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ORIGINAL INVESTIGATION

Causal influences of neuroticism on mental health and cardiovascular disease

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Abstract

We investigated the relationship between neuroticism and 16 mental and 18 physical traits using summary results of genome-wide association studies for these traits. LD score regression was used to investigate genetic correlations between neuroticism and the 34 health outcomes. Mendelian randomization was performed to investigate mutual causal relationships between neuroticism and the 34 health outcomes. Neuroticism genetically correlates with a majority of health-related traits and confers causal effects on 12 mental traits (major depressive disorder (MDD), insomnia, subjective well-being (SWB, negatively), schizophrenia, attention-deficit/hyperactivity disorder, alcohol dependence, loneliness, anorexia nervosa, anxiety disorder, bipolar disorder, obsessive–compulsive disorder, and psychiatric disorders) and two physical diseases (cardiovascular disease and hypertensive disease). Conversely, MDD, SWB, and insomnia have a causal effect on neuroticism. We highlighted key genes contributing to the causal associations between neuroticism and MDD, including *RBFOX1, RERE, SOX5,* and *TCF4*, and those contributing to the causal associations between neuroticism and cardiovascular diseases, including *MAD1L1*, *ARNTL*, *RERE*, and *SOX6*. The present study indicates that genetic variation mediates the causal influences of neuroticism on mental health and cardiovascular diseases.

Introduction

Neuroticism is one of the five higher order factors taxonomically defining one's personality. The modern conception of neuroticism was initially introduced by Hans Eysenck and his contemporaries when it was defined in Freudian theory terms (Ormel et al. 2013). Currently, the consensus has neuroticism as the tendency to experience negative emotions, including anxiety, fear, sadness, anger, guilt, disgust, irritability, loneliness, worry, self-consciousness, dissatisfaction, hostility, embarrassment, reduced self-confidence, and feelings of vulnerability, in reaction to various types of stress, and to place themselves into situations that foster negative affect (Jeronimus et al. 2014; Specht et al. 2011). The individual differences in neuroticism scores show moderate to

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high stability across much of the adult life course (Wray et al. 2007).

Mounting evidence suggests that neuroticism has profound significance for mental health (Lahey 2009; Ormel et al. 2013). Specifically, people who score higher in the neuroticism dimension have a greater propensity for psychiatric conditions, such as anxiety, somatoform, obsessive–compulsive disorder (OCD), as well as schizophrenia (SZ), bipolar disorder (BD), major depression disorder (MDD), and attention-deficit hyperactivity disorder (ADHD) (Kendler and Myers 2010; Kotov et al. 2010; Lonnqvist et al. 2009; Michielsen et al. 2014; Schirmbeck et al. 2015; Van Os and Jones 2001). Furthermore, several studies linked higher levels of neuroticism to an increase in all-cause mortality (Gale et al. 2016). Neuroticism also contributes to other phenomena that correlate strongly with psychological distress, for example, persistent low subjective well-being (SWB), and physical health problems (Heller et al. 2004; Okbay et al. 2016). Previous studies had quantified neuroticism's cross-sectional association with common mental disorders (CMDs), but also revealed the strong predictive effect of neuroticism with CMDs in prospective association (Kotov et al. 2010; Lahey 2009; Lonnqvist et al. 2009; Van Os and Jones 2001). Discovered connections between neuroticism and CMDs have promoted the assumption that neuroticism is an independent, etiologically informative risk factor, which may actively contribute to the progress of CMDs.

A vital role of neuroticism in mental health has long been documented, but whether the association of neuroticism with psychopathology is determined by inherited genetic variants remains elusive. Previous studies indicated that the possible explanation for associations between neuroticism and these various mental disorders may be due to shared genetic components. Genetic correlations have been identified between neuroticism and anorexia nervosa, MDD, and SZ, and attributed to the genes with pleiotropic effects (Gale et al. 2016; Hill et al. 2019). In addition, some of the subfactors of neuroticism were also genetically associated with BD, ADHD, and autism spectrum disorder (ASD) (Hill et al. 2019). Furthermore, previous studies reported moderate to high genetic correlations between neuroticism and obsessive–compulsive symptoms (Bergin et al. 2014; Taylor et al. 2011). Twin studies have shown considerable overlaps between the genetic factors of neuroticism and those conferring risk for internalizing disorders, such as anxiety and depression (Hettema et al. 2006).

Recently, genome-wide association studies (GWAS) have begun to map the loci that are associated with neuroticism (Luciano et al. 2018; Smith et al. 2016), as well as ones contributing both to neuroticism and psychiatric disorders (Barlow et al. 2014; Lo et al. 2017; Smeland et al. 2017). Current evidence strongly supports the importance of neuroticism in the genetic etiology of mental disorders. However, causal relationships between neuroticism and a wide range of human health outcomes, especially physical conditions, remain largely unknown.

Mendelian randomization (MR) is an analytic technique that uses genetic variants as instrumental variables to test for causative association between an exposure and an outcome (Lawlor et al. 2008). MR is becoming increasingly efficient and cost-effective when applied to ever-growing data curated from recent GWAS. Recently, the GSMR (Generalized Summary-data-based MR) had been developed by leveraging power from multiple genetic variants accounting for linkage disequilibrium (LD) between the variants (Zhu et al. 2018).

Here, we hypothesize that genetic liability of neuroticism may confer risk to mental health and some kinds of physical diseases. In the present study, we used LD score regression to trace the genetic correlations of neuroticism to a panel of mental and physical conditions. We further used the GSMR to perform a multi-SNP MR analysis on summary results presented in GWAS datasets to test the causal associations between neuroticism and these conditions. Finally, we curated and compared genome-wide risk genes for neuroticism and 13 traits causally influenced by neuroticism. For further dissection, we have concentrated on the connection of neuroticism to MDD and cardiovascular diseases (CVDs), two major causes of morbidity in world populations.

