General Psychiatry

Exploring the influences of education, intelligence and income on mental disorders

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ABSTRACT

Background Previous studies have shown that educational attainment (EA), intelligence and income are key factors associated with mental disorders. However, the direct effects of each factor on major mental disorders are unclear.

Aims We aimed to evaluate the overall and independent causal effects of the three psychosocial factors on common mental disorders.

Methods Using genome-wide association study summary datasets, we performed Mendelian randomisation (MR) and multivariable MR (MVMR) analyses to assess potential associations between the 3 factors (EA, N=766 345; household income, N=392 422; intelligence, N=146 808) and 13 common mental disorders, with sample sizes ranging from 9907 to 807 553. Inverse-variance weighting was employed as the main method in the MR analysis.

Results Our MR analysis showed that (1) higher EA was a protective factor for eight mental disorders but contributed to anorexia nervosa, obsessive-compulsive disorder (OCD), bipolar disorder (BD) and autism spectrum disorder (ASD); (2) higher intelligence was a protective factor for five mental disorders but a risk factor for OCD and ASD; (3) higher household income protected against 10 mental disorders but confers risk for anorexia nervosa. Our MVMR analysis showed that (1) higher EA was a direct protective factor for attention-deficit/hyperactivity disorder (ADHD) and insomnia but a direct risk factor for schizophrenia, BD and ASD; (2) higher intelligence was a direct protective factor for schizophrenia but a direct risk factor for major depressive disorder (MDD) and ASD; (3) higher income was a direct protective factor for seven mental disorders, including schizophrenia, BD, MDD, ASD, post-traumatic stress disorder, ADHD and anxiety disorder.

Conclusions Our study reveals that education, intelligence and income intertwine with each other. For each factor, its independent effects on mental disorders present a more complex picture than its overall effects.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Educational attainment (EA), intelligence and income are vital psychosocial factors associated with mental disorders. However, the direct effects of each factor on major mental disorders need to be further elucidated.

WHAT THIS STUDY ADDS

⇒ Untangled, independent effects of these psychosocial factors on mental disorders are more complex than their overall effects. Our study suggests that higher EA or higher intelligence may exert independent detrimental effects on some mental disorders; while high income is a direct protective factor for most common mental disorders.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In the clinical practice for mental disorders, taking into account each of the psychosocial factors may provide additional granularity necessary for proper disease-specific prevention and management.

of higher EA on occupations and income are also positive and direct. As two vital dimensions of socioeconomic status, EA and income also correlate with a variety of social and health outcomes.[3] Social epidemiology demonstrates that both lower-level EA and lower socioeconomic position are strongly associated with poorer health, a higher risk of illness and higher mortality.[4]

Although the overall effects of each of the three psychosocial factors are deemed beneficial, determining causality in conventional observational studies of mental diseases is a challenge. Recently, the Mendelian randomisation (MR) technique has been widely employed to evaluate causality between risk factors and diseases.[5–7] In MR, causality is examined by using germline genetic variants as instruments for quantifying the effect of an exposure on a specific outcome. It was reported that higher EA was associated with an increased risk for bipolar disorder (BD) but a decreased risk for attention-deficit/

