

1 **Genetic correlations between pain phenotypes and** 2 **depression and neuroticism**

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16 Running title: Genetic correlations between pain and psychiatric traits

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18

19 **Abstract**

20 Correlations between pain phenotypes and psychiatric traits such as depression and
 21 the personality trait of neuroticism are not fully understood. The purpose of this study
 22 was to identify whether eight pain phenotypes, depressive symptoms, major
 23 depressive disorders, and neuroticism are correlated for genetic reasons. Eight pain
 24 phenotypes were defined by a specific pain-related question in the UK Biobank
 25 questionnaire. First we generated genome-wide association summary statistics on
 26 each pain phenotype, and estimated the common SNP-based heritability of each trait
 27 using GCTA. We then estimated the genetic correlation of each pain phenotype with
 28 depressive symptoms, major depressive disorders and neuroticism using the the
 29 cross-trait linkage disequilibrium score regression (LDSC) method integrated in the
 30 LD Hub. Third, we used the LDSC software to calculate genetic correlations among
 31 pain phenotypes. All pain phenotypes were heritable, with pain all over the body
 32 showing the highest heritability ($h^2=0.31$, standard error=0.072). All pain phenotypes,
 33 except hip pain and knee pain, had significant and positive genetic correlations with
 34 depressive symptoms, major depressive disorders and neuroticism. The largest
 35 genetic correlations occurred between neuroticism and stomach or abdominal pain
 36 ($r_g=0.70$, $P=2.4 \times 10^{-9}$). In contrast, hip pain and knee pain showed weaker evidence
 37 of shared genetic architecture with these negative emotional traits. In addition, many
 38 pain phenotypes had positive and significant genetic correlations with each other
 39 indicating shared genetic mechanisms. Pain at a variety of body sites is heritable
 40 and genetically correlated with depression and neuroticism. This suggests that pain,
 41 neuroticism and depression share partially overlapping genetic risk factors.

42 **Key words:** Genetic correlation, pain, genome-wide association study, UK Biobank,
 43 depression, neuroticism

44 INTRODUCTION

45 Pain is a global public health priority. In the Global Burden of Diseases Study 2015,
 46 low back and neck pain were, by far, the leading cause of years lived with disability
 47 (YLDs) worldwide, with migraine also ranked among the top ten causes.¹ Some
 48 other leading causes of YLDs such as musculoskeletal disorders and diabetes are
 49 also highly likely to feature pain as a prominent symptom. It was estimated that 20%
 50 of adults suffer from pain globally and that 10% adults are diagnosed with chronic
 51 pain each year.² Chronic pain, i.e. pain that has persisted beyond normal tissue
 52 healing time (usually taken as 3 months) can arise from many causes, but is often
 53 idiopathic or difficult to classify pathophysiologically.³ It is recognized to have
 54 significant genetic contributions to its development,⁴ as well as environmental
 55 components. Improving our understanding of the genetic contributions to the
 56 experience of pain could help our understanding of its aetiology and prevention, and
 57 might also offer opportunities for personalised medicine and drug targeting based on
 58 identified genetic variants. Although some genetic studies have focused on pain in
 59 specific body sites and have suggested possible genetic variants associated with
 60 pain phenotypes,⁵ the overall understanding of the genetic contributions of pain
 61 remain unclear. Current limitations in our knowledge include: 1. the extent to which
 62 pain as a phenotype is determined by additive genetic components mainly
 63 represented by single nucleotide polymorphisms (SNPs); 2. whether the genetic
 64 mechanisms of pain in different body sites or in different disorders are similar or
 65 different; and 3. whether the genetic connections between pain phenotypes and
 66 other common co-morbidities are similar or different. Addressing these questions
 67 brings further challenges when the severity and the frequency of pain are taken into
 68 account.

