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Investigation on the genetic factors on blood pressure, anxiety, depressive symptoms, psychoticism, and psychological well-being.

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Abstract

Background: High blood pressure is a major risk factor for cardiovascular disease and is thought to be related to psychological issues. Yet, it is unclear what causes high blood pressure and what causes anxiety, depressive symptoms, neuroticism, and subjective well-being.

Aim: Anxiety, depressive symptoms, neuroticism, and subjective well-being were all examined in the current investigation to determine whether there are genetic causes for these conditions.

Methods: Eight large-scale genome-wide association study datasets for hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, anxiety, depressive symptoms, neuroticism, and subjective well-being were subjected to Mendelian randomization (MR) analyses using the generalized retrospective MR analysis method.

Results: The multimodal causal link for both blood pressure and the four psychological functioning was found to have a causal effect of DBP on neuroticism, and 1074 independent instrumental single nucleotide polymorphisms were discovered by the incorporated Heterogeneity in Dependent Instruments-outlier test.

Conclusion: Neuroticism is a direct causative result of DBP. Proper blood pressure control may lessen neuroticism, mood disorders that increase neuroticism, and cardiovascular problems.

Key-words: High blood pressure , Hypertension, Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Pulse pressure, Anxiety, Depressive symptoms, Neuroticism.

Introduction

Fluid dynamic theories state that the pressure of flowing blood against the blood arteries causes blood pressure (BP). Blood pressure (BP) is measured in millimeters of mercury (mm Hg) and expressed in terms of systolic blood pressure (SBP, maximum pressure) and diastolic blood pressure (DBP, minimum pressure), which represents the pressure in blood vessels during heart contractions and rest periods, respectively. When the SBP is >140 mm Hg and/or the DBP readings are higher than >90 mm Hg for two consecutive days, the body is said to be in a condition of hypertension. More than 25% of people worldwide have hypertension, which is a major risk factor for the emergence of various illnesses that impact the entire body, especially heart and circulation conditions. 2 Several research organisation have looked into the comorbidity of hypertension with psychosocial and mental illnesses despite the fact that the aetiology of hypertension is not entirely understood. Yet, it is still unknown and occasionally debatable how hypertension and psychological illnesses are related. 3 An emotional response to stress, anxiety is a sensation of worry, dread, and uneasiness. Pessimism, poor mood, low energy, anxiety, and physical aches

are some of the signs of depression. 4 Being prone to negative feelings including anxiety, fear, distress, dissatisfaction, despair, rage, and guilt is a personality trait known as neuroticism.

Survey questions on life satisfaction, positive affect, and happiness are used to gauge subjective well-being. Based on data from cross-sectional and prospective research, a recent contentious systematic review and meta-analysis hypothesized a link between anxiety and an elevated risk of hypertension. 5 The pathophysiological mechanisms underpinning the link between changed BP and psychosocial states are unknown or inconsistent, despite mounting evidence to the contrary. It is yet unclear how BP affects anxiety, depressive symptoms, neuroticism, and subjective well-being. Generic variations that contribute to a trait can be found using genome-wide association studies (GWASs). There are GWASs that take into account neuroticism, anxiety, depressive symptoms, and subjective well-being that can offer human genetic data about these psychological states. Based on GWAS summary data, Mendelian randomization (MR) analysis is a prominent technique for examining the bidirectional genetic causal effects between two characteristics. 6 7 This approach can be used to investigate the genetic causes of BP's impact on psychological states.
Hence, using large GWAS data samples, this study set out to investigate the causal links between BP and anxiety, depressive symptoms, neuroticism, and subjective well-being.

Methods and materials

Study design

We conducted simultaneous two-sample MR analyses to investigate the relationship between the exposure (a risk factor) and the result (a phenotype). The exposure-related genetic variations were chosen as the instrumental variables. The four BP traits—SBP, DBP, pulse pressure (PP), and hypertension—were regarded as the exposure in one direction of the MR analysis, while the four psychological states—anxiety, depressive symptoms, neuroticism, and subjective well-being—were handled as the outcome. This assignment was switched around for the MR analysis in the opposite way. The research was divided into three stages: **(1)** gathering summary-level GWAS data for the eight traits, **(2)** looking into genetic variations as potential instrumental variables, and **(3)** calculating the causal effects of the exposure on the result.

