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Reciprocal interaction between depression and pain: results from a comprehensive bidirectional Mendelian randomization study and functional annotation analysis

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Abstract

To understand a putative causal link for depression and pain, we retrieved summary statistics from genome-wide association studies conducted for pain at 7 different body sites (N = 151,922-226,683) and major depression disorder (MDD, $N_{case/control}$ = 246,363/561,190). We conducted a bidirectional Mendelian randomization analysis using distinct genome-wide association studies-identified single nucleotide polymorphisms for each trait as instrumental variables and performed several sensitivity analyses to verify Mendelian randomization assumptions. We also conducted functional annotation analysis using 396 tissue-specific annotations from the roadmap project. Across 7 different body sites, genetic predisposition to depression was associated with pain at the neck/shoulder (odds ratio [OR] = 1.08 per one log-unit increase in depression risk, 95% confidence interval [CI]: 1.06-1.10), back (OR = 1.05, 95% CI: 1.04-1.07), abdominal/stomach (OR = 1.03, 95% CI: 1.02-1.04), as well as headache (OR = 1.10, 95% CI: 1.07-1.12), but not with pain on the face, hip, and knee. In the reverse direction, genetically instrumented multisite chronic pain (OR = 1.78 per one increment in the number of pain site, 95% CI: 1.51-2.11) and headache (OR = 1.55 per one log-unit increase in headache risk, 95% CI = 1.13-2.10) were associated with MDD. Functional annotation analysis showed differential clustering patterns where depression clustered closely with headache and neck/shoulder pain, exhibiting substantial brain tissue enrichment. Our study indicates that depression is a causal risk factor for headache and pain localized at neck/shoulder, back, and abdominal/stomach, rather than pain at face, hip, and knee, and suggests common neurological pathologies underlying the development of depression, headache, and neck/shoulder pain.

Keywords: Depression, Pain, Mendelian randomization study, Functional annotation analysis, Causal inference, Genetics

1. Introduction

Depression and pain are 2 common and deleterious disorders that cause substantial economic and societal burden. Clinical observations have long recognized the comorbidity and interaction between depression and pain, where both conditions often coexist, respond to similar treatments, aggravate each other, and share common biological mechanisms.[20]

Despite a highly heterogeneous and chronic nature of depression and pain, both traits exhibit a significant genetic component in its development. For example, a recent study has meta-analyzed 807,553 individuals (246,363 cases and 561,190 controls) from the 3 largest genome-wide association studies (GWAS) of depression and identified 102 independent variants, 269 genes, and 15 gene-sets associated with major depression disorder (MDD), including genes and pathways associated with synaptic structure and neurotransmission.[14] Similarly, the polygenic architecture of pain has been elucidated by a GWAS of multisite chronic pain (MCP) conducted in ~380,000 UK Biobank participants, which identified independent lead single-nucleotide polymorphisms (SNPs) at 39 risk loci.[16] Furthermore, site-specific GWAS(s) have been performed for pain at different body parts including neck/shoulder,[25] back,[30] head,[22] and knee[23] and identified GWAS-significant genetic variants ranging from 3 loci (associated with back, knee, or neck/shoulder pain) to 28 loci (associated with headache).

The relationship between depression and pain has been studied to some extent, yet the results remain uncertain. A recent genetic correlation analysis has identified positive and significant shared genetic basis of MDD with headache (r_g = 0.39), neck/shoulder pain (r_g = 0.40), stomach/abdominal pain (r_g = 0.53),

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and back pain ($r_g = 0.36$), but not with facial, hip, or knee pain (all r_g close to 0).[24] These estimates can reflect pleiotropy, where specific genetic alleles increase risk to both phenotypes, but it can also reflect a directional and/or causal association. The latter can be examined by Mendelian randomization (MR) design, which uses genetic variants as instrumental variables (IVs) and makes causal inference. So far, only 2 MR studies have been performed to explore a putative causal relationship regarding depression and pain, both in a format of secondary or complementary analysis. One study did not find any causal relationship between MDD and headache,[24] whereas the other identified a causal effect between MDD and MCP in both directions.[16]

As additional MDD-associated loci have been discovered and novel statistical approaches have been developed, we aim to update and extend previous findings by conducting a bidirectional MR, leveraging summary statistics of the largest GWAS conducted in MDD and localized pain at 7 different body sites. We complement our bidirectional MR with a cell-type specific functional annotation analysis to partition the heritability and to understand the shared genetic origin across traits.

2. Materials and methods

We conduct the current MR study applying a standard two-sample framework where the IV-exposure and IV-outcome associations are from 2 GWAS (Supplementary Fig. 1, available at http://links.lww.com/PAIN/B367).

2.1. Major depression disorder genome-wide association studies

The largest GWAS of MDD was conducted meta-analyzing data on 246,363 cases of self-reported clinical diagnosis of depression or self-reported broad depression and 561,190 controls, all of European ancestry.[14] A total of 102 independent variants (biallelic common SNPs, $P<5 \times 10^{-8}$) were identified. We included these 102 SNPs as our $IVs_{(MDD)}$ and extracted $IV_{(MDD)}$-MDD associations (beta-coefficients, standard errors) from the MDD GWAS (Supplementary Table 1, available at http://links.lww.com/PAIN/B367).