69 Mental health disorders are among the commonest co-morbidities of pain.⁶⁻⁷
70 Depression was ranked as the third most important cause of disability worldwide,
71 and anxiety is also a leading cause.¹ The personality trait of neuroticism shows a
72 high phenotypic and genetic association with depression, anxiety and with reports of
73 physical and mental disorders.⁸⁻¹⁰ Neuroticism is also reckoned to cause a large
74 burden of ill health and health-related expenditure.¹¹ Specific pain phenotypes
75 including migraine, facial pain, neck pain, abdominal pain, low back pain, and
76 fibromyalgia have been shown to be associated with depression and anxiety.¹²⁻¹⁷
77 This epidemiological coexistence between pain and psychiatric traits could arise in
78 part because of shared genetic factors.¹⁸⁻¹⁹ Understanding the genetic correlation
79 between pain and psychiatric traits may help to elucidate their degree of shared
80 genetic architecture and provide a framework for future causal inference.²⁰ It has
81 been proposed that some pain phenotypes (such as migraine, back pain) and some
82 psychiatric traits (such as depression or neuroticism) share common genetic
83 components.²¹⁻²⁴ However, the genetic correlations between multiple pain
84 phenotypes in different body sites, and those between pain phenotypes and
85 depressive symptoms, major depressive disorders and neuroticism, have not been
86 reported systematically, to the best of our knowledge.

87 The recently released UK Biobank cohort has recorded eight broadly-defined pain
88 phenotypes, generated from a specific pain question: headache, facial pain, neck or
89 shoulder pain, back pain, stomach or abdominal pain, hip pain, knee pain, and pain
90 all over the body.²⁵ This has made it possible for researchers to identify genetic
91 variants associated with each pain phenotype. In addition, when combining genome-
92 wide association study (GWAS) summary statistics with the cross-trait linkage
93 disequilibrium score regression (LDSC) method implemented in the online LD hub

94 tool (<http://ldsc.broadinstitute.org/ldhub/>) and the LDSC software
95 (<https://github.com/bulik/ldsc>), researchers can estimate the genetic correlations
96 between selected phenotypes.²⁶

97 In order to identify genetic correlations between pain phenotypes and depression
98 and the personality trait of neuroticism, as well as the genetic correlations among
99 pain phenotypes, we generated GWAS summary statistics on eight pain phenotypes
100 in different body sites based on the UK Biobank cohort and adapted the cross-trait
101 LDSC method through the LD hub and the LDSC software.

102

103 **MATERIALS AND METHODS**

104 **Participants**

105 Over 500,000 people aged between 40 and 69 years were recruited by the UK
106 Biobank cohort in 2006-2010 across England, Scotland and Wales. A detailed
107 clinical, demographic, and lifestyle questionnaire was completed by all participants.
108 Biological samples (blood, urine and saliva) were also provided for future analysis.
109 Further information on the UK Biobank cohort can be found at www.ukbiobank.ac.uk.
110 Ethical approval was granted by the National Health Service National Research
111 Ethics Service (reference 11/NW/0382). The current study was conducted under
112 approved UK Biobank data application number 4844.

113 DNA extraction and quality control (QC) were standardized and the detailed method
114 can be found at <http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/DNA-Extraction-at-UK-Biobank-October-2014.pdf>. Genotyping was obtained from the
115 bespoke Affymetrix UK Biobank chips. The Wellcome Trust Centre for Human
116 Genetics at Oxford University was in charge of standard QC procedures for
117

genotyping results. The detailed QC steps can be found at <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580>.

In March 2018, The UK Biobank released an updated version of the genetic information (including directly genotyped genotypes and imputed genotypes) of 501,708 samples to all approved researchers. The detailed QC steps of imputation were described by Bycroft et al.²⁷

Definitions of pain phenotypes

We used a specific pain-related questionnaire adapted by the UK Biobank, which included the 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. More than one option could be selected. (UK Biobank Questionnaire field ID: 6159)

For each pain phenotype, cases were defined as those who selected the specific pain site option for the above question, regardless of whether they had selected other options. For example, headache cases are those who selected the 'Headache' option; Facial pain cases are those who selected the 'Facial pain' option; etc.

For each GWAS analysis, controls were those who selected the 'None of the above' option. Thus we used the same 'no pain' control population for all pain phenotypes in different body sites.