Materials and methods

Datasets and quality control

Summary results of GWAS for 17 mental and 18 physical conditions were included in the analyses (Table 1). The mental conditions were selected based on each condition's frequency and importance, and the physical conditions were selected based on each condition's significance within human non-communicative chronic disorders. The trait psychiatric disorders included the collection of psychological/psychiatric problem, mania/bipolar disorder/manic depression, schizophrenia, anxiety/panic attacks. The cardiovascular disease (CVD) included a panel of cardiovascular conditions recruited by the UKB (Supplementary File) (Sudlow et al. 2015). In this study, we used CVD to specifically denote the collection of cardiovascular conditions used the UKB dataset, and used CVDs to denote all cardiovascular conditions. All participants were of European origins. Per condition sample sizes have ranged from 7556 to 694,649. Detailed information of these included studies is summarized in Table 1. We compared SNP alleles between the neuroticism dataset and each of the other datasets and performed the following quality control steps: (1) SNPs were fileted based on INFO $\geq$ 0.90 if it exists; (2) each SNP was

Table 1 Summary information of the datasets

	Trait	Author (year)	PMID	Cases	Controls	*N*
Mental traits	Neuroticism	Nagel et al. (2018)	29,942,085	NA	NA	390,278
	Alcohol dependence	Walters et al. (2018)	30,482,948	11,569	34,999	46,568
	Attention-deficit/hyperactivity disorder	Demontis et al. (2018)	30,478,444	20,183	35,191	55,374
	Anorexia nervosa	Duncan et al. (2017)	28,494,655	3495	10,982	14,477
	Anxiety disorder	Otowa et al. (2016)	26,857,599	NA	NA	17,310
	Autism spectrum disorder	Grove et al. (2019)	30,804,558	18,382	27,969	46,350
	Bipolar disorder	Ruderfer et al. (2018)	29,906,448	20,129	21,524	41,653
	Loneliness	Gao et al. (2017)	27,629,369	NA	NA	7556
	Major depressive disorder	Wray et al. (2018)	29,700,475	135,458	344,901	480,359
	Obsessive–compulsive disorder	IOCDF-GC et al. (2017)	28,761,083	2688	7952	10,640
	Posttraumatic stress disorder	Duncan et al. (2017)	28,439,101	2424	7113	9937
	Subjective well-being	Okbay et al. (2016)	27,089,181	NA	NA	298,420
	Schizophrenia	Ruderfer et al. (2018)	29,906,448	33,426	32,541	65,967
	Tourette syndrome	Yu et al. (2019)	30,818,990	4819	9488	14,307
	Insomnia	Jansen et al. (2019)	30,804,565	109,402	277,131	386,533
	Alzheimer's disease	Jansen et al. (2019)	30,617,256	71,880	383,378	455,258
	Psychiatric disorders	Sudlow et al. (2015)	25,826,379	2564	109,774	112,338
Physical traits	Type 2 diabetes	Xue et al. (2018)	30,054,458	62,892	596,424	659,316
	Coronary artery disease	Nikpay et al. (2015)	26,343,387	60,801	123,504	184,305
	epilepsy	Anney et al. (2014)	25,087,078	8696	26,157	34,853
	Cardiovascular disease	Sudlow et al. (2015)	25,826,379	14,510	97,828	112,338
	Dyslipidemia	Sudlow et al. (2015)	25,826,379	16,818	95,520	112,338
	Hypertensive disease	Sudlow et al. (2015)	25,826,379	32,689	79,649	112,338
	Body mass index	Pulit et al. (2019)	30,239,722	NA	NA	694,649
	Peripheral vascular disease	Sudlow et al. (2015	25,826,379	1816	110,522	112,338
	Varicose veins	Sudlow et al. (2015)	25,826,379	2637	109,701	112,338
	Inflammatory bowel disease	Liu et al. (2015)	26,192,919	12,882	21,770	34,652
	Osteoarthritis	Sudlow et al. (2015)	25,826,379	11,133	101,205	112,338
	Osteoporosis	Sudlow et al. (2015)	25,826,379	2084	110,254	112,338
	Hemorrhoids	Sudlow et al. (2015)	25,826,379	3826	108,512	112,338
	Hernia abdominopelvic cavity	Sudlow et al. (2015)	25,826,379	7115	105,223	112,338
	Peptic ulcer	Sudlow et al. (2015)	25,826,379	2254	110,084	112,338
	Allergic rhinitis	Sudlow et al. (2015)	25,826,379	6603	105,735	112,338
	Asthma	Sudlow et al. (2015)	25,826,379	14,473	97,865	112,338
	Cancer	Sudlow et al. (2015)	25,826,379	11,632	100,706	112,338

compared between the two datasets and SNPs with conflicting alleles between each pair of datasets were excluded; (3) the alleles and effects of the datasets were harmonized. For palindromic SNPs, we employed allele frequency (FRQ) filtering to determine whether the alleles from the two GWASs were derived from the same reference panel or not (SNPs with FRQ difference between the two GWASs ≥ 0.20 were deemed as a mapping from opposite reference panels).

Genetic correlation analysis

GWAS summary results were utilized to analyze the genetic correlations of neuroticism with the 34 health conditions using LD score regression (Bulik-Sullivan et al. 2015a; b). The 1000 Genome project phase 3 (Genomes Project et al. 2015) was used to estimate the LD structure for European populations, which was obtained from the LD score regression website (Bulik-Sullivan et al. 2015a, b; Finucane et al. 2015). SNPs were filtered by 1.1 million variants, a subset of 1000 Genomes and HapMap3, with MAF above 0.05. Adjustment for multiple tests was achieved by calculating the false discovery rate (FDR).