Noteworthily, this MDD GWAS contained UK Biobank participants, which overlap to some extent (28%) with the localized pain GWAS. We therefore additionally extracted 44 MDD-associated SNPs identified by an earlier GWAS comprising 135,458 cases and 344,901 controls, all of European ancestry, to conduct a sensitivity analysis.[32] There the GWAS contains a small proportion of participants from UK Biobank (N = 29,740, 6%), resulting in a minimal overlap with the pain GWAS.

2.2. Pain genome-wide association studies

Large-scale GWAS(s) on pain by different body sites were conducted analyzing the UK Biobank participants (N = 151,922-226,683). Information was collected through a specific pain-related questionnaire, which included a question "In the last month have you experienced any of the following that interfered with your usual activities?". The options were: (1) headache; (2) facial pain; (3) neck or shoulder pain; (4) back pain; (5) stomach or abdominal pain; (6) hip pain; (7) knee pain; (8) pain all over the body; (9) none of the above; (10) prefer not to say.[24] Here, we included pain at 7 specific sites, namely headache, neck/shoulder, back, abdominal/stomach, facial, knee, and hip. For each pain phenotype, cases were defined as those who selected a specific pain site option, regardless of whether they had selected other options. Controls were those who selected the "none of the above" option. We did not include "pain all over the body" because this measure, taken as a proxy for chronic widespread pain, represents a different clinical syndrome from localized chronic pain and does not necessarily directly reflect chronic pain at 7 body sites. Alternatively, we obtained data from a large GWAS on MCP with 387,649 UK Biobank participants, all of European ancestry.[16] Multisite chronic pain was measured as the number of body sites (from 0 to 7 sites) at which pain had lasted for at least 3 months.

We extracted the $IV_{(MDD)}$-pain associations (beta-coefficients, standard errors) from each of the 7 pain GWAS(s) (Supplementary Table 1, available at http://links.lww.com/PAIN/B367). We also retrieved the full-set GWAS summary data for functional annotation analysis.

Because depression and pain often co-occur, we next tried to explore whether pain affects depression onset (opposite to the aforementioned depression to pain relationship). For most site-specific pain, for example, knee, back, shoulder/neck, less than 3 GWAS-significant SNPs were discovered, making the analysis underpowered. We therefore included only 2 pain phenotypes with better power: headache defined as self-reported broad-sense headache with 28 independently associated SNPs (Supplementary Table 2, available at http://links.lww.com/PAIN/B367) and MCP with 39 independently associated SNPs (Supplementary Table 3, http://links.lww.com/PAIN/B367).

2.3. Lifestyle factors genome-wide association studies

Pain, as an objective assessment, is highly heterogeneous and influenced by other factors. We therefore incorporated summary statistics from the GWAS of several heritable lifestyle exposures, including smoking,[21] alcohol consumption,[21] physical activity,[8] educational attainment,[19] and body mass index (BMI).[33] We first tested the association between each localized pain and the 5 lifestyle factors, and then included IVs associated with these lifestyle factors in a multivariable MR (MVMR) analysis to adjust for their effects.

Characteristics of all GWAS data are summarized in Supplementary Table 4 (available at http://links.lww.com/PAIN/B367). The GWAS summary data do not contain any personal information, and the original GWAS have obtained ethical approval from relevant ethics review committees.

2.4. Statistical analysis

2.4.1. Mendelian randomization analysis

We first evaluated a bidirectional causal relationship between depression and pain, applying several MR approaches including a random-effect inverse variance-weighted method (IVW),[6] a weighted median approach,[4] and an MR-Egger regression.[3]

Briefly, the random-effect IVW pools estimate from each IV and provides causal estimation assuming all IVs are valid or are invalid in a way that overall pleiotropy is balanced to be zero. Complementary to IVW, we also used a weighted median approach, which provides consistent estimates even when up to 50% of the analyzed genetic variants are invalid IVs. Finally, we performed MR-Egger regression to test for bias due to directional pleiotropy, where the average of direct effects of the tested genetic variants on outcome is nonzero. The heterogeneity between IVs was tested using Cochran Q test.

Three important model assumptions need to be satisfied for MR to yield unbiased causal estimates. Namely, IVs should be

robustly associated with the exposure (*relevance*), affect outcome only through the exposure (*exclusion restriction*), and should not be associated with confounders in the exposure–outcome relationship (*exchangeability*). We therefore performed important sensitivity analyses to validify model assumptions. For example, we excluded palindromic IVs or IVs that were associated with potential confounding traits according to GWAS catalog (https://www.ebi.ac.uk/gwas/). We also used an MVMR approach to adjust for potential horizontal pleiotropy acting through confounders such as smoking, alcohol consumption, BMI, and levels of education.[7] All MR analyses were conducted using the "TwoSampleMR" package in R software version 3.6.0.[11] The causal estimates with binary exposures, including MDD and localized pain, represent the change in the outcome per unit change in the exposure on the log odds scale, whereas the causal estimates for multisite chronic pain, a numeric exposure ranging from 0 to 7 pain sites, represent the change in the outcome per one increment in the number of pain sites.