INTRODUCTION

Intelligence, education and income are three fundamental determinants of human health and well-being. Intelligence is a basic indicator of cognitive ability and a major correlate of human health outcomes.[1] Higher intelligence has positive direct effects on educational attainment (EA), higher-status occupations and income.[2] The effects
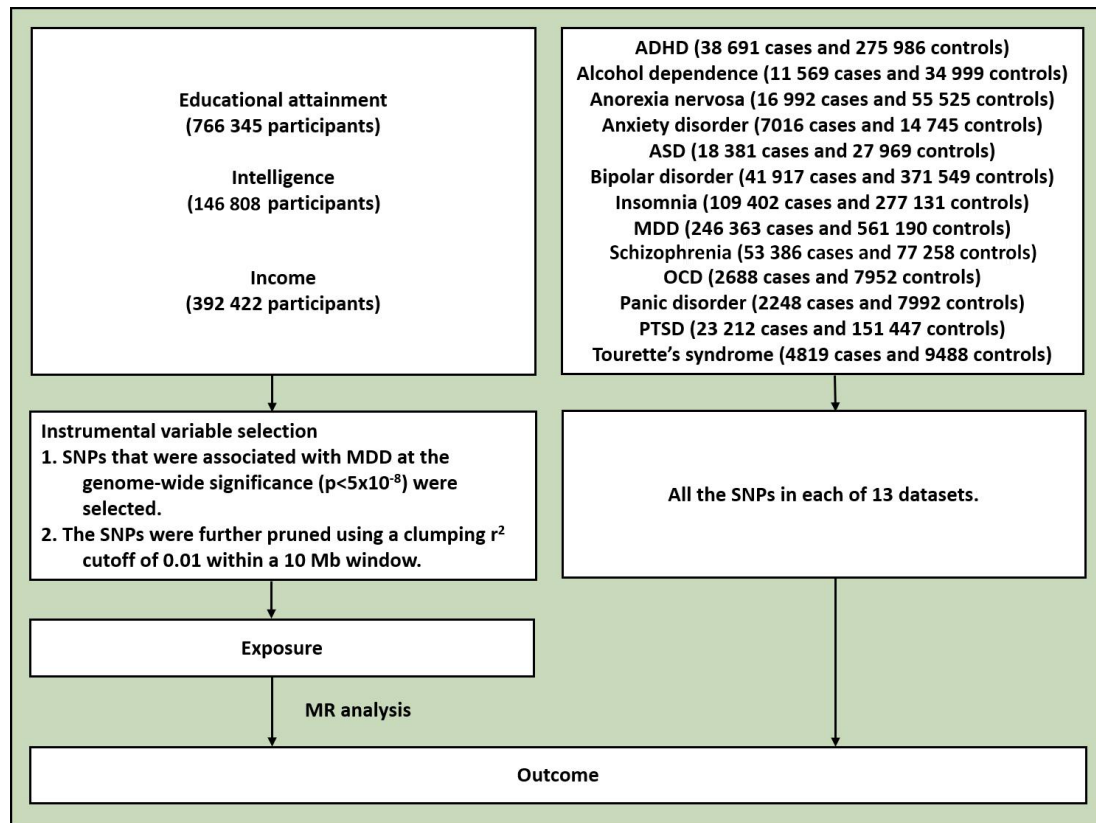
Figure 1 Flowchart of the study. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; MDD, major depressive disorder; MR, Mendelian randomisation; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; SNPs. single-nucleotide polymorphisms.

hyperactivity disorder (ADHD),[8][9] while higher EA or intelligence confers a causal effect on autism spectrum disorder (ASD) but protects against ADHD (OR: 0.78).[10][11]

Here, we hypothesise that the overall effects of each of the three factors on mental disorders may be partially mediated or confounded by each other. To disentangle these relationships, we conducted univariable MR analysis and multivariable MR (MVMR) analyses and compared the overall effects of each of these factors on mental diseases to their direct effects on the same set of conditions.

METHODS
Genome-wide association study (GWAS) summary datasets
The design of the study is shown in figure 1. The study used publicly available GWAS summary results. Table 1 lists the GWAS datasets used in this study. The datasets on EA contained 766 345 participants.[12] The GWAS datasets of household income and intelligence (fluid intelligence score) were obtained from Yang Lab (https://yanglab. westlake.edu.cn/),[13] containing 392 422 and 146 808 participants, respectively. The participants of the income and intelligence datasets came from the UK Biobank, consisting of ~500 000 volunteers aged 40–69 recruited between 2006 and 2010 across the United Kingdom.[14] Detailed information on the UK Biobank cohort can be found on its website (https://www.ukbiobank.ac.uk/).

The insomnia dataset was obtained from the Center for Neurogenomics and Cognitive Research.[15] The largest GWAS summary datasets for the other 12 mental disorders, namely, ADHD, alcohol dependence, anorexia nervosa, anxiety disorder, ASD, BD, major depressive disorder (MDD), obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD), schizophrenia and Tourette's syndrome (TS), were obtained from the Psychiatric Genomics Consortium. Sample sizes ranged from 9907 to 807 553 for the mental disorders. All the participants in the datasets were of European origin.

Genetic correlation analysis
The genetic correlations between the 3 factors and the 13 mental disorders were appraised by linkage disequilibrium (LD) score regression.[16] The LD structure of the genetic variants was derived from the 1000 Genome Project Phase 3 in European populations. Multiple testing was accounted for by the false discovery rate (FDR) procedure (FDR<0.05).