Bidirectional MR analysis

Bidirectional causal associations between neuroticism and the 34 traits were inferred using GSMR (Zhu et al. 2018), and FDR was calculated for the 68 tests. This method utilizes summary-level data to test for putative causal associations between a risk factor (exposure) and an outcome using independent genome-wide significant SNPs as instrumental variables as an index of the exposure. Instrumental variants were selected based on default $P \leq 5 \times 10^{-8}$ and further pruned using a clumping r^2 cutoff of 0.01. When the threshold was surpassed by less than 10 SNPs, a P value threshold of 1×10^{-5} was used; when more than 10,000 SNPs surpassed the default threshold, further analysis was limited to the top 10,000 most significant SNPs. HEIDI outlier detection was used to filter genetic instruments that showed clear pleiotropic effects on the exposure phenotype and the outcome phenotype. We used a P value threshold of 0.01 for the outlier detection analysis in HEIDI, which removes 1% of SNPs by chance if there is no pleiotropic effect.

The method estimates a putative causal effect of the exposure on the outcome (b_{xy}) as a function of the relationship between the SNP's effects on the exposure (b_{zx}) and the SNP's effects on the outcome (b_{zy}), given the assumption that the effect of non-pleiotropic SNPs on an exposure (x) should be related to their effect on the outcome (y) in an independent sample only via mediation through the phenotypic causal pathway (b_{xy}). The estimated causal effect coefficients (b_{xy}) are approximately equal to the natural log odds ratio for a case–control trait. An odds ratio of 2 can be interpreted as a doubled risk compared with the population prevalence of a binary trait for every standard deviation increase in the exposure trait. Criteria for significant causal association included both the absolute value of effect size $b_{xy} \geq 0.10$ and FDR < 0.05.

To explore the mechanisms underlying the causal associations between neuroticism and MDD, CVD, and HD, we mapped the instrumental SNPs into their host genes. FUMA was used to map SNPs to genes and identify LD-independent genomic regions (Watanabe et al. 2017). All genes located within 10 kb vicinity of each variant were mapped. Therefore, these mapped genes contributed to the causal effects between neuroticism and MDD, CVD, and HD.

Curation of GWAS genes and gene overlapping analysis

We obtained GWAS results (including meta-analysis) of the 14 traits with a causal association with neuroticism from the GWAS Catalog database (https://www.ebi.ac.uk/gwas/) (Buniello et al. 2019). Quality control steps: (1) studies with sample size of ≥ 2000 were retained; (2) studies with mixed phenotypes were removed; (3) genes in MHC regions were removed due to the high LD within the MHC region, which may inflate the gene overlapping analysis; (4) pharmacogenetic studies were excluded. The results of quality control steps are listed in Supplementary Table 1.

Analysis of overlaps between gene sets of each trait with those of neuroticism was conducted using R package SuperExactTest (Wang et al. 2015), with the total gene number in the genome being set as 30,000.

All the statistical analyses were conducted in R 3.6.1 or Python 3.7 environment. A more detailed description of the methods is provided in the Supplementary File.

Results

Genetic correlations

Genetic correlation analyses indicated that neuroticism has a significant genetic correlation with all the 16 mental conditions, and with 8 out of the 18 physical conditions studied (Supplementary Table 2, Fig. 1a). In particular, a relatively high genetic correlation was detected between neuroticism and SWB ($r_g = -0.68$) and MDD (0.67), followed by anxiety disorder, loneliness, psychiatric disorders, insomnia, alcohol dependence, and OCD (r_g in range of 0.31–0.54). The average absolute r_g for correlations between neuroticism and mental conditions was 0.34 ± 0.18, while the average absolute r_g between neuroticism and physical conditions was 0.11 ± 0.05.

MR analysis

In the MR analysis, neuroticism displayed a causal effect on 12 out the 16 mental conditions (MDD, insomnia, SWB, SZ, ADHD, alcohol dependence, loneliness, anorexia nervosa, anxiety disorder, BD, OCD, and psychiatric disorders) and two physical conditions (hypertensive disease (HD) and CVD) (Table 2 and Fig. 1c). Conversely, MDD, insomnia, and reduced SWB displayed a causal effect on neuroticism. The SNPs and genes contributing to the causal effect between neuroticism and MDD are listed in Supplementary Tables 3–4. The SNPs and genes contributing to the causal effect of neuroticism on CVD and HD are listed in Supplementary Tables 5–6. Figure 2 depicts outcomes of specific analysis which uncovered genes mediating the causal effects between neuroticism and MDD, CVD, and HD. The genetic correlation coefficient and MR effect size for each trait are shown in Fig. 1b.

The mental and physical traits can be grouped into four classes based on their relationship with neuroticism (see Fig. 1d). At the first level, traits do not have any genetic relationship with neuroticism, while the traits residing at the second level and the neuroticism share some genetic

