Abstract

We conducted a bidirectional Mendelian randomization study to examine the causal effects of six personality traits (anxiety, neuroticism, extraversion, openness to experience, agreeableness and conscientiousness) on back pain associated with health care use and the causal effect of back pain on the same risk factors. Genetic instruments for the personality traits and back pain were obtained from the largest published genome-wide association studies conducted in individuals of European ancestry. We used inverse weighted variance meta-analysis and Causal Analysis Using Summary Effect for primary analyses and sensitivity analyses to examine evidence for causal associations. We interpreted exposure-outcome associations as being consistent with a causal relationship if results of at least one primary analysis were statistically significant after accounting for multiple statistical testing (p-value < 0.0042), and the direction and magnitude of effect estimates were concordant between primary and sensitivity analyses. We found evidence for statistically significant bidirectional causal associations between neuroticism and back pain, with odds ratio 1.51 (95% confidence interval 1.37; 1.67) of back pain per neuroticism sum score standard deviation, p-value = 7.80e-16; and beta = 0.12, se = 0.04 of neuroticism sum score standard deviation per log odds of back pain, p-value = 2.48e-03. Other relationships did not meet our predefined criteria for causal association.

Perspective

The significant positive feedback loop between neuroticism and back pain highlights the importance of considering neuroticism in the management of patients with back pain.

Key words: Big Five, anxiety, low back pain, risk factor, causality

Introduction

Back pain is a major cause of disability worldwide. According to the Global Burden of Disease Study 2015, low back pain together with neck pain were the leading causes of global years lived with disability in 1990-2015 [50]. The lifetime prevalence of back pain is as high as 39% and varies widely depending on the population [19]. There are many known risk factors of back pain, including genetics, lifestyle traits, social status, psychological factors and personality [11,38,52]. Investigating the causal relationships between possible risk factors and back pain is an important step toward understanding the disease etiology and discovering new methods of pain management and medical treatment. The gold standard of studying causal relations is randomized control trials (RCTs). However, for most lifestyle, social and personality traits RCTs are not a feasible option. Modern developments in genomics research offer an opportunity to conduct a good approximation of an RCT – Mendelian randomization (MR) analysis. MR has a level of evidence somewhere between traditional observational studies and RCTs [9].

Personality traits and mental health problems are an important group of back pain risk factors. Among them depression is by far the most common mental disorder associated with back pain [38,52]. Anxiety and the "Big Five" personality traits (neuroticism, extraversion, openness to experience, agreeableness, conscientiousness) are associated with chronic back pain as well [20,43]. Emotions and personality not only influence the risk of back pain but also modify the perception of pain and can influence the results of treatment [1,14]. For instance, higher scores of agreeableness may reflect that people are more likely to relieve their emotional distress through relying on social support [20]. This may be protective against chronic back pain, since it is known that there is an association between its development and stressful stimuli [8]. Also, patients with high levels of conscientiousness may suffer less from back pain because of acceptance of life with the condition

[22], whereas those with low levels of conscientiousness may have more difficulties due to lack of motivation to follow recommendations for the treatment of pain [37]. Moreover, previously we have shown that major depressive disorder (MDD) has a moderate-magnitude causal association with chronic back pain (odds ratio [OR] = 1.41, 95% confidence interval [CI] 1.27; 1.58) [52]. This might be partially explained by central sensitization being more likely to develop in patients with anxiety and depression disorders and playing a vital role in the chronification of back pain [16,41]. On the other hand, disease experience may alter patients' behavior, for instance making them less prone to seeking new experiences and induce patients to control their movements carefully [20]. These various examples illustrate why causal relationships of back pain with personality traits are an important area of inquiry.

The aim of this study was to conduct a bidirectional MR study between back pain and six personality traits: anxiety and the "Big Five" personality traits (extraversion, agreeableness, openness, conscientiousness, and neuroticism). We hypothesized that personality traits would have causal effects on back pain and that, conversely, back pain would have causal effects on personality traits.

Methods

Data used

The study was conducted using the largest publicly available genome-wide association study (GWAS) results for the respective traits. Research approvals involved the UK Biobank Research Ethics Committee (#11/NW/0382) and the VA Puget Sound Health Care System (MIRB 00903). The informed consent was obtained from each subject involved in the study. All the data were obtained from individuals of European ancestry, providing greater sample size and statistical power and mitigating confounding by ancestry [9]. Each dataset passed the quality control and unification procedure employing tools integrated into the GWAS-MAP platform [42].

