Supplementary information

Supplementary Information 1. Functional annotation analysis of major depression disorder and seven localized pain.

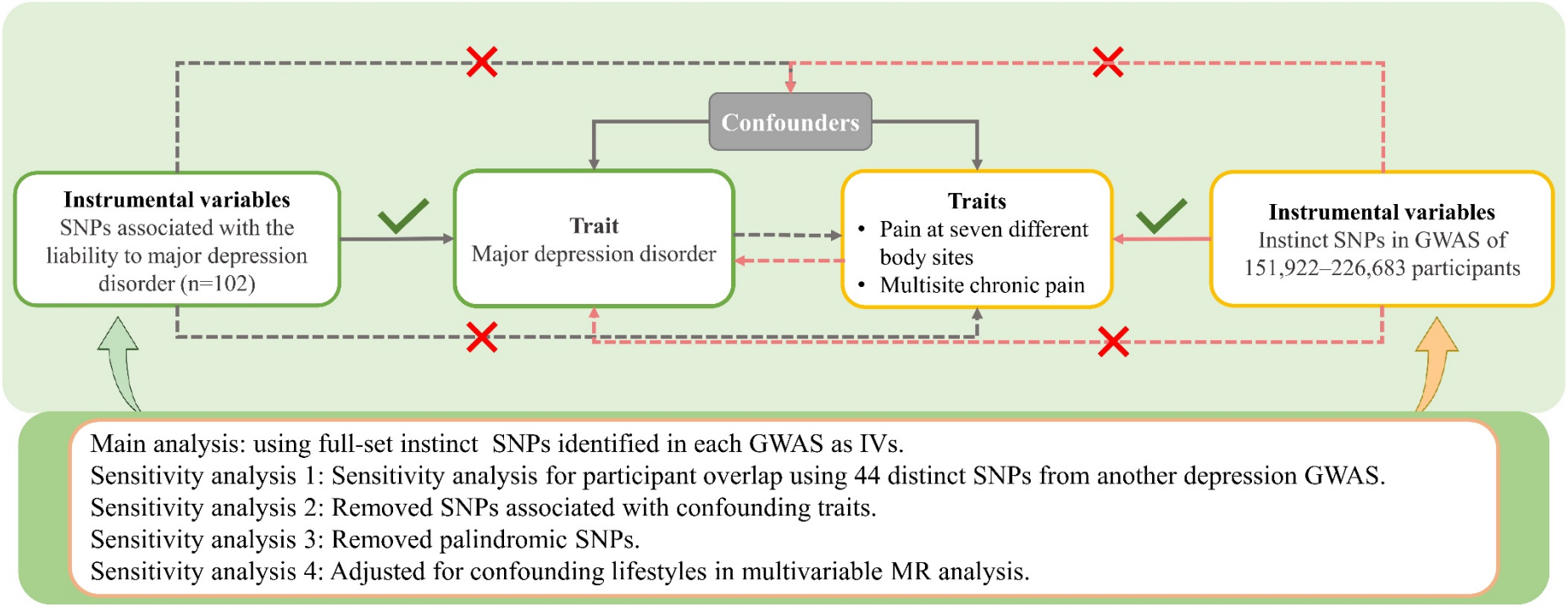
To understand the (dis)similarity across traits, we further partitioned heritability using stratified-LD score regression (LDSC) leveraging genome-wide genetic variants of pain and MDD [1]. This method partitions SNPs into functional categories and calculates category-specific enrichment based on the 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.

We performed analyses using 396 annotations (http://www.roadmapepigenomics.org/overview) constructed by the Roadmap project from narrow peaks in six chromatin marks, consisting of DNase hypersensitivity, three histone modification marks (H3K4me3, H3K4me1 and H3K36me3), and two acetylation marks (H3K9ac and H3K27ac), in a set of 88 primary cell types / tissues. Each cell-type-specific annotation corresponds to a histone mark in a single cell type (for example, H3K27ac in CD19 immune cells) and there are 396 such annotations in total. The Roadmap annotations is the largest existing epigenomic mapping dataset that contains ~100 cell types and six different chromatin marks. The six chosen marks are core epigenomic marks informative for gene activity and expression – specifically, DNase hypersensitivity denoting regions of accessible chromatin; H3K27ac and H3K9ac associated with increased activation of enhancer and promotor regions; H3K4me3 associated with promotor regions; H3K4me1 associated with enhancer regions; and H3K36me3 associated with transcribed regions [2]. Noteworthily, enhancer associated marks, like H3K27ac which tags both enhancer and promotor activity, are considered more informative for tissue-specific disease enrichment [2].

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 (for example, SNPs with any of the six histone modifications in any hematopoietic and immune cells were considered as one big category). All functional annotation analyses were conducted using the LDSC software [1, 3], and enrichment values were transformed into color scale

and visualized by hierarchical clustering.

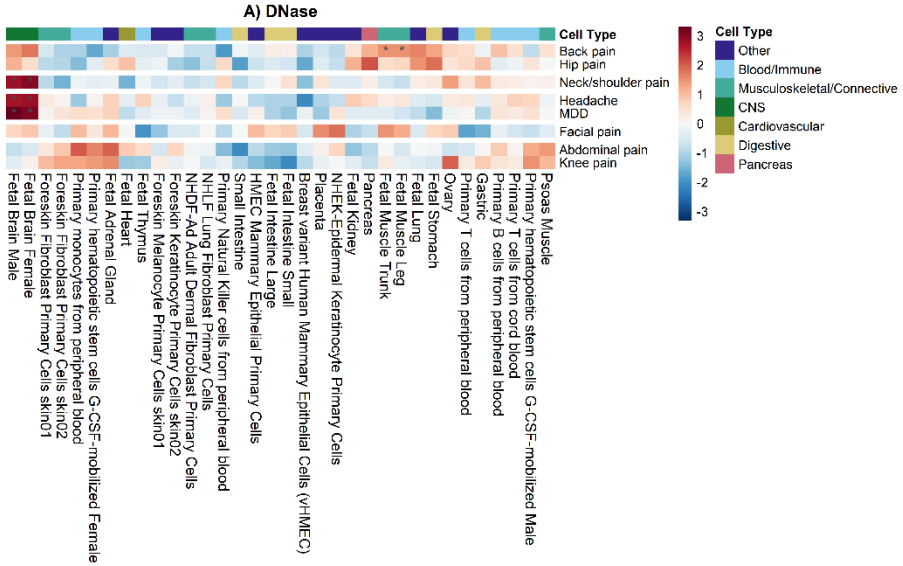
Supplementary Figure 1. Framework for the bidirectional Mendelian randomization study design of pain and major depression disorder.



