Is there a causal relationship between executive function and liability to mental health and substance use? A Mendelian randomisation approach

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Abstract

Background: Executive function consists of several cognitive control processes that are able to regulate lower level processes. Poorer performance in tasks designed to test executive function is associated with a range of psychopathologies such as schizophrenia, major depressive disorder (MDD) and anxiety, as well as with smoking and alcohol consumption. Despite these well-documented associations, whether they reflect causal relationships, and if so in what direction, remains unclear. We aimed to establish whether there is a causal relationship between a latent factor for performance on multiple executive function tasks – which we refer to as common executive function (cEF) – and liability to schizophrenia, MDD, anxiety, smoking initiation, alcohol consumption, alcohol dependence and cannabis use disorder (CUD), and the directionality of any relationship observed.

Methods: We used a two-sample bidirectional Mendelian randomisation (MR) approach using genome-wide association study (GWAS) summary data from large cohorts (N=17,310 to 848,460) to examine whether causal relationships exist, and if so in which direction.

Results: We found evidence of a causal effect of increased cEF on reduced schizophrenia liability (IVW: OR=0.10; 95% CI 0.05 to 0.19; p-value=3.43×10^{-12}), reduced MDD liability (IVW: OR=0.52; 95% CI 0.38 to 0.72; p-value=5.23×10^{-05}), decreased drinks per week (IVW: β=-0.06; 95% CI -0.10 to -0.02; p-value=0.003), and reduced CUD liability (IVW: OR=0.27; 95% CI 0.12 to 0.61; p-value=1.58×10^{-03}). We also found evidence of a causal effect of increased schizophrenia liability on decreased cEF (IVW: β=-0.04; 95% CI -0.04 to -0.03; p-value=3.25×10^{-27}), as well as smoking initiation on decreased cEF (IVW: β=-0.06; 95%CI -0.09 to -0.03; p-value=6.11×10^{-05}).

Conclusion: Our results indicate a potential bidirectional causal relationship between a latent factor measure of executive function (cEF) and schizophrenia liability, a possible causal effect of increased cEF on reduced MDD liability, CUD liability, and alcohol consumption, and a possible causal effect of smoking initiation on decreased cEF. These results suggest that executive function should be considered as a potential risk factor for some mental health and substance use outcomes, and may also be impacted by mental health (particularly schizophrenia). Further studies are required to improve our understanding of the underlying mechanisms of these effects, but our results suggest that executive function may be a promising intervention target. These results may therefore inform the prioritisation of experimental medicine studies (e.g., of executive function interventions), for both mental health and substance use outcomes, to improve the likelihood of successful translation.

Introduction

The ability to perform nearly all of the activities required for daily living is mediated by executive function (EF)[1] – the ability to perform self-directed behaviour toward a goal and to enable self-regulation. The prefrontal cortex is the neural substrate of EF, including cognitive control functions that regulate lower-level processes such as decision making[1]. There are different aspects of EF, including inhibitory control, working memory and task switching.

EF is thought to be impaired in individuals with a range of mental health problems[1], and there is evidence that it is also associated with substance use[2]. For example, poorer EF has been observed among individuals with schizophrenia[1,3–5], major depressive disorder (MDD)[6,7], and anxiety[8,9], as well as in people who smoke both cigarettes[10,11] and cannabis[12,13] and consume alcohol[10,14]. The direction of association between EF and these phenotypes is unclear[1], with some studies suggesting EF deficits prior to these[2] and others suggesting they occur after[3]. It is unclear whether these associations represent causal pathways, and if so what the direction of any causal effect might be. EF is potentially modifiable[15], and drug repurposing analyses for a common EF factor (cEF) score[16] have suggested that this cEF may also be modifiable. Therefore, if we can better understand the relationship between EF and mental health and substance use outcomes, this will help to inform intervention development.

Mendelian randomisation (MR) is a well-established method for causal inference, which relies on approximations of Mendel's laws of segregation and random assortment[17]. MR is based on instrumental variable (IV) analysis, with single nucleotide polymorphisms (SNPs) that are robustly associated with the exposure used as IVs. MR is subject to three core assumptions:

i) the genetic instrument is robustly associated with the exposure of interest (relevance), ii) there is no confounding of the genetic instrument and the outcome (independence), and iii) the genetic instrument only influences the outcome via the exposure (exclusion restriction). There are different MR methods that test potential violations of these assumptions and therefore a consistent effect estimate across different approaches would provide greater evidence of a truly causal effect, robust to the assumptions of MR. MR minimises the effect of confounding variables as the genetic variants are randomly assigned at conception[18]. It also overcomes issues around reverse causation as these genetic variants precede any outcomes[19].

Summary data from genome-wide association studies (GWAS) can be used as the genetic instruments in MR. A recent GWAS of cEF score, conducted in the UK Biobank (European ancestry), identified 90 genome-wide significant hits[16]. The factor score was created from five different EF tasks – trail making, symbol-digit substitution, digit span, prospective memory, and pairs memory – using confirmatory factor analysis. Unlike, previous studies focusing on specific EF tasks, the cEF incorporates multiple facets which may better capture the cognitive component of psychopathology. In particular, single executive function tasks are noisy measures of executive functioning, with large method variance components reflecting lower level cognitive processes (the "task impurity problem"[20]). By combining multiple tasks, we can create a more "pure" measure of executive functioning. Further, past work has shown that this common component is correlated with – but separable from – IQ, and is genetically associated with psychopathology over and above the genetic influence of other cognitive factors[16].