In the primary analyses, we utilized GWAS data on six personality traits (anxiety, neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness) and a GWAS meta-analysis of back pain (Table 1). Anxiety was measured in the UK Biobank [45] sample and defined as a binary trait with 1,092 cases and 360,102 controls. Results of GWAS were obtained from the open access Neale Lab database (http://www.nealelab.is/uk-biobank). This GWAS was conducted using linear regression analysis. The phenotype "Anxiety disorders" is coded in the Neale Lab database as "KRA_PSY_ANXIETY", which is a code manually curated by collaborators from the FinnGen project [25]. It combines the F40 through F48 medical codes ("Neurotic, stress-related and somatoform disorders") from the 10th Revision of the International Statistical Classification of Diseases (ICD-10) (see https://risteys.finngen.fi/endpoints/KRA_PSY_ANXIETY for more details on phenotype definition). GWAS results for neuroticism were also provided by UK Biobank [36]. The phenotype was evaluated based on a summed neuroticism score obtained from 12 dichotomous items of the Eysenck Personality Questionnaire Revised Short Form (EPQ-RS) [12], and then standardized before association analysis. Data on other personality traits were obtained

from the Genetics of Personality Consortium (GPC) (https://tweelingenregister.vu.nl/gpc). Phenotypic values of openness to experience, agreeableness and conscientiousness were assessed as summed scores from NEO Five-Factor Inventory [10], while the extraversion latent score was calculated using an Item-Response Theory (IRT) approach harmonizing data from various inventories [47,48]. Unlike the GWAS on back pain, GWASs on all personality traits were conducted using linear regression models. The back pain GWAS used for main analyses represents the results of meta-analysis performed by the DBDS Genetic Consortium and GO consortium [2], comprising 119,110 cases and 909,847 controls in the total sample. The binary back pain phenotype was reconstructed from the ICD-10 M54 code "Dorsalgia". Here we refer to this phenotype as "back pain associated with health care use" (BP-HC). The corresponding GWAS results were transferred from the GRCh38 to GRCh37 genomic build using the liftOver tool (https://github.com/broadinstitute/liftover/) prior to the analyses.

Table 1. GWAS summary statistics for personality traits and back pain associated with health care use (BP-HC) employed in the main analyses

Another GWAS on back pain was employed for *post hoc* MR analyses excluding sample overlap between exposure and outcome. These data were derived from the seventh release of the FinnGen study [25]. The phenotype was defined as "M13 Dorsalgia" based on ICD-10 codes from electronic health records (see https://r7.risteys.finngen.fi/phenocode/M13_DORSALGIA for more details). The GWAS was performed with logistic regression and included 44,509 cases and 227,388 controls.

Additionally, we used data on sixteen potential confounders representing psychosocial (smoking, education, alcohol consumption, physical activity, sleep duration and depression) and cardiovascular (blood pressure, plasma lipid levels, type 2 diabetes and obesity) risk factors of back pain to conduct sensitivity analyses. More information on all the data used is provided in Supplemental Table 1.

Genetic correlations and heritability

We assessed the genetic correlations between personality traits and BP-HC to check whether there is a shared genetic background that can mediate their co-occurrence. At first, we reformatted the GWAS data using GenomicSEM v0.0.2 R package [13] and then utilized the LD Score regression tool [5] to compute SNP-based heritability of the traits and genetic correlations between them. The statistical significance threshold for heritability estimates was set at p-value < 0.007 = 0.05/7 and for genetic correlation coefficients it was defined as p-value < 0.008 = 0.05/6.