SNP: single nucleotide polymorphism; GWAS: genome-wide association study; IV: instrumental variables.

Solid arrows represent the association exists in the framework, while dash arrows indicate the association may exist or not. Green ticks mean the association should be valid for MR assumptions (*relevance*), while red crosses represent that the existence of such association would violate MR assumptions (*exclusion restriction* and *exchangeability*).

Supplementary Figure 2. Heat maps showing bi-clustering of traits and cell-types over six histone marks. We performed 396 cell-type-specific annotation analysis in pain at different body sites and in MDD. We compared these enrichment results using a heat map. Each checker reflects the beta coefficient z-score, scaled by traits. Red indicates enrichment, blue indicates depletion. Deeper color represents stronger magnitude of effects. Asterisk represents statistical significance withstood correction ($P < 0.05/396$). The category of cell types is color coded to the left. A) DNase, B) H3K27ac, C) H3K36me3, D) H3K4me1, E) H3K4me3 and F) H3K9ac.



B) H3K27ac
Cell Type
Hip pain
Back pain
MDD
Neck/shoulder pain
Headache
Facial pain
Abdominal pain
Knee pain
Stomach Smooth Muscle
Rectal Smooth Muscle
Duodenum Smooth Muscle
Colon Smooth Muscle
Ovary
Liver
Placenta Amnion
Fetal Adrenal Gland
Right Ventricle
Placenta
Fetal Muscle Trunk
Skeletal Muscle Female
Fetal Muscle Leg
Spleen
Lung
Fetal Stomach
Adipose Nuclei
Right Atrium
Left Ventricle
NHLF Lung Fibroblast Primary Cells
NHDF-Ad Adult Dermal Fibroblast Primary Cells
Osteoblast Primary Cells
Aorta
Primary mononuclear cells from peripheral blood
Primary T helper naive cells from peripheral blood 1
Primary T killer naive cells from peripheral blood
Foreskin Melanocyte Primary Cells skin03
Primary Natural Killer cells from peripheral blood
Fetal Thymus
Primary T cells from peripheral blood
Primary T helper 17 cells PMA-I stimulated
Primary T helper memory cells from peripheral blood 1
Gastric
Pancreas
Primary B cells from peripheral blood
Foreskin Melanocyte Primary Cells skin01
Primary T regulatory cells from peripheral blood
Primary T helper cells PMA-I stimulated
Primary T helper cells from peripheral blood
Primary T helper naive cells from peripheral blood 2
Primary T cells effector memory enriched from peripheral blood
Thymus
Primary hematopoietic stem cells G-CSF-mobilized Female
Foreskin Fibroblast Primary Cells skin02
Foreskin Fibroblast Primary Cells skin01
Primary T killer memory cells from peripheral blood
Primary T helper memory cells from peripheral blood 2
HMEC Mammary Epithelial Primary Cells
Primary monocytes from peripheral blood
Fetal Intestine Small
Fetal Intestine Large
NHEK-Epidermal Keratinocyte Primary Cells
Foreskin Keratinocyte Primary Cells skin03
Small Intestine
Psoas Muscle
Esophagus
Sigmoid Colon
Colonic Mucosa
Rectal Mucosa Donor 31
Rectal Mucosa Donor 29
Brain Substantia Nigra
Brain Hippocampus Middle
Brain Cingulate Gyrus
Pancreatic Islets
Brain Inferior Temporal Lobe
Brain Angular Gyrus
Brain Anterior Caudate
Brain Dorsolateral Prefrontal Cortex
3
2
1
0
-1
-2
-3
Cell Type
Blood/Immune
Musculoskeletal/Connective
Other
Adipose
Cardiovascular
Liver
CNS
Digestive
Pancreas

C) H3K36me3
Cell Type
Abdominal pain
Facial pain
Knee pain
Neck/shoulder pain
MDD
Hip pain
Back pain
Headache
Fetal Adrenal Gland
Liver
Fetal Brain Male
Colon Smooth Muscle
NHEK-Epidermal Keratinocyte Primary Cells
Foreskin Keratinocyte Primary Cells skin03
Rectal Smooth Muscle
Duodenum Mucosa
Fetal Intestine Large
Small Intestine
Skeletal Muscle Female
Skeletal Muscle Male
Ovary
Breast Myoepithelial Primary Cells
Aorta
Fetal Heart
Breast variant Human Mammary Epithelial Cells (vHMEC)
Psoas Muscle
HMEC Mammary Epithelial Primary Cells
Osteoblast Primary Cells
NHDF-Ad Adult Dermal Fibroblast Primary Cells
Adipose Nuclei
Foreskin Melanocyte Primary Cells skin03
Left Ventricle
Primary T helper naive cells from peripheral blood 1
Primary T helper memory cells from peripheral blood 2
Primary T killer naive cells from peripheral blood
Primary T killer memory cells from peripheral blood
Primary B cells from peripheral blood
Primary B cells from cord blood
Fetal Kidney
Rectal Mucosa Donor 31
Duodenum Smooth Muscle
Stomach Mucosa
Rectal Mucosa Donor 29
Primary hematopoietic stem cells G-CSF-mobilized Male
Primary hematopoietic stem cells G-CSF-mobilized Female
Right Atrium
Fetal Thymus
Primary T helper memory cells from peripheral blood 1
Primary monocytes from peripheral blood
Primary T helper cells PMA-I stimulated
Primary hematopoietic stem cells short term culture
Primary T helper cells from peripheral blood
Primary Natural Killer cells from peripheral blood
Fetal Lung
Primary hematopoietic stem cells
Gastric
Foreskin Melanocyte Primary Cells skin01
Spleen
Right Ventricle
Esophagus
Lung
Fetal Stomach
NHLF Lung Fibroblast Primary Cells
Placenta Amnion
Pancreas
Foreskin Keratinocyte Primary Cells skin02
Fetal Intestine Small
Colonic Mucosa
Sigmoid Colon
Placenta
Thymus
Primary mononuclear cells from peripheral blood
Primary T cells effector memory enriched from peripheral blood
Primary T helper 17 cells PMA-I stimulated
Primary T regulatory cells from peripheral blood
Primary T helper naive cells from peripheral blood 2
Primary T cells from peripheral blood
Primary T cells from cord blood
Primary neutrophils from peripheral blood
Stomach Smooth Muscle
Pancreatic Islets
Fetal Muscle Leg
Brain Substantia Nigra
Foreskin Fibroblast Primary Cells skin02
Foreskin Fibroblast Primary Cells skin01
Fetal Muscle Trunk
Brain Cingulate Gyrus
Brain Anterior Caudate
Brain Inferior Temporal Lobe
Brain Hippocampus Middle
Brain Angular Gyrus
Ganglion Eminence derived primary cultured neurospheres
Cortex derived primary cultured neurospheres
Fetal Brain Female
Brain Germinal Matrix
Brain Dorsolateral Prefrontal Cortex
Cell Type
Other
Blood/Immune
CNS
Musculoskeletal/Connective
Adipose
Cardiovascular
Liver
Digestive
Pancreas
3
2
1
0
-1
-2
-3