We examined whether there were causal relationships between EF and a range of mental health and substance use phenotypes, and the direction of any effect – for example, does poor mental health lead to poorer EF, or vice versa? We did this by applying a two-sample MR approach, where the SNP-exposure and SNP-outcome estimates are obtained from genome-wide association studies (GWAS) in independent samples and used to estimate causal effects. We focused on schizophrenia, MDD, anxiety, smoking initiation, alcohol consumption (drinks per week), alcohol dependence, and cannabis use disorder (CUD), using a bidirectional approach to determine the causal direction of these relationships.

Methods

Data Sources

We used GWAS data from several studies, shown in Table 1. To minimise sample overlap, we excluded some samples that contributed to the original GWAS in our analyses, as indicated in Table 1.

Table 1. GWAS for executive function, mental health and substance use outcomes.

Phenotype	Author	Sample	Final N
Executive function	Hatoum et al, 2020[16]	UKBB	427,037
Schizophrenia	Schizophrenia Working Group of the PGC, 2020[21]	PGC	Cases = 69,369 Controls = 236,642
Major depressive disorder	Wray et al, 2018[22]	PGC, excluding UKBB and 23andMe	Cases = 45,396 Controls = 97,250
Anxiety	Otowa et al, 2016[23]	ANGST	Cases = 5,712 Controls = 11,598
Smoking initiation	Liu et al, 2019[24]	GSCAN, excluding UKBB	848,460
Drinks per week	Liu et al, 2019[24]	GSCAN, excluding UKBB	630,154
Alcohol dependence	Walters et al 2018[25]	PGC Substance Use Disorders working group	Cases = 8,485 Controls = 20,272
Cannabis use disorder	Johnson et al, 2020[26]	PGC Substance Use Disorders working group, iPSYCH and deCODE	Cases = 14,080 Controls = 343,736

UKBB= UK Biobank, PGC= Psychiatric Genomics Consortium, ANGST= Anxiety NeuroGenetics Study, GSCAN= GWAS and Sequencing Consortium of Alcohol and Nicotine use

Executive function. We used summary data from the most recent GWAS of cEF[16], which identified 90 independent genome-wide significant ($p<5x10^{-08}$) SNPs associated with a cEF score, where a higher score reflects increased EF.

Schizophrenia. We used summary data from the most recent Psychiatric Genomics Consortium (PGC) GWAS of schizophrenia[21], which identified 294 independent genome-wide significant SNPs. Cases mostly included participants diagnosed with schizophrenia (although diagnoses of other psychotic disorders were also included in some samples).

Major depressive disorder (MDD). We used summary data from the most recent PGC GWAS of MDD[22], which identified 44 independent genome-wide significant SNPs. Cases of MDD were either diagnosed by a clinical professional, or through structured interviews with trained interviewers, using the DSM IV, ICD-9 or ICD-10 criteria.

Anxiety. We used summary data from a GWAS of anxiety[23], which identified one independent genome-wide significant SNP. In this meta-analysis, there were up to five different anxiety disorder phenotypes included in the nine samples from seven independent cohorts. Lifetime DSM-based anxiety disorder diagnostic assessments were available for all cohorts except for the Rotterdam study, in which only one-year prevalence was assessed. Each study assessed DSM-based criteria for the following six-lifetime clinical phenotypes: generalised anxiety disorder (GAD), panic disorder, agoraphobia, social phobia, specific phobia and MDD, however, any subject reporting a mood disorder only was removed from analyses.

Smoking initiation. We used summary data from the most recent GWAS of smoking initiation[24], which identified 378 conditionally independent genome-wide significant SNPs

associated with ever being a regular smoker (current or former). Participants were asked whether they had smoked more than 100 cigarettes in their lifetime and whether they had ever smoked every day for at least a month or ever smoked regularly. To obtain summary statistics for the full sample included in the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN) GWAS excluding UK Biobank data, we meta-analysed results from GWAS of 23andMe, Inc. only data and all results excluding UK Biobank and 23andMe. The meta-analysis was conducted using the genome-wide association meta-analysis (GWAMA) software[27].

Drinks per week. We used summary data from the most recent GWAS of drinks per week[24], which identified 99 conditionally independent genome-wide significant SNPs associated with the average number of drinks a participant reported drinking each week. Participants were asked about the number of alcoholic beverages they had in the past week and the average number of drinks per week than they had in the past year. Data were log-transformed prior to the GWAS. This measure did not account for the type of alcohol consumed and for any study with ranges, the mid-range value was used. Again, to obtain summary statistics for the full GSCAN GWAS excluding UK Biobank data, we meta-analysed results from GWAS of 23andMe only data and all results excluding UK Biobank and 23andMe.