Definitions of depression and neuroticism

The phenotypes of depression and neuroticism were defined by the psychological cohorts collected by the LD hub.²⁸⁻³¹ The original researchers of these cohorts agreed to share the GWAS summary statistics on depression and neuroticism with

the LD hub for generating genetic correlations. Therefore, we selected the 'Psychiatric diseases' option and the 'Personality traits' option in the LD hub to include the depression and neuroticism traits. These traits are: Depressive symptoms,²⁸ Neuroticism (x 2 studies),²⁹⁻³⁰ Major depressive disorder.³¹ However, for neuroticism, we only chose the version used by Okbay et al,³⁰ as it is a GWAS meta-analysis publication, the results of which included the results from van den Berg et al.²⁹

Statistical analysis

Generating the heritabilities of all pain phenotypes

In this study, genome-wide complex trait analysis (GCTA) was used to calculate narrow-sense SNP-based heritabilities based on the genomic-relatedness-based restricted maximum-likelihood (GREML) approach.³²

Generating GWAS summary statistics of all pain phenotypes

In this study, genotype data were analysed in BGENIE (<https://jmarchini.org/bgenie/>), as recommended by UK Biobank. Routine QC steps included: removing SNPs with INFO scores less than 0.1, SNPs with minor allele frequency less than 0.5%, or SNPs that failed Hardy-Weinberg tests $P < 10^{-6}$. SNPs on the X and Y chromosomes and mitochondrial SNPs were also removed. We further removed those whose ancestry was not white British based on principal component analysis, those who were related at least another participant in the cohort (a cut-off value of 0.025 in the generation of the genetic relationship matrix) and those who failed QC. Association tests based on standard Frequentist association were performed using BGENIE adjusting for age, sex, body mass index (BMI), 9 population principal components, genotyping arrays, and assessment centers.

Generating genetic correlations between pain phenotypes and depression and neuroticism by the LD hub

The LD hub has gathered 235 published GWAS summary statistics of different disorders worldwide. Those GWAS summary statistics were compared against researcher-uploaded GWAS summary statistics of a phenotype of interest to generate genetic correlations between the phenotype and 235 phenotypes.²⁶

In order to identify genetic correlations between pain phenotypes and the depression and neuroticism traits, we used the cross-trait LDSC method through the LD Hub v1.9.0.²⁶ The LD Hub estimates the bivariate genetic correlations of a phenotype with other traits using individual SNP allele effect sizes and the average LD in a region. In this study, as there are altogether three depression and neuroticism traits available in the LD hub, those with P values less than 0.002 (0.05/24, 8 pain phenotypes and 3 psychiatric phenotypes) should be considered significant surviving Bonferroni correction for multiple testing.

Generating genetic correlations among pain phenotypes using the LDSC software

The LDSC software is a Linux version of the online LD hub tool. It is used to calculate the genetic correlations between two traits at a time while the LD hub can output the genetic correlations between one trait and many traits at the same time. In this study, as there were altogether 28 pair combinations among eight pain phenotypes, those with P values less than 0.0018 (0.05/28) should be considered significant surviving Bonferroni correction for multiple testing.

RESULTS

The heritabilities and the GWAS summary statistics of all pain phenotypes

The specific pain question received 775,252 responses to all options answered by 501,708 UK Biobank participants during the initial assessment visit (2006-2010).

Table 1 summarises the numbers of cases and controls in the GWAS of the eight pain phenotypes.

The narrow-sense SNP heritabilities of each pain phenotype are presented in the Table 2. Pain all over the body had the greatest heritability among all pain phenotypes ($h^2=0.31$, standard error (SE)=0.072). Knee pain has the lowest heritability ($h^2=0.08$, SE=0.029). The SNP heritabilities of other pain phenotypes were between 0.11 to 0.24.

Genetic correlations between pain and depression and neuroticism

Through the genetic correlation analysis, we identified multiple significant and positive correlations between pain phenotypes and depression and neuroticism. (Table 2, Figure 1) A supplementary table is provided to show the genetic correlations between pain phenotypes and all available psychiatric and personality traits in the LD hub (Supplementary Table 1).

Depression and eight pain phenotypes:

For depressive symptoms, all pain phenotypes had significant and positive genetic correlations with depression except hip pain and knee pain. The largest genetic correlation occurred with pain all over the body ($rg=0.69$, $P=1.4 \times 10^{-27}$), followed by stomach or abdominal pain ($rg=0.67$, $P=5.7 \times 10^{-7}$). For hip pain and knee pain, although there were positive genetic correlations with depressive symptoms ($rg=0.34$ and 0.12 , correspondingly), the associations did not survive Bonferroni correction ($P=0.03$ and 0.13 , correspondingly). The values of the genetic correlations between other pain phenotypes and depressive symptoms were between $rg=0.33$ and 0.55 , and all were statistically significant after adjustment for multiple testing.