MR analysis
The MR analyses were performed using three techniques implemented in TwoSampleMR,[17] including inverse-variance weighted (IVW), weighted median and MR-Egger. The IVW model was used as the main method. Directional pleiotropy was evaluated by the intercept

Table 1 Summary information of the datasets

Trait	Year	First author	PMID	N_{case}	$N_{control}$	N
EA	2018	Lee JJ	30038396	NA	NA	766 345
Intelligence	2019	Jiang L	31768069	NA	NA	146 808
Income	2019	Jiang L	31768069	NA	NA	392 422
ADHD	2023	Demontis D	36702997	38 691	275 986	314 677
Alcohol dependence	2018	Walters RK	30482948	11 569	34 999	46 568
Anorexia nervosa	2019	Watson HJ	31308545	16 992	55 525	72 517
Anxiety disorder	2016	Otowa T	26857599	7016	14 745	21 761
ASD	2019	Grove J	30804558	18 381	27 969	46 350
BD	2021	Mullins N	34002096	41 917	371 549	413 466
Insomnia	2019	Jansen PR	30804565	109 402	277 131	386 533
MDD	2019	Howard DM	30718901	246 363	561 190	807 553
OCD	2017	Arnold PD	28761083	2688	7952	10 640
Panic disorder	2021	Forstner AJ	31712720	2248	7992	9907
PTSD	2019	Nievergelt CM	31594949	23 212	151 447	174 659
Schizophrenia	2022	Trubetskoy V	35396580	53 386	77 258	130 644
TS	2019	Yu D	30818990	4819	9488	14 307

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; EA, educational attainment; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; TS, Tourette's syndrome.

from the MR-Egger regression. The heterogeneity of the MR analysis was evaluated by Cochran's Q test (p<0.05) and I^2 statistics ($I^2>0.25$). The significant associations were determined by an IVW-based FDR <0.05. For each MR analysis, genome-wide significant single-nucleotide polymorphisms ($p<5\times10^{-8}$) in the exposure dataset were used to select independent variables (IVs) by a clumping r^2 value of 0.01 in a 10 Mb window.

MVMR analysis
An MVMR analysis was used to estimate the direct effect of each exposure on each of the mental disorders. The MVMR analyses were performed using the TwoSampleMR package.[17]

RESULTS
Genetic correlations
For the three psychosocial factors, high and positive inter-correlations were detected (r_g: 0.63–0.81) (online supplemental table 1). The three psychosocial factors had overall negative genetic correlations with the 13 mental disorders (figure 2A and online supplemental table 2). Notably, ADHD demonstrated the strongest negative correlation with all the three psychosocial factors (r_g: −0.41 to −0.53). ASD had positive correlations with EA (r_g: 0.21) and intelligence (r_g: 0.20). OCD was positively correlated with EA (r_g: 0.24) and income (r_g: 0.14). Anorexia nervosa was also positively correlated with EA (r_g: 0.25) and income (r_g: 0.16).

MR analysis
Considering the genetic correlations between the three factors and the intertwined influences of these factors on each mental disorder, we called the associations revealed by the MR analysis 'overall causal effects'.

For the three psychosocial factors, their causal associations with each other were strong and bidirectional (OR: 1.44–2.17) (online supplemental table 3). Specifically, intelligence confers causal effects on EA (OR: 1.50) and income (OR: 1.44), EA confers causal effects on intelligence (OR: 2.17) and income (OR: 1.99), and income confers causal effects on EA (OR: 1.88) and intelligence (OR: 1.99).

The causal effects of the three studied factors on the mental disorders are shown in table 2, figure 2 and online supplemental table 4. Higher EA served as a protective factor for eight mental disorders, including panic disorder (OR: 0.68), ADHD (OR: 0.72), TS (OR: 0.73), alcohol dependence (OR: 0.75), MDD (OR: 0.84), insomnia (OR: 0.86), PTSD (OR: 0.94) and anxiety disorder (OR: 0.95), but as a risk factor for anorexia nervosa (OR: 1.44), OCD (OR: 1.29), BD (OR: 1.38) and ASD (OR: 1.21).

Higher intelligence was a protective factor for five mental disorders, including schizophrenia (OR: 0.63), ADHD (OR: 0.85) and insomnia (OR: 0.93), but a risk factor for ASD (OR: 1.15).