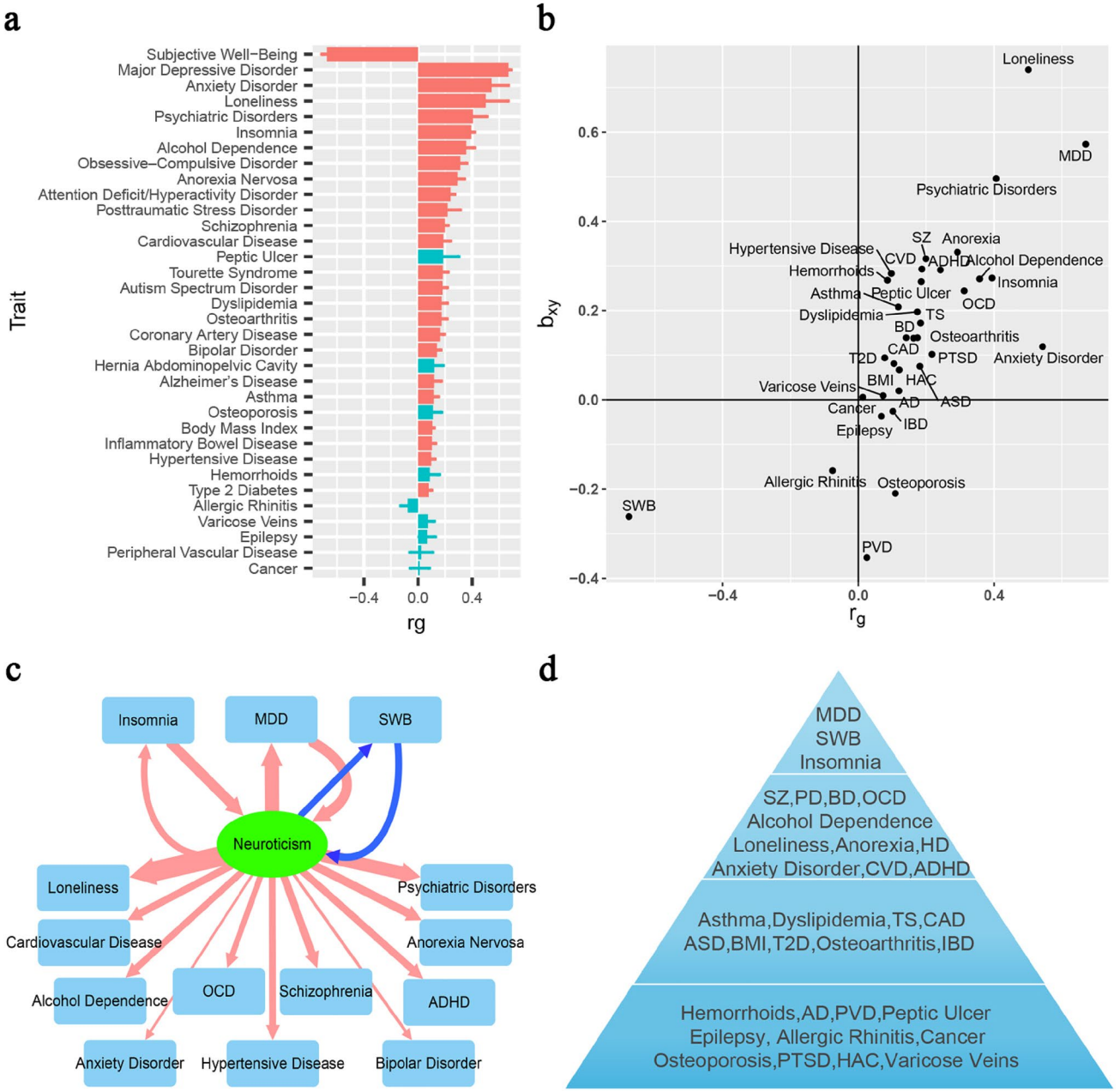

Fig. 1 Relationships of neuroticism to each of correlating traits. *AD* Alzheimer's disease, *ADHD* attention-deficit/hyperactivity disorder, *ASD* autism spectrum disorder, *BD* bipolar disorder, *BMI* waist-to-hip ratio adjusted for body mass index, *CAD* coronary artery disease, *CVD* cardiovascular disease, *HAC* hernia abdominopelvic cavity, *IBD* inflammatory bowel disease, *MDD* major depressive disorder, *OCD* obsessive–compulsive disorder, *PTSD* posttraumatic stress disorder, *PVD* peripheral vascular disease, *SWB* subjective well-being, *SZ* schizophrenia, *T2D* type 2 diabetes, *TS* Tourette syndrome, *HAC* hernia abdominopelvic cavity, *PVD* peripheral vascular disease, *HD* hypertensive disease, *PD* psychiatric disorders. **a** Genetic correlation of neuroticism with all traits assessed. Red bars indicate FDR ≤ 0.05, and blue bars indicate FDR > 0.05; the lines in each bar indicate standard error. **b** Genetic correlation coefficient and Mendelian randomization effect size for each trait. **c** Mendelian randomization analysis of neuroticism with all traits assessed. Arrowed lines show a causal effect from a source node to a targeted node; red lines show positive coefficient, and blue lines show negative coefficient; the thickness of lines is relative to the absolute value of the coefficient. **d** Pyramid depicting the hierarchy of the relationship between all traits connected to neuroticism