For major depressive disorder, the genetic correlation results were similar to those for depressive symptoms. The largest genetic correlation was with stomach or abdominal pain ($rg=0.53$, $P=0.0005$), followed by pain all over the body ($rg=0.43$, $P=5.6 \times 10^{-6}$). However, the rg values of hip pain and knee pain were 0.04 and -0.07, which were also statistically insignificant ($P=0.80$ and 0.53, correspondingly). The values of the genetic correlations between other pain phenotypes and major depressive disorder were between $rg=0.34$ and 0.40, and all were statistically significant.

Neuroticism and eight pain phenotypes:

With neuroticism, stomach or abdominal pain had the largest genetic correlation ($rg=0.70$, $P=2.4 \times 10^{-9}$). Headache followed next with $rg=0.50$ and $P=2.2 \times 10^{-72}$. All genetic correlations with other pain phenotypes (except hip pain and knee pain) were positive and significant with rg values between 0.30 and 0.50. For hip pain and knee pain, although there were positive genetic correlations with neuroticism, the correlations were statistically insignificant.

Genetic correlations among pain phenotypes

Through the LDSC software, we identified multiple significant and positive correlations among pain phenotypes (Table 3). The largest positive and significant genetic correlation was between neck or shoulder pain and back pain ($rg=0.83$, $P=2.11 \times 10^{-100}$), followed by hip pain and pain all over the body ($rg=0.81$, $P=0.0004$). Neck or shoulder pain had positive and significant genetic correlations with all other pain phenotypes ($0.52 < rg < 0.83$), this was the same for pain all over the body ($0.36 < rg < 0.81$). Among all all pain phenotypes, hip pain only had three positive and significant genetic correlations (neck or shoulder pain, back pain and pain all over the body) with other pain phenotypes.

DISCUSSION

Eight self-reported pain phenotypes, from different sites across the body, were all heritable and showed a broad pattern of partially shared genetic architecture with each other. We also found evidence that pain shared genetic architecture with depressive symptoms, major depressive disorder and neuroticism for most sites across the body. Hip pain and knee pain was the exception, in showing weak and non-significant genetic correlations with depressive symptoms, major depressive disorder and neuroticism.

The nature of the relationship between pain phenotypes and depression has been uncertain. Epidemiological studies have identified that depression is reported more often by patients reporting pain and also that pain is a risk factor for the future development of depression.³³ Patients with psychosomatic conditions suffer from psychiatric disorders (such as depression) and physical diseases (such as bodily pain), and their co-occurrence is associated with greater disability than either condition alone.³⁴ Although the exact mechanisms linking these conditions are not clear, genetic mechanisms are implied through shared biological pathways, such as gene expression in biological networks, the endocannabinoid system, the hypothalamic-pituitary-adrenal axis and inflammatory pathways.³⁵ Our study answered a specific question about depression: to what extent is each pain phenotype genetically correlated with depression? Our genetic correlation results between headache, facial pain, neck or shoulder pain, stomach or abdominal pain, back pain, pain all over the body and depression are all consistent in direction with known epidemiological associations.¹²⁻¹⁷ This suggests that share genetic risk factors are likely to partly explain their phenotypic correlations. However, the genetic

correlations between hip pain and knee pain and depression were contrary to previous observations that depression and knee pain or hip pain are strongly related.³⁶ Previous studies have shown that knee pain from osteoarthritis increases a person's risk of developing subsequent depression.³⁷ A systematic review of the relationship between knee pain and multiple psychiatric traits also found an association between depression and knee pain.³⁸ While genetic factors may contribute to the pain at different sites, our findings suggest that non-genetic factors may be more important in the co-occurrence of knee or hip pain with depression.