D) H3K4me1
Cell Type
Back pain
Hip pain
Headache
Neck/shoulder pain
MDD
Knee pain
Abdominal pain
Facial pain
Right Atrium
Left Ventricle
Fetal Adrenal Gland
Stomach Smooth Muscle
Duodenum Smooth Muscle
Ovary
Rectal Smooth Muscle
Colon Smooth Muscle
Pancreas
Gastric
Psoas Muscle
Fetal Stomach
Fetal Lung
Right Ventricle
Lung
Spleen
Primary hematopoietic stem cells G-CSF-mobilized Male
Primary hematopoietic stem cells G-CSF-mobilized Female
Primary hematopoietic stem cells
Adipose Nuclei
HMEC Mammary Epithelial Primary Cells
Fetal Thymus
Breast variant Human Mammary Epithelial Cells (vHMEC)
Foreskin Keratinocyte Primary Cells skin02
Primary monocytes from peripheral blood
Primary neutrophils from peripheral blood
Esophagus
Skeletal Muscle Male
Fetal Muscle Trunk
Placenta Amnion
Skeletal Muscle Female
Fetal Muscle Leg
Placenta
NHEK-Epidermal Keratinocyte Primary Cells
Foreskin Keratinocyte Primary Cells skin03
Primary B cells from peripheral blood
Primary B cells from cord blood
Colonic Mucosa
Liver
Primary mononuclear cells from peripheral blood
Primary hematopoietic stem cells short term culture
Fetal Kidney
Fetal Heart
Osteoblast Primary Cells
NHDF-Ad Adult Dermal Fibroblast Primary Cells
Foreskin Fibroblast Primary Cells skin01
Thymus
Foreskin Fibroblast Primary Cells skin02
NHLF Lung Fibroblast Primary Cells
Breast Myoepithelial Primary Cells
Aorta
Primary T helper cells from peripheral blood
Primary T helper cells PMA-I stimulated
Primary T helper naive cells from peripheral blood 2
Primary T regulatory cells from peripheral blood
Primary T helper memory cells from peripheral blood 1
Primary T helper memory cells from peripheral blood 2
Primary T cells effector memory enriched from peripheral blood
Primary T killer memory cells from peripheral blood
Primary T helper naive cells from peripheral blood 1
Primary T helper 17 cells PMA-I stimulated
Primary T killer naive cells from peripheral blood
Primary T cells from cord blood
Primary T cells from peripheral blood
Foreskin Melanocyte Primary Cells skin03
Primary Natural Killer cells from peripheral blood
Foreskin Melanocyte Primary Cells skin01
Small Intestine
Duodenum Mucosa
Fetal Intestine Small
Fetal Intestine Large
Sigmoid Colon
Rectal Mucosa Donor 29
Stomach Mucosa
Rectal Mucosa Donor 31
Brain Cingulate Gyrus
Brain Anterior Caudate
Brain Hippocampus Middle
Brain Substantia Nigra
Brain Inferior Temporal Lobe
Brain Angular Gyrus
Pancreatic Islets
Brain Dorsolateral Prefrontal Cortex
Ganglion Eminence derived primary cultured neurospheres
Cortex derived primary cultured neurospheres
Fetal Brain Female
Fetal Brain Male
Brain Germinal Matrix
4
2
0
-2
-4
Cell Type
Other
Blood/Immune
CNS
Musculoskeletal/Connective
Adipose
Cardiovascular
Liver
Digestive
Pancreas

E) H3K4me3
Cell Type
Facial pain
Hip pain
Back pain
Knee pain
Abdominal pain
Headache
Neck/shoulder pain
MDD
HMEC Mammary Epithelial Primary Cells
Breast variant Human Mammary Epithelial Cells (vHMEC)
Primary T helper naive cells from peripheral blood 1
NHLF Lung Fibroblast Primary Cells
Foreskin Keratinocyte Primary Cells skin03
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Skeletal Muscle Female
Adipose Nuclei
Skeletal Muscle Male
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Right Atrium
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Fetal Muscle Leg
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Primary neutrophils from peripheral blood
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Foreskin Melanocyte Primary Cells skin01
Lung
Right Ventricle
Aorta
Stomach Smooth Muscle
Ovary
Primary hematopoietic stem cells
Sigmoid Colon
Duodenum Smooth Muscle
Gastric
Fetal Brain Male
Primary monocytes from peripheral blood
Primary B cells from peripheral blood
Primary B cells from cord blood
Pancreatic Islets
Small Intestine
Liver
Colon Smooth Muscle
Pancreas
Primary hematopoietic stem cells G-CSF-mobilized Male
Rectal Smooth Muscle
Fetal Heart
Primary T killer memory cells from peripheral blood
Primary T helper memory cells from peripheral blood 2
Primary T helper memory cells from peripheral blood 1
Primary T cells from cord blood
Primary T cells effector memory enriched from peripheral blood
Primary T helper memory cells from peripheral blood 1
Primary T cells from peripheral blood
Primary Natural Killer cells from peripheral blood
Fetal Lung
Duodenum Mucosa
Primary T helper cells from peripheral blood
Primary T helper cells PMA-I stimulated
Primary T helper 17 cells PMA-I stimulated
Primary T regulatory cells from peripheral blood
Primary T helper naive cells from peripheral blood 2
Thymus
Primary T killer naive cells from peripheral blood
Primary mononuclear cells from peripheral blood
Stomach Mucosa
Fetal Thymus
Rectal Mucosa Donor 31
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Placenta Amnion
Placenta
Fetal Intestine Small
Fetal Intestine Large
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Fetal Kidney
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Foreskin Fibroblast Primary Cells skin01
Fetal Brain Female
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Brain Dorsolateral Prefrontal Cortex
Brain Angular Gyrus
Brain Cingulate Gyrus
Brain Hippocampus Middle
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Brain Inferior Temporal Lobe
Brain Substantia Nigra
Cell Type
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Adipose
Cardiovascular
Liver
Digestive
Pancreas
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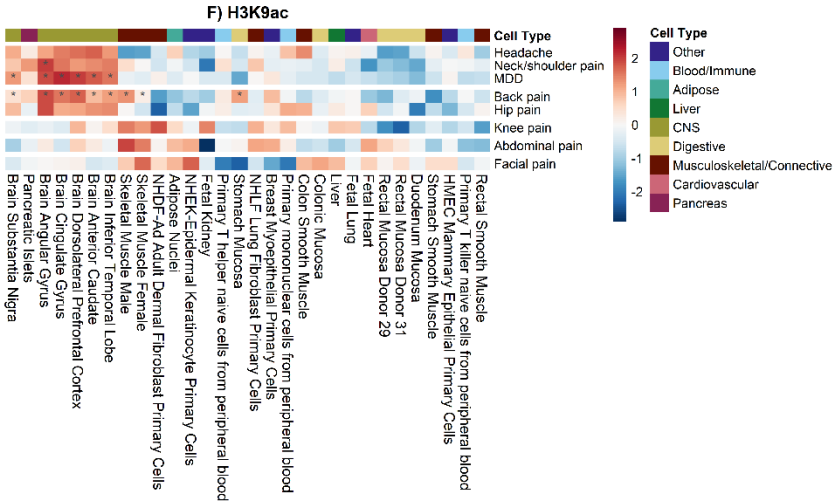
-2