2.4.2. Functional annotation analysis

To understand the (dis)similarity across traits, we further partitioned heritability using stratified-LD score regression leveraging genome-wide genetic variants of 7 localized pain and MDD.[9] This method partitions SNPs into functional categories and calculates category-specific enrichment based on the assumption that a category of SNPs is enriched for heritability if SNPs with high linkage disequilibrium to that category have higher χ^2 statistics than SNPs with low linkage disequilibrium to that category. Details of our functional annotation analysis are presented in Supplementary Note 1 (available at http://links.lww.com/PAIN/B367).

We further divided those 396 cell-type–specific annotations into 9 broad groups (adipose, central nervous system (CNS), digestive system, cardiovascular, musculoskeletal and connective tissue, immune and blood, liver, pancreas, and other) by taking a union of the cell-type–specific annotations within each group (eg, SNPs with any of the 6 histone modifications in any hematopoietic and immune cells were considered as one big category). All functional annotation analyses were conducted using the LD score regression software,[5,9] and enrichment values were transformed into color scale and visualized by hierarchical clustering.

To account for multiple comparisons, we considered a *P*-value smaller than 0.05 as suggestive significance; a Bonferroni-corrected *P*-value was applied based on the specific numbers of comparisons made in each analysis.

3. Results

As shown in **Table 1**, across 7 different body sites, genetic predisposition to depression was associated with pain on the neck/shoulder (odds ratio [OR] = 1.08, 95% confidence interval [CI]: 1.06-1.10, $P = 6.5 \times 10^{-17}$), back (OR = 1.05, 95% CI: 1.04-1.07, $P = 8.5 \times 10^{-11}$), abdominal/stomach (OR = 1.03, 95% CI: 1.02-1.04, $P = 2.1 \times 10^{-7}$), as well as headache (OR = 1.10, 95% CI: 1.07-1.12, $P = 7.3 \times 10^{-15}$). All *P*-values passed Bonferroni-corrected threshold using the IVW method ($P < 0.05/7$). The results remained consistent in both magnitude and direction using the weighted median approach. We did not observe any apparent horizontal pleiotropy as indicated by MR-Egger intercepts where all *P*-values for intercepts were greater than 0.05. Because MR-Egger regression produces twice as large standard errors as that of IVW, as expected, confidence intervals from MR-Egger were slightly inflated. Noteworthily, the effect of depression on back pain attenuated to null in the MR-Egger regression (OR = 0.99, $P = 0.78$). On the contrary, we did not observe any significant effect of depression with pain on face (OR = 1.00, $P = 0.07$), hip (OR = 1.01, $P = 0.06$), or knee (OR = 0.99, $P = 0.10$).

Sensitivity analysis removing palindromic IVs (**Table 1**) revealed similar findings on that genetically predicted depression increased sensitivity of pain on head, neck/shoulder, back, as well as abdominal/stomach, but not pain on face, hip, or knee. Consistent findings were observed excluding IVs associated with important potential confounders in genome-wide significance as revealed by the GWAS catalog (**Table 1**) as well as using 44 MDD-associated IVs identified in an earlier GWAS possessing negligible sample overlap with pain GWAS (Supplementary Table 5, available at http://links.lww.com/PAIN/B367). These results corroborated each other and support the robustness of our primary findings.

Among 5 lifestyle exposures, genetically predicted BMI, smoking, education, and alcohol consumption were significantly associated with at least one localized pain after Bonferroni-correction ($P < 0.05/35 = 0.0014$, **Fig. 1** and Supplementary Table 6, available at http://links.lww.com/PAIN/B367). Adjusting for all confounders simultaneously in one multivariable MR model did not alter our results (headache: OR = 1.08, $P = 3.2 \times 10^{-40}$; neck/shoulder pain: OR = 1.05, $P = 6.8 \times 10^{-17}$; back pain: OR = 1.03, $P = 2.2 \times 10^{-9}$; abdominal/stomach pain: OR = 1.02, $P = 7.4 \times 10^{-18}$). No significant association was observed for facial, hip, or knee pain. Adjusting for each confounder sequentially revealed similar findings (**Table 2**).

Perhaps not surprisingly, our reverse directional MR identified a significant causal association of pain with depression (**Table 3**). We found that genetic predisposition to multisite chronic pain was associated with the risk of depression, and the results were consistent across different sets of IVs (all IVs: OR = 1.78, $P = 1.6 \times 10^{-11}$; removing palindromic IVs: OR = 1.78, $P = 2.4 \times 10^{-10}$; removing pleiotropic IVs: OR = 1.67, $P = 8.9 \times 10^{-9}$), statistical methods (weighted median: OR = 1.48, $P = 8.3 \times 10^{-7}$), or adjustment for known confounding lifestyle factors (**Table 2**, adjusted for all lifestyle factors: OR = 1.83, $P = 9.9 \times 10^{-15}$). Due to limited availability of headache-associated IVs, estimates of headache with depression displayed larger statistical uncertainty and directional inconsistency (**Table 3**, all IVs: IVW, OR = 1.55, 95% CI, 1.13-2.10, $P = 0.005$; MR-Egger, OR = 0.77, 96% CI, 0.30-1.98, $P = 0.59$; weighted median, OR = 1.42, 95% CI, 1.07-1.88, $P = 0.01$). No substantial pleiotropy was detected by MR-Egger intercept (P for intercept =0.14).