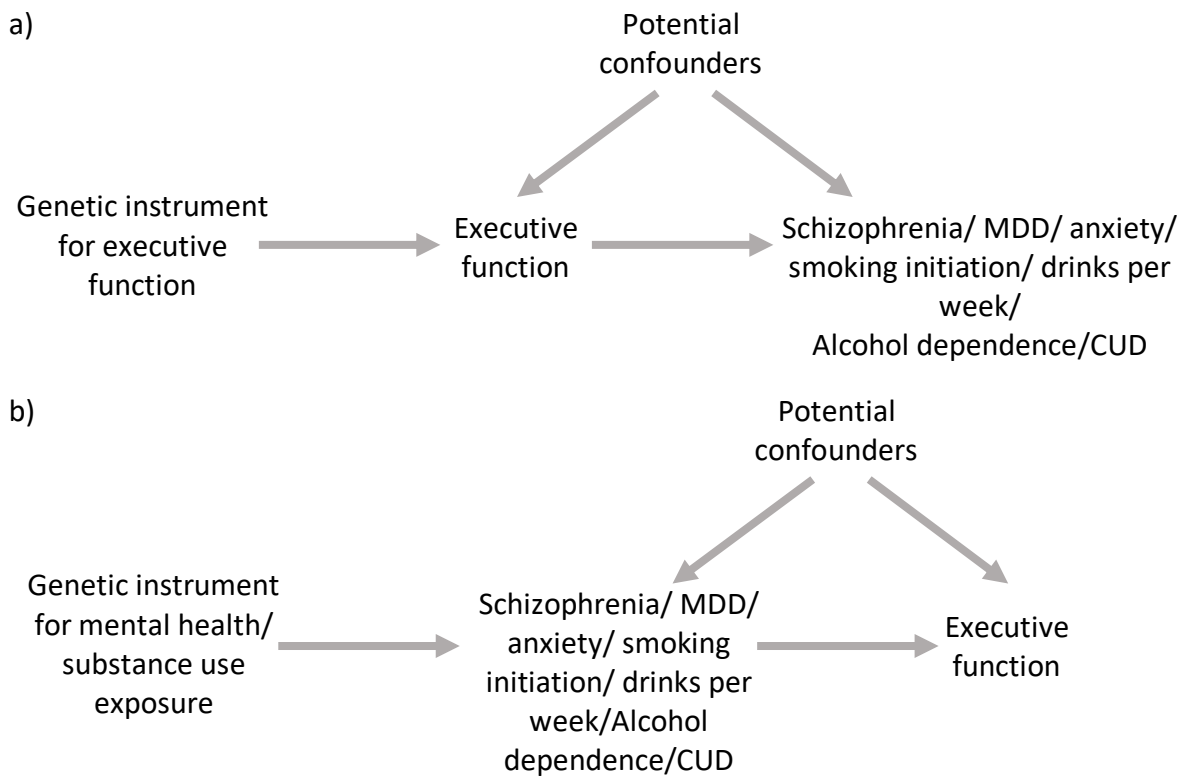
Alcohol Dependence. We used summary data from the PGC substance use disorders working group GWAS of alcohol dependence[25], which identified one conditionally independent genome-wide significant SNPs in their European GWAS associated with alcohol dependence. Alcohol dependence cases were those that met criteria for DSM-IV or DSM-III-R alcohol dependence diagnosis.

Cannabis Use Disorder (CUD). We used summary data from the most recent GWAS of CUD[26] from the PGC substance use disorders working group, iPSYCH and deCODE which identified 2 conditionally independent genome-wide significant SNPs associated with CUD. CUD cases were those that met criteria for DSM-5, DSM-IV, DSM-III-R or ICD-10 cannabis abuse or dependence.

Statistical analyses

The analysis plan for this study was pre-registered on the Open Science Framework (https://osf.io/j3tb5). We conducted two-sample MR analyses using R (version 4.0.3)[28] and the package TwoSampleMR (version 0.5.0)[29,30]. In order to assess potential bidirectional pathways, we conducted two-sample MR analyses with cEF as the exposure for one direction, and as the outcome in the other direction (see Figure 1), when assessing causal relationships with liability to schizophrenia, MDD, anxiety, smoking initiation, drinks per week, alcohol dependence and CUD.

Figure 1. Bidirectional two-sample Mendelian randomisation between a common executive function factor score and liability to mental health and substance use outcomes



Directed acyclic graph for the potential causal effects being examined with a) executive function as the exposure and liability to mental health and substance use phenotypes as the outcomes and b) liability to mental health and substance use phenotypes as the exposures and executive function as the outcome. MDD=Major depressive disorder, CUD=Cannabis use disorder