Data collection and extraction

Figure 1, describes the current study's flowchart. First, the GWAS datasets for the four psychological states from European populations were gathered. The MR-base database provided the dataset for the anxiety GWAS. 8 The UK Biobank (UKB), Genetic Epidemiology Research on Adult Health and Aging (GERA), and Psychiatric Genetics Consortium provided the depressive symptoms GWAS dataset (PGC). 9 The UKB and Genetics of Personality Consortium provided the neuroticism GWAS dataset (GPC). 10 We evaluated every disease using accepted diagnostic standards. The summary association statistics from 59 cohorts were used in a meta-analysis to create the subjective well-being GWAS dataset. Primary subjective well-being, life satisfaction, positive affect, and post hoc subjective well-being were the four phenotypical panels into which subjective well-being was divided.

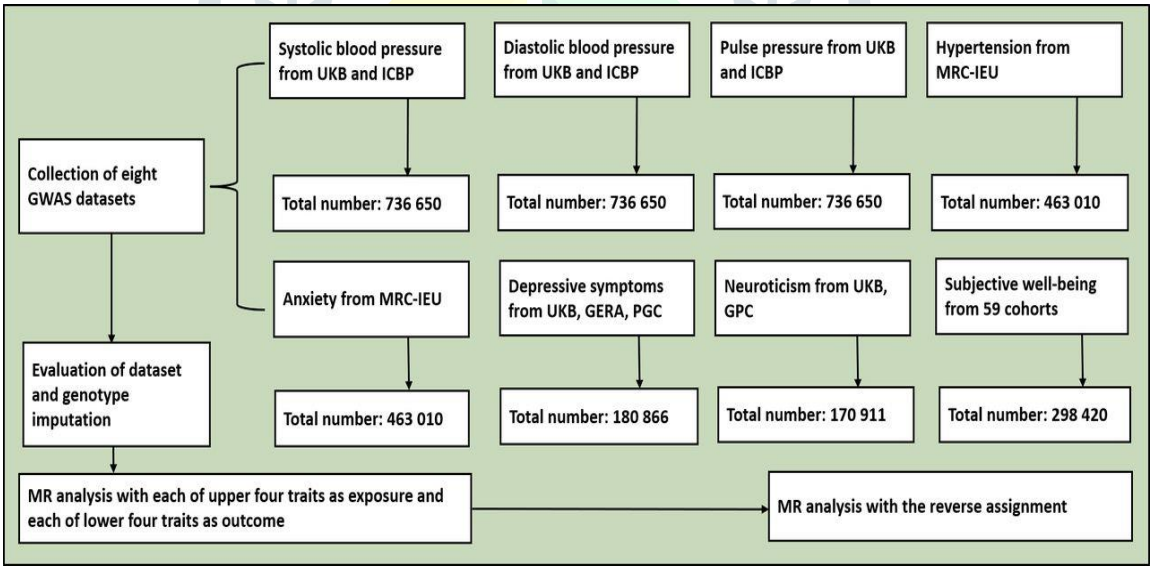

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Figure 1: Study flowchart. GERA, Genetic Epidemiology Research on Adult Health and Aging; GPC, Genetics of Personality Consortium; GWAS, genome-wide association study; MR, Mendelian randomization; PGC, Psychiatric Genetics Consortium; UKB, UK Biobank; ICBP, International Consortium for Blood Pressure; MRC-IEU, Medical Research Council-Integrative Epidemiology Unit.

DBP and SBP GWAS data were taken from the Guo et al. study. 11 The PP GWAS dataset was included because PP has been presented as a way to distinguish between SBP and DBP and is thought to be a standalone risk factor for whole-body diseases (table 1). 12 With the greatest sample size in the MR-base database, the hypertension GWAS dataset included includes abnormal blood pressure, which is defined as SBP >140 mm Hg and/or DBP >90 mm Hg on 2 consecutive days. 8 Each GWAS had participant samples that were entirely of European descent. All first investigations had received ethical approval.