Because depression and pain showed a strong genetic component (SNP-heritability), we further partitioned such heritability by cell-type–specific annotations. As presented in Supplementary Figure 2 and Supplementary Table 7 (available at http://links.lww.com/PAIN/B367), different clustering patterns were observed comparing cell-type–specific enrichment for depression with 7 localized pain. At 5 of the 6 chromatin marks, especially in 3 enhancer-related marks that are suggested to be more informative for tissue-specific disease enrichment (H3K27ac, H3K9ac, and H3K4me1), depression clustered closely with headache and neck/shoulder pain and exhibited substantial brain tissue components.

4. Discussion

To the best of our knowledge, this is the first comprehensive genetic analysis that systemically interrogates a causal

Table 1

Genetic predisposition to major depression disorder and risk of pain: the results from Mendelian randomization analysis.

Methods	# SNP	OR (95% CI)	*P*	*P* for intercept or heterogeneity	# SNP	OR (95% CI)	*P*	*P* for intercept or heterogeneity	# SNP	OR (95% CI)	*P*	*P* for intercept or heterogeneity
	Full set				Remove SNPs associated with confounding traits				Remove palindromic SNPs			
Multisite chronic pain												
IVW	102	**1.28 (1.23-1.34)**	**2.9×10^{-27}**	**< 0.001**	76	**1.26 (1.20-1.33)**	**1.1×10^{-18}**	**< 0.001**	89	**1.27 (1.21-1.33)**	**5.6×10^{-22}**	**< 0.001**
MR-Egger	102	1.14 (0.95-1.37)	0.16	0.21	76	1.07 (0.87-1.32)	0.53	0.11	89	1.13 (0.93-1.38)	0.21	0.24
Weighted median	102	**1.19 (1.14-1.24)**	**2.5×10^{-14}**		76	**1.18 (1.12-1.25)**	**1.3×10^{-9}**		89	**1.18 (1.12-1.24)**	**1.0×10^{-10}**	
Headache												
IVW	95	**1.10 (1.07-1.12)**	**7.3×10^{-15}**	**< 0.001**	69	**1.07 (1.05-1.10)**	**1.1×10^{-7}**	**< 0.001**	83	**1.09 (1.06-1.12)**	**2.3×10^{-11}**	**< 0.001**
MR-Egger	95	1.06 (0.96-1.16)	0.26	0.44	69	1.00 (0.90-1.11)	0.95	0.16	83	1.07 (0.96-1.18)	0.21	0.68
Weighted median	95	**1.11 (1.08-1.13)**	**5.9×10^{-15}**		69	**1.06 (1.03-1.10)**	**5.7×10^{-5}**		83	**1.09 (1.06-1.12)**	**2.3×10^{-9}**	
Neck/shoulder pain												
IVW	102	**1.08 (1.06-1.10)**	**6.5×10^{-17}**	**< 0.001**	76	**1.07 (1.05-1.09)**	**3.6×10^{-10}**	**0.002**	89	**1.07 (1.05-1.10)**	**1.6×10^{-13}**	**< 0.001**
MR-Egger	102	1.04 (0.96-1.12)	0.35	0.27	76	1.03 (0.95-1.12)	0.48	0.40	89	1.04 (0.97-1.13)	0.28	0.44
Weighted median	102	**1.06 (1.04-1.09)**	**4.6×10^{-9}**		76	**1.05 (1.03-1.08)**	**9.0×10^{-5}**		89	**1.06 (1.03-1.08)**	**2.8×10^{-6}**	
Back pain												
IVW	95	**1.05 (1.04-1.07)**	**8.5×10^{-11}**	**0.03**	69	**1.06 (1.03-1.08)**	**2.1×10^{-7}**	**0.01**	83	**1.05 (1.03-1.07)**	**3.5×10^{-8}**	**0.02**
MR-Egger	95	0.99 (0.93-1.06)	0.78	0.06	69	0.97 (0.90-1.06)	0.54	0.05	83	0.99 (0.93-1.06)	0.77	0.09
Weighted median	95	**1.05 (1.03-1.07)**	**2.3×10^{-5}**		69	**1.05 (1.02-1.08)**	**4.5×10^{-4}**		83	**1.04 (1.02-1.07)**	**3.3×10^{-4}**	
Abdominal/stomach pain												
IVW	102	**1.03 (1.02-1.04)**	**2.1×10^{-7}**	**0.005**	76	**1.02 (1.01-1.03)**	**7.5×10^{-5}**	0.05	89	**1.02 (1.01-1.03)**	**4.5×10^{-6}**	**0.01**
MR-Egger	102	1.02 (0.98-1.06)	0.38	0.71	76	1.00 (0.96-1.05)	0.84	0.43	89	1.02 (0.98-1.06)	0.29	0.95
Weighted median	102	**1.03 (1.01-1.04)**	**9.4×10^{-5}**		76	**1.02 (1.01-1.03)**	**2.2×10^{-3}**		89	**1.02 (1.01-1.04)**	**1.1×10^{-3}**	
Facial pain												
IVW	102	1.00 (0.99-1.01)	0.07	0.64	76	1.00 (0.99-1.01)	0.15	0.43	89	1.00 (0.99-1.01)	0.31	0.66
MR-Egger	102	1.00 (0.98-1.02)	0.73	0.43	76	0.99 (0.97-1.02)	0.51	0.30	89	1.00 (0.98-1.02)	0.79	0.98
Weighted median	102	1.00 (0.99-1.01)	0.27		76	1.00 (0.99-1.01)	0.40		89	1.00 (0.99-1.01)	0.31	
Hip pain												
IVW	102	1.01 (0.99-1.02)	0.06	0.77	76	1.01 (1.00-1.02)	0.02	0.72	89	1.01 (1.00-1.02)	0.03	0.96
MR-Egger	102	0.99 (0.96-1.03)	0.69	0.39	76	1.02 (0.97-1.06)	0.48	0.86	89	1.00 (0.96-1.04)	0.91	0.54
Weighted median	102	1.00 (0.99-1.02)	0.67		76	1.01 (0.99-1.02)	0.48		89	1.01 (0.99-1.02)	0.45	
Knee pain												
IVW	102	0.99 (0.98-1.01)	0.10	**0.01**	76	0.99 (0.98-1.01)	0.23	0.07	89	0.99 (0.97-1.00)	0.04	**0.02**
MR-Egger	102	0.98 (0.93-1.03)	0.46	0.71	76	0.98 (0.92-1.04)	0.50	0.69	89	0.98 (0.93-1.04)	0.55	0.94
Weighted median	102	0.98 (0.96-1.00)	0.02		76	0.98 (0.96-1.00)	0.04		89	0.98 (0.96-0.99)	0.01	

