvented (provided core assumptions are met).²⁰

We capitalize on the availability of large genetic samples and sophisticated methods to elucidate the nature of the relationship between schizophrenia and CVD. Using summary-level data of genome wide association studies (GWAS), we: (1) compute genetic correlations to determine genome-wide overlap between schizophrenia and CVD risk, (2) perform univariable MR to test if liability to schizophrenia causally increases CVD risk, (3) perform univariable MR to test if liability to CVD causally increases schizophrenia risk, and (4) perform multivariable MR to test if key health behaviors mediate effects of liability to schizophrenia on CVD risk.

Methods

The analysis plan was pre-registered at <https://osf.io/fprew>.

Data

We employed European-based estimates from the largest available GWAS on schizophrenia.²¹ Cases were individuals diagnosed with schizophrenia spectrum disorder based on DSM-IV criteria. For CVD, we selected 8 phenotypes often linked to schizophrenia, for which sufficiently large GWAS were available (supplement). These entailed 2 *clinical endpoints*: coronary artery disease²² and heart failure,²³ and 6 *markers of CVD risk*: systolic blood pressure,²⁴ diastolic blood pressure,²³ heart rate variability (HRV),²⁵ QT interval,²⁶ early repolarization ECG pattern,²⁷ and dilated cardiomyopathy ECG pattern²⁷ (phenotype definitions in [table 1](#)). For multivariable MR, we selected 5 potential mediators of effects of liability to schizophrenia on CVD. These capture health behaviors, or their downstream consequences, particularly prevalent among individuals with schizophrenia: smoking (initiation²⁸ and lifetime smoking²⁰), body mass index (BMI),²⁹

physical activity,³⁰ lipid levels (total cholesterol and triglycerides³¹— may be increased as a result of anti-psychotic medication), and type-2-diabetes.³² For MR, overlap between some of the exposure and outcome samples was prevented by excluding overlapping UK-Biobank participants. For further explanation see Supplement.

Genetic Correlations

Genetic correlations were computed using linkage disequilibrium score (LDSC) regression.³³ The genetic correlation is based on the estimated slope from the regression of the product of z -scores from 2 GWAS on the LD score and represents the covariation between 2 traits based on all polygenic effects captured by the included SNPs. We filtered GWAS summary statistics to only include the 1 290 028 million SNPs from the HapMap3 European reference panel, used to provide the genome-wide LD information.^{33,34}

Univariable Mendelian Randomization

We conducted bi-directional MR to assess evidence for causal effects of liability to schizophrenia on CVD risk, and vice versa, of liability to CVD on schizophrenia risk. MR relies on 3 main assumptions ([figure 1A](#)). “Horizontal pleiotropy,” a variant associating with multiple traits, may violate assumptions 2 and 3, if the variant associates with the outcome directly or via a confounding factor.¹⁸

The main method was inverse-variance weighted (IVW) regression. Independent SNPs that reached genome-wide significance ($P < 5E-08$) in the exposure GWAS were extracted to form instrumental variables. SNP-outcome effects were obtained from the outcome GWAS. A ratio estimate was obtained by dividing the effect a SNP has on the outcome by the effect it has on the exposure. Individual SNP-effects were weighted by the inverse of their variance and estimates of all SNPs combined. IVW provides the first indication of whether the exposure causes the outcome, assuming all assumptions are met. To verify its validity, we applied 6 sensitivity methods: First, weighted median regression which can provide a consistent causal estimate even when <50% of the weight of the instrument does not satisfy the MR assumptions.³⁵ Second, weighted mode regression, the estimate of which is reliable as long as the most frequent SNP-effects are contributed by valid SNPs.³⁶ Third, MR-Egger regression, which explicitly tests for horizontal pleiotropy.³⁷ Instead of being fixed to zero, the intercept is freely estimated and can be interpreted as the average horizontally pleiotropic effect. Crucially, MR-Egger relies on 2 assumptions: the INstrument Strength Independent of Direct Effect (InSIDE; meaning that any pleiotropic effects should not be correlated with the instrument strength) assumption and the NO Measurement Error (NOME) assumption. An important limitation is that MR-Egger has markedly lower statistical power than IVW. Fourth,

Table 1. Overview of the main phenotypes, details on their reference and how they were measured, the number of independent, genome-wide significant Single Nucleotide Polymorphisms (SNP) identified in the GWAS and genetic correlations between schizophrenia and the cardiovascular disease phenotypes