F) H3K9ac
Cell Type
Headache
Neck/shoulder pain
MDD
Back pain
Hip pain
Knee pain
Abdominal pain
Facial pain
Rectal Smooth Muscle
Primary T killer naive cells from peripheral blood
HMEC Mammary Epithelial Primary Cells
Stomach Smooth Muscle
Duodenum Mucosa
Rectal Mucosa Donor 31
Rectal Mucosa Donor 29
Fetal Heart
Fetal Lung
Liver
Colonic Mucosa
Colon Smooth Muscle
Primary mononuclear cells from peripheral blood
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NHLF Lung Fibroblast Primary Cells
Stomach Mucosa
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Adipose Nuclei
NHDF-Ad Adult Dermal Fibroblast Primary Cells
Skeletal Muscle Female
Skeletal Muscle Male
Brain Inferior Temporal Lobe
Brain Anterior Caudate
Brain Dorsolateral Prefrontal Cortex
Brain Cingulate Gyrus
Brain Angular Gyrus
Pancreatic Islets
Brain Substantia Nigra
2
1
0
-1
-2
Cell Type
Other
Blood/Immune
Adipose
Liver
CNS
Digestive
Musculoskeletal/Connective
Cardiovascular
Pancreas

Supplementary Table 1. Characteristic of the 102 major depression disorder associated instruments.

SNP	A1	A2	EAF	Beta	SE	P-value	Confounding traits
rs1002656	T	C	0.70	-0.0210	0.0024	4.84E-19	General factor of neuroticism
rs10061069	C	G	0.22	-0.0250	0.0026	5.17E-22	Well-being spectrum (multivariate analysis)
rs10149470	A	G	0.49	-0.0206	0.0021	6.88E-22	Extremely high intelligence, Cognitive ability, Autism
rs1021363	A	G	0.35	0.0226	0.0023	3.77E-23	
rs1045430	T	G	0.48	-0.0226	0.0022	4.44E-25	Neuroticism
rs10774600	T	C	0.17	-0.0133	0.0030	1.07E-05	
rs10789214	T	C	0.57	0.0137	0.0022	3.81E-10	
rs10817969	T	G	0.72	0.0169	0.0024	1.32E-12	
rs10890020	A	G	0.52	-0.0267	0.0022	3.31E-34	
rs10913112	T	C	0.38	-0.0214	0.0023	1.72E-20	
rs1095626	T	C	0.58	-0.0285	0.0022	6.31E-39	
rs11135349	A	C	0.47	-0.0250	0.0022	2.18E-30	
rs113188507	A	G	0.28	0.0234	0.0025	2.94E-21	
rs1152578	T	C	0.44	-0.0152	0.0022	4.19E-12	
rs11579246	A	G	0.91	0.0320	0.0037	8.07E-18	
rs12052908	A	T	0.53	-0.0211	0.0022	3.98E-22	
rs1226412	T	C	0.79	0.0232	0.0027	3.35E-18	
rs12624433	A	G	0.26	0.0191	0.0025	2.16E-14	Neuroticism, Self-reported math ability (MTAG)
rs12923444	A	C	0.56	-0.0237	0.0023	1.76E-24	
rs12966052	C	G	0.18	-0.0187	0.0028	3.76E-11	
rs12967143	C	G	0.70	-0.0256	0.0024	1.61E-27	Well-being spectrum (multivariate analysis)
rs12967855	A	G	0.33	0.0207	0.0023	1.32E-19	Educational attainment (years of education)
rs13084037	A	G	0.77	-0.0217	0.0025	1.79E-17	
rs1343605	A	C	0.38	0.0231	0.0022	1.62E-25	
rs1354115	A	C	0.62	0.0186	0.0022	4.39E-17	
rs1409379	T	C	0.76	0.0164	0.0025	8.26E-11	
rs141954845	A	G	0.39	0.0179	0.0022	1.18E-15	
rs143186028	T	G	0.18	0.0244	0.0028	7.23E-18	
rs1448938	A	G	0.42	0.0172	0.0022	3.74E-15	Gut microbiome composition (winter)
rs1466887	T	C	0.55	-0.0125	0.0022	1.37E-08	
rs1568452	T	C	0.39	0.0293	0.0022	3.08E-40	
rs16887442	T	C	0.43	0.0148	0.0022	1.25E-11	
rs169235	A	G	0.75	-0.0170	0.0025	1.61E-11	Neuroticism
rs17641524	T	C	0.21	-0.0243	0.0027	7.90E-20	Educational attainment (MTAG), Primary biliary cholangitis
rs1890946	T	C	0.47	-0.0194	0.0022	8.62E-19	
rs1933802	C	G	0.45	-0.0198	0.0022	1.36E-19	
rs1956373	T	G	0.74	-0.0169	0.0025	6.08E-12	
rs1982277	T	C	0.76	0.0206	0.0026	1.28E-15	
rs198457	T	C	0.19	-0.0213	0.0028	5.41E-14	Neuroticism, Life satisfaction
rs200949	A	G	0.87	0.0433	0.0034	2.13E-37	
rs2029865	A	T	0.45	-0.0184	0.0022	4.02E-17	
rs2043539	A	G	0.42	0.0220	0.0022	8.32E-24	
rs2187490	T	G	0.91	-0.0152	0.0039	8.49E-05	
rs2247523	C	G	0.53	-0.0159	0.0021	9.05E-14	
rs2509805	T	C	0.32	0.0191	0.0024	4.92E-16	
rs2568958	A	G	0.62	0.0336	0.0022	4.45E-52	Body mass index, weight
rs263645	A	T	0.54	0.0176	0.0022	6.92E-16	
rs2670139	T	C	0.76	-0.0177	0.0025	2.19E-12	
rs2876520	C	G	0.53	-0.0187	0.0022	2.65E-17	Well-being spectrum (multivariate analysis)
rs301799	T	C	0.57	-0.0254	0.0022	4.05E-31	Thyroid peroxidase antibody positivity
rs30266	A	G	0.33	0.0323	0.0023	1.99E-45	loneliness measure
rs3099439	T	C	0.53	-0.0208	0.0022	1.61E-21	Neuroticism
rs3213572	A	G	0.47	0.0196	0.0021	5.51E-20	
rs33431	T	C	0.61	0.0121	0.0022	4.69E-08	
rs34488670	T	C	0.79	-0.0193	0.0027	4.69E-13	Age of smoking initiation (MTAG), Risk-taking tendency