Table 2 Mendelian randomization analysis of neuroticism with all traits

	Trait	Mendelian randomization				Reverse Mendelian randomization			
		b_{xy} (s.e.)	*P*	FDR	*N*	b_{xy} (s.e.)	*P*	FDR	*N*
Mental traits	Alcohol dependence	**0.271 (0.062)**	$\mathbf{1.19\times10^{-5}}$	$\mathbf{7.36\times10^{-5}}$	129	– 0.005 (0.009)	0.601	0.691	25[a]
	ADHD	**0.291 (0.042)**	$\mathbf{2.54\times10^{-12}}$	$\mathbf{1.92\times10^{-11}}$	128	0.074 (0.020)	2.37×10^{-4}	1.01×10^{-3}	12
	Anorexia nervosa	**0.331 (0.080)**	$\mathbf{3.89\times10^{-5}}$	$\mathbf{1.87\times10^{-4}}$	129	– 0.003 (0.008)	0.714	0.759	27[a]
	Anxiety disorder	**0.119 (0.033)**	$\mathbf{3.53\times10^{-4}}$	$\mathbf{1.41\times10^{-3}}$	128	0.017 (0.009)	0.044	0.103	16[a]
	ASD	0.075 (0.045)	0.093	0.186	129	0.012 (0.010)	0.22	0.332	58[a]
	Bipolar disorder	**0.139 (0.048)**	$\mathbf{3.91\times10^{-3}}$	$\mathbf{1.40\times10^{-2}}$	123	0.017 (0.007)	9.76×10^{-3}	3.00×10^{-2}	115
	Loneliness	**0.740 (0.176)**	$\mathbf{2.56\times10^{-5}}$	$\mathbf{1.34\times10^{-4}}$	119	0.002 (0.008)	0.828	0.853	16[a]
	MDD	**0.573 (0.025)**	$\mathbf{5.37\times10^{-120}}$	$\mathbf{3.65\times10^{-118}}$	124	**0.407 (0.021)**	$\mathbf{1.91\times10^{-81}}$	$\mathbf{6.49\times10^{-80}}$	44
	OCD	**0.244 (0.094)**	$\mathbf{9.41\times10^{-3}}$	$\mathbf{3.00\times10^{-2}}$	126	0.003 (0.008)	0.665	0.729	22[a]
	PTSD	0.102 (0.276)	0.712	0.759	124	– 0.005 (0.008)	0.48	0.628	22[a]
	SWB	**– 0.262 (0.023)**	$\mathbf{3.07\times10^{-30}}$	$\mathbf{5.22\times10^{-29}}$	105	**– 0.285 (0.039)**	$\mathbf{3.91\times10^{-13}}$	$\mathbf{3.32\times10^{-12}}$	24
	Schizophrenia	**0.316 (0.040)**	$\mathbf{2.12\times10^{-15}}$	$\mathbf{2.06\times10^{-14}}$	117	0.089 (0.009)	4.89×10^{-22}	6.65×10^{-21}	65
	Tourette syndrome	0.172 (0.081)	0.035	0.087	125	0.004 (0.008)	0.595	0.691	28[a]
	Insomnia	**0.273 (0.016)**	$\mathbf{3.34\times10^{-64}}$	$\mathbf{7.57\times10^{-63}}$	128	**0.403 (0.049)**	$\mathbf{1.12\times10^{-16}}$	$\mathbf{1.27\times10^{-15}}$	15
	Alzheimer's disease	0.020 (0.015)	0.159	0.274	128	– 0.038 (0.021)	0.069	0.147	58
	Psychiatric disorders	0.496 (0.195)	0.011	0.033	126	0.055 (0.020)	6.26×10^{-3}	2.10×10^{-2}	34[a]
Physical traits	Type 2 diabetes	0.094 (0.057)	0.1	0.189	111	0.035 (0.015)	0.024	0.063	158
	CAD	0.138 (0.066)	0.036	0.087	124	0.004 (0.015)	0.809	0.846	56
	Epilepsy	– 0.037 (0.058)	0.516	0.65	119	– 0.021 (0.013)	0.113	0.208	20[a]
	CVD	**0.293 (0.091)**	$\mathbf{1.20\times10^{-3}}$	$\mathbf{4.53\times10^{-3}}$	125	0.035 (0.018)	0.048	0.109	42[a]
	Dyslipidemia	0.197 (0.086)	0.023	0.063	125	– 0.022 (0.014)	0.13	0.233	37
	Hypertensive disease	**0.283 (0.069)**	$\mathbf{4.13\times10^{-5}}$	$\mathbf{1.87\times10^{-4}}$	123	0.014 (0.015)	0.336	0.486	36
	BMI	0.081 (0.013)	1.54×10^{-9}	1.05×10^{-8}	120	0.044 (0.010)	1.44×10^{-5}	8.16×10^{-5}	181[b]
	PVD	– 0.354 (0.253)	0.161	0.274	106	0.040 (0.029)	0.176	0.285	15[a]
	Varicose veins	0.009 (0.194)	0.962	0.962	126	– 0.010 (0.018)	0.591	0.691	41[a]
	IBD	– 0.026 (0.052)	0.613	0.691	124	0.011 (0.006)	0.053	0.116	71[b]
	Osteoarthritis	0.139 (0.102)	0.171	0.284	126	0.037 (0.021)	0.074	0.152	32[a]
	Osteoporosis	– 0.210 (0.222)	0.344	0.487	125	0.019 (0.021)	0.379	0.526	30[a]
	Hemorrhoids	0.268 (0.163)	0.099	0.189	126	0.019 (0.026)	0.468	0.624	20[a]
	HAC	0.067 (0.124)	0.588	0.691	126	– 0.018 (0.022)	0.408	0.555	28[a]
	Peptic ulcer	0.265 (0.209)	0.205	0.321	126	– 0.012 (0.024)	0.608	0.691	24[a]
	Allergic rhinitis	– 0.159 (0.126)	0.208	0.321	126	0.021 (0.018)	0.232	0.343	45[a]
	Asthma	0.208 (0.090)	0.021	0.06	125	0.008 (0.017)	0.62	0.691	30
	Cancer	0.006 (0.100)	0.955	0.962	126	– 0.015 (0.022)	0.497	0.638	29[a]

ADHD attention-deficit/hyperactivity disorder, *ASD* autism spectrum disorder, *BMI* waist-to-hip ratio adjusted for body mass index, *CAD* coronary artery disease, *CVD* cardiovascular disease, *HAC* hernia abdominopelvic cavity, *IBD* inflammatory bowel disease, *MDD* major depressive disorder, *OCD* obsessive–compulsive disorder, *PTSD* posttraumatic stress disorder, *PVD* peripheral vascular disease, *SWB* subjective well-being, *s.e.* standard error

[a]*P* value threshold of 1×10^{-5} was used

[b]Top 10,000 most significant SNPs were used. Significant associations ($b_{xy}>0.10$ and FDR < 0.05) were in bold, and red color denotes significant negative causal associations

background. Traits at the third level both share a genetic background with neuroticism, and are causally influenced by neuroticism. Fourth-level traits (at the top) display both high genetic correlations and mutually causal relationships with neuroticism.