Mendelian randomization analysis

Overview of Mendelian randomization and analysis pipeline

Mendelian randomization (MR) is an *in silico* approach that aims to test for causal relationship between two traits: an exposure (considered as a cause) and an outcome (considered as a consequence of the exposure). The concept of MR is quite similar to the one utilized in RCTs. In MR, genetic variants associated with a higher risk of development of exposure trait are analogues to the intervention in RCTs. Thus, the carriers of such exposure-associated genetic variants can be

related to the affected group and the non-carriers refer to the control group. The genetic variants are usually represented as single nucleotide polymorphisms (SNPs) and traditionally called instrumental variables (IVs). Classical MR requires IVs to meet specific assumptions: (i) IVs must be associated with the exposure; (ii) IVs should not affect the outcome apart from through the exposure (no horizontal pleiotropy); and (iii) there should be no association of IVs with any of the confounders of the exposure-outcome relationship. The information on association between the genetic variants and exposure or outcome is commonly taken from the results of GWAS of a corresponding trait. Similar to the randomization of intervention in RCTs, there is a random allocation of genetic variants in MR, but unlike RCTs, this is a "natural" randomization due to the random distribution of genotypes in populations under the genetic laws, such as Mendel's laws of segregation and independent assortment, crossing over and random fertilization. Genetic variants are independent of environmental factors, so these environmental factors are assumed to be equally distributed between individuals with different genotypes. This makes MR less prone to confounding in comparison to observational studies [44]. The notable distinction between effect estimates in MR and RCTs is that MR provides estimates of a life-long "intervention", whereas RCTs assess short-term effects [46]. Negative MR results should be interpreted with caution: absence of the statistically significant signal does not necessarily mean no causality between traits.

In the current study, we used a protocol which we developed previously [52]. This protocol applies two MR methods: inverse variance weighted meta-analysis, IVW [18,23], and Causal Analysis Using Summary Effect estimates, CAUSE [34] and includes primary, sensitivity and *post hoc* analyses. This protocol was previously used for studying causal effects of psychosocial [52] and cardio-vascular (Suri, 2023) risk factors on back pain and *vice versa*. The present study continues this

earlier work, considering these risk factors as potential confounders of causal relationships between personality traits and back pain (Supplemental Table 1).

Selection of instrumental variables

Instrumental variables for both IVW and CAUSE were selected in three steps. First, we found genetic variants overlapping between exposure and outcome datasets. Then, we performed clumping of these variants utilizing PLINK 1.9 [7,39] (10000 kb window, $r^2 > 0.001$ threshold for correlation between SNPs, minor allele frequency (MAF) < 0.05 filter, p-value ≤ 5e-08 and p-value ≤ 1e-03 statistical significance thresholds for IVW and CAUSE, respectively). Finally, we kept only those SNPs that passed the harmonization of exposure and outcome data procedure implemented in the TwoSampleMR v0.5.5 [18] and cause v1.0.0.0274 (https://github.com/jean997/cause) R packages. The selected IVs can be considered as strong (F-statistic > 10) and meeting the first MR assumption, though we did not require IVs to be replicated in other GWASs as it is recommended for the IVW analysis [18].

Primary Mendelian randomization analysis

For IVW and CAUSE analyses we employed standard functions (with default settings) from the TwoSampleMR and cause R packages, respectively. The statistical significance threshold for MR results was set at p-value < 0.0042 = 0.05/(6*2), where 6 is the total number of exposure-outcome trait pairs and 2 reflects the bidirectionality of the analyses. For those trait pairs that passed the significance threshold at least in one of the methods in primary analysis (criterion 1) and provided effect estimates concordant by direction and magnitude between IVW and CAUSE (criterion 2), we conducted sensitivity analyses.

Sensitivity Mendelian randomization analysis

Sensitivity analyses attempted to control for horizontal pleiotropy and confounding effects reflecting violation of the second and the third MR assumptions, respectively. In IVW sensitivity analysis this was implemented in two steps: (i) we filtered out the IVs associated with potential confounders and personality traits other than the one considered as exposure or outcome in each exposure-outcome trait pair being analyzed; (ii) and we used the MR-PRESSO v1.0 [49] tool to identify and exclude horizontal pleiotropy outliers. In CAUSE sensitivity analysis, we used a similar approach, but only controlled for potential confounding (without excluding horizontal pleiotropy outliers); no manual correction for horizontal pleiotropy was made since it is embedded in the model of the CAUSE method.

When all the sensitivity analyses were done, we collated the direction of the effect estimates from all the primary and sensitivity analyses. If the direction of effect estimates were the same across these analyses (criterion 3), we inferred the data to be concordant with the hypothesis of causal effect of exposure on outcome.