The genetic relationships between pain phenotypes and neuroticism are also of interest and are similar to those between pain and depression. Neuroticism was identified to be a potential risk factor for elevated pain responses in laboratory pain in healthy children, and can likely exacerbate pain responses when coupled with fear of bodily sensations.³⁹ Neuroticism has also been independently associated with greater pain catastrophizing and pain-related anxiety.⁴⁰ Our genetic correlation results were consistent with findings from epidemiological studies of headache,⁴¹ neck or shoulder pain,⁴² back pain,⁴³ and pain all over the body.⁴⁴ No previous studies have shown epidemiological data for the relationships between neuroticism and facial pain or stomach or abdominal pain. It was also suggested from our study that there were no significant genetic relationships between knee pain or hip pain and neuroticism. To our knowledge, no previous studies have specifically examined the epidemiological relationships between neuroticism and hip pain or knee pain. Our findings suggest that hip pain and knee pain may belong to a separate pain group and should be considered separately when designing studies of the genetic relationships between pain and psychiatric disorders.

A significant and positive correlation between a pain phenotype and a psychiatric trait reflects share genetic architecture. This can reflect pleiotropy, where specific genetic alleles give risk to both phenotypes, but it can also reflect mediated pleiotropy where there is a directional or causal association between these traits.²⁰ It is also possible for positive genetic correlations to be generated by misclassification of pain as depression, or major depression as pain.⁴⁵ Whilst this seems unlikely to explain the convergent genetic correlation of neuroticism with pain, it will be important to examine whether there is subgroup heterogeneity amongst individuals with pain on depression that can be explained by variation on the other trait.

This paper also reported the genetic correlations among pain phenotypes in different body sites. Many pain phenotypes have positive and significant genetic correlations with each other indicating the common genetic mechanisms behind different pain phenotypes. This common mechanism is less likely to be represented by a few genes with large effects, but to reflect many genetic variants with smaller effects. It is biologically plausible for back pain and neck or shoulder pain to demonstrate the largest genetic correlation ($rg=0.83$) since causal genetic factors could have plausible detrimental effects across the whole spine. For other genetic correlations such as that between hip pain and pain all over the body ($rg=0.81$), the reason is less apparent and merits further research.

The highest narrow-sense heritability among all pain phenotypes in this study was 0.31 for pain all over the body. The heritabilities of all other pain phenotypes were moderate. The narrow-sense heritability does not take gene-gene interactions, gene-environment interactions, or the contribution from rare variants into account, and is therefore likely to be an under estimate of the true heritability. This is the first report of the heritabilities for facial pain ($h^2=0.24$), stomach or abdominal pain ($h^2=0.14$), to

the best of our knowledge, and suggests important genetic contributions to chronic pain at all body sites.

Arguably the greatest strength of the current study was the large size of the UK Biobank sample. This provided the largest single sample size for many of the pain phenotypes studied here compared with previous GWAS studies of pain.⁵ Nevertheless, potential limitations should also be taken into account. The phenotyping in UK Biobank was based on a single specific non-standard pain-related question. This means that all pain phenotypes were broadly-defined and unfiltered by other potentially relevant information on the nature, duration or intensity of the pain. Similar limitations also apply to the psychological traits measured in UK Biobank and elsewhere.⁴⁶ In future, new pain questionnaires may be administered to participants in UK Biobank, and this will allow for more detailed and focused phenotyping for use in future analyses.

In summary, we have identified significant and positive genetic correlations between multiple pain phenotypes and depression and neuroticism, suggesting that the known associations between these traits are partly due to shared genetic architecture. In contrast, we have suggested that the known epidemiological relationships between hip and knee pain and depression are not caused primarily by common genetic factors, prompting a search for other explanations. In addition, we have showed that many pain phenotypes are heritable and have positive and significant genetic correlations with each other. This indicates that common genetic risk factors confer liability to pain at many different sites across the body, suggesting shared risk factors and, potentially, disease mechanisms.

These findings contribute to the understanding of the genetic and biological mechanisms for individual pain phenotypes, depression and neuroticism. In addition,

the findings also represent an early but important step towards the identification of causal associations between pain phenotypes and psychiatric disorders and identifying subgroup heterogeneity.

CONFLICTS OF INTEREST

Ian Deary is a participant in UK Biobank. Other authors declare no conflict of interests.

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Figure legends:

Figure 1. The genetic correlations between eight pain phenotypes and depressive symptoms, major depressive disorders and neuroticism

Please note, the genetic correlations between these traits and hip pain and knee pain were not significant ($P > 0.002$, Table 2).