Gene overlaps

GWAS results of the 14 traits are listed in Supplementary Tables 7–20. Except for OCD and anxiety disorder, each trait showed significant over-representation of overlapped genes with neuroticism (Supplementary Table 21). Especially, 304

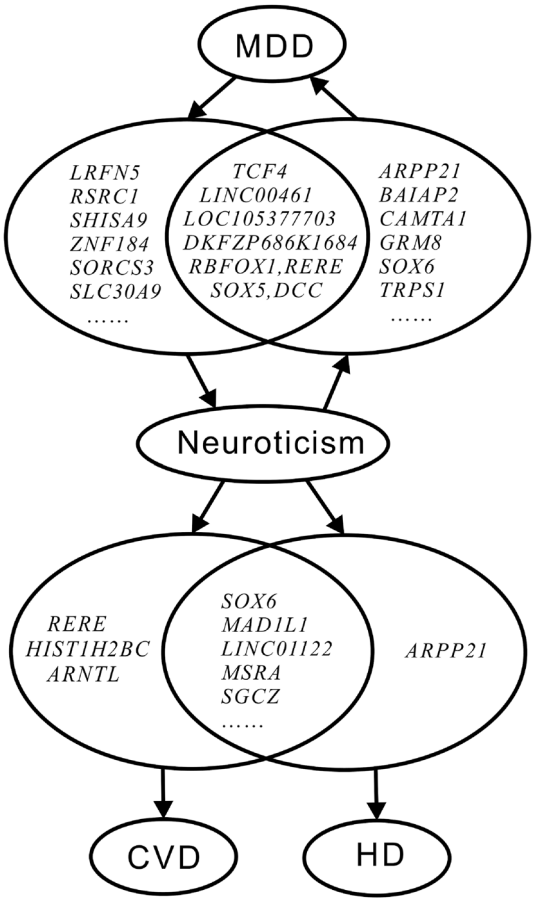

Fig. 2 Key genes mediating the causal effects between neuroticism and MDD, CVD, and HD. *MDD* major depressive disorder, *CVD* cardiovascular disease, *HD* hypertensive disease

out of 590 GWAS risk genes for SWB (significant overlapping, P = 0; FDR = 0) and 218 out of 791 GWAS risk genes for MDD (significant overlapping, $P = 1.47 \times 10^{-166}$; FDR $= 1.03 \times 10^{-165}$) were overlapped with those for neuroticism.

Discussion

The profound significance of neuroticism for public health is evidenced by the fact that the estimated economic costs of neuroticism exceed those of common mental disorders (Cuijpers et al. 2010). Higher scores for neuroticism are associated with an increased risk for various mental disorders, and, somewhat less consistently, with certain aspects of physical health. A well-known case is the type A behavior pattern (TABP) as a coronary risk factor. An overall association between the TABP and CHD has been well established (Smith and MacKenzie 2006). The prevailing model to explain this association is that type A individuals show higher levels of cardiovascular and neuroendocrine responses to stressors compared with their more relaxed Type B counterparts. Type D (i.e., distressed) personality is another kind of personality associated with CHD (Denollet 2005; Denollet et al. 1996). One of the two factors of this construct—negative affectivity—corresponds closely to neuroticism (Denollet 2005).

The evidence supporting the association of neuroticism with mental health and cardiovascular risk is convincing, the emphasis at present is to determine the mechanisms involved. The concept that personality influences health seems straightforward, but the explication of mechanisms underlying mind–body associations is conceptually complex and methodologically challenging due to inconsistent findings and alternative interpretations (Smith and MacKenzie 2006).

We outline the models of mechanisms for neuroticism into two broad categories, physiological reactions to stressors and health-related behavior alterations. Within the psychological reaction category, neuroticism influences the appraisal of potentially stressful life circumstances and coping responses and leads to various negative affections, including depression, anxiety, hostility, and anger, which are also risk factors for CVDs (Barth et al. 2004; Chida and Steptoe 2009). Physiological mechanisms underlying psychological reactions include neuroendocrine responses, inflammation, autonomic function (Schneiderman et al. 2005). Another category concerns patterns of behavioral changes. Personality influences health-relevant daily habits (e.g., smoking, diet, and exercise) relate to negative health behaviors, which could mediate the association between personality and disease (Booth-Kewley and Vickers 1994). Higher neuroticism could lead to unhealthy behaviors such as poor diet, smoking, sleep disturbances, physical inactivity, or lower treatment adherence (Chida and Steptoe 2009). Neuroticism has higher comorbidity with alcohol and drug dependence, conduct disorders, and antisocial personality (Khan et al. 2005). Of note is that the two aspects are not independent and mutually exclusive, but rather act together to link neuroticism to elevated cardiovascular risk.

Our results indicate that neuroticism may confer risk to mental health and CVDs through genetic variation, therefore, reveal a novel mechanism by which neuroticism influences the risk for mental disorders and CVDs. It is a more fundamental way compared with theories derived from psychological effects and health behaviors. The evidence derived from genetic variants as instrumental variables indicates that the mediating effects are most likely etiologically causal in nature compared with other mechanisms. Undoubtedly, the psychological, behavioral, and genetic mechanisms and pathways operate in a synergistic and integrative way to promote cardiovascular changes and related clinical manifestations.

Recently, genetic correlations of neuroticism with some health conditions have been reported. Gale et al. examined genetic correlations of neuroticism with 9 mental traits and 8 physical health-related outcomes, and reported significant positive associations between neuroticism and MDD, anorexia nervosa, and SZ (Gale et al. 2016). Nagel et al. investigated 9 mental traits and 26 other traits, and detected significant positive genetic correlations between neuroticism and 11 health characteristics, including MDD, ADHD, anorexia nervosa, SZ, intracranial volume, and significant negative genetic correlations between neuroticism and SWB, height, age of first child, intelligence quotient (IQ), and educational attainment (Nagel et al. 2018). Using GWAS results from the UK Biobank (UKB), Hill et al. (2019) found that neuroticism significantly correlates with 20 out of the 32 studied conditions; the resultant list of correlates included SZ, MDD, anorexia nervosa, ADHD, and SWB (negatively).