We used independent genome-wide significant SNPs for the exposure of interest as instruments in the MR analyses, except when anxiety, alcohol dependence and CUD were the exposures, where we used a p-value threshold of $1x10^{-05}$ to select SNPs due to the low number of genome-wide significant SNPs. We excluded all SNPs in linkage disequilibrium (LD) using an r^2 of 0.001, a window of 10000 kb and the European 1000 genomes reference panel. Where there were palindromic SNPs, we tried to infer the positive strand based on allele frequencies, but if this was not possible, then these SNPs were also excluded. Where an exposure SNP was not available in the outcome data, we attempted to identify a suitable proxy SNP using the LDproxy tool from LDlink[31]. We pruned the SNPs extracted to $r^2 \geq 0.8$ and

extracted the first SNP that was present in the exposure and outcome data. After exclusions and identifying any proxy SNPs we searched for the remaining cEF SNPs in the outcome GWAS (73 for schizophrenia, 85 for MDD, 83 for anxiety, 82 for smoking initiation, 83 for drinks per week, 73 for alcohol dependence and 73 for CUD) and the remaining mental health and substance use exposure SNPs in the cEF outcome (175 for schizophrenia, 29 for MDD, 17 for anxiety, 187 for smoking initiation, 67 for drinks per week, 19 for alcohol dependence and 37 for CUD). The GWAS summary statistics for the exposure and outcome in each analysis were harmonised so that the SNP allele-exposure and SNP allele-outcome associations were in the same direction.

We used several different MR methods to assess these putative causal relationships: inverse-variance weighted (IVW)[32], MR-Egger[33], weighted median[34], simple mode and weighted mode[35], and Steiger filtering[36] MR methods. We used the IVW approach as our main method with the other methods used as sensitivity analyses.

The IVW approach constrains the intercept to pass through zero, assuming no horizontal pleiotropy. We tested for heterogeneity between the individual SNPs included in the genetic instrument using Cochran's test of heterogeneity. The MR-Egger method tests for overall directional pleiotropy by not constraining the intercept to pass through zero. If the intercept is not zero then this is indicative of directional horizontal pleiotropy. We also assessed heterogeneity between the individual SNPs whilst adjusting for any directional pleiotropy for the MR-Egger method using Rucker's Q test. We used the weighted median method to obtain estimates under the assumption that at least 50% of the SNPs satisfy the MR assumptions and are valid IVs. Finally, we used the mode-based approaches to obtain estimates for the largest cluster of SNPs, where SNPs not in that cluster could be invalid. The

206 weighted method accounts for the largest weights of SNPs. We also conducted single SNP
207 and leave-one-out analyses.

208 Where we found evidence of a bidirectional causal relationship, we ran Steiger filtering. This
209 allows orientation of the direction of effect where the underlying biology of genetic variants
210 is less clear, by identifying which SNPs explain more variance in the outcome than the
211 exposure and then repeating the MR analyses excluding those SNPs to rule out reverse
212 causation[36].

213 In cases where we found evidence for a causal effect between a given exposure and
214 outcome, we present plots of these results in the Supplementary Material. These plots
215 include scatter plots of the SNP-exposure and SNP-outcome associations with the causal
216 effect estimates from each MR method presented, forest plots for causal effects of each
217 SNP in the instrument (which can indicate if heterogeneity is present), plots presenting the
218 leave-one-out results and funnel plots of each SNP included in the instrument, where a
219 symmetrical plot indicates that the effects of each SNP included are similar to the average
220 effect and asymmetry may indicate horizontal pleiotropy.

221 We calculated weighted and unweighted regression dilution I-squared statistics for each
222 analysis[37], presented in Supplementary Table S1, which give an indication of the amount of
223 bias in the 'NO Measurement Error' (NOME) assumption in the MR-Egger estimate[34]. If the I-
224 squared statistic is 0.9 or above this indicates minimal bias in the MR-Egger estimate and
225 therefore we present the MR-Egger results for these associations. If either the weighted or
226 unweighted I-squared statistics were between 0.6 and 0.9, this may indicate regression
227 dilution bias and therefore we ran simulation extrapolation (SIMEX) corrections, to obtain
228 bias-adjusted point estimates for MR-Egger and we present these results in place of MR-

Egger. Anything below 0.6 means that the bias may be too large and therefore we do not report either the SIMEX correction or the MR-Egger results. We also estimated the mean F-statistic for each analysis, indicative of instrument strength, where a value under 10 may indicate a weak instrument[37].

Data availability

The data used in this study are publicly-available GWAS data for cEF (available upon request by contacting the authors), schizophrenia (https://www.med.unc.edu/pgc/download-results/scz/), MDD (https://www.med.unc.edu/pgc/download-results/mdd/), anxiety (https://www.med.unc.edu/pgc/download-results/angst/?choice=Other+GWAS+DataAnxiety+Neuro+Genetics+Study+%28ANGST%29), smoking initiation and drinks per week (data with UK Biobank and 23andMe removed can be found here: https://conservancy.umn.edu/handle/11299/201564, and for 23andMe data access needs to be requested (see below), alcohol dependence (https://figshare.com/articles/dataset/sud2018-alc/14672187) and CUD (https://figshare.com/articles/dataset/sud2020-cud/14842692). The full GWAS summary statistics for the 23andMe discovery data set will be made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. Please visit https://research.23andme.com/collaborate/#dataset-access/ for more information and to apply to access the data.

Code availability

The analysis code that forms the basis of the results presented here is available from the University of Bristol's Research Data Repository (http://data.bris.ac.uk/data/), DOI : To be made available upon publication).

Results

Our two-sample MR results for the causal effects of cEF on mental health and substance use outcomes are presented in Table 2.