Phenotype	GWAS reference	How the phenotype was measured	Sample size	<i>n</i> SNPs	Genetic correlation with schizophrenia
Schizophrenia	Ripke et al, 2020	Cases were individuals diagnosed with a schizophrenia spectrum disorder, based on DSM-IV criteria	53 386 cases 77 258 controls	185 (European)	—
Coronary artery disease	Nelson et al, 2017	Cases were individuals with a fatal or nonfatal myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG), chronic ischemic heart disease, or angina	71 602 cases 260 875 controls	56	$rg = -0.02$, SE = 0.03, $P = .439$
Heart failure	Shah et al, 2020	Cases were individuals with a clinical diagnosis of heart failure of any aetiology (no inclusion criteria based on left ventricle ejection fraction)	47 309 cases 930 014 controls	12	$rg = -0.01$, SE = 0.04, $P = .696$
Systolic blood pressure	Evangelou et al, 2018	Mean of 2 systolic blood pressure measurements (if available), manual or automatic (or both). Measured in millimetres of mercury (mmHg)	757 601	237	$rg = -0.01$, SE = 0.02, $P = .699$
Diastolic blood pressure	Evangelou et al, 2018	Mean of 2 diastolic blood pressure measurements (if available), manual or automatic (or both). Measured in millimetres of mercury (mmHg)	757 601	158	$rg = 0.001$, SE = 0.02, $P = .965$
Heart rate variability	Nolte et al, 2017	The root mean square of the successive differences of inter beat intervals (RMSSD), which reflects heart rate variability	46 952 exposure sample 26 523 outcome sample	9	$rg = -0.01$, SE = 0.05, $P = .850$
QT interval	Arking et al, 2014	The time from the start of the Q wave to the end of the T wave as read from an ECG. Individuals were excluded if there was atrial fibrillation, atrial flutter, presence of QRS duration >120 msec or presence of left/right bundle branch block	103 331	68	$rg = 0.04$, SE = 0.03, $P = 0.142$
Early repolarization ECG-pattern	Verweij et al, 2020	The height of a specific point of the electrocardiogram (ECG), +44 msec after the R wave, which coincided with the early repolarization criteria. The genome-wide significant SNPs were followed up in an independent cohort (Lifelines) to confirm their association with early repolarization diagnosis (1,253 cases, 11,463 controls); 2 were significant at the Bonferroni level and 5 showed suggestive association, more than expected by chance. Combined in a IVW-regression analysis, there was strong evidence that these SNPs causally predict early repolarization pattern.	63 700	9	$rg = -0.02$, SE = 0.04, $P = .600$
Dilated cardiomyopathy ECG-pattern	Verweij et al, 2020	The height of a specific point on electrocardiogram (ECG), -18 msec before the R wave, which showed strong overlap with dilated cardiomyopathy risk. The genome-wide significant SNPs were followed up in an independent cohort (UK biobank) to confirm their association with dilated cardiomyopathy diagnosis (1,375 cases, 241,325 controls). Combined in a IVW-regression analysis, there was strong evidence that these SNPs causally predict dilated cardiomyopathy pattern.	63 700	34	$rg = 0.004$, SE = 0.04, $P = .892$

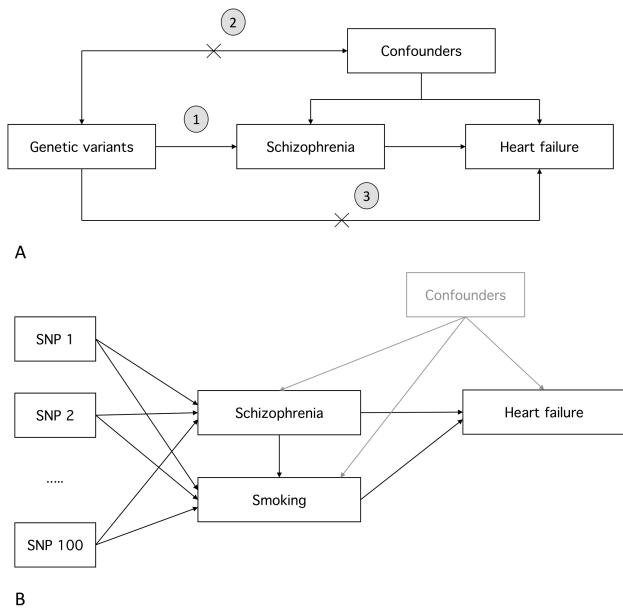


Fig. 1. Mendelian randomization (MR). (A) MR relies on 3 assumptions; the genetic variants in the instrument must (1) associate robustly with the exposure (e.g. schizophrenia), (2) be independent of confounders, and (3) not directly affect the outcome (e.g. heart failure), except through their effect on the exposure. (B) Multivariable MR allows an additional variable, besides the main exposure. We tested whether key health behaviours mediate the effect of schizophrenia on cardiovascular disease. E.g., if the inclusion of smoking (considerable) decreases the direct effect of schizophrenia on heart failure, it implies that smoking mediates the relationship.