rs34653192	C	G	0.32	-0.0196	0.0024	3.39E-16	
rs34937911	T	C	0.88	0.0244	0.0034	5.39E-13	
rs35553410	T	C	0.75	-0.0159	0.0025	2.18E-10	
rs3793577	A	G	0.47	-0.0211	0.0022	5.58E-22	Neuroticism, Life satisfaction
rs3823624	T	C	0.81	0.0294	0.0028	1.61E-26	Sleep duration
rs4346585	T	C	0.70	-0.0163	0.0024	4.87E-12	
rs45510091	A	G	0.95	0.0463	0.0049	7.74E-21	Feeling miserable
rs4772087	T	C	0.37	0.0209	0.0023	2.34E-20	
rs56314503	T	G	0.75	-0.0203	0.0025	1.28E-16	
rs56887639	A	G	0.73	-0.0171	0.0024	6.04E-13	
rs57344483	A	G	0.93	-0.0241	0.0041	5.26E-09	
rs58104186	A	G	0.47	0.0190	0.0022	3.56E-18	
rs58621819	A	T	0.79	-0.0169	0.0027	2.17E-10	Heel bone mineral density
rs59283172	A	G	0.11	-0.0174	0.0036	1.18E-06	
rs5995992	T	C	0.72	-0.0301	0.0024	2.60E-35	
rs60157091	T	C	0.52	0.0205	0.0022	5.54E-21	Well-being spectrum (multivariate analysis)
rs61902811	A	G	0.37	-0.0289	0.0022	5.17E-39	
rs61990288	A	G	0.51	-0.0249	0.0021	1.96E-31	
rs62091461	T	C	0.23	-0.0199	0.0026	1.75E-14	
rs62188629	A	G	0.31	0.0169	0.0024	6.15E-13	
rs67436663	C	G	0.24	-0.0141	0.0025	2.83E-08	
rs6783233	T	C	0.28	0.0177	0.0024	1.14E-13	
rs7030813	T	C	0.37	0.0251	0.0022	8.88E-30	
rs7117514	A	G	0.54	-0.0166	0.0022	3.64E-14	
rs7193263	A	G	0.67	-0.0206	0.0023	3.83E-19	
rs7198928	T	C	0.62	0.0219	0.0022	3.71E-23	
rs7200826	T	C	0.26	0.0270	0.0025	3.09E-28	Well-being spectrum (multivariate analysis)
rs7227069	A	G	0.43	0.0242	0.0022	2.13E-28	
rs7241572	A	G	0.20	0.0200	0.0027	2.56E-13	
rs725616	T	C	0.36	0.0135	0.0022	1.06E-09	
rs72710803	A	C	0.91	-0.0247	0.0038	1.35E-10	
rs75581564	A	G	0.12	0.0248	0.0034	3.49E-13	
rs7585722	T	C	0.85	-0.0215	0.0030	5.47E-13	
rs7624336	T	G	0.21	0.0092	0.0027	0.000548	
rs7659414	A	C	0.58	-0.0089	0.0022	4.32E-05	
rs7685686	A	G	0.58	0.0173	0.0022	5.52E-15	
rs7758630	A	T	0.41	-0.0165	0.0022	7.79E-14	
rs7807677	T	C	0.55	0.0211	0.0022	5.40E-22	
rs78337797	T	G	0.88	0.0229	0.0034	1.37E-11	
rs7837935	T	G	0.15	-0.0226	0.0031	1.15E-13	Neuroticism
rs7932640	T	C	0.44	0.0227	0.0022	3.40E-25	
rs8037355	T	C	0.56	-0.0192	0.0022	1.52E-18	
rs913930	A	G	0.64	-0.0219	0.0023	1.03E-21	Neuroticism
rs9363467	T	C	0.60	0.0158	0.0023	2.50E-12	
rs9545360	A	C	0.18	-0.0167	0.0029	6.70E-09	
rs9592461	A	G	0.49	0.0243	0.0022	1.17E-28	Well-being spectrum (multivariate analysis)
rs997934	T	C	0.38	0.0163	0.0023	4.60E-13	

SNP: single nucleotide polymorphism; A1: effect allele; A2: other allele; EAF: effect allele frequency.

Supplementary Table 2. Characteristic of the 28 headache associated instruments.