Higher income conferred a protective effect on 9 out of the 13 mental disorders, including panic disorder (OR: 0.41), schizophrenia (OR: 0.68), MDD (OR: 0.74), ADHD (OR: 0.76), TS (OR: 0.75),
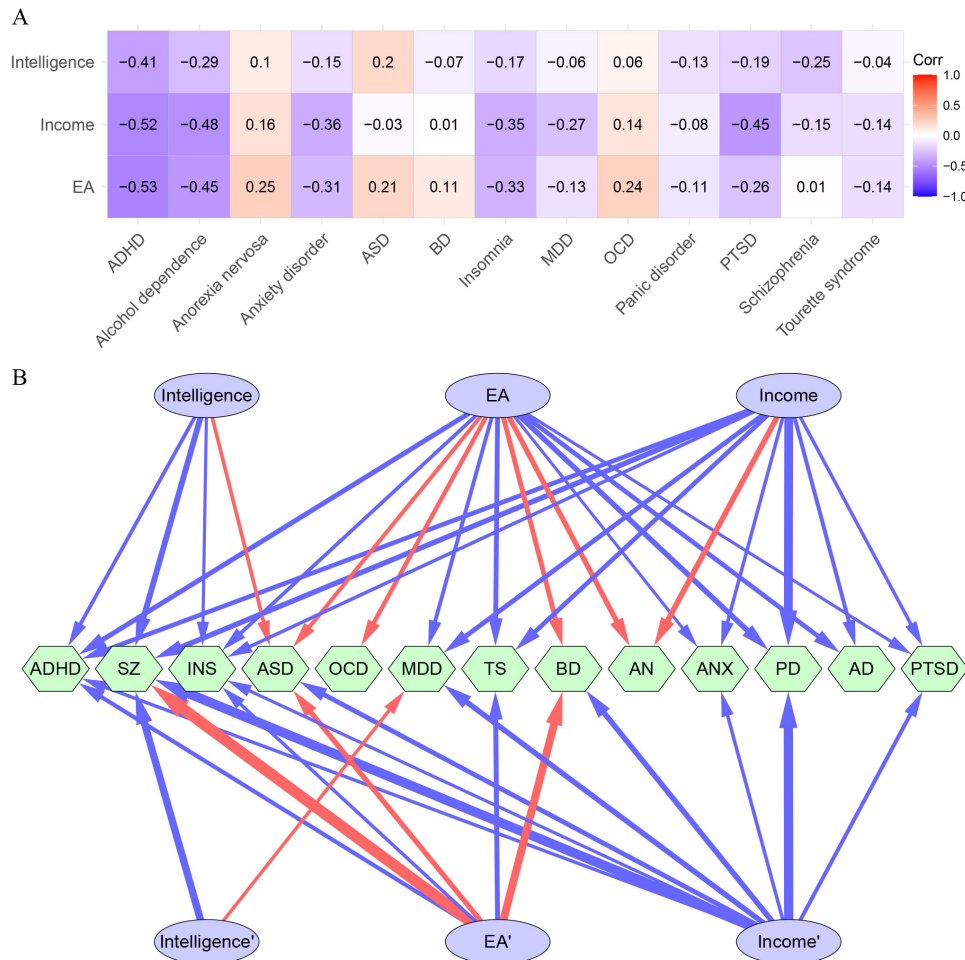
Figure 2 Genetic correlations and causal associations between the three psychosocial factors and the mental disorders. (A) Genetic correlations between the three psychosocial factors and the mental disorders. (B) Significant overall and independent causal effects of the three factors on the mental disorders. The upper lines are causal effects in the Mendelian randomisation analysis, and the bottom lines are causal effects in the multivariable Mendelian randomisation analysis. The red colour represents positive causal effects, and the blue colour represents negative causal effects. The width of the edges is relative to the absolute value of the effect sizes. AD, alcohol dependence; ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ANX, anxiety disorder; ASD, autism spectrum disorder; BD, bipolar disorder; EA, educational attainment; INS, insomnia; MDD, major depressive disorder; MR, Mendelian randomisation; OCD, obsessive-compulsive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; SZ, schizophrenia; TS, Tourette's syndrome.

alcohol dependence (OR: 0.83), PTSD (OR: 0.89), anxiety disorder (OR: 0.89) and insomnia (OR: 0.89). However, higher income was a risk factor for anorexia nervosa (OR: 1.52).

The average overall causal effects (OR) were 0.99 (0.26), 0.96 (0.13) and 0.88 (0.26) for EA, intelligence and income, respectively.

MR sensitivity analysis showed that the directions from different models were largely the same (online supplemental table 4). The MR-Egger regression did not support directional pleiotropy in the MR analysis (MR-Egger intercept <0.01). The evidence of directional pleiotropy for the IVs from the MR-Egger regression was minimal, indicating the robustness of the main results. There was evidence supporting the potential heterogeneity among the individual IV effect estimates.

MVMR analysis

Further exploration of the direct causal effects of each factor on the mental disorders was conducted with the aid of MVMR, which is capable of accounting for the influence of synergistic factors. Here, we called the associations revealed by MVMR 'direct' or 'independent' causal effects.