In our study, we found that neuroticism shows a correlation with all mental conditions studied and nearly half of physical conditions and characteristics, with relatively higher correlations between neuroticism and MDD, SWB (negatively), anxiety, loneliness, and insomnia. In addition to replicating previously reported correlations of neuroticism with SZ, anorexia nervosa, AD, and ADHD, our study detected novel genetic connections between neuroticism and loneliness, insomnia, alcohol dependence, OCD, and TS. For physical conditions, our study identified genetic correlations of neuroticism with asthma, CVD, dyslipidemia, osteoarthritis, coronary artery disease, body mass index (BMI), inflammatory bowel disease, HD, and type 2 diabetes. Predictably, the average correlation of neuroticism with mental conditions was stronger than that observed for neuroticism and physical conditions.

Even if previous studies have detected correlations between neuroticism and health-related traits, the causality of these relationships has rarely been tested. Nagel et al. reported a significant causal effect of neuroticism on depression, anxiety disorder, ADHD, SWB, SZ, IQ, and educational attainment, as well as a reverse causal effect of some traits on neuroticism, including depression, ADHD, SWB, SZ, childhood obesity, intracranial volume, height, age of first child, IQ, and educational attainment.

Presented results suggest that neuroticism has a close genetic relationship with all major mental conditions, and in most cases, these relationships are causal. We augmented the study of Nagel et al. by identifying additional traits genetically influenced by neuroticism, including insomnia, alcohol dependence, loneliness, anorexia nervosa, BD, and OCD. Thus, etiological evidence for the previous observation that high scores for neuroticism predate the onset and development of any CMD, and that their effects rarely decline over time (Jeronimus et al. 2016) is provided. Furthermore, our study shows a causal relationship between neuroticism and CVDs, pointing at the strength of the mind–body relationship underlining at least some physical conditions. In this light, it is important to note a handful of genes and protein products recently shown to contribute both to psychological traits, including neuroticism, and physical diseases. The causal role of neuroticism in the development of a physical disease may inform a pathway to truly personalized, prevention-driven medicine.

In agreement with the above results, we observed significant enrichment of overlapping genes between neuroticism and the majority of the 14 traits tested. Especially, half of GWAS risk genes of SWB and more than a quarter of risk genes of MDD were overlapped with those of neuroticism.

Given together, neuroticism showed the closest relationship with MDD and SWB, as evidenced by strong genetic correlation, large bidirectional causal effect, and striking enrichment of overlapping genes between neuroticism and the above two mentioned characteristics. This might probably attribute to the shared genetic factors, and these shared genetic factors have vertical genetics pleiotropy, which may cause some related intermedia phenotypes to be causally correlated.

A strong association between neuroticism and an increased risk of MDD has been previously reported in two large population cohorts (Navrady et al. 2017), consistent with previous cross-sectional observations that neuroticism is most strongly associated with depressive disorders (Kotov et al. 2010). However, molecular mechanisms underlying the associations of neuroticism and MDD remain elusive. In this study, we revealed a panel of genes contributing to both the causal effect of neuroticism on MDD and those contributing to the causal effect of MDD on neuroticism, including *DCC*, *LINC00461, DKFZP686K1684, LOC105377703, RBFOX1, RERE, SOX5,* and *TCF4*. Each of these genes has been previously identified as a genome-wide gene for each of the two traits. Therefore, these genes are plausible key contributors to the bidirectional causal associations of the two conditions.

The transcription factor 4 encoding gene, *TCF4*, was one of the first genome-wide risk loci for SZ (Stefansson et al. 2009). Later, in some works, this gene was implicated in MDD (Wray et al. 2018), insomnia (Jansen et al. 2019), Pitt–Hopkins syndrome, and other neurodevelopmental disorders (Forrest et al. 2014). It plays a role in lymphoid tissue development and epithelial–mesenchymal transition (Forrest et al. 2014). *DCC* plays a key role in axon guidance and nerve regeneration (Finci et al. 2015), and is a genome-wide risk gene for MDD (Wray et al. 2018), neuroticism (Nagel et al. 2018; Okbay et al. 2016), intelligence (Savage et al. 2018), cognitive ability (Lee et al. 2018), and educational attainment (Lee et al. 2018). *LINC00461* locus encodes one of the most highly conserved lncRNA, which is predominantly expressed in the brain (Deguchi et al. 2017). Previous GWASs have implicated it in MDD

(Nagel et al. 2018) and neuroticism (Baselmans et al. 2019; Luciano et al. 2018; Nagel et al. 2018). *RBFOX1* regulates tissue-specific alternative splicing, and have being implicated in neurodevelopmental and neuropsychiatric disorders, including MDD (Hyde et al. 2016; Wray et al. 2018), ASD (Grove et al. 2019), and neuroticism (Baselmans et al. 2019; Luciano et al. 2018; Okbay et al. 2016). DKFZP686K1684 and LOC105377703 are two ncRNAs with unknown functions. The function of *RERE* is discussed later.

SWB is an indicator of happiness or satisfaction. The highest negative correlation between neuroticism and SWB observed in our study was similar to the results of two previous studies (Hill et al. 2019; Nagel et al. 2018), which is not surprising as all three studies, including the present one, utilized the same dataset for SWB (Okbay et al. 2016). The high negative correlation between neuroticism and SWB and the negative causal effect of neuroticism on SWB points towards an overall detrimental effect of neuroticism on mental health.

In addition to its association with mental and physical diseases, neuroticism also influences one's social life. This effect is evident from a high genetic correlation between neuroticism and loneliness and an extremely high causal effect of neuroticism on loneliness ($b_{xy}=0.74$). These results are consistent with the previously reported genetic correlation between neuroticism and social deprivation (Hill et al. 2019), suggesting an extended role of neuroticism in one's social behavior and activity.