Table 1: Summary of European genome-wide association study data on various blood pressure, anxiety, depressive symptoms, neuroticism and subjective well-being traits.

Traits	Sample size	SNPs	Reference (DOI)
Systolic blood pressure	736 650	7 070 522	10.1038 /s41467-020-17002-0
Diastolic blood pressure	736 650	7 142 798	10.1038 /s41467-020-17002-0
Pulse pressure	736 650	7 071 236	10.1038 /s41467-020-17002-0
Hypertension	463 010	9 851 867	https://gwas.mrcieu.ac.uk/datasets/ukb-b-12493/
Anxiety	463 010	9 851 867	https://gwas.mrcieu.ac.uk/datasets/ukb-b-11311/
Depressive symptoms	180 866	6 524 474	10.1038 /ng.3552
Neuroticism	170 911	6 524 432	10.1038 /ng.3552
Subjective well-being	298 420	2 268 675	10.1038 /ng.3552

DOI, Digital Object Identifier; SNPs, single nucleotide polymorphisms.

Each study includes a thorough explanation of participant characteristics. One research was the only one to include all subjects. According to the original publications' descriptions, genotyping was carried out on genomic DNA isolated from blood samples using conventional techniques using a variety of commercially available genotyping arrays. The 1000 Genomes Project reference panel and IMPUTE2 software were used to impute genotypes. 13 All biallelic single nucleotide polymorphisms (SNPs) and SNPs with an imputation score > 0.9 were taken into account for the following analysis for each GWAS dataset, whereas ambiguous SNPs were discarded. An SNP's alleles in the second dataset were reversed if it was mapped to opposing strands in either dataset.

MR Analysis

MR analysis uses instrumental variables, which are predicted to be free of confounding variables, to infer the plausible causation of a link between the exposure and the outcome. 14 Genetic variants are considered as instrumental factors to test for causation in MR tests utilising GWAS data. Exploiting GWAS data with large independent samples can significantly increase the power of an MR analysis since genetic variations may be pleiotropic or correlated,15 which increases the power of an analysis. Three conditions must be met for genetic variations to be employed as instrumental variables: they must be (1) related to the exposure, (2) only have an impact on the outcome through the exposure, and (3) unrelated to variables.

The Genome-wide Complex Trait Analysis tool (V.1.93.3 beta2) was used to explore bidirectional causal links between each psychological state and each BP trait in the framework of Generalized Summary-data-based MR (GSMR).17 This method is based on summary-level data, using independent genome-wide significant SNPs as instrumental variables, that is, an index of the exposure to test for putative causal associations between a risk factor (exposure) and an outcome. Instrumental variants were selected based on the default GWAS threshold of $p \leq 5 \times 10-8$. An LD (linkage disequilibrium) threshold of r2=0.05 was used to identify independent SNPs based on the European population as referenced within the 1000 Genomes Project (phase 3). Heterogeneity in Dependent Instruments (HEIDI)-outlier detection was used to filter genetic instruments that had obvious pleiotropic effects on the exposure and outcome. A threshold p value of 0.01 was used for the HEIDI analysis.18 We used an F-statistic >10 to define SNPs as valid instrumental variables. Ten was the minimum number of instrumental SNPs required. The power for the MR analysis was calculated using an online calculator (http://sb452.shinyapps.io/power/). P values were adjusted using the Bonferroni method, multiplying by 32 for multiple tests.

Results

The collected GWAS summary datasets are provided in table 1 below. For SBP, DBP, and PP, the maximum sample size was 736 650, and the minimum was 463 010 for hypertension. Anxiety had a maximum sample size of 463 010, and neuroticism had a minimum sample size of 170 911. The BP and psychological state datasets did not contain any subjects. With BP traits as exposure and psychological states as outcome, hypertension and DBP had significant causal effects on neuroticism ($p=8.8\times10-6$ and 0.026, respectively, table 2). After adjusting for multiple tests, only DBP was significantly associated with neuroticism (bxy=0.003 6, table 2; pbonferroni =0.000 28). There were 1074 independent instrumental SNPs, which were significantly associated with DBP but not with neuroticism (online supplemental table 1 and figure 2). These instrumental SNPs,

with F-statistic >10, were independent with an LD r2 less than 0.05 and survived the HEIDI-outlier analysis that removes horizontal pleiotropic SNPs with p<0.01. No significant causal effects were found for other BP traits and each psychological state.