The results of the MVMR analysis are shown in table 3 and figure 2B. We found that higher EA is independently associated with an increased risk for schizophrenia (OR: 3.43), BD (OR: 2.11) and ASD (OR: 1.43) and a decreased risk for ADHD (OR: 0.80) and insomnia (OR: 0.90). In the MVMR analysis, the average effect sizes (OR values) of EA on the mental disorders increased substantially and became largely detrimental (OR_MR: 0.99 vs OR_MVMR: 1.30). In particular, the effects of EA on schizophrenia and BD

Table 2 Causal effects of the three factors on the mental disorders in the Mendelian randomisation analysis

Exposure	Outcome	B (SE)	OR (95% CI)	N_IV	P value	FDR
EA	ADHD	−0.333 (0.018)	0.72 (0.69 to 0.74)	457	<0.001	6.63E−78
EA	Alcohol dependence	−0.286 (0.042)	0.75 (0.69 to 0.82)	460	<0.001	1.57E−10
EA	Anorexia nervosa	0.364 (0.077)	1.44 (1.24 to 1.67)	458	<0.001	7.64E−06
EA	Anxiety disorder	−0.056 (0.020)	0.95 (0.91 to 0.98)	454	<0.001	8.83E−03
EA	ASD	0.192 (0.036)	1.21 (1.13 to 1.30)	460	<0.001	5.15E−07
EA	BD	0.323 (0.066)	1.38 (1.21 to 1.57)	463	<0.001	3.90E−06
EA	Insomnia	−0.154 (0.013)	0.86 (0.84 to 0.88)	458	<0.001	1.13E−32
EA	MDD	−0.175 (0.028)	0.84 (0.79 to 0.89)	461	<0.001	2.63E−09
EA	OCD	0.253 (0.064)	1.29 (1.14 to 1.46)	461	<0.001	2.06E−04
EA	Panic disorder	−0.390 (0.160)	0.68 (0.49 to 0.93)	462	0.015	0.023
EA	PTSD	−0.064 (0.015)	0.94 (0.91 to 0.97)	462	<0.001	5.99E−05
EA	Schizophrenia	0.050 (0.082)	1.05 (0.90 to 1.23)	461	0.536	0.674
EA	TS	−0.313 (0.056)	0.73 (0.66 to 0.82)	460	<0.001	1.36E−07
Income	ADHD	−0.280 (0.035)	0.76 (0.70 to 0.81)	86	<0.001	2.69E−14
Income	Alcohol dependence	−0.191 (0.085)	0.83 (0.70 to 0.98)	88	0.024	0.036
Income	Anorexia nervosa	0.421 (0.119)	1.52 (1.21 to 1.92)	87	<0.001	8.43E−04
Income	Anxiety disorder	−0.121 (0.033)	0.89 (0.83 to 0.95)	87	<0.001	5.53E−04
Income	ASD	−0.010 (0.068)	0.99 (0.87 to 1.13)	88	0.884	0.907
Income	BD	−0.069 (0.130)	0.93 (0.72 to 1.20)	88	0.595	0.682
Income	Insomnia	−0.121 (0.022)	0.89 (0.85 to 0.93)	88	<0.001	1.91E−07
Income	MDD	−0.302 (0.047)	0.74 (0.67 to 0.81)	86	<0.001	1.26E−09
Income	OCD	0.151 (0.102)	1.16 (0.95 to 1.42)	87	0.139	0.192
Income	Panic disorder	−0.885 (0.255)	0.41 (0.25 to 0.68)	87	<0.001	1.06E−03
Income	PTSD	−0.116 (0.025)	0.89 (0.85 to 0.93)	89	<0.001	1.01E−05
Income	Schizophrenia	−0.382 (0.156)	0.68 (0.50 to 0.93)	88	0.014	0.023
Income	TS	−0.282 (0.111)	0.75 (0.61 to 0.94)	87	0.011	0.019
Intelligence	ADHD	−0.158 (0.028)	0.85 (0.81 to 0.90)	78	<0.001	6.24E−08
Intelligence	Alcohol dependence	−0.115 (0.055)	0.89 (0.80 to 0.99)	78	0.035	0.051
Intelligence	Anorexia nervosa	0.160 (0.109)	1.17 (0.95 to 1.45)	77	0.143	0.192
Intelligence	Anxiety disorder	−0.005 (0.026)	0.99 (0.95 to 1.05)	76	0.833	0.879
Intelligence	ASD	0.144 (0.048)	1.15 (1.05 to 1.27)	78	<0.001	4.66E−03
Intelligence	BD	−0.032 (0.096)	0.97 (0.80 to 1.17)	78	0.741	0.826
Intelligence	Insomnia	−0.068 (0.018)	0.93 (0.90 to 0.97)	78	<0.001	2.75E−04
Intelligence	MDD	−0.005 (0.044)	0.99 (0.91 to 1.09)	78	0.909	0.909
Intelligence	OCD	−0.047 (0.084)	0.95 (0.81 to 1.12)	78	0.575	0.682
Intelligence	Panic disorder	−0.046 (0.217)	0.96 (0.62 to 1.46)	78	0.834	0.879
Intelligence	PTSD	−0.011 (0.021)	0.99 (0.95 to 1.03)	78	0.579	0.682
Intelligence	Schizophrenia	−0.454 (0.135)	0.63 (0.49 to 0.83)	78	<0.001	1.49E−03
Intelligence	TS	−0.052 (0.081)	0.95 (0.81 to 1.11)	77	0.519	0.674