Post hoc analysis

For exposure-outcome trait pairs that had statistically significant MR effects in the primary analysis, but involved sample overlap, we conducted a *post hoc* analysis using an independent GWAS of back pain from the FinnGen biobank to account for bias due to overlapping samples. This analysis was restricted to the IVW method only, with no sensitivity analyses. If the effect estimate was concordant by its direction and magnitude with estimates from the main MR analysis, we concluded that the effect was observed not due to sample overlap but because of causality.

Rescaling the Mendelian randomization effect estimates to the logistic scale

For anxiety, which is a binary trait analyzed using a linear regression model, we transformed the IVW and CAUSE effect estimates from the linear to the logistic scale. We performed this both in forward and reverse MR using the formulae described in [31,32]. Thus, in forward MR we multiplied the effect estimate beta MR by the coefficient $pr * (1 - pr)$, while for the reverse MR the coefficient was equal to $\frac{1}{pr*(1-pr)}$. We set the prevalence (pr) of anxiety to 0.003 based on the number of cases and controls in the corresponding GWAS.

Estimation of the detectable Mendelian randomization effect

To evaluate the magnitude of detectable MR effect under the defined statistical threshold p-value < 0.0042 and statistical power of 80% we assessed the corresponding non-centrality parameter (NCP) of the chi-squared distribution with one degree of freedom to be 13.74. Then for every exposure-outcome pair we calculated the proportion of exposure trait variance explained (R^2) by instrumental variables (IVs) as follows: $R^2 = \frac{\sum_i z_i^2}{N_{exposure}}$, where $z_i^2 = \left(\frac{\beta_{exposure_i}}{se_{exposure_i}}\right)^2$ is the test statistics for the ith IV from the GWAS on exposure and $N_{exposure}$ is its sample size. Only the IVs from primary IVW analyses were accounted for. Further we computed the linear beta MR effect as $\beta_{MR_{linear}} = \sqrt{\frac{NCP}{R^2 * N_{outcome}}}$, where $N_{outcome}$ is the sample size of outcome GWAS.

Since back pain and anxiety are binary traits, we had to transform the linear effect estimates to the logistic scale. This was done according to the formula: $\beta_{MR_{logistic}} = \beta_{MR_{linear}} * \frac{\sqrt{pr_{exposure}*(1-pr_{exposure})}}{\sqrt{pr_{outcome}*(1-pr_{outcome})}}$, where $pr_{exposure}$ and $pr_{outcome}$ are the prevalence of exposure and

outcome, respectively. If one of the traits from the exposure-outcome pair was continuous, we substituted the corresponding part of the fraction (numerator or denominator) with 1.

For those continuous personality traits that were not standardized (all of them apart from neuroticism) we estimated the standard deviation (SD) of the phenotype to transform the estimates of the detectable MR effect to the scale of the corresponding GWAS (see Supplemental Table 1). The SD values were evaluated as the square root of the phenotypic variance calculated based on the subset of independent statistically insignificant SNPs as described by Winkler et al. [53]. A list of independent genetic variants was obtained using PLINK v1.9 software, using the --indep-pairwise option. The MR estimates were divided by SD in cases in which the personality trait was considered as the exposure and was multiplied by SD otherwise.

Finally, we hypothesized the expected direction of the causal effect based on the other studies [20,22,37]. Thus, we assumed neuroticism to be positively correlated with BP-HC, whereas agreeableness, conscientiousness, extraversion and openness to experience to have a negative direction of effect. Since anxiety is positively correlated with neuroticism, we expected anxiety to have a positive correlation with BP-HC as well.

All the intermediate parameter values used for estimation of the detectable MR effect and the final effect estimates are given in Supplemental Tables 2 and 3.

Overlapping sample bias estimation

The GWAS samples for analyses of BP-HC, anxiety and neuroticism involved UK Biobank participants. According to Burgess et al. [6], this could bias the causal effect estimate in IVW in case of weak IVs. Although we performed our analyses using IVs strongly associated with the exposure

trait (p-value < 5e-08, F-statistic > 10), and reinforced the IVW results with estimates from CAUSE method which is robust to sample overlap, we additionally evaluated the bias in IVW effect estimates and inflation of type 1 error introduced by sample overlap between exposure and outcome traits both in forward and reverse MR. To do this we employed the online tool (https://sb452.shinyapps.io/overlap/) implementing the approach described by Burgess et al. [6]. The proportion of exposure variance explained by IVs (R^2) was assessed as described above and represented in Supplemental Tables 2 and 3 alongside the information on outcome trait prevalence. The sample sizes for corresponding traits are given in Supplemental Table 1. The observational estimate bias was approximated as $1/E(F - statistic) = 0.1$.