Schizophrenia. We found strong evidence of a causal effect of increased cEF on reduced odds of schizophrenia (IVW: OR=0.10; 95% CI 0.05 to 0.19; p-value=3.43×10^{-12}) for all methods except MR Egger, which we were unable to estimate due to violation of the NOME assumption (See Supplementary Table S1). These results were in a consistent direction across the different MR analyses (Supplementary Figure S1). However, we did observe evidence of heterogeneity for the IVW estimate (Supplementary Figure S2) and some asymmetry in the funnel plot (Supplementary Figure S3), although our leave one out analyses did not indicate that a single SNP was driving the association (Supplementary Figure S4). Steiger filtering indicated that only 41% of SNPs instrumenting cEF explained more variance in cEF than schizophrenia, and results were attenuated when repeating analyses with this subset of SNPs. However, these results were in the same direction as the main results (Supplementary Table 2).

Major depressive disorder. We found strong evidence of a causal effect of increased cEF on reduced odds of MDD (IVW: OR=0.52; 95% CI 0.38 to 0.72; p-value=5.23×10^{-05}). These results were in a consistent direction across the different MR analyses (Supplementary Figure S5), and there was evidence of a causal effect for all methods except simple mode and MR Egger, which again we unable to estimate due to violation of the NOME assumption. Here we also found evidence of heterogeneity for the IVW estimate (Supplementary Figure S6), and some asymmetry in the funnel plot (Supplementary Figure S7); however, leave one out analyses did not indicate that a single SNP was driving the

association (Supplementary Figure S8). Steiger filtering indicated that 81% of SNPs instrumenting cEF explained more variance in cEF than MDD, but again results were similar to the main results when using this subset of SNPs (Supplementary Table 2).

Anxiety. We did not find evidence of a causal effect of cEF on anxiety liability (IVW: OR=0.49; 95% CI 0.19 to 1.23; p-value=0.13).

Smoking initiation. We did not find clear evidence of a causal effect of cEF on smoking initiation (IVW: OR=0.87; 95% CI 0.74 to 1.02; p-value=0.09) for any of the MR analyses.

Drinks per week. We found some evidence of a causal effect of increased cEF on decreased number of alcoholic drinks per week consumed (IVW: β=-0.06; 95% CI -0.10 to -0.02; p-value=0.003). These results were in a consistent direction across the different MR analyses (Supplementary Figure S9), although there was only evidence of a causal effect for the IVW method. We also found evidence of heterogeneity here (Supplementary Figure S10) and slight asymmetry in the funnel plot (Supplementary Figure S11); however, leave one out analyses did not indicate that a single SNP was driving the association (Supplementary Figure S12).

Alcohol dependence. We did not find clear evidence of a causal effect of cEF on alcohol dependence liability (IVW: OR=0.50; 95% CI 0.23 to 1.28; p-value=0.08) for any of the MR analyses.

Cannabis Use Disorder (CUD). We found strong evidence of a causal effect of increased cEF on reduced odds of CUD (IVW: OR=0.27; 95% CI 0.12 to 0.61; p-value=1.58×10^{-03}) for all methods except MR Egger, which we were unable to estimate due to violation of the NOME assumption (See Supplementary Table S1). These results were in a consistent direction

297 across the different MR analyses (Supplementary Figure S13). However, we did observe
298 evidence of heterogeneity for the IVW estimate (Supplementary Figure S14) and slight
299 asymmetry in the funnel plot (Supplementary Figure S15), although our leave one out
300 analyses did not indicate that a single SNP was driving the association (Supplementary
301 Figure S16).

Table 2. Two-sample Mendelian randomisation results with executive function (cEF) as the exposure.

Outcome	Method	NSNPs	OR or beta (95% CI)	P-value	Heterogeneity test p-value	Directional pleiotropy intercept (95% CI; p-value)
Schizophrenia	IVW	73	0.10 (0.05, 0.19)	$3.43x10^{-12}$	$3.52x10^{-61}$	
	MR Egger[a]	-	-	-	-	-
	Weighted median	73	0.15 (0.09, 0.24)	$1.12x10^{-15}$		
	Simple mode	73	0.11 (0.04, 0.33)	$2.04x10^{-04}$		
	Weighted mode	73	0.12 (0.05, 0.29)	$1.53x10^{-05}$		
MDD	IVW	85	0.52 (0.38, 0.72)	$5.23x10^{-05}$	$8.22x10^{-03}$	
	MR Egger[a]	-	-	-	-	-
	Weighted median	85	0.45 (0.30, 0.67)	$1.12x10^{-04}$		
	Simple mode	85	0.36 (0.13, 1.10)	0.06		
	Weighted mode	85	0.33 (0.12, 0.96)	0.05		
Anxiety	IVW	83	0.49 (0.19, 1.23)	0.13	0.09	
	MR Egger[b]	83	0.39 ($3.67x10^{-4}$, 420.28)	0.79		0.002 (-0.05, 0.06; 0.94)
	Weighted median	83	0.31 (0.09, 1.07)	0.07		
	Simple mode	83	0.09 (0.004, 2.03)	0.14		
	Weighted mode	83	0.16 (0.009, 2.99)	0.23		
Smoking initiation	IVW	82	0.87 (0.74, 1.02)	0.09	2.64×10^{-67}	
	MR Egger[a]	-	-	-	-	-
	Weighted median	82	0.88 (0.78,0.99)	0.04		
	Simple mode	82	0.81 (0.51,1.29)	0.39		
	Weighted mode	82	0.81 (0.49, 1.37)	0.44		
Drinks per week	IVW	83	-0.06 (-0.10, -0.02)	0.003	$8.81x10^{-26}$	
	MR Egger[a]	-	-	-	-	-
	Weighted median	83	-0.05 (-0.08, -0.01)	0.008		
	Simple mode	83	-0.05 (-0.14, 0.04)	0.29		
	Weighted mode	83	-0.04 (-0.12, 0.04)	0.33		