Table 2: Results of Generalized Summary-data-based Mendelian Randomization analysis

Exposure trait	Outcome trait	bxy	SE	P value	SNPs
DBP	Anxiety	0.012 6	0.006 7	0.061	1087
DBP	Depressive symptoms	0.000 2	0.000 9	0.828	1091
DBP	Neuroticism	0.003 6	0.000 8	<0.001	1074
DBP	SWB	−0.001 2	0.000 8	0.111	941
Hypertension	Anxiety	0.620 9	0.697 7	0.374	84
Hypertension	Depressive symptoms	0.057 1	0.093 0	0.540	84
Hypertension	Neuroticism	0.188 3	0.084 6	0.026	84
Hypertension	SWB	−0.038 8	0.080 1	0.628	68
PP	Anxiety	0.012 7	0.006 4	0.049	842
PP	Depressive symptoms	−0.000 5	0.000 8	0.588	836
PP	Neuroticism	−0.001 2	0.000 8	0.119	822
PP	SWB	0.001 2	0.000 7	0.092	727
SBP	Anxiety	0.004 2	0.004 0	0.287	1024
SBP	Depressive symptoms	−0.000 5	0.000 5	0.302	1024
SBP	Neuroticism	0.000 3	0.000 5	0.585	1006
SBP	SWB	0.000 4	0.000 5	0.355	881

DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure; SNPs, single nucleotide polymorphisms; SWB, subjective well-being.

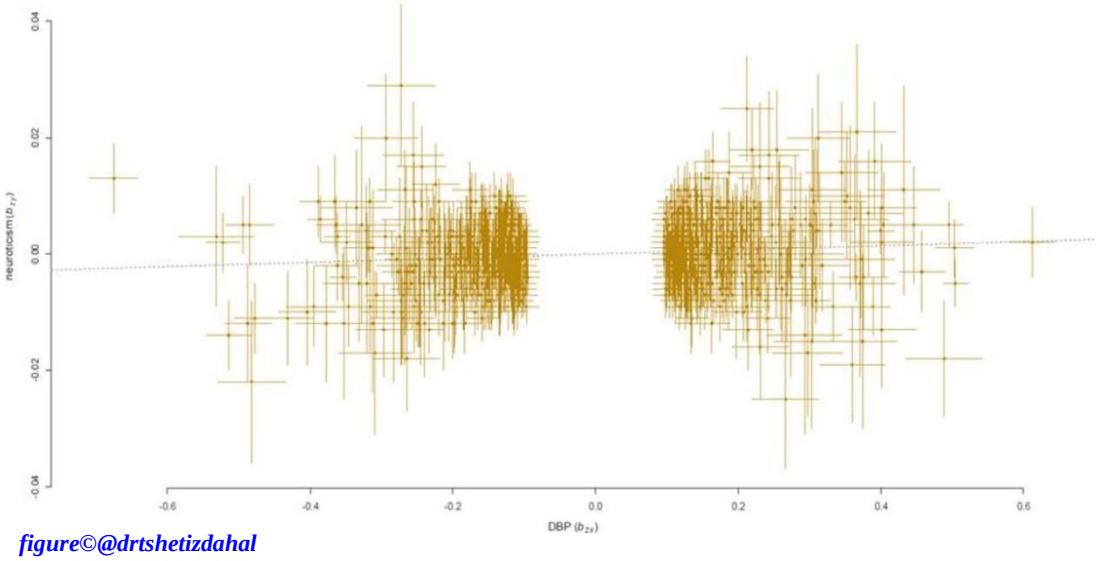

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Figure 2: The causal effects of DBP on neuroticism. The dotted lines denote effect sizes (bxy). DBP, diastolic blood pressure.

After SNP clumping and HEIDI-outlier filtering, less than the default threshold of 10 independent instrumental variations were preserved in the study, according to the reverse causal effects analysis. Due to the complexity of anxiety, depressive symptoms, neuroticism, and subjective well-being, results from a small number of independent instrumental variants may be skewed. Without this threshold, no meaningful causal link between any psychological state and any BP attribute was discovered. Given the sample size for the pertinent variant-outcome relationships and an alpha of 5%, the power of our MR analysis in all pairs of exposure and outcomes was >90%.