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; CI, confidence interval; EA, educational attainment; FDR, false discovery rate; IVW, inverse-variance weighted; MDD, major depressive disorder; N_IV, number of instrumental variable; OCD, obsessive-compulsive disorder; OR, odds ratio; PTSD, post-traumatic stress disorder; SE, standard error; TS, Tourette's syndrome.

remarkably increased, and the protective effects of EA on alcohol dependence, panic disorder, PTSD and MDD disappeared.

The average causal effect of intelligence on the mental disorders did not change after MVMR (OR_MR: 0.96 vs OR_MVMR: 0.97). The protective effects

Table 3 Causal effects of the three factors on the mental disorders in the multivariable Mendelian randomisation analysis

Exposure	Outcome	B (SE)	OR (95% CI)	N_IV	P value	FDR
EA	ADHD	−0.22 (0.04)	0.80 (0.74 to 0.87)	435	<0.001	1.88E−07
EA	Alcohol dependence	−0.15 (0.10)	0.86 (0.71 to 1.04)	441	0.125	0.212
EA	Anorexia nervosa	0.16 (0.17)	1.17 (0.84 to 1.63)	436	0.358	0.499
EA	Anxiety disorder	0.01 (0.04)	1.01 (0.93 to 1.10)	430	0.788	0.884
EA	ASD	0.36 (0.08)	1.43 (1.22 to 1.67)	441	<0.001	2.85E−05
EA	BD	0.75 (0.15)	2.11 (1.57 to 2.83)	444	<0.001	3.83E−06
EA	Insomnia	−0.11 (0.03)	0.90 (0.85 to 0.95)	439	<0.001	7.50E−04
EA	MDD	0.02 (0.06)	1.02 (0.90 to 1.15)	443	0.795	0.884
EA	OCD	0.17 (0.14)	1.19 (0.90 to 1.57)	443	0.219	0.356
EA	Panic disorder	0.20 (0.36)	1.22 (0.61 to 2.47)	443	0.573	0.721
EA	PTSD	0.06 (0.03)	1.07 (1.00 to 1.14)	443	0.046	0.092
EA	Schizophrenia	1.23 (0.17)	3.43 (2.44 to 4.83)	443	<0.001	6.32E−11
EA	TS	−0.33 (0.13)	0.72 (0.56 to 0.92)	442	<0.001	0.034
Income	ADHD	−0.11 (0.04)	0.90 (0.82 to 0.98)	63	0.012	0.037
Income	Alcohol dependence	−0.22 (0.11)	0.80 (0.65 to 1.00)	63	0.047	0.092
Income	Anorexia nervosa	0.33 (0.19)	1.39 (0.95 to 2.02)	61	0.087	0.162
Income	Anxiety disorder	−0.12 (0.05)	0.88 (0.80 to 0.97)	62	0.013	0.037
Income	ASD	−0.31 (0.09)	0.73 (0.61 to 0.87)	63	<0.001	1.41E−03
Income	BD	−0.41 (0.17)	0.67 (0.48 to 0.92)	62	0.015	0.037
Income	Insomnia	−0.08 (0.03)	0.93 (0.87 to 0.98)	63	0.015	0.037
Income	MDD	−0.40 (0.07)	0.67 (0.59 to 0.77)	61	<0.001	1.45E−07
Income	OCD	0.15 (0.16)	1.16 (0.86 to 1.58)	63	0.333	0.481
Income	Panic disorder	−0.95 (0.40)	0.39 (0.18 to 0.85)	62	0.017	0.039
Income	PTSD	−0.19 (0.04)	0.83 (0.77 to 0.89)	62	<0.001	2.29E−06
Income	Schizophrenia	−0.99 (0.20)	0.37 (0.25 to 0.55)	62	<0.001	2.68E−06
Income	TS	−0.11 (0.14)	0.90 (0.68 to 1.18)	63	0.445	0.598
Intelligence	ADHD	−0.06 (0.03)	0.95 (0.89 to 1.00)	52	0.047	0.092
Intelligence	Alcohol dependence	0.01 (0.07)	1.01 (0.88 to 1.16)	52	0.848	0.894
Intelligence	Anorexia nervosa	−0.02 (0.12)	0.98 (0.77 to 1.24)	52	0.873	0.896
Intelligence	Anxiety disorder	0.01 (0.03)	1.01 (0.95 to 1.07)	52	0.816	0.884
Intelligence	ASD	0.06 (0.06)	1.07 (0.95 to 1.19)	52	0.266	0.407
Intelligence	BD	−0.18 (0.11)	0.84 (0.68 to 1.03)	52	0.100	0.177
Intelligence	Insomnia	0.01 (0.02)	1.01 (0.97 to 1.05)	52	0.806	0.884
Intelligence	MDD	0.11 (0.04)	1.12 (1.02 to 1.22)	52	0.014	0.037
Intelligence	OCD	−0.06 (0.10)	0.94 (0.77 to 1.15)	52	0.561	0.721
Intelligence	Panic disorder	0.06 (0.26)	1.06 (0.64 to 1.76)	52	0.815	0.884
Intelligence	PTSD	0.00 (0.02)	1.00 (0.96 to 1.05)	52	0.992	0.992
Intelligence	Schizophrenia	−0.67 (0.13)	0.51 (0.40 to 0.66)	52	<0.001	1.38E−06
Intelligence	TS	0.10 (0.09)	1.11 (0.92 to 1.32)	52	0.271	0.407