CI, confidence interval; IVW, inverse variance-weighted; MR, Mendelian randomization; OR, odds ratio; SNP, single-nucleotide polymorphisms.

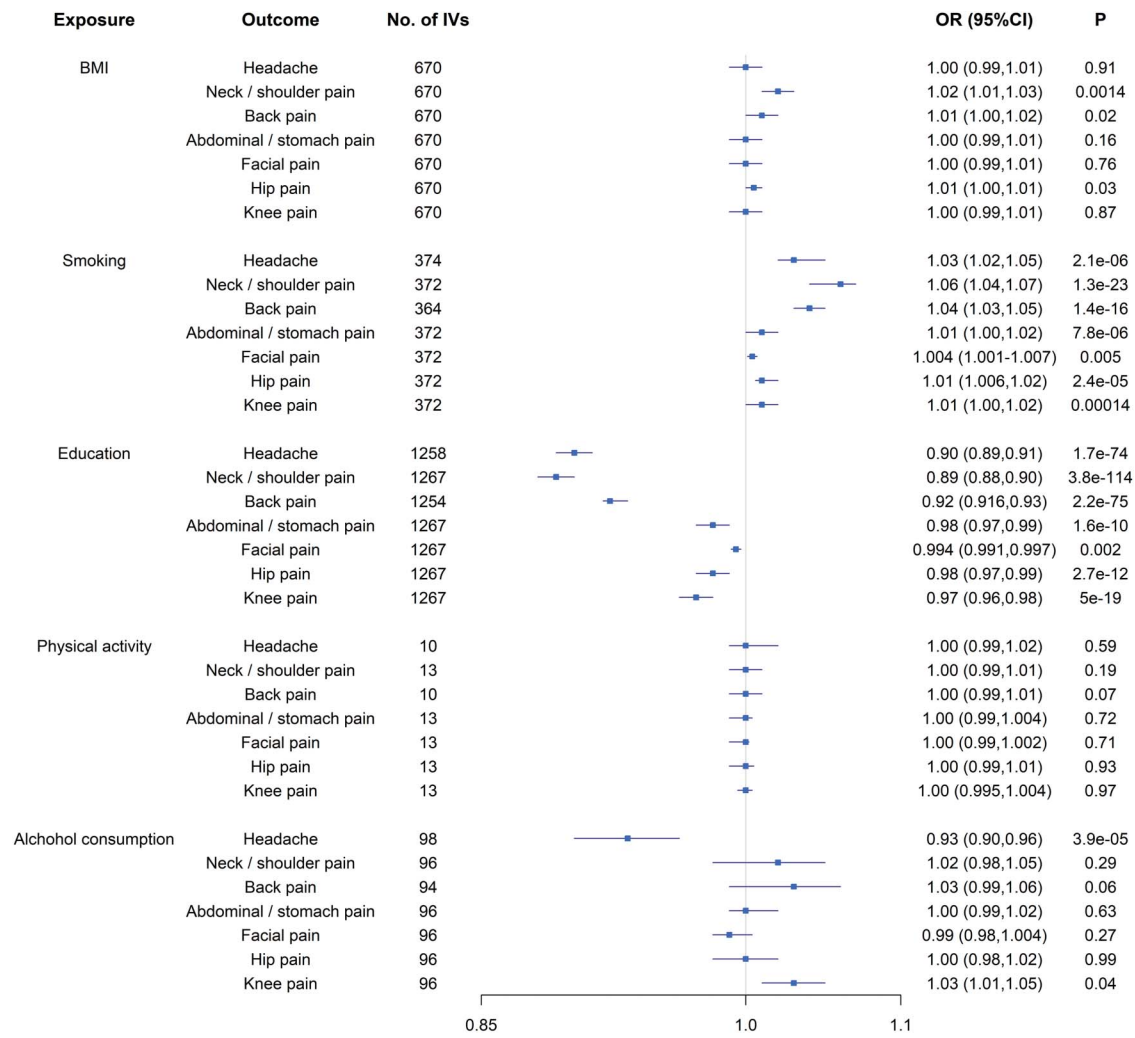

Figure 1. The putative causal effect of known confounding factors on pain: the results from Mendelian randomization analysis using the IVW approach. Squares and horizontal bars represent the odds ratios and confidence intervals of factor with the risk of pain, respectively. BMI, body mass index; CI, confidence interval; IVW, inverse-variance weighted approach; OR, odds ratio.

relationship between depression and pain, 2 highly complicated and entangled disorders. We found evidence supporting for a connection between depression and pain at specific body sites such as head, neck/shoulder, back, and abdominal/stomach, but not at other sites including face, hip, or knee. We further discovered a brain tissue enrichment in depression, neck/shoulder pain, and headache, suggesting a neural mechanism underlying the causal link.

Our findings are in line with a previous report that has quantified the genetic correlation between depression and pain and found significantly shared genetic architecture of depression with headache (r_g = 0.39), neck/shoulder pain (r_g = 0.40), back pain (r_g = 0.36), and abdominal/stomach pain (r_g=0.53), but not with facial, hip, or knee pain (all r_g close to 0).[24] Consistent with these results, we identified that genetic predisposition to depression targeted pain on certain body areas (head, neck/shoulder, back, and abdominal/stomach) rather than others (face, hip, and knee). The negative findings regarding facial, hip, or knee pain contradict observations from conventional epidemiological investigations. For example, a cohort study has followed 3006 patients and reported that depression increased the risk of temporomandibular disorders, a subgroup of facial pain problem (RR = 2.1, 95% CI = 1.5-3.0, P = 0.001).[17] Another cohort study that has followed 3407 patients with osteoarthritis for 2 years found that depression was significantly associated with knee pain worsening.[27] Moreover, a cross-sectional study of 2515 adult participants has suggested that elevated depression scores were significantly and independently associated with disabling chronic hip pain.[29] Although genetic factors are likely to contribute to pain at different sites, our negative findings suggest that nongenetic triggers may be more relevant in the co-occurrence of facial, knee, or hip pain with depression. However, although our results suggest a strong evidence of null association of depression with facial, hip, and knee pain (ORs virtually equal to 1), we had limited power for these 3 pain traits due to small sample sizes. Therefore, our results need to be confirmed when larger GWAS data become available.

For those 4 body areas (head, neck/shoulder, back, and abdominal/stomach) where we have identified significant causal associations, the nature of such relationship remains uncertain with 2 potential explanations—a true causal relationship or confounding by pleiotropic factors. We attempted to reduce the likelihood of confounding through statistical approaches such as using curated IVs without pleiotropic effects, MR-Egger regression, and MVMR. The highly consistent results between MVMR adjusting for different covariates and our main analysis

Table 2

Theresults from multivariable Mendelian randomization analysis adjusting for confounders.