MR pleiotropy residual sum and outlier (MR-PRESSO) analysis,³⁸ which consists of 3 steps: testing for horizontal pleiotropy (global test), correcting for horizontal pleiotropy using outlier removal (outlier test) and evaluating significant differences in the causal estimate before and after outlier removal (distortion test). Fifth, generalized summary data-based MR (GSMR).³⁹ GSMR provides high statistical power by using low levels of LD between the SNPs and considering sampling variation in the estimated effects of all SNPs. Pleiotropic SNPs are removed with the HEIDI-outlier procedure. Sixth, Steiger filtering which corrects for reverse causality.⁴⁰ The Steiger test was used to identify and then exclude SNPs that explained a larger amount of variance in the outcome, compared to the exposure.

We also performed leave-one-out analyses, repeating IVW after removing each SNP, and computed Cochran's Q to assess heterogeneity between SNP-estimates in each instrument. To assess instrument strength, we computed the F -statistic ($F > 10$ is sufficiently strong). To assess whether the NOME assumption was satisfied for MR-Egger we computed the I^2_{GX} statistic.⁴¹ If I^2_{GX} is higher than 0.9, bias due to violation of the NOME assumption is not likely. When $I^2_{GX} = 0.6-0.9$, bias can be corrected for with simulation extrapolation (SIMEX) MR-Egger.

An MR finding was considered robust when results were consistent across methods. Because sensitivity methods rely on stricter assumptions than IVW, they are less powerful. Their statistical evidence, but not effect size, will therefore be weaker, even for a true effect. We describe findings as showing no clear evidence, weak evidence, evidence or strong evidence for a causal effect, taking into account IVW and the sensitivity methods, adhering to the broad interpretation of P -values described by Sterne and Davey Smith (2001).⁴² We consider a finding to be consistent across sensitivity methods if the beta coefficient is in the same direction and of comparable size (or larger). Analyses were performed in R (3.6.3), using packages: "TwoSampleMR," "GSMR," "psych," and "MR-PRESSO."

Multivariable Mendelian Randomization

Using multivariable MR, health behaviours were added to see whether effects of liability to schizophrenia as the exposure on CVD as the outcome diminished, which could indicate mediation (figure 1B).⁴³ For each univariable analysis we added each health behavior separately (we did not combine them to prevent violation of linearity and homogeneity assumptions⁴⁴). We evaluated robustness with multivariable MR-Egger, computed the Sanderson-Windmeijer conditional F statistic for instrument strength, and computed an adaption of the Cochran's Q statistic to detect heterogeneity (see Supplement for more information).

Results

Genetic Correlations

Genetic correlations, reflecting overlap between genome-wide liability to schizophrenia and CVD, were all close to zero (table 1).

Univariable Mendelian Randomization

Instruments for schizophrenia and CVD were sufficiently strong (supplementary table S1). Bi-directional univariable MR results are depicted in table 2.

Liability to Schizophrenia on CVD. There was evidence that liability to schizophrenia causally increases heart failure risk (beta_{IVW} = 0.027, 95% confidence intervals = 0.003–0.051, $P = 0.027$). Weighted median and weighted mode regression confirmed this with consistent effect sizes, but weaker statistical evidence. GSMR showed much stronger evidence for a positive effect, of greater magnitude (beta = 0.266, CIs = 0.25–0.281, $P = 3.3E-251$). While the MR-Egger intercept showed strong evidence for horizontal pleiotropy (−0.013, CIs = −0.019 to −0.007, $P = 9.4E-05$; supplementary table S2), its slope also indicated strong evidence for a positive effect (beta = 0.220,

Table 2. Results of univariable, bidirectional Mendelian randomization analyses between liability to schizophrenia (SCZ) and coronary artery disease (CAD), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart failure (HF), heart rate variability (HRV), QT interval (QT), early repolarization ECG pattern (ERP), and dilated cardiomyopathy ECG pattern (DCM)