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; CI, confidence interval; EA, educational attainment; FDR, false discovery rate; MDD, major depressive disorder; N_IV, number of instrumental variable; OCD, obsessive-compulsive disorder; OR, odds ratio; PTSD, post-traumatic stress disorder; SE, standard error; TS, Tourette's syndrome.

of intelligence vanished in ADHD and insomnia. Notably, in MVMR, higher intelligence was a risk factor for MDD (OR: 1.12). Higher intelligence remained a protective factor for schizophrenia (OR: 0.51).

The overall effects of household income on the mental disorders had little change in the MVMR analysis (OR_MR: 0.88 vs OR_MVMR: 0.82). After adjustments for EA and intelligence in the MVMR analysis, higher income ceased to serve as a protective or risk

factor for anorexia nervosa, alcohol dependence and TS but turned into a protective factor for BD (OR: 0.67) and ASD (OR: 0.73). After the MVMR adjustment, higher income remained a protective factor for schizophrenia (OR: 0.37), insomnia (OR: 0.93), MDD (OR: 0.67), anxiety disorder (OR: 0.88), PTSD (OR: 0.83), panic disorder (OR: 0.39) and ADHD (OR: 0.90).

DISCUSSION
Main findings

In this study, we comprehensively explored the genetic relationships between 3 psychosocial factors and 13 common mental disorders. We observed overall negative genetic correlations between three psychosocial factors and the mental disorders. However, several mental disorders have positive correlations with EA or income, including ASD, anorexia nervosa, BD and OCD. These genetic correlations were largely consistent with those uncovered by MR analysis.

Of note, the strongest negative genetic correlations with all three psychosocial factors were observed for ADHD. This finding should be interpreted as the protection offered by the genetic components associated with high EA (OR: 0.72), intelligence (OR: 0.85) and income (OR: 0.76). This observation is consistent with results from previous studies.[10 18 19] However, in the MVMR, the observed protective effect of intelligence on ADHD was diminished (OR: 0.95). Our results indicate the strong confounding effects of the three psychosocial factors on ADHD. It seems that the protective effects of intelligence on ADHD are chiefly mediated by EA and income.

In some cases, the results of MR and MVMR analyses differed substantially. For example, our MR analysis highlighted the protective effects of EA on eight mental disorders, which were somewhat counterbalanced by the risks for anorexia nervosa (OR: 1.44), OCD (OR: 1.29), BD (OR: 1.38) and ASD (OR: 1.21). However, the MVMR analysis pointed towards the direct detrimental effects of EA on several mental disorders. In other words, the unfavourable effects of EA on mental disorders became apparent after subtracting the confounding influences of the other two factors. Although the MR results did support the protective effects of EA on MDD (OR: 0.84), this protection disappeared after MVMR-guided dissection (OR: 1.02). Our results suggest that the survey-observed negative associations between EA and MDD should be attributed to the confounding protective effect of income.

Our MR analysis showed that higher intelligence was a protective factor for three mental disorders (schizophrenia, ADHD and insomnia) but a risk factor for ASD (OR: 1.15). In MVMR, higher intelligence turned from a neutral to a risk factor for MDD (OR: 1.12). Notably, higher intelligence remained an independent protective factor for schizophrenia (OR: 0.51). After MVMR-guided adjustment for confounders, higher intelligence was

no longer marked as a protective factor for ADHD and insomnia.