Results

Genetic correlations and heritability

Analysis of trait heritability estimates showed that only four (BP-HC, neuroticism, extraversion and openness to experience) out of seven traits demonstrated statistically significant SNP-based heritability (Supplemental Table 4). These heritability estimates varied from 5.31% for extraversion to 10.07% for openness to experience. Only two traits (neuroticism and openness to experience) were statistically significantly genetically correlated with BP-HC. Both traits showed moderate magnitude of genetic correlation of about 35%.

Mendelian randomization analysis

In the forward MR primary analysis, only neuroticism showed a statistically significant effect on BP-HC (see Table 2, Supplemental Tables 5 and 6). Both IVW and CAUSE primary results passed the significance threshold and demonstrated close effect estimates (IVW: beta = 0.41, OR = 1.51, 95% CI 1.37; 1.67; CAUSE: gamma = 0.38). We detected statistically significant heterogeneity between the 91 IVs used in primary IVW analysis (see Supplemental Table 5), which was eliminated after performing sensitivity analysis. Results of sensitivity analysis (Table 2, Supplemental Tables 5 and 7) for neuroticism were concordant with the results from primary MR. The *post hoc* analysis using GWASs without sample overlap was concordant with the primary MR results as well (Supplemental Table 8). For other personality traits we did not observe a sufficient number of IVs for IVW analyses. For anxiety, extraversion and conscientiousness there were no IVs at all.

Table 2. Causal effect of personality risk factors on back pain associated with health care use (BP-HC)

Similar to the forward MR analysis, in the reverse MR we observed only one statistically significant signal, for neuroticism (see Table 3, Supplemental Tables 9 – 11). It was significant in both methods used in the primary analysis and the effect estimates for each were consistent (IVW: beta = 0.12; CAUSE: gamma = 0.10). IVs used in primary IVW analysis were heterogeneous (Supplemental Table 9). The heterogeneity was removed after sensitivity IVW analysis. Although there were only two IVs that remained in sensitivity IVW analysis, the direction of the effect observed for these was the same as that in the primary MR and sensitivity CAUSE analyses. In *post hoc* analysis (Supplemental Table 8) we obtained an effect estimate which was close to the values from the primary MR. No other personality traits had statistically significant associations in the reverse MR.

Table 3. Causal effect of back pain associated with health care use (BP-HC) on personality risk factors

Detectable Mendelian randomization effect

We evaluated the magnitude of detectable MR effect in forward (Supplemental Table 2) and reverse (Supplemental Table 3) primary analyses assuming 80% statistical power. The largest detectable effect in forward MR was found for neuroticism (beta = 0.11, OR = 1.12) assuming a positive direction of the effect. For conscientiousness and openness to experience the estimated detectable MR effect on BP-HC was beta = -0.04 assuming a negative correlation, which corresponds to OR = 0.96. In reverse MR detectable effect estimates on average were more extreme and varied from beta = -2.40 for conscientiousness to beta = 1.25 for anxiety (OR = 3.50).

Notably, a large detectable effect in the reverse MR was also estimated for openness to experience (beta = -2.28).

Overlapping sample bias

Analysis of relative bias in IVW effect estimates from forward and reverse MR analyses considering anxiety and neuroticism showed modest bias of 0.003 and stable type 1 error of 0.05. It should be noted that for these traits the detected CAUSE effects were similar to those obtained in IVW in both magnitude and direction, and the results from *post hoc* analysis for neuroticism confirmed findings from the main analysis. This all adds credibility to the observed IVW effect estimates and allows us to conclude that IVW results are reliable, despite the sample overlap.