Exposure	Outcome	SNPs		Inverse variance weighted		Weighted median		Weighted mode		MR-Egger		SNPs		GSMR	
		<i>n</i>	Beta (95% CI)	<i>P</i>	Beta (95% CI)	<i>P</i>	Beta (95% CI)	<i>P</i>	Beta (95% CI)	<i>P</i>	Beta (95% CI)	<i>n</i>	Beta (95% CI)	<i>P</i>	
<i>Clinical endpoints</i>															
SCZ	CAD	177	0.002 (-0.026 to 0.030)	.886	0.012 (-0.020 to 0.045)	.464	0.052 (-0.031 to 0.136)	.222	0.113 (0.018 to 0.243)	.025	0.169	-0.004 (-0.026 to 0.018)	.712		
SCZ	HF	177	0.027 (0.003 to 0.051)	.027	0.026 (-0.006 to 0.058)	.107	0.024 (-0.071 to 0.119)	.626	0.220 (0.129 to 0.312)	4.5E-06	171	0.266 (0.25 to 0.281)	3.3E-251		
<i>Risk markers</i>															
SCZ	SBP	175	-0.012 (-0.294 to 0.270)	.933	0.053 (-0.108 to 0.213)	.520	0.163 (-0.243 to 0.570)	.432	0.878 (-0.460 to 2.217)	.200	137	0.178 (0.088 to 0.267)	1.0E-04		
SCZ	DBP	175	0.054 (-0.101 to 0.208)	.495	0.037 (-0.052 to 0.126)	.414	-0.155 (-0.524 to 0.215)	.413	0.563 (-0.063 to 1.189)	.080	148	0.054 (0.004 to 0.104)	.035		
SCZ	HRV	149	0.019 (0.003 to 0.036)	.024	0.020 (-0.003 to 0.043)	.083	0.036 (-0.021 to 0.092)	.214	-0.004 (-0.075 to 0.056)	.902	147	0.016 (0.007 to 0.030)	.038		
SCZ	QT	161	0.152 (-0.154 to 0.459)	.329	0.217 (-0.230 to 0.664)	.342	0.410 (-0.406 to 1.225)	.326	-0.253 (-1.481 to 0.975)	.687	160	0.150 (-0.161 to 0.452)	.352		
SCZ	ERP	177	0.020 (0.001 to 0.038)	.040	0.016 (-0.007 to 0.039)	.176	0.005 (-0.050 to 0.061)	.850	0.001 (-0.066 to 0.067)	.982	171	0.016 (0.002 to 0.030)	.031		
SCZ	DCM	177	0.004 (-0.014 to 0.021)	.694	0.008 (-0.015 to 0.030)	.511	-1.4E-04 (-0.053 to 0.053)	.996	0.093 (0.020 to 0.166)	.014	170	-0.001 (-0.015 to 0.014)	.917		
<i>Clinical endpoints</i>															
CAD	SCZ	51	-0.018 (-0.092 to 0.056)	.642	-0.006 (-0.063 to 0.051)	.827	-0.004 (-0.073 to 0.065)	.902	0.009 (-0.171 to 0.189)	.921	45	-0.032 (-0.069 to 0.005)	.093		
HF	SCZ	10	-0.109 (-0.238 to 0.020)	.100	-0.041 (-0.184 to 0.102)	.575	-0.032 (-0.208 to 0.144)	.727	0.063 (-0.317 to 0.443)	0.753	9	-0.120 (-0.232 to -0.008)	.034		
<i>Risk markers</i>															
SBP	SCZ	230	0.008 (-2.1E-04 to 0.017)	.056	0.009 (0.001 to 0.017)	.030	0.009 (-0.005 to 0.024)	.209	0.016 (-0.007 to 0.038)	.176	199	0.006 (0.002 to 0.011)	.009		
DBP	SCZ	154	-0.008 (-0.018 to 0.001)	.088	-0.005 (-0.015 to 0.004)	.253	-0.004 (-0.017 to 0.009)	.551	-0.026 (-0.049 to -0.003)	.030	138	-0.002 (-0.007 to 0.004)	.498		
HRV	SCZ	9	-0.034 (-0.217 to 0.149)	.715	-0.13 (-0.33 to 0.07)	.203	-0.103 (-0.333 to 0.127)	.404	-0.107 (-0.531 to 0.317)	.637	9	-0.037 (-0.192 to 0.118)	.639		
QT	SCZ	65	-4.0E-04 (-0.004 to 0.003)	.806	2.9E-05 (-0.003 to 0.003)	.986	2.9E-04 (-0.003 to 0.004)	.879	1.5E-04 (-0.005 to 0.006)	.957	60	-0.002 (-0.004 to -4E-05)	.174		
ERP	SCZ	8	-0.003 (-0.191 to 0.185)	.978	-0.014 (-0.183 to 0.155)	.873	-0.015 (-0.213 to 0.183)	.510	-0.022 (-0.357 to 0.513)	.938	8	-0.004 (-0.124 to 0.115)	.954		
DCM	SCZ	32	0.003 (-0.087 to 0.093)	.953	0.006 (-0.098 to 0.110)	.907	0.008 (-0.115 to 0.131)	.902	-0.057 (-0.284 to 0.170)	.624	30	0.024 (-0.045 to 0.093)	.496		