Alcohol dependence	IVW	73	0.50 (0.23, 1.09)	0.08	0.17	
	MR Egger[a]	-	-	-	-	-
	Weighted median	73	0.37 (0.12, 1.14)	0.92		
	Simple mode	73	0.33 (0.02, 5.61)	0.44		
	Weighted mode	73	0.47 (-0.04, 5.36)	0.55		
CUD	IVW	73	0.27 (0.12, 0.61)	1.58×10^{-03}	6.17×10^{-09}	
	MR Egger[a]	-	-	-	-	-
	Weighted median	73	0.14 (0.06, 0.35)	1.84×10^{-05}		
	Simple mode	73	0.05 (0.007, 0.38)	4.56×10^{-03}		
	Weighted mode	73	0.08 (0.01, 0.47)	7.19×10^{-03}		

[a]NO Measurement Error (NOME) assumption violated for MR-Egger and value below 0.6, therefore no results presented. [b]I-squared value between 0.6 and 0.9 so SIMEX correction is presented instead of MR-Egger. MDD=Major depressive disorder, CUD=Cannabis use disorder, OR-odds ratio, CI=confidence interval, IVW=Inverse-variance weighted, MR=Mendelian randomisation, SNP=Single nucleotide polymorphism.

Our two-sample MR results for causal effects of the mental health and substance use phenotypes on cEF are presented in Table 3.

Schizophrenia. We found strong evidence of a causal effect of increased odds of schizophrenia on decreased cEF (IVW: β=-0.04; 95% CI -0.04 to -0.03; p-value=3.25×10^{-27}). These results were in a consistent direction across the different MR analyses (Supplementary Figure S17). However, we did observe evidence of heterogeneity for the IVW estimate (Supplementary Figure S18) and some asymmetry in the funnel plot (Supplementary Figure S19), although there was little evidence of directional pleiotropy from the SIMEX estimate and our leave one out analyses did not indicate that a single SNP was driving the association (Supplementary Figure S20). Steiger filtering indicated that all SNPs instrumenting schizophrenia explained more variance in schizophrenia than cEF; therefore these analyses were not repeated (Supplementary Table 2).

MDD. We did not find evidence of a causal effect of MDD liability on cEF (IVW: β=-0.02; 95% CI -0.05 to 0.01; p-value=0.31) using IVW. However, evidence was stronger using other sensitivity methods and the direction of effect was consistent across all approaches i.e., for increased odds of MDD on decreased cEF. Steiger filtering indicated that all SNPs instrumenting schizophrenia explained more variance in MDD than cEF; therefore these analyses were not repeated (Supplementary Table 2).

Anxiety. We did not find evidence of a causal effect of anxiety liability on cEF (IVW: β=8.69×10^{-04}; 95% CI -0.003 to 0.005; p-value=0.68) for any of the MR analyses.

Smoking initiation. We found strong evidence of a causal effect of smoking initiation on decreased cEF (IVW: β=-0.06; 95% CI -0.09 to -0.03; p-value=6.11×10^{-05}) and there was

evidence of this causal effect using the weighted median method but not the other MR methods, although the direction of effect was consistent (Supplementary Figure S21). We did find evidence of heterogeneity for the IVW estimate (Supplementary Figure S22) and slight asymmetry in the funnel plot (Supplementary Figure S23); however, our leave one out analyses did not indicate that a single SNP was driving the association (Supplementary Figure S24).

Drinks per week. We did not find clear evidence of a causal effect of cEF on number of alcoholic drinks per week consumed (IVW: β=-0.007; 95% CI -0.17 to 0.16; p-value=0.93).

Alcohol dependence. We did not find clear evidence of a causal effect of alcohol dependence liability on cEF (IVW: β=-3.31x10^{-03}; 95% CI -8.21x10^{-03} to 1.65x10^{-03}; p-value=0.09) for any of the MR analyses.

Cannabis Use Disorder (CUD). We did not find clear evidence of a causal effect of CUD liability on cEF (IVW: β=-6.42x10^{-03}; 95% CI -0.01 to 9.56x10^{-04}; p-value=0.09) for any of the MR analyses.