Discussion

Investigating the causal relationships between risk factors and back pain is an important step toward understanding its underlying mechanisms and developing novel trajectories of pain management and treatment. We have demonstrated bidirectional causal associations between neuroticism level and BP-HC. These results are concordant with epidemiological observations that a high level of neuroticism increases the risk of pain in general, modifies pain perception and treatment response, and increases chances of pain chronification [4,24,26,37]. One of the possible mechanisms of the neuroticism influence on BP-HC is through pain catastrophizing and increasing of pain anxiety [28]. Possible mechanisms of the reverse influence (BP-HC on neuroticism levels) could be partially explained by the fact that the quality of life of patents with back pain decreases as back pain severity increases. To our knowledge, this is the first time a causal effect of back pain on neuroticism has been reported. Both forward and reverse effects were positive in the current work, indicating a possible positive feedback loop between neuroticism and BP-HC, meaning that back pain could lead to greater neuroticism, which in turn can cause more pain. Our findings are in line with the diathesis-stress model of personality and pain [51] which assumes that a diathesis (such as a personality trait or premorbid personality functioning) and stressors (such as physiological stress of pain and the psychosocial stress associated with chronic pain disability) interact in a nonlinear way and may aggravate each other. It means that not only may a diathesis influence the probability of being exposed to stressful stimuli, but also diatheses may determine which types of events a person interpret as stressors [33]. The diathesis-stress model shows that comprehensive assessment of both personality function and stressful factors prior to manifestation of pain is crucial for better understanding of the aims, expectations, and limitations of pain treatment.

Since neuroticism is a risk factor for depression [55], bidirectionality of the association between neuroticism and BP-HC contrasts with our findings for MDD. Previously we have observed causal relationship of MDD on back pain but not *vice versa* [52]. Given the current results for neuroticism and conservative nature of our MR protocol, which resulted in a single IV in sensitivity analysis of back pain against MDD in our recent study, we may speculate, that back pain still can have reverse causation on MDD as on neuroticism level. However, further studies are needed.

We did not observe evidence for causality between other personality traits and back pain. This might be due to the lack of statistical power and absence of IVs for the IVW MR for several traits. However, the CAUSE method was not impacted by a paucity of IVs, yet it also failed to find evidence of statistically significant causal associations for other personality traits. The GWASs for extraversion, openness to experience, agreeableness and conscientiousness had smaller sample sizes than the one for neuroticism ($N < 65,000$). We did not detect significant result for anxiety either and had no IVs in forward IVW analysis at all; however, anxiety had sample size comparable with neuroticism. Most likely, we simply had low statistical power for anxiety, as for other personality traits but neuroticism. We may also speculate that alternative approaches to anxiety phenotype measurement may have resulted in a bigger number of cases, providing greater statistical power in GWAS and more IVs for MR analyses. For the given sample sizes and current phenotype definitions available, the estimated detectable effects were substantial, varying from beta = -2.40 to beta = 1.25. We cannot claim the absence of causal signals before much bigger GWASs are incorporated in frames of the MR analysis.

Beside the modest sample size for several personality traits, the study has other limitations. Firstly, for the primary analyses for neuroticism and anxiety, we used GWASs that had sample overlap with the GWAS of BP-HC. This potentially increases the type 1 error of the analysis and could

bias effect estimates [6]. However, our estimates of overlapping sample bias suggested that the likelihood of such bias is negligible. Moreover, the results of *post hoc* analyses when using non-overlapping samples were concordant with the main analyses. Secondly, the results are applicable only for European population. GWASs of samples with other ancestries are much needed so that the relationships between personality traits and BP-HC in other populations can be studied using MR. Thirdly, it is known that personality traits as well as back pain are vulnerable to assortative mating bias [29,30]. There is no general solution for this possible issue, but there is a growing evidence for efficiency of a family-based design in MR [3,17]. However, our *post hoc* results obtained on GWAS from another population (from Finland biobank) increases the confidence that our results are valid. Finally, in the current study we utilized medical codes to identify back pain cases, which creates a heterogeneous sample with highly varying pain locations and duration. In general, this might decrease the statistical power of the analysis and reduce the number of IVs, though in this case it could be compensated by a very large sample size [27]. In addition, it is possible that we did not detect the expected causal effects of psychological factors because the back pain phenotype we used was not restricted to chronic back pain exclusively, while many previously described associations were observed specifically in the setting of chronic back pain [16,20,43]. Although we can hypothesize that patients with back pain seeking healthcare treatment most likely have chronic pain [15,21,35], there may still be a substantial proportion of people with acute back pain in our GWAS sample and this might have affected our findings.

Our results support the general clinical practice of considering personality traits in multidisciplinary treatment programs for chronic back pain [20,37,40,54]. The significant positive feedback loop between neuroticism and back pain highlights the potential importance of recognizing neuroticism in patients with back pain.

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