We reported SIMEX-corrected values for MR-Egger when I_{G^2} statistic was <0.9 (see [supplementary table S2](#)). SNPs, n = total number of SNPs included in the analysis, SE = standard error, GSMR = Generalized Summary Data-Based Mendelian randomization.

CI = 0.129–0.312, $P = 4.5E-06$). There was strong evidence for heterogeneity across SNPs (Cochran's Q $P = 2.3E-04$; [supplementary table S3](#)). MR-PRESSO detected one outlier, but eliminating it did not have a large impact ([supplementary table S4](#)). Steiger filtering did not find SNPs that explained more variance in the outcome than the exposure, suggesting no reverse causality ([supplementary table S5](#)). While leave-one-out analysis showed SNP rs13107325 to have a relatively large impact, the effect size and statistical evidence remained considerable after removal ([supplementary figure S1](#)). In sum, horizontal pleiotropy notwithstanding, there is consistent evidence for a causal, increasing effect of liability to schizophrenia on heart failure across all included (sensitivity) methods.

There was evidence that liability to schizophrenia causally increases early repolarization pattern ($\beta_{IVW} = 0.020$, CI = 0.001–0.038, $P = .040$). While weighted median and GSMR confirmed this, weighted mode and MR-Egger regression did not ($\beta = 0.005$, CI = -0.050 – 0.061 , $P = .850$, and $\beta = 0.001$, CI = -0.066 – 0.067 , $P = .982$, respectively). There was strong evidence for heterogeneity ($P = 6.8E-09$), but the MR-Egger intercept indicated that this was not due to horizontal pleiotropy ($P = .580$). MR-PRESSO detected one outlier, which did not impact the results. Steiger filtering excluded one SNP resulting in a slightly weaker effect.

There was evidence that liability to schizophrenia causally increases HRV ($\beta_{IVW} = 0.019$, CI = $2.5E-03$ to 0.036 , $P = 0.024$). Weighted median, weighted mode and GSMR were consistent, while MR-Egger was not. There was evidence for heterogeneity ($P = 0.009$), but this was likely not due to horizontal pleiotropy (MR-Egger intercept $P = 0.499$). Excluding one outlier with MR-PRESSO did not impact the results, while excluding 6 SNPs with Steiger filtering slightly attenuated the effect. No other analyses showed clear evidence for association ([supplementary table 2](#)).

Liability to CVD on Schizophrenia Risk. There was weak evidence that increased systolic blood pressure causally increases schizophrenia risk ($\beta_{IVW} = 0.008$, CI = $-2.1E-04$ to 0.017 , $P = .056$), confirmed by all sensitivity methods. There was strong evidence for heterogeneity ($P = 4.6E-68$), but the MR-Egger intercept indicated that this was not due to horizontal pleiotropy ($P = 0.491$). MR-PRESSO detected 14 outliers, yet elimination of these SNPs did not change the results. Steiger filtering removed 16 SNPs, resulting in even stronger evidence ($\beta_{IVW} = 0.010$, CI = 0.003 – 0.016 , $P = 0.006$). Leave-one-out analysis showed that removing SNP rs11191548 considerably decreased the effect size and weakened statistical evidence ([supplementary figure S2](#)).

There was very weak evidence that liability to increased diastolic blood pressure decreases schizophrenia risk ($\beta_{IVW} = -0.008$, CI = -0.018 – 0.001 , $P = .088$), but this was not corroborated by sensitivity analyses. No other analyses showed clear evidence for association ([supplementary table 2](#)).