SNP	A1	A2	EAF	Beta	SE	P-value	Confounder
rs1011121	G	A	0.59	-0.0080	0.0014	1.46E-08	
rs1050316	T	G	0.65	-0.0098	0.0015	1.54E-11	Platelet count
rs10774231	C	T	0.58	-0.0082	0.0014	4.55E-09	
rs11172113	C	T	0.41	-0.0202	0.0014	4.92E-47	Migraine, Medication use, Coronary artery disease, Lung function (FEV1/FVC)
rs12134493	A	C	0.12	0.0136	0.0021	1.93E-10	Migraine
rs12740679	G	C	0.26	0.0110	0.0016	3.66E-12	
rs1555132	A	C	0.36	0.0083	0.0015	1.16E-08	
rs17220352	G	A	0.24	0.0104	0.0016	9.42E-11	
rs2036465	C	A	0.80	-0.0093	0.0017	4.01E-08	
rs2072806	G	C	0.13	-0.0121	0.0021	5.30E-09	
rs2362290	A	G	0.21	-0.0141	0.0017	6.25E-16	
rs2895526	A	T	0.47	-0.0086	0.0014	4.61E-10	
rs34097149	C	T	0.02	-0.0297	0.0046	1.33E-10	
rs3748784	G	A	0.51	-0.0078	0.0014	1.75E-08	
rs4596713	T	C	0.57	-0.0078	0.0014	2.30E-08	
rs4909945	C	T	0.70	0.0087	0.0015	5.13E-09	Platelet aggregation
rs4941139	C	T	0.34	0.0093	0.0015	2.22E-10	
rs56304645	T	C	0.23	0.0102	0.0016	5.74E-10	
rs56349329	A	G	0.16	-0.0104	0.0019	3.69E-08	
rs6606710	C	T	0.41	0.0084	0.0015	8.44E-09	Neuroticism
rs7300001	G	A	0.08	-0.0144	0.0025	8.86E-09	General cognitive ability
rs7555006	G	A	0.44	0.0081	0.0014	5.87E-09	
rs77804065	T	C	0.22	0.0130	0.0017	5.87E-15	Feeling guilty, Neuroticism
rs78438709	G	A	0.07	-0.0186	0.0027	8.57E-12	
rs8614	A	C	0.18	0.0105	0.0018	4.25E-09	Self-reported math ability, Smoking initiation
rs9349379	G	A	0.40	-0.0110	0.0014	3.59E-15	Migraine, Coronary heart disease, Cervical artery dissection, Alcohol consumption, blood pressure
rs9486715	C	A	0.33	0.0171	0.0015	2.58E-31	
rs9490318	T	C	0.15	0.0124	0.0019	1.72E-10	

SNP: single nucleotide polymorphism; A1: effect allele; A2: other allele; EAF: effect allele frequency.

Supplementary Table 3. Characteristics of the 39 multisite chronic pain associated instruments.

SNP	A1	A2	EAF	Beta	SE	P-value	Confounder
9:140251458_g_a	G	A	0.123	-0.0277	0.0037	5.30E-14	
rs10259354	G	A	0.2983	0.0147	0.0026	3.00E-08	
rs10888692	C	G	0.4301	-0.0143	0.0025	5.30E-09	
rs10992729	C	T	0.3344	0.0158	0.0026	1.10E-09	
rs11079993	G	T	0.3825	-0.0173	0.0025	5.70E-12	
rs11599236	T	C	0.4058	0.0138	0.0025	3.30E-08	Depressed affect, Feeling miserable, Neuroticism, Educational attainment
rs11751591	G	A	0.1516	0.0214	0.0034	2.70E-10	
rs11786084	G	A	0.3328	-0.0145	0.0026	2.30E-08	
rs11871043	T	C	0.4213	0.0149	0.0025	1.70E-09	
rs12071912	C	T	0.3163	-0.0153	0.0026	5.30E-09	
rs12435797	G	T	0.1859	-0.0173	0.0031	3.70E-08	
rs12537376	A	G	0.3969	0.0151	0.0025	1.70E-09	
rs12765185	T	A	0.2669	-0.0151	0.0027	3.90E-08	Educational attainment
rs13135092	A	G	0.08071	-0.0328	0.0044	1.50E-13	HDL cholesterol levels, white blood cell count, Insomnia, Alcohol use disorder, Age of smoking initiation
rs13136239	G	A	0.3508	0.0141	0.0026	3.60E-08	Borderline personality disorder
rs1443914	T	C	0.475	0.0162	0.0024	2.80E-11	
rs17474406	G	A	0.01805	-0.0492	0.0088	2.40E-08	
rs1946247	T	G	0.1389	-0.019	0.0035	4.90E-08	
rs197422	C	A	0.3794	-0.015	0.0025	2.00E-09	
rs1976423	A	C	0.4968	-0.014	0.0024	8.20E-09	
rs2006281	C	T	0.4981	0.0135	0.0024	3.40E-08	
rs2183271	T	C	0.3578	-0.014	0.0025	3.10E-08	Educational attainment (MTAG)
rs2386584	T	G	0.3835	-0.0166	0.0025	2.80E-11	
rs2424248	G	A	0.1255	0.023	0.0037	3.70E-10	
rs28428925	G	A	0.1365	-0.0214	0.0035	1.40E-09	
rs285026	G	T	0.4297	-0.0138	0.0025	1.90E-08	
rs34811474	G	A	0.2285	0.0192	0.0029	2.70E-11	Lung function (FVC), General cognitive ability, Intelligence, Educational attainment, Body mass index, Osteoarthritis
rs4852567	A	G	0.2834	0.0149	0.0027	4.30E-08	
rs59898460	T	C	0.4044	0.0169	0.0025	9.20E-12	
rs61883178	C	A	0.1696	-0.0208	0.0033	2.00E-10	
rs62098013	G	A	0.3631	-0.0169	0.0026	4.00E-11	Smoking initiation
rs6478241	A	G	0.365	0.0149	0.0025	3.10E-09	Migraine without aura
rs6770476	C	T	0.289	-0.0154	0.0027	9.40E-09	Neuroticism
rs6869446	T	C	0.3861	-0.0144	0.0025	9.50E-09	
rs6907508	A	G	0.1146	-0.0217	0.0038	1.10E-08	HDL cholesterol levels x alcohol consumption
rs6926377	A	C	0.294	-0.0155	0.0027	7.90E-09	
rs6966540	T	C	0.3762	-0.0139	0.0025	3.30E-08	Heel bone mineral density
rs7628207	T	C	0.1766	0.0195	0.0032	8.40E-10	
rs7798894	A	T	0.2888	0.0153	0.0027	1.60E-08	

SNP: single nucleotide polymorphism; A1: effect allele; A2: other allele; EAF: effect allele frequency.

Supplementary Table 4. Information and source of GWAS data used for analyses.