344 **Table 3.** Two-sample Mendelian randomisation results with executive function (cEF) as the outcome.
345

Exposure	Method	NSNPs	Beta (95% CI)	P-value	Heterogeneity test p-value	Directional pleiotropy intercept (95% CI; p-value)
Schizophrenia	IVW	175	-0.04 (-0.04, -0.03)	$3.25x10^{-27}$	$3.04x10^{-72}$	
	MR Egger[b]	175	-0.05 (-0.07, -0.03)	$5.77x10^{-05}$		$9.0x10^{-04}$ ($-6.13x10^{-04}$, 0.002; 0.24)
	Weighted median	175	-0.03 (-0.03, -0.02)	$8.08x10^{-21}$		
	Simple mode	175	-0.04 (-0.06, -0.01)	$2.14x10^{-03}$		
	Weighted mode	175	-0.04 (-0.06, -0.02)	$7.93x10^{-04}$		
MDD	IVW	29	-0.02 (-0.05, 0.01)	0.31	$3.45x10^{-19}$	
	MR Egger[a]	-	-	-	-	-
	Weighted median	29	-0.03 (-0.05, -0.01)	0.01		
	Simple mode	29	-0.04 (-0.08, -0.006)	0.03		
	Weighted mode	29	-0.03 (-0.06, -0.002)	0.04		
Anxiety	IVW	17	$8.69x10^{-04}$ (-0.003, 0.005)	0.68	0.17	
	MR Egger[a]	-	-	-	-	-
	Weighted median	17	$7.19x10^{-04}$ (-0.004, 0.006)	0.78		
	Simple mode	17	0.004 (-0.007, 0.01	0.49		
	Weighted mode	17	0.002 (-0.007, 0.01)	0.67		
Smoking Initiation	IVW	187	-0.06 (-0.09, -0.03)	$6.11x10^{-05}$	$4.23x10^{-88}$	
	MR Egger[a]	-	-	-	-	-
	Weighted median	187	-0.04 (-0.07, -0.01)	$2.61x10^{-03}$		
	Simple mode	187	-0.01(-0.11, 0.08	0.80		
	Weighted mode	187	-0.01(-0.12, 0.09)	0.82		

Drinks per Week	IVW	67	-0.007 (-0.17, 0.16)	0.93	$1.09x10^{-51}$	
	MR Egger[a]	-	-	-	-	-
	Weighted median	67	-0.05 (-0.16, 0.07	0.45		
	Simple mode	67	-0.10 (-0.31, 0.11)	0.34		
	Weighted mode	67	-0.05 (-0.15, 0.06)	0.41		
Alcohol dependence	IVW	19	$-3.31x10^{-03}$ ($-8.21x10^{-03}$, $1.65x10^{-03}$)	0.19	0.08	
	MR Egger[b]	19	$-3.74x10^{-03}$ (-0.01, $3.66x10^{-03}$)	0.33		$1.93x10^{-05}$ ($-1.99x10^{-03}$, $2.03x10^{-03}$; 0.99)
	Weighted median	19	$-3.67x10^{-03}$ ($-9.78x10^{-03}$, $2.44x10^{-03}$)	0.24		
	Simple mode	19	$-3.69x10^{-03}$ (-0.01, $7.25x10^{-03}$)	0.52		
	Weighted mode	19	$-4.28x10^{-03}$ (-0.01, $3.58x10^{-03}$)	0.30		
CUD	IVW	37	$-6.42x10^{-03}$ (-0.01, $-9.56x10^{-04}$)	0.09	$1.71x10^{-08}$	
	MR Egger[a]	-	-	-	-	-
	Weighted median	37	$-5.16x10^{-03}$ (-0.01, $1.98x10^{-03}$)	0.16		
	Simple mode	37	$-4.65x10^{-03}$ (-0.02, $9.96x10^{-03}$)	0.54		
	Weighted mode	37	$-3.65x10^{-03}$ (-0.02, 0.01)	0.61		

[a]NO Measurement Error (NOME) assumption violated for MR-Egger and value below 0.6, therefore no results presented. [b]I-squared value between 0.6 and 0.9 so SIMEX correction is presented instead of MR-Egger. MDD=Major depressive disorder, CUD=Cannabis use disorder, OR-odds ratio, CI=confidence interval, IVW=Inverse-variance weighted, MR=Mendelian randomisation, SNP=Single nucleotide polymorphism.

Discussion

We examined whether there was evidence of causal effects of cEF on schizophrenia, MDD, anxiety, smoking initiation, drinks per week, alcohol dependence and CUD. We also examined the reverse direction (i.e., causal effects of mental health and substance use on cEF). Evidence of a causal effect in both directions may be indicative of a bidirectional relationship or some other underlying common risk factor.

Our main findings were evidence of a causal relationship between increased cEF and reduced schizophrenia liability in both directions. Steiger filtering supported the finding of bidirectional effects, despite some attenuation of results for cEF on schizophrenia. This causal effect supports previous observational studies, which have found that people with schizophrenia have poorer EF[1,3–5]; however, our MR analyses provide evidence that these associations may reflect causal pathways. The fact that we find causal effects between schizophrenia liability and cEF in both directions may point to this association being bidirectional or due to an underlying common risk factor.