Discussion

Main Findings

The link between high blood pressure and psychological factors is evident because high blood pressure is a major risk factor for cardiovascular disease. Yet, it is difficult to separate the causative relationships between blood pressure and anxiety, depressive symptoms, neuroticism, and subjective well-being. In this work, we have used GSMR analysis methods for the first time and discovered a causal relationship between DBP and neuroticism. The use of MR in this work was predicated on the beliefs that genetic variants are connected to the exposure factor, are unrelated to confounding factors related to the result, and must influence the outcome through the exposure factor.

To determine the causal connection between the exposure factors and the result, the MR approach is devised. 14. Because of their stability and randomness, genetic variants from GWASs are typically treated as instrumental variants; however, they may cause horizontal pleiotropy, in which variants affect exposure and outcome traits through distinct mechanisms (uncorrelated pleiotropy) or through a shared heritable factor. 15 The GSMR method integrates the HEIDI-outlier test to find loci that influence several phenotypes, such as pleiotropy effects on the exposure and outcome, and is thought to be more effective than previous summary data-based MR approaches19, 20. 21.

Limitations

Modern large-scale GSMR analysis uses random genetic variants as instrumental variables, which may represent lifelong influences and boost the precision of the analysis results, to eliminate the biases brought on by confounding factors in observational studies. The current research does have some possible drawbacks, though. First, while the GSMR's integrated HEIDI-outlier test can find loci affecting several phenotypes, such as pleiotropy impacts on the exposure and outcome21, the possibility of residual pleiotropy cannot be entirely ruled out. To assess the independence of variations and analysis outcomes, more techniques are needed. Second, the results may not apply to other populations because the current analysis focused mostly on populations of European ancestry. Thirdly, a strict Bonferroni correction was applied to evaluate the positive MR findings, which might have resulted in false-negative findings and reduced the proportion of false-positive results.

Implications

One of the essential indicators, blood pressure serves as an important gauge of blood circulation. About 1000 SNPs have been strongly linked to this complicated variable by extensive GWASs, and BP has a 30%–60% heritability. 22 By engaging the sympathetic nervous system, certain psychological elements including mental stress and worry can raise blood pressure suddenly and increase blood fluidity. 23 Fear, rage, and happiness all raise blood pressure, and in people with more labile blood pressure, emotional effects are more variable. 24 A drop in blood pressure in placebo groups is frequently observed in pharmacological investigations of hypertension, which is distinct from spontaneous remission and regression to the mean effect when comparing placebo groups with untreated groups. 25 26. As blood pressure serves as a conduit between the brain and the heart and can thus influence the emergence of personality traits, its involvement in psychosomatic medicine is implicit. People with neuroticism are frequently critical of themselves, can be sensitive to criticism from others, and are prone to anxiety, worry, hostility, rage, and despair. One of the main contributing factors to anxiety and mood disorders is neuroticism. 27 High levels of mental stress are more common in neurotic people, and this can cause blood pressure to rise and cardiovascular problems. 28

Hence, proper blood pressure control may lessen neuroticism, mood disorders that exacerbate neuroticism, and cardiovascular diseases.

Conclusion

In conclusion, using GWAS datasets with large sample sizes, we found that, among the causal relationship between BP and psychological states, DBP had a causal effect on neuroticism but not on the other psychological states of anxiety, depressive symptoms, or subjective well-being. Since the independent instrumental SNPs for these four psychological states are limited, future studies are required to explore the causal relationship between psychological states and BP.

Ethics Statements and Ethics Approval

Patient consent for publication, Not required. This study involves human participants but the Bioethics Committee of LSMU, Rivne, Ukraine exempted this study. Participants gave informed consent to participate in the study before taking part.

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Author's Contribution

Dr. Jeby Abraham conceived and designed the analysis, collected the data, Dr Jainy Abraham contributed data or analysis tools, and Dr. Tshetiz Dahal performed the analysis as well as wrote the paper.

Conflict of Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.