Analysis	Traits	Consortium	Participants	Web source	Inclusion criteria
Main analysis	Major depressive disorder	UK Biobank, 23andMe and Psychiatric Genomics Consortium (**main analysis**)	807,553 individuals of European ancestry (246,363 cases and 561,190 controls), of which 361,315 individuals (127,552 cases and 233,763 controls) were from UK Biobank	https://datashare.is.ed.ac.uk/handle/10283/3203	1) In UK biobank, case and control status were defined based on the response to the question "Have you ever seen a general practitioner / psychiatrist for nerves, anxiety, tension or depression?", and individuals were excluded if self-reporting bipolar disorder, schizophrenia, personality disorder or taking antipsychotic medications. 2) In 23andMe, MDD was defined based on responses to web-based surveys, with individuals that self-reported as having received a clinical diagnosis or treatment for depression classified as cases. 3) In PGC, case and control status were defined based on clinically-derived phenotypes for MDD.
	Headache	UK Biobank	224,073 individuals of European ancestry (74,761 cases and 149,312 controls)	https://figshare.com/articles/fourpainphenotypes1/7699556 https://figshare.com/articles/fourpainphenotype2/7699583	Localized pain were defined based 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. Cases were those who selected the specific pain site option for the above question, regardless of whether they had selected other options. Controls were those who selected the "none of the above" option.
	Facial pain		151,922 individuals of European ancestry (2,610 cases and 149,312 controls)		
	Neck / shoulder pain		203,306 individuals of European ancestry (53,994 cases and 149,312 controls)		
	Stomach / abdominal pain		157,529 individuals of European ancestry (8,217 cases and 149,312 controls)		
	Back pain		193,303 individuals of European ancestry (4,3991 cases and 149,312 controls)		
	Hip pain		159,428 individuals of European ancestry (10,116 cases and 149,312 controls)		
	Knee pain		171,516 individuals of European ancestry (22,204 cases and 149,312 controls)		
	Multisite chronic pain		387,649 individuals of European ancestry	http://dx.doi.org/10.5525/gla.researchdata.822	Phenotype were the number of sites with chronic pain (0 to 7 sites), which was defined relying on the above pain question plus one question "whether this pain had lasted for 3 months or longer". Those who answered that they had chronic pain "all over the body" were excluded as there is some evidence that this phenotype relating to widespread pain can be substantially different from more localized chronic pain.
Sensitivity analysis	BMI	UK Biobank, GIANT consortium	~700,000 participants of European ancestry	https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	
	Education	Social Science Genetic Association Consortium	1,131,881 individuals of European ancestry	www.thessgac.org/data.	
	Exercise	UK Biobank	91,105 participants of European ancestry	http://biobank.ctsu.ox.ac.uk/crystal/docs.cgi?id=1	
	Smoking	GWAS & Sequencing Consortium of Alcohol and Nicotine	1.2 million individuals of European ancestry	https://genome.psych.umn.edu/index.php/GSCAN	
	Alcohol consumption				
	Major depressive disorder	Psychiatric Genomics Consortium, deCODE, GenScotland, GERA, iPSYCH, UK Biobank and 23andMe (**sensitivity analysis**)	480,395 individuals of European ancestry (135,458 cases and 344,901 controls), of which 29,740 individuals (14,260 cases and15,480 controls) were from UK biobank	https://www.nature.com/articles/s41588-018-0090-3	For majority of the cohorts included in this GWAS, cases were individuals clinically-diagnosed with MDD, while those with other psychiatric disorders, such as bipolar disorder and non-affective psychosis, were excluded from the cases and controls.

Supplementary Table 5. Sensitivity analysis using 44 depression associated instruments from a GWAS with minimal sample overlap with UK biobank.

Methods	#SNP	OR (95%CI)	P-value	P-value for intercept / heterogeneity
Multisite chronic pain				
Inverse variance weighted	36	1.13 (1.08-1.18)	**4.25E-07**	1.46E-08
MR Egger	36	0.98 (0.70-1.36)	0.88	0.40
Weighted median	36	1.10 (1.05-1.16)	**2.18E-05**	
Headache				
Inverse variance weighted	34	1.04 (1.02-1.07)	**6.40E-05**	4.61E-03
MR Egger	34	0.98 (0.85-1.14)	0.82	0.43
Weighted median	34	1.04 (1.02-1.07)	**7.97E-04**	
Neck / shoulder pain				
Inverse variance weighted	36	1.04 (1.02-1.07)	**3.43E-05**	3.75E-03
MR Egger	36	0.97 (0.84-1.12)	0.66	0.31
Weighted median	36	1.04 (1.02-1.07)	**5.58E-04**	
Back pain				
Inverse variance weighted	34	1.03 (1.01-1.05)	**2.38E-03**	4.41E-03
MR Egger	34	1.00 (0.86-1.15)	0.95	0.63
Weighted median	34	1.02 (1.00-1.05)	0.09	
Abdominal / stomach pain				
Inverse variance weighted	36	1.02 (1.01-1.03)	**8.31E-05**	0.17
MR Egger	36	1.07 (1.00-1.15)	0.05	0.15
Weighted median	36	1.02 (1.00-1.03)	0.01	
Facial pain				
Inverse variance weighted	36	1.00 (0.99-1.01)	0.81	0.08
MR Egger	36	1.00 (0.96-1.05)	0.87	0.84
Weighted median	36	1.00 (1.00-1.01)	0.38	
Hip pain				
Inverse variance weighted	30	1.01 (1.00-1.02)	0.17	0.63
MR Egger	30	1.01 (0.93-1.09)	0.90	0.95
Weighted median	30	1.00 (0.99-1.02)	0.57	
Knee pain				
Inverse variance	36	1.00 (0.98-1.01)	0.76	0.02

weighted				
MR Egger	36	1.09 (0.97-1.22)	0.14	0.13
Weighted median	36	0.99 (0.98-1.01)	0.53	

IVW: inverse-variance weighted approach; OR: odds ratio; CI: confidence interval

Supplementary Table 6. Multivariable Mendelian randomization adjusting for traits likely to confound the depression-pain relationship.