Personality is commonly seen as an inherited trait that remains stable across the lifespan. Due to the general belief that neuroticism is a risk factor for various mental disorders and distress, previous work heavily emphasized the effect of neuroticism on various medical conditions. In contrast, our present work, along with the study of Nagel et al., indicates that the scores for neuroticism may be affected by an individual's mental status, too, stressing on bidirectionality of the relationship between neuroticism and mental disorders. The discovery of neuroticism-promoting influence on insomnia and reduced SWB is of clinical relevance. In the case of insomnia, the discovery of its bidirectional causal connections to neuroticism may bring hope for the patients seeking personality improvement, since the sleeping problems are more amenable to modification than the neuroticism itself. The negative genetic correlation and the bidirectional negative causal connections between neuroticism and SWB indicate that either mutually detrimental effects or reciprocally inhibiting mechanisms shared between these conditions are at play. It is tempting to speculate that an individual's neuroticism may be improved by increasing one's feeling of happiness, which can be achieved by social interventions or in course of psychotherapy. Together, our results point towards a potential avenue for possible amelioration of maladaptive personality traits, and therefore, for decreasing the risks for the relevant mental disorders by improving the quality of sleep, and/or by enhancing the feeling of happiness or satisfaction.

For physical conditions, neuroticism may genetically exert an effect on CVD and HD. CVDs account for a large proportion of the total disability and morbidity (DALYs and Collaborators 2018). Hypertension is a major risk factor for CVDs, contributing to a large proportion of cardiovascular deaths (Lim et al. 2012). Neuroticism has been reported to be correlated with stroke and increased coronary heart disease mortality (Jokela et al. 2014), but biological mechanisms underlying their associations are poorly understood. Our findings may have implications in the prevention and personalized treatment of CVDs. The American Heart Association (AHA) advocated screening depression in all patients with CADs (Lichtman et al. 2008). Our results suggest that it may be useful to screen neuroticism in patients with CVDs, since improved treatment may be reached by including psychological or psychiatric interventions for subgroups with higher neuroticism.

Here, we explored critical biological molecules and potential mechanisms contributing to the links between neuroticism and CVDs. Of particular interest are *MAD1L1*, *ARNTL*, *RERE*, *LINC01122*, and *SOX6*. All these genes were found both to mediate the causal effect of neuroticism to CVD, and to confer genome-wide risks for the two conditions. None of these genes is a novice in the field of neurodevelopment. The arginine-glutamic acid dipeptide (RE) repeats gene (*RERE*) is located in the proximal 1p36 region critical for neurodevelopment (Zoltewicz et al. 2004). Heterozygous variants in the *RERE* gene have been reported to be associated with a neurodevelopmental disorder with or without anomalies of the brain, eye, or heart (NEDBEH) (Jordan et al. 2018). In addition, *RERE* is also one of the candidate genes for CHARGE syndrome (Issekutz et al. 2005) and 1p36 deletion syndrome (Zaveri et al. 2014), sharing the features of the developmental delay, intellectual disability, congenital heart disease, cardiovascular malformations, and cardiomyopathy (Fregeau et al. 2016; Issekutz et al. 2005; Jordan et al. 2018; Zaveri et al. 2014). Mouse models implicate *RERE* in cerebellar foliation and the migration and maturation of Purkinje cells (Kim and Scott 2014) as well as in ventricular septal defects (Kim et al. 2018). *LINC01122* is a non-coding RNA that was linked to depression (Nagel et al. 2018), insomnia (Jansen et al. 2019), Tourette syndrome (Yu et al. 2019), neuroticism (Nagel et al. 2018), and CVDs (Kichaev et al. 2019). *MAD1L1* play a role in cell cycle control and has been implicated in the genetic susceptibility for MDD (Howard et al. 2018), SZ (Ripke et al. 2013), BD (Psychiatric 2011), neuroticism (Luciano et al. 2018; Nagel et al. 2018), and CVDs (Kichaev et al. 2019). The protein encoded by *SOX6* is a transcriptional activator that plays a versatile regulatory role in vertebrate development,

including normal development of the central nervous system and maintenance of cardiac and skeletal muscle cells (Hagiwara 2011). GWASs implicated it in neuroticism (Baselmans et al. 2019; Luciano et al. 2018; Nagel et al. 2018), hypertension or blood pressure (Ehret et al. 2016; Giri et al. 2019; Kichaev et al. 2019; Lu et al. 2015; Takeuchi et al. 2018), and CVDs (Kichaev et al. 2019; van der Harst and Verweij 2018), while molecular physiology research pointed at its direct contribution to the prevention of the cardiac hypertrophy (Huang et al. 2015). The presence of both neurodevelopmental and cardiovascular phenotypes in the spectrum of the effects pertained to each of these genes is remarkable.

Our study had several strengths. First, we analyzed the data for a larger set of traits, especially for mental traits. Second, for each trait, only well-powered datasets were included, and a threshold of MR effect coefficient was used to select the strongest factors. Furthermore, to avoid potential population heterogeneity across the studies, we limited our analysis to individuals of European ancestry.

However, several limitations should also be noted. First, to focus attention on mental conditions, a relatively small number of physical traits was included in the study, thus, necessitating future exploring of the association of neuroticism with physical conditions in detail. Second, amounts of samples comprising different datasets varied substantially—from a minimum of 7,556 samples for loneliness to 694,649 samples for BMI; this imbalance may result in uneven power across the traits. Finally, as our analysis was limited to a genetic component of each trait, presented results should be interpreted cautiously, with the understanding that human traits result from a complex web of interactions among a plethora of psycho-social-environmental factors.

Conclusions

In summary, our findings reveal genetic relationships between neuroticism and various health conditions and shed light on mechanisms underlying their phenotypic relationships.

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Author contributions FZ and MX conceived and designed the study. FZ performed the data analysis and wrote the manuscript. FZ, AB, and MX revised the manuscript. CZ, XZ, JC, HC, and MX contributed to the data preparation and interpretation of the results. All the authors reviewed and approved the final version of the manuscript.

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Data availability The present study was based on a secondary analysis of GWAS data and all data generated during the study are included in this published article.

Declarations

Conflict of interest There are no conflicts of interest for any author.

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