Multivariable Mendelian Randomization

For relationships with evidence of causality, multivariable results are shown in [figure 2](#). Other multivariable results are in [supplementary tables S6–S21](#). The conditional F-statistic indicated sufficient instrument strength, except for physical activity which ranged between ~ 8 and ~ 11 ([table S15](#)).⁴⁵ Most health behaviors had a larger impact on heart failure than did liability to schizophrenia. When added in multivariable MR, only BMI had a noteworthy impact on the direct effect of liability to schizophrenia on heart failure. BMI *increased* the causal effect of liability to schizophrenia by $\sim 70\%$ ($\beta_{IVW} = 0.046$, CI = 0.01 – 0.083 , $P = .013$). MR-Egger confirmed the effect size and direction and the intercept indicated no horizontal pleiotropy ($P = .537$; [supplementary table S16](#)). BMI itself showed a positive association with heart failure ($\beta_{IVW} = 0.447$, CI = 0.34 – 0.555 , $P = 3.4E-16$), suggesting it is negatively associated with schizophrenia. We conducted post-hoc analyses with underweight (versus normal weight) and overweight (vs normal weight) as potential mediators (Supplement). Underweight did not change the main effect, while overweight increased it by $\sim 30\%$ (conditional F-statistic for underweight was low (2.28)). The effect of liability to schizophrenia on HRV remained consistent after adding health behaviors. The effect of liability to schizophrenia on early repolarization pattern decreased when adding BMI, total cholesterol and triglycerides, with 70% ($\beta_{IVW} = 0.006$, CI = -0.017 to 0.028 , $P = .617$), 65% ($\beta_{IVW} = 0.007$, CI = -0.017 – 0.031 , $P = .549$), and 60% ($\beta_{IVW} = 0.008$, CI = -0.016 – 0.032 , $P = .538$), respectively. MR-Egger results were consistent.

Discussion

We computed genome-wide genetic correlations between schizophrenia and eight important CVD phenotypes, all of which were nearly zero. Using MR, there was evidence that liability to schizophrenia causally increases heart failure risk. This effect was not mediated by health behaviors in multivariable MR. There was also evidence that liability to schizophrenia causally increases early repolarization pattern, largely mediated by BMI and lipid levels. There was evidence that liability to schizophrenia increases HRV, a direction of effect contrasting clinical observations. Finally, there was weak evidence that increased systolic blood pressure increases schizophrenia risk.

The lack of evidence for genetic correlation between schizophrenia and CVD is striking, given consistent phenotypic correlations³ and the fact that a considerable amount of the risk variants for schizophrenia are located in genes relevant for cardiological functioning, such as calcium channels. In contrast, considerable positive genetic correlations between schizophrenia and immune-mediated diseases mirrored earlier epidemiological