The observed causal effect of increased cEF on reduced MDD liability is also interesting, as previous studies have provided mixed evidence for the directionality of this relationship[6,7]. We did not find strong evidence of a causal effect of MDD on cEF using the IVW approach; however, evidence was stronger when using other MR methods, and the direction of effect we observed was negative and consistent across these. It may also be possible that there is lower power in the MDD instrument than the cEF instrument, due to the lower number of SNPs, which may also be why we do not observe a consistent effect of MDD on cEF. Therefore, we cannot rule out the possibility of a bidirectional relationship and Steiger filtering suggested that the effects could be bidirectional as well. We cannot draw any

372 strong conclusions from our results regarding anxiety and cEF. Whilst we do not find
373 evidence of a causal relationship, this does not mean that there is definitely no effect, but
374 rather that our study may have lacked the power to detect a causal effect here, particularly
375 given that we find some evidence of a possible causal effect of MDD on cEF in our sensitivity
376 analyses and previous studies have reported high genetic correlations between MDD and
377 anxiety[38]. Thus the association found in previous studies needs further investigation still[8,9].

378 Finally, we also found some evidence of a causal effect of smoking initiation on decreased
379 cEF and increased cEF on decreased drinks per week and reduced CUD liability, all in a
380 consistent direction with previous observational studies[10–14]. However, evidence for the
381 smoking and drinks per week findings was weak, so further studies examining this would be
382 useful.

383 Our results are in contrast to a previous study which used latent causal variable (LCV)
384 analyses and did not find evidence of any causal effects of cEF on schizophrenia, MDD,
385 anxiety, alcohol use disorder or other traits examined[16]. LCV analysis relies on the
386 assumption that there is a latent variable that mediates the genetic correlation between
387 two traits and uses whole genome summary statistics to estimate genetic causality. One
388 trait is partially genetically causal for the other if it is strongly genetically correlated with the
389 LCV. However, LCV aims to capture the overall direction of causality and therefore may be
390 less appropriate for relationships where a bidirectional effect may be present, as we
391 observe in our study. Whereas MR does allow for for bidirectional relationships[39]. Although,
392 LCV has better control for pleiotropy[16], meaning the difference between our results and
393 those in the previous LCV analysis may reflect the presence of pleiotropy, which we were
394 unable to directly test for in several of our analyses. We were able to test this for our MR of

schizophrenia on cEF and found no evidence of pleiotropy. However, this should be considered when interpreting our other results.

Limitations

There are a number of limitations to our study that should be considered when interpreting these results. First, there could be low statistical power to detect causal effects for some of the analyses. In particular, where anxiety, alcohol dependence and CUD are the exposures there were a low number of genome-wide significant SNPs. To overcome this issue we lowered the p-value threshold for our MR analyses to $1x10^{-5}$, but this means that any interpretation of these results should be approached with caution and revisiting this causal relationship when larger GWAS are available would be valuable. Second, in the majority of our analyses (i.e., in both directions for schizophrenia, MDD, smoking initiation, drinks per week and CUD) evidence of heterogeneity was observed in the IVW estimates, which could suggest that horizontal pleiotropy is present (e.g., that independent pathways are responsible for the influence of SNPs on the exposure and outcome). Therefore, caution should be used when interpreting these results. However, we did test for violations of other MR assumptions using additional MR sensitivity analyses and the direction of the results were consistent with the direction of the main results. Despite this, in a number of our analyses we could not test for directional pleiotropy due to the I-squared estimate being too low.

Finally, MR is also subject to some general limitations[40]. For example, the 'Winner's curse' can occur when the SNPs used are based on the discovery GWAS only (as opposed to combined discovery and replication results), meaning that SNP-trait effects may be overestimated. This can mean that the MR estimate is biased towards the null. Thus, the

focus of our results is on the direction of effect as opposed to the size of any causal effects, although the latter may still be somewhat informative.

Conclusion

Our findings suggest a bidirectional causal relationship between cEF and schizophrenia liability, where increased schizophrenia liability is associated with decreased cEF and vice versa, as well as causal effects of increased cEF on reduced MDD liability and CUD liability and decreased drinks per week, and a causal effect of smoking initiation on decreased cEF. These results require further study to better understand the mechanisms behind these causal effects. Future research would benefit from better powered GWAS for anxiety where a lack of power may explain why we did not detect any causal effects. Our results may inform prioritisation of experimental medicine studies (e.g., of interventions targeting EF) to improve the likelihood of successful translation and suggest that these interventions may be useful prior to the onset of schizophrenia and MDD in particular.

Acknowledgements: We thank all the contributors to the consortia we have used GWAS results from in our analyses. We would like the thank the research participants and employees of 23andMe for making this work possible.

Funding: This work was supported by the UK Medical Research Council Integrative Epidemiology Unit at the University of Bristol (Grant ref: MC_UU_00011/7) and the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. HMS is supported by the European Research Council (Grant ref: 758813 MHINT). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care. ASH acknowledges funding from that National Institute on Drug Abuse (Grant ref: T32DA007261).

Competing interests: None

Author contributions: Conceptualization: MRM, ZER; Methodology: SMIB, ZER; Formal Analysis: SMIB, ZER; Resources: MRM; Data Curation: ZER; Writing—Original Draft: SMIB, ZER; Writing—Review and Editing: SMIB, HMS, ASH, MRM, ZER; Supervision: MRM, ZER; Project Administration: MRM, ZER; Funding Acquisition: MRM.

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