Methods	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	xOR (95% CI)	*P*	OR (95% CI)	*P*
	Adjust for all		Adjust for BMI		Adjust for smoking		Adjust for education		Adjust for alcohol		Adjust for exercise	
MDD on pain												
Multisite chronic pain	**1.16 (1.14-1.19)**	**3.1×10^{-39}**	**1.20 (1.17-1.24)**	**8.0×10^{-31}**	**1.19 (1.15-1.22)**	**4.9×10^{-29}**	**1.20 (1.17-1.22)**	**1.2×10^{-65}**	**1.22 (1.17-1.26)**	**1.4×10^{-28}**	**1.22 (1.18-1.27)**	**4.4×10^{-25}**
Headache	**1.08 (1.07-1.10)**	**3.2×10^{-40}**	**1.09 (1.07-1.11)**	**5.4×10^{-25}**	**1.08 (1.06-1.10)**	**1.6×10^{-21}**	**1.08 (1.07-1.09)**	**1.4×10^{-41}**	**1.08 (1.06-1.10)**	**6.9×10^{-20}**	**1.08 (1.06-1.10)**	**8.3×10^{-15}**
Neck/shoulder pain	**1.05 (1.04-1.06)**	**6.8×10^{-17}**	**1.07 (1.05-1.08)**	**4.4×10^{-18}**	**1.05 (1.04-1.07)**	**4.8×10^{-15}**	**1.06 (1.05-1.07)**	**2.6×10^{-32}**	**1.06 (1.05-1.08)**	**9.5×10^{-17}**	**1.07 (1.05-1.08)**	**2.3×10^{-17}**
Back pain	**1.03 (1.02-1.04)**	**2.2×10^{-9}**	**1.04 (1.02-1.05)**	**7.5×10^{-8}**	**1.04 (1.02-1.05)**	**1.8×10^{-9}**	**1.04 (1.03-1.05)**	**2.0×10^{-18}**	**1.04 (1.03-1.06)**	**9.4×10^{-11}**	**1.05 (1.03-1.06)**	**2.5×10^{-12}**
Abdominal/stomach pain	**1.02 (1.01-1.03)**	**7.4×10^{-18}**	**1.02 (1.01-1.03)**	**1.7×10^{-10}**	**1.02 (1.01-1.03)**	**8.1×10^{-11}**	**1.02 (1.01-1.03)**	**2.0×10^{-18}**	**1.02 (1.01-1.03)**	**1.1×10^{-10}**	**1.02 (1.01-1.03)**	**4.1×10^{-8}**
Facial pain	1.004 (1.001-1.007)	0.01	1.005 (1.001-1.009)	0.01	1.004 (1.00-1.01)	0.03	**1.01 (1.00-1.02)**	**3.3×10^{-5}**	1.005 (1.001-1.009)	0.01	1.004 (1.00-1.008)	0.05
Hip pain	1.00 (0.99-1.01)	0.45	1.00 (0.99-1.01)	0.22	1.00 (0.99-1.01)	0.37	1.006 (1.00-1.01)	0.01	1.00 (0.99-1.01)	0.11	1.00 (0.99-1.01)	0.10
Knee pain	1.00 (0.99-1.01)	0.87	1.01 (0.99-1.02)	0.31	0.99 (0.98-1.00)	0.13	1.00 (0.99-1.01)	0.90	1.00 (0.98-1.004)	0.27	0.99 (0.98-1.00)	0.19
Pain on MDD												
Multisite chronic pain	**1.83 (1.57-2.13)**	**9.9×10^{-15}**	**1.82 (1.61-2.06)**	**1.6×10^{-21}**	**1.73 (1.52-1.98)**	**5.5×10^{-16}**	**1.78 (1.51-2.10)**	**7.5×10^{-12}**	**1.87 (1.71-2.04)**	**2.1×10^{-43}**	**1.42 (1.14-1.76)**	**1.5×10^{-3}**
Headache	**2.62 (2.22-3.10)**	**1.16×10^{-29}**	**3.04 (2.58-3.59)**	**6.4×10^{-40}**	**2.61 (2.31-2.95)**	**7.7×10^{-54}**	**1.17 (1.10-1.24)**	**1.5×10^{-7}**	**3.32 (2.92-3.77)**	**9.1×10^{-76}**	**1.23 (1.16-1.31)**	**1.4×10^{-11}**

Table 3