Rg: genetic correlation

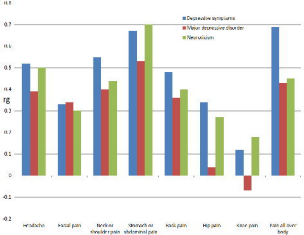


Table 1. The sample numbers available for GWAS on eight pain phenotypes

Pain phenotypes	Cases	Controls
Headache	74,761	149,312
Facial pain	2,610	149,312
Neck or shoulder pain	53,994	149,312
Stomach or abdominal pain	8,217	149,312
Back pain	43,991	149,312
Hip pain	10,116	149,312
Knee pain	22,204	149,312
Pain all over body	5,670	149,312

Table 2. The SNP-based heritabilities (h^2) of eight pain phenotypes from the UK Biobank cohort and their genetic correlations with depressive symptoms, major depression and neuroticism

Pain phenotypes	Heritability		Depressive symptoms		Major depressive disorder		Neuroticism	
	h^2 (SE)	P	rg	P	rg	P	rg	P
Headache	0.21 (0.015)	1.6×10^{-206}	0.52	1.6×10^{-46}	0.39	1.6×10^{-11}	0.50	2.2×10^{-72}
Facial pain	0.24 (0.12)	3.2×10^{-41}	0.33	2×10^{-4}	0.34	0.01	0.30	1.0×10^{-5}
Neck or shoulder pain	0.11 (0.017)	1.3×10^{-153}	0.55	3.4×10^{-30}	0.40	5.8×10^{-8}	0.44	5.3×10^{-7}
Stomach or abdominal pain	0.14 (0.050)	6.5×10^{-54}	0.67	5.7×10^{-7}	0.53	5×10^{-4}	0.70	2.4×10^{-9}
Back pain	0.11 (0.020)	1.5×10^{-67}	0.48	1.5×10^{-14}	0.36	3×10^{-5}	0.40	1.7×10^{-13}
Hip pain	0.12 (0.041)	4.5×10^{-56}	0.34	0.03	0.04	0.80	0.27	0.04
Knee pain	0.08 (0.029)	4.1×10^{-56}	0.12	0.13	-0.07	0.53	0.18	0.002
Pain all over body	0.31 (0.072)	5.9×10^{-74}	0.69	1.4×10^{-27}	0.43	5.6×10^{-6}	0.45	3.4×10^{-17}

P values < 0.002 (0.05/24) were considered as significant. Those significant rg values were in bold.

SE: standard error

rg : genetic correlation

Table 3. The genetic correlations among all pain phenotypes based on the UK Biobank

	Headache		Facial pain		Neck or shoulder pain		Stomach or abdominal pain		Back pain		Hip pain		Knee pain	
	rg	P	rg	P	rg	P	rg	P	rg	P	rg	P	rg	P
Facial pain	0.44	1.06 x 10 ⁻¹⁰												
Neck or shoulder pain	0.61	1.39 x 10 ⁻⁹⁴	0.52	3.27 x 10 ⁻¹⁰										
Stomach or abdominal pain	0.56	8.01 x 10 ⁻¹⁰	0.60	9.16 x 10 ⁻⁵	0.67	3.3 x 10 ⁻¹²								
Back pain	0.53	2.79 x 10 ⁻³⁶	0.47	4.50 x 10 ⁻⁷	0.83	2.11 x 10 ⁻¹⁰⁰	0.56	5.61 x 10 ⁻⁶						
Hip pain	0.32	0.002	0.86	0.002	0.69	1.79 x 10 ⁻⁵	0.38	0.12	0.54	0.0004				
Knee pain	0.39	3.70 x 10 ⁻¹³	0.33	0.01	0.53	1.53 x 10 ⁻¹⁴	0.53	0.0002	0.46	3.29 x 10 ⁻⁸	0.36	0.03		
Pain all over body	0.62	4.69 x 10 ⁻⁵²	0.43	6.51 x 10 ⁻⁵	0.79	1.45 x 10 ⁻⁴⁷	0.73	2.58 x 10 ⁻⁷	0.69	1.46 x 10 ⁻²⁹	0.81	0.0004	0.36	5.56 x 10 ⁻⁵

P values < 0.0018 (0.05/28) were considered as significant. Those significant rg values were in bold.

rg: genetic correlation