After MVMR-guided adjustment for confounders, higher income behaved as a protective factor for 9 out of the 13 mental disorders, including schizophrenia (OR: 0.37), BD (OR: 0.67), ASD (OR: 0.73), MDD (OR: 0.67), anxiety disorder (OR: 0.88), insomnia (OR: 0.93), panic disorder (OR: 0.39), PTSD (OR: 0.83) and ADHD (OR: 0.90). In summary, both the overall and the independent effects of income on the mental disorders were beneficial (OR_MR: 0.88 vs OR_MVMR: 0.82).

The observed causal influences of the three factors on schizophrenia are worth specific attention. In the MR analysis, the effects of EA on schizophrenia were non-significant, while the other two factors conferred robust protective effects on this psychiatric condition. In the MVMR analysis, EA conferred the highest causal effect on schizophrenia (OR: 3.43), while the other two factors strongly protected against schizophrenia, with the protective effect of higher income being the highest (OR: 0.37).

The observed protective roles of higher income and higher intelligence in schizophrenia were consistent with the large body of accumulated evidence.[20–23] In our study, EA behaved as a risk factor for schizophrenia, which is consistent with the genetic findings that additional years of schooling are genetically associated with an increased risk for this psychiatric condition.[21 24] However, previous cohort survey studies revealed lower risks of schizophrenia in cohorts with additional years of education.[25] The paradoxical relationships between genetic prediction and cohort observations may be due to a reverse causation bias, namely, obvious impairments of school performance after the onset of psychotic symptoms in individuals with schizophrenia. Moreover, patients with schizophrenia are less likely to enter higher education due to premorbid cognitive impairments.[26]

BD genetically overlaps with schizophrenia. While being associated with some cognitive deficits, BD predisposes individuals to certain creativity and cognitive adeptness, thus being distinct from schizophrenia in its neurodevelopmental aspects. The distribution of educational levels of patients with BD is similar to that in the general population.[27] A detrimental effect of EA on BD was detectable in our analyses, although at a smaller scale than that seen for schizophrenia. Our MR analysis showed that EA was an overall risk factor for BD (OR: 1.38). In MVMR, its causal effects were much stronger than those of BD (OR: 2.11). Therefore, higher EA is a remarkable risk factor for BD.

Another interesting case is anorexia nervosa, where the detrimental effects of both EA and income were relatively strong in MR but diminished to non-significance in the results of MVMR. Performance at school or educational level is positively associated with the risk of eating disorders, and striving for perfection is proposed as an explanation for this association.[28 29] In a previous MR study, a higher EA adjusted for intelligence was reported to be associated with a higher risk of anorexia nervosa.[30] Our

MR analysis indicates that, in addition to higher EA, higher household income is also an overall risk factor for anorexia nervosa. However, neither EA nor income could independently confer risk for anorexia nervosa in the MVMR analysis.

In summary, when the independent effects of the three factors were accounted for, higher EA represented a risk factor for mental health, higher income served as a definite protective factor, and the impacts of intelligence on the mental disorders appeared to be mixed. However, when the much higher prevalence and population disease burden of MDD are taken into consideration along with the detrimental effects of intelligence on MDD, an overall trend describing the influence of intelligence on these mental disorders becomes unfavourable.

To some extent, intelligence represents the inherent mental capacity of a human being, EA may reflect a process of socialisation from birth to adulthood, and income denotes the outcome of this socialisation. Our results suggest that the protective effects of EA and intelligence on mental disorders, as observed in the MR analysis, mainly stem from the mediating effects of income. It seems that higher intelligence or high EA will be of little benefit to mental health when they cannot be translated into higher socioeconomic status. Education is a long and stress-increasing process. While a majority of mental problems occur at the life stage of studying, the higher socioeconomic outcomes of EA compensate for the toll the study period took on mental health, with an outcome depending on all of the above and reflected in a cumulative incidence of mental disorders within the lifetime.

Limitations

Although the MR framework provides an advantage over traditionally designed epidemiological studies, several limitations of our study should be noted. In particular, both MR and MVMR analyses concentrate exclusively on the genetic liability to studied traits, with no regard to their environmental components. Moreover, as the heritability of intelligence may be in a non-linear relationship with socioeconomic status, a more granular view on the correlation puzzle of multiple factors connecting mental disorders with psychosocial factors is warranted. We should also emphasise that observed relationships may not be translatable into actionable items through socioeconomic interventions. Pleiotropy is a well-known source of bias in MR analyses, especially in non-homogenous datasets. While the MR-Egger procedure did not support directional pleiotropy in our study, some evidence supporting the potential heterogeneity among the individual IV effect estimates was reported.

Implications

Here, we dissect the complexity of causal connections between EA, intelligence, income and 13 common mental disorders. The results of this study may aid in clarifying inconsistencies noted in previously published research and add some insights to the current understanding of the relationship between psychosocial factors and mental disorders.

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