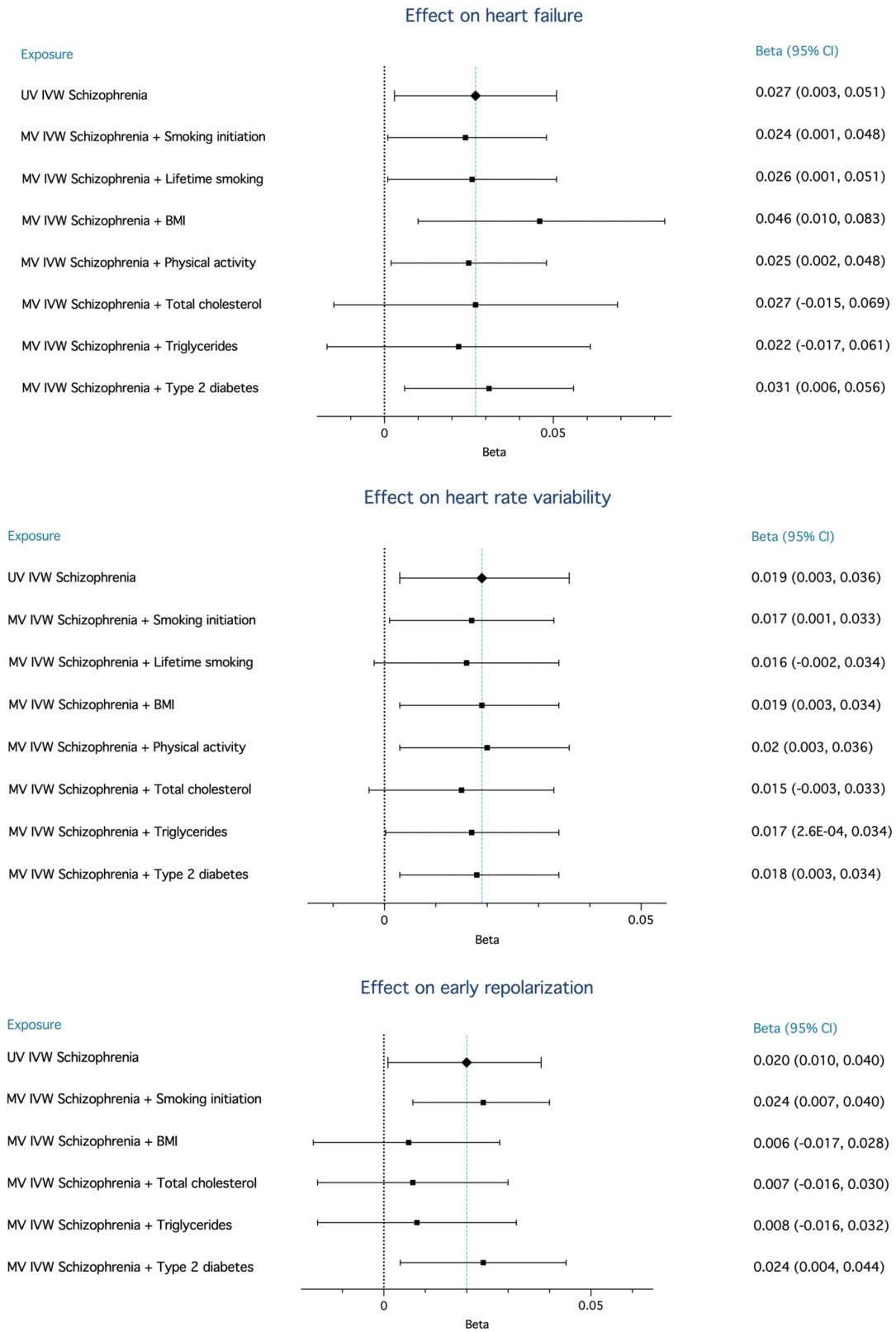


Fig. 2. Forest plots of multivariable Mendelian randomization (MR) analyses of liability to schizophrenia on heart failure (A), heart rate variability (B), and early repolarization (C), showing the direct effect of liability to schizophrenia on the respective outcomes. Each health behaviour was added in a separate analysis. Lifetime smoking and physical activity could not be added for C, because there was considerable sample overlap.

evidence.⁴⁶ Our findings indicate that there is minimal shared genetic etiology, implying that phenotypic associations between schizophrenia and cardiovascular disease are due to other mechanisms. However, since a genetic correlation is computed on a genome-wide scale, it may also be that only a subset of variants overlaps, with the average shared signal being weak. Moreover, our analyses test the effects of liability to schizophrenia, and not a schizophrenia diagnosis *per se*. It may be that an actual diagnosis, and all detrimental factors associated with it, drive associations with cardiovascular disease and we were not able to capture that.

With MR, we found evidence that liability to schizophrenia causally increases CVD. MR employs a selection of genetic variants, as opposed to the genome-wide approach for genetic correlations. MR might therefore find an association that was “cancelled out” by opposing effects in a genome-wide correlation.⁴⁷ There was robust evidence that liability to schizophrenia increases heart failure risk, confirming its high prevalence among individuals with schizophrenia.⁴⁸ MR’s powerful premise and the robustness across sensitivity analyses allows us to say with more certainty that this is due to causal effects. Important to note is that the MR-Egger intercept indicated horizontal pleiotropy, such that genetic variants for schizophrenia also exerted some effect on heart failure, independent of schizophrenia. The effect on heart failure was not mediated by health behaviors, which is particularly noteworthy for smoking – smoking rates among individuals with schizophrenia are high and smoking increases cardiovascular mortality.¹⁷ Our findings are in line with the notion that schizophrenia is characterized by a systemic dysregulation of the body, including inflammation and oxidative stress, which promotes cardiac alterations and ultimately heart failure.^{9,49} This implies that changing health behaviors—while useful to improve health—is not sufficient to reduce cardiovascular mortality among patients with schizophrenia. To prevent heart failure, priority should lie with optimal treatment and early-stage interventions, thereby preventing detrimental systemic effects. Finally, it should be noted that we did not find clear evidence for an effect of liability to schizophrenia on coronary artery disease (CAD), which is surprising as CAD can be an underlying cause of heart failure. This may indicate that causal effects on heart failure do not run through pathways typical to CAD (e.g. atherosclerosis), but rather through pathways related to the myocardium itself (e.g. contractility or electrical function).⁵⁰ A post hoc multivariable MR analysis confirmed that the direct effect of liability to schizophrenia on heart failure remained the same after adding CAD (supplementary table S22).