Methods	# SNP	OR (95%CI)	P-value	P-value for intercept / heterogeneity	# SNP	OR (95%CI)	P-value	P-value for intercept / heterogeneity	# SNP	OR (95%CI)	P-value	P-value for intercept / heterogeneity	# SNP	OR (95%CI)	P-value	P-value for intercept / heteroge neity	# SNP	OR (95%CI)	P-value	P-value for intercept / heteroge neity
	BMI				SMOKING				EDUCATION				PHYSICAL ACTIVITY				ALCOHOL CONSUMPTION			
Headache																				
IVW	670	1.00 (0.99-1.01)	0.91	**< 0.001**	374	**1.03 (1.02-1.05)**	**2.1×10^{-6}**	**< 0.001**	1258	**0.90 (0.89-0.91)**	**1.7×10^{-74}**	**< 0.001**	10	1.00 (0.99-1.02)	0.59	**< 0.001**	98	**0.93 (0.90-0.96)**	**3.9×10^{-5}**	**< 0.001**
MR-Egger	670	**0.93 (0.90-0.96)**	**2.1×10^{-6}**	< 0.001	374	0.99 (0.94-1.04)	0.70	0.12	1258	**0.88 (0.85-0.92)**	**9.1×10^{-11}**	0.17	10	1.00 (0.98-1.03)	0.73	0.90	98	**0.88 (0.82-0.94)**	**1.6×10^{-4}**	0.05
Weighted median	670	0.99 (0.97-1.00)	0.04		374	**1.03 (1.01-1.04)**	**7.0×10^{-5}**		1258	**0.91 (0.90-0.92)**	**2.8×10^{-51}**		10	1.00 (0.99-1.003)	0.28		98	**0.90 (0.86-0.94)**	**3.7×10^{-6}**	
Neck / shoulder pain																				
IVW	670	**1.02 (1.01-1.03)**	**1.4×10^{-3}**	**< 0.001**	372	**1.06 (1.04-1.07)**	**1.3×10^{-23}**	**< 0.001**	1267	**0.89 (0.88-0.90)**	**3.8×10^{-114}**	**< 0.001**	13	1.00 (0.99-1.01)	0.19	0.07	96	1.02 (0.98-1.05)	0.29	**< 0.001**
MR-Egger	670	0.98 (0.96-1.01)	0.21	0.01	372	1.02 (0.97-1.06)	0.51	0.07	1267	**0.88 (0.85-0.91)**	**4.2×10^{-13}**	0.37	13	1.00 (0.99-1.01)	0.37	0.85	96	0.94 (0.86-1.03)	0.21	0.08
Weighted median	670	1.01 (0.99-1.02)	0.42		372	**1.05 (1.04-1.07)**	**1.1×10^{-13}**		1267	**0.90 (0.88-0.91)**	**4.1×10^{-71}**		13	1.00 (0.99-1.01)	0.26		96	1.03 (0.99-1.08)	0.19	
Back pain																				
IVW	670	1.01 (1.00-1.02)	0.02	< 0.001	364	**1.04 (1.03-1.05)**	**1.4×10^{-16}**	**< 0.001**	1254	**0.92 (0.916-0.93)**	**2.2×10^{-75}**	**< 0.001**	10	1.00 (0.99-1.01)	0.07	0.92	94	1.03 (0.99-1.06)	0.06	**0.005**
MR-Egger	670	0.99 (0.97-1.01)	0.45	0.09	364	1.02 (0.98-1.07)	0.26	0.37	1254	**0.94 (0.92-0.97)**	**1.2×10^{-4}**	0.15	10	1.00 (0.99-1.01)	0.97	0.55	94	0.99 (0.91-1.09)	0.90	0.39
Weighted median	670	1.00 (0.99-1.01)	0.83		364	**1.04 (1.03-1.05)**	**1.1×10^{-9}**		1254	**0.92 (0.91-0.94)**	**1.3×10^{-38}**		10	1.00 (0.99-1.01)	0.54		94	1.02 (0.97-1.06)	0.42	
Abdominal / stomach pain																				
IVW	670	1.00 (0.99-1.01)	0.16	**0.002**	372	**1.01 (1.00-1.02)**	**7.8×10^{-6}**	< 0.001	1267	**0.98 (0.97-0.99)**	**1.6×10^{-10}**	**0.003**	13	1.00 (0.99-1.004)	0.72	0.04	96	1.00 (0.99-1.02)	0.63	0.11
MR-Egger	670	0.99 (0.98-1.01)	0.28	0.09	372	0.99 (0.97-1.01)	0.45	0.06	1267	0.99 (0.99-1.01)	0.53	0.21	13	1.00 (0.99-1.005)	0.68	0.44	96	0.94 (0.90-0.99)	0.01	0.004
Weighted median	670	1.00 (0.99-1.01)	0.68		372	**1.01 (1.00-1.02)**	**4.0×10^{-3}**		1267	**0.99 (0.98-0.995)**	**1.5×10^{-3}**		13	1.00 (0.99-1.004)	0.86		96	1.00 (0.97-1.02)	0.78	
Facial pain																				
IVW	670	1.00 (0.99-1.01)	0.76	0.24	372	**1.004 (1.001-1.007)**	**0.005**	< 0.07	1267	**0.994 (0.991-0.997)**	**2.0×10^{-3}**	**< 0.001**	13	1.00 (0.99-1.002)	0.71	0.32	96	0.99 (0.98-1.004)	0.27	0.23
MR-Egger	670	1.00 (0.99-1.01)	0.55	0.44	372	1.01 (0.99-1.02)	0.43	0.90	1267	1.00 (0.99-1.01)	0.55	0.63	13	1.00 (0.99-1.001)	9.34	0.14	96	0.98 (0.96-1.01)	0.15	0.27
Weighted median	670	1.00 (0.99-1.01)	0.87		372	1.00 (1.00-1.01)	0.04		1267	**0.99 (0.98-1.00)**	**0.009**		13	1.00 (0.99-1.002)	0.63		96	0.99 (0.98-1.01)	0.28	
Hip pain																				
IVW	670	1.005 (1.00-1.01)	0.03	0.18	372	**1.01 (1.006-1.02)**	**2.4×10^{-5}**	**0.08**	1267	**0.98 (0.97-0.99)**	**2.7×10^{-12}**	0.17	13	1.00 (0.99-1.005)	0.93	**< 0.001**	96	1.00 (0.98-1.02)	0.99	0.18
MR-Egger	670	1.01 (0.99-1.02)	0.31	0.83	372	1.01 (0.99-1.04)	0.23	0.79	1267	0.98 (0.97-1.00)	0.06	0.91	13	1.00 (0.99-1.01)	0.36	0.22	96	0.99 (0.95-1.04)	0.83	0.81
Weighted median	670	1.01 (0.99-1.02)	0.08		372	1.01 (1.00-1.02)	0.02		1267	**0.98 (0.97-0.99)**	**6.3×10^{-7}**		13	1.00 (0.99-1.004)	0.87		96	1.01 (0.98-1.04)	0.54	
Knee pain																				
IVW	670	1.00 (0.99-1.01)	0.87	**< 0.001**	372	**1.01 (1.00-1.02)**	**1.4×10^{-4}**	**< 0.001**	1267	**0.97 (0.96-0.98)**	**5.0×10^{-19}**	**< 0.001**	13	1.00 (0.995-1.004)	0.97	0.31	96	**1.03 (1.01-1.05)**	**0.04**	0.07
MR-Egger	670	0.99 (0.97-1.01)	0.46	0.46	372	1.02 (0.98-1.05)	0.35	0.99	1267	**0.95 (0.93-0.98)**	**1.7×10^{-4}**	0.20	13	1.00 (0.993-1.007)	0.99	1.00	96	0.98 (0.92-1.05)	0.62	0.18
Weighted median	670	1.00 (0.99-1.01)	0.57		372	1.01 (0.99-1.02)	0.17		1267	**0.97 (0.96-0.98)**	**8.2×10^{-12}**		13	1.00 (0.99-1.002)	0.40		96	1.03 (0.99-1.07)	0.14	

IVW: inverse-variance weighted approach; OR: odds ratio; CI: confidence interval

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