Genetic predisposition to pain and risk of major depression disorder: the results from Mendelian randomization analysis.

Methods	Full set				Remove SNPs associated with confounding traits				Remove palindromic SNPs			
	# SNP	OR (95% CI)	*P*	*P* for intercept or heterogeneity	# SNP	OR (95% CI)	*P*	*P* for intercept or heterogeneity	# SNP	OR (95% CI)	*P*	*P* for intercept or heterogeneity
Multisite chronic pain on MDD												
IVW	37	**1.78 (1.51-2.11)**	**1.6×10^{-11}**	**< 0.001**	26	**1.67 (1.40-1.98)**	**8.9×10^{-9}**	**< 0.001**	34	**1.78 (1.49-2.12)**	**2.4×10^{-10}**	**< 0.001**
MR-Egger	37	1.60 (0.68-3.79)	0.28	0.81	26	2.28 (0.88-5.94)	0.19	0.52	34	1.57 (0.65-3.80)	0.32	0.78
Weighted median	37	**1.48 (1.27-1.73)**	**8.3×10^{-7}**		26	**1.48 (1.22-1.79)**	**5.4×10^{-5}**		34	**1.48 (1.26-1.74)**	**1.9×10^{-6}**	
Headache on MDD												
IVW	26	**1.55 (1.13-2.10)**	**0.005**	**< 0.001**	20	**1.77 (1.18-2.66)**	**0.005**	**< 0.001**	23	**1.35 (1.06-1.70)**	**0.01**	**0.02**
MR-Egger	26	0.77 (0.30-1.98)	0.59	0.14	20	0.59 (0.16-2.16)	0.44	0.10	23	0.77 (0.39-1.53)	0.47	0.11
Weighted median	26	**1.42 (1.07-1.88)**	**0.01**		20	**1.77 (1.25-2.49)**	**0.001**		23	**1.41 (1.07-1.85)**	**0.01**	

CI, confidence interval; IVW, inverse variance-weighted; MDD, major depression disorder; MR, Mendelian randomization; OR, odds ratio.

reflect the effect of depression on pain independent of potential confounding factors including smoking, alcohol intake, physical activity, educational attainment, and obesity, and careful analyses into additional confounders are warranted.

We further discovered that genetically predicted multisite chronic pain also increased the risk of depression. Such bidirectional relationship corroborates clinical observations as well as animal behavioral experiments on a reciprocal interaction between pain and depression, where depressive-like conditions exacerbate pain perception and the presence of chronic pain aggravates depressive-like behaviors.[20] Indeed, prospective studies have suggested a reciprocal association between depression and headache where headache increased the likelihood of incident depression (RR = 1.44, 95% CI = 1.32-1.56)[28] and depression was significantly associated with recurrent headache (OR = 1.6, 95% CI = 1.2-2.1, $P = 0.001$).[2] Our result regarding genetic predisposition to headache and risk of depression needs to be validated by future studies due to its limited number of IVs and large statistical uncertainty.