There was evidence that liability to schizophrenia increases early repolarization pattern, corroborating reports that early repolarization disproportionately affects patients with schizophrenia.^{51,52} Historically, this pattern

was considered normal,⁵³ but recent evidence linked it to an increased risk of sudden cardiac death.⁵⁴ Sudden cardiac death is particularly prevalent in patients with schizophrenia, making early repolarization an important risk marker. The association with early repolarization pattern declined when correcting for BMI, total cholesterol, and triglycerides. This helps elucidate the, currently poorly understood, etiology of early repolarization and suggests that among individuals with schizophrenia this pattern can be improved by lowering BMI and lipid levels.⁵⁴

Liability to schizophrenia was associated with higher HRV, while patients present with lower HRV in the clinic—partly due to anti-psychotic use.^{55,56} This discrepancy may be explained by the fact that we employed 2 separate GWAS (one for schizophrenia, a separate one for HRV). The number of individuals with a schizophrenia diagnosis – and thus antipsychotic use—was likely low in the HRV GWAS. Another consideration is that the HRV GWAS data were not corrected for heart rate, which correlates strongly with HRV and is usually higher in individuals with schizophrenia.⁸ Finally, lower HRV may result from the systemic presentation of schizophrenia, which our measure of liability did not capture. Studies tracking HRV before and after schizophrenia is diagnosed would help clarify our findings.

There was evidence that higher systolic, but not diastolic, blood pressure increases schizophrenia risk. This corroborates a large cohort study reporting that, in men, higher blood pressure in adolescence predicts schizophrenia in adulthood.⁵⁷ Higher blood pressure has also been reported in individuals who were at risk of, but had not yet developed, psychosis.⁵⁸ Combined, this suggests that dysfunction of the autonomic nervous system precedes schizophrenia onset. A potentially important confounder is smoking, as it affects both blood pressure⁵⁹ and schizophrenia.⁶⁰ However, in a post-hoc multivariable MR analysis, we found no change in effect when adding smoking (supplementary table S23).

Our study has some important strengths. We were able to conduct powerful analyses, investigating disorders with a low prevalence on the population level (especially schizophrenia). In addition to computing genetic correlations, we applied a wide range of rigorous MR sensitivity methods, which increases the robustness of our inferences, including multivariable MR which allowed us to investigate important mediators. Combined, this has kept the risk of bias from horizontal pleiotropy and reverse causality to a minimum. There are also limitations to consider. Schizophrenia is a severe illness and those who suffer most may not have been able to participate in research, causing selection bias.^{61,62} For early repolarization and dilated cardiomyopathy, it should be taken into consideration that these do not reflect the whole pattern, but rather a particular amplitude of the ECG that corresponds with the beginning of the respective patterns. For some relationships, there may have

been temporality issues. Schizophrenia often arises in early adulthood, whereas heart failure and coronary artery disease develop later in life. Testing heart failure and coronary artery disease as exposures for schizophrenia is therefore imperfect. However, genetic risk to CVD can already have an impact early in life and therefore causal relationships are plausible.⁶³ Assortative mating, dynastic effects (“genetic nurture”) and residual population stratification could not be accounted for – future within-family Mendelian randomization analyses may be able to reduce such bias.⁶⁴ Another limitation that warrants attention is the fact that we based our primary analyses on European ancestry individuals only. When we attempted to replicate 2 of the main findings, increasing effects of liability to schizophrenia⁶⁵ on heart failure⁶⁶ and of blood pressure⁶⁷ on schizophrenia risk, we found effects in the same direction, but without clear evidence for causality (supplementary table S24; GWAS were not available for heart rate variability and early repolarization pattern).

In conclusion, we showed that a shared genetic etiology is not the most likely mechanism underlying associations between schizophrenia and CVD. There was, however, evidence that liability to schizophrenia causally increases the risk of heart failure and early repolarization pattern. While the effect on early repolarization pattern was largely mediated by BMI and lipid levels, the effect on heart failure remained stable after adding key health behaviors. This implies that effective treatment and intervention in early psychosis is important to decrease excess cardiovascular mortality. Tracking of physical health and screening for CVD is currently done less frequently than advised in clinical guidelines, and start of treatment is often delayed.⁶⁸ More thorough screening throughout psychiatric treatment must become a priority, in order to decrease the stark mortality gap between schizophrenia patients and individuals from the general population.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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