Generally, the present MR study provides evidence supporting a putative causal relationship between depression and pain. The main etiological hypothesis is that these 2 disorders are linked by common underlying neurobiological mechanisms. At the tissue level, the functional brain reorganization in depression and pain has been investigated by a multitude of neuroimaging studies. The results have shown that emotional processing in depressed patients is topologically shifted towards the insular areas involved in pain perception and processing.[26] At the molecular level, monoamine neurotransmitters, including serotonin, dopamine, and norepinephrine, have been found to typically involve in the pathologies of both depression and pain.[15] For example, with depletion of serotonin and norepinephrine, as occurs in depression, the pain signals from the body, which are suppressed under normal conditions, are amplified with more attention and emotion involved.[1] Moreover, common genetic and epigenetic modifications might also mediate the interaction between depression and pain. SNP Val66Met in the BNDF gene, which encodes for brain-derived neurotrophic factor, has been shown to modify the relationship between life stress and depression[13] and increase the vulnerability to chronic multisite musculoskeletal pain.[10] Rats experiencing stress-induced visceral pain have shown an increase in DNA methylation at the glucocorticoid receptor promoter and a decrease at the corticotropin-releasing factor genes in the amygdala, demonstrating the involvement of central epigenetic mechanisms in regulating pain-depression morbidity.[31] Despite findings identified from animal models, our cell-type–specific annotation analysis, which leveraged human genome-wide information, has demonstrated a substantial enrichment in brain tissues of depression, headache, and neck/shoulder pain, supporting the hypothesis of neurobiological mechanisms underlying depression and pain.

Our current study has several advantages. We controlled for bias arising from population stratification by restricting participants to individuals of European ancestry. We conducted several important sensitivity analyses to verify MR model assumptions. We selected the most significant independent SNPs identified by the largest depression or pain GWAS, so all were robustly associated with exposure of interest, guaranteeing "relevance" assumption. We performed several statistical approaches to reduce pleiotropic effects and to satisfy "exclusion restriction" and "exchangeability" assumption.

Nevertheless, limitations should be acknowledged. First, despite using the hitherto largest GWAS for MDD and 7 localized pain, our statistical power remains limited for relatively small odds

ratio detected in each association. In addition, overfitting might be a concern because both MDD and pain GWAS contain UK Biobank data (up to 28% participant overlap). We conducted a sensitivity analysis using 44 MDD-associated SNPs identified in an early GWAS possessing negligible overlap with pain GWAS and observed highly consistent results with our main analysis. Such consistency reinforced the robustness of our findings and reduced the likelihood of overfitting and false positives to the minimal. Furthermore, the pain phenotype in UK Biobank was based on a single uniformed question. This means that all pain phenotypes were broadly defined and self-reported, unfiltered by other potentially relevant information on the nature, duration, or intensity of the pain. Similar concerns apply to the depression measurement. An updated analysis is warranted when the new and more detailed, validated pain-related questionnaire will be administered. Also, the original pain GWAS(s) did not take into account whether participants were taking antidepressants when answering their pain questionnaires. Antidepressants have been found to relieve pain in depressed patients, which might misclassify pain cases into nonpain controls. However, the impact of such misclassification might be small due to 2 reasons. First, evidence from randomized clinical trials has demonstrated that antidepressants can relieve but can hardly eliminate pain, meaning individuals under treatment could still experience moderate pain feelings.[12,18] Given the pain phenotypes in the original GWAS(s) were defined as binary questions (having vs not having pain), most of the participants with antidepressant treatment could still report a "Yes" in their pain questionnaires and contribute correctly as a case to the GWAS(s). Second, such misclassification, if exists, would drive our pain-MDD relationship towards null, contrary to the significant results observed by our study. Moreover, due to the minimal significant genetic signals that have been identified contributing to the pain at body sites except headache, our analysis targeting the pain-on-depression relationship was limited to headache only. An updated analysis is necessitated for the effects of site-specific pain on depression when more signals are discovered. Finally, because the participants in our present study were of European ancestry, we cautioned that the generalizability of our results is confined to European-ancestral populations.

To conclude, we have identified a causal connection between depression and pain at specific body sites such as head, neck/shoulder, back, and abdominal/stomach, but not at other body sites including face, hip, or knee. We have further revealed a brain tissue enrichment in depression, headache, and neck/should pain, which suggests possible common neurological pathways underpinning the causal association. Our findings contribute to the understanding of genetic and biological mechanisms for individual pain phenotypes and depression.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Summary statistics for the genetic associations with MDD, seven localized pain, multisite chronic pain, and five lifestyle factors were obtained from the corresponding GWAS listed in Supplementary Table 4 (available at http://links.lww.com/PAIN/B367). The authors thank all the investigators for sharing the data. XJ designed the study. BT and XJ analyzed the data, interpreted the results, and wrote the manuscript. Dr. Xia Jiang is supported by a starting package from the Swedish Research Council and Forskningsrådet för hälsa, arbetsliv och välfärd.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B367.

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