Supplementary Information

Supplementary Table 1 Detailed information on the field identification and codes for participants included in the United Kingdom Biobank. ICD-10, the International Classification of Diseases, 10th Revisions; ICD-9, the International Classification of Diseases, 9th Revision.

Supplementary Table 2 The International Classification of Diseases (ICD) codes and self-reported codes for excluded diseases.

Supplementary Table 3 The prevalence of fracture in male, female and pooled samples with or without major depressive disorder (MDD) and the prevalence of MDD in male, female and pooled samples with or without fracture.

Supplementary Table 4 The prevalence of fracture in different age groups with or without major depressive disorder (MDD) and the prevalence of MDD in different age groups with or without fracture.

Supplementary Table 5 The information of 74 lead single nucleotide polymorphisms (SNPs) for major depressive disorder (MDD) with the risk of fracture.

Supplementary Table 6 Baseline characteristics of participants and comparison between individuals with and without major depressive disorder (MDD) and fracture. BMD, bone mineral density; BMI, body mass index.

Supplementary Table 7 The results of genetic correlation and cross-trait analysis beween major depressive disorder (MDD) and fracture. rg = genetic correlation, se = standard error of rg, P value= p-value for rg, gcov_int, gcov_int_se = cross-trait LD Score regression intercept and standard error. nc1@p9, nc2@p9, and nc12@p9 = the number of causal variants for trait1, trait2 and both, respectively; nc@p9 = number of trait-influencing variants specific to MDD; rho_beta = the correlation of effect sizes within the shared polygenic component; rg = genetic correlation; concordant_fraction = the proportion of shared variants with concordant direction of effect in both traits on all shared variants; $\pi 1$, $\pi 2$, and $\pi 12$ = polygenicity of trait1, trait2 and both, respectively.

Supplementary Table 8 Distinct genomic loci shared between major depressive disorder (MDD) and fracture at conjunctional false discovery rate (conjFDR) < 0.05.

Supplementary Table 9 The results of Summary-data-based Mendelian Randomization (SMR) analyses for the expression of *SGIP1* (ENSG00000118473)

with major depressive disorder (MDD) and fracture in spinal cord (cervical) and muscle (gastrocnemius).

Supplementary Table 10 The general biological functions of 53 genes.

Supplementary Fig.1 The matching information of 39 965 patients with fracture.

Supplementary Fig.2 The prevalence rate in different age groups. Panel A: the prevalence rate for fracture with or without major depressive disorder (MDD). Panel B: the prevalence rate for MDD with or without fracture.

Supplementary Fig.3 The association of genetically predicted major depressive disorder (MDD) with fracture and vice versa in male and female.

Supplementary Fig.4 The annotation of genetic associations with Functional mapping and annotation (FUMA). Panel A: the result of genome-wide association study (GWAS) catalog reported genes. Panel B: Multi-marker Analysis of GenoMic Annotation (MAGMA) tissue expression analysis results. Per-tissue enrichment of expression of genes based on Genotype-Tissue Expression (GTEx) RNA-seq data for left 30 general and right 54 specific tissue types.

Supplementary Fig.5 A simple illustration of the assumptive mechanism: the potential implication of the *SGIP1* gene in the pathology of major depressive disorder (MDD) and fracture.

Supplementary Table 1 Detailed information on the field identification and codes for participants included in UK Biobank.

Description	Field IDs	Codes
Depression *	41270	F320, F321, F322, F323, F328, F329, F330, F331, F332, F333, F334, F338, F339
Depression †	41203	296.1, 300.4, 311 M484, M4840, M4842, M4844, M4845, M4846, M4847, M4848, M4849; M84, M840, M8400, M8401, M8402, M8403, M8404, M8405, M8406, M8407, M8408, M841, M8410, M8411, M8412, M8413, M8414, M8415, M8416, M8417, M8418, M8419, M842, M8421, M8422, M8423, M8424, M8425, M8426, M8427, M8428, M843, M8430, M8435, M8436, M8437, M8438, M8439, S02, S020, S0200, S0201, S021, S0210, S0211, S022, S0220, S0221, S023, S0230, S0231, S024, S0240, S0241, S025, S0250, S0251, S026, S0260, S0261, S027, S0270, S0271, S028, S0280, S0281, S029, S0290, S0291, S12, S120, S1200, S121, S1210, S122, S1220, S127, S1270, S128, S1280, S1281, S129, S1290, S1291, S22, S220, S2200, S221, S2210, S222, S2220, S223, S2230, S2231, S224, S2241, S225, S2250, S2251, S228, S2280, S229, S2290, S32, S320, S3200, S321, S3210, S3211, S322, S3220, S323, S3230, S3231, S324, S3240, S3241, S325, S3250, S3251, S327, S3270, S3271, S328, S3280, S3281, S42, S420, S4200, S4201, S421, S4210, S422, S4220, S4221, S423, S4230, S4231, S424, S4240, S4241, S427, S4270, S4271, S428, S4280, S429, S4290, S52, S520, S5200, S5201, S521, S5210, S5211, S522, S5220, S5221, S523, S5230, S5231, S524, S5240, S5241, S525, S5250, S5251, S526, S5260, S5261, S527, S5270, S5271, S528, S5280, S5281, S529, S5290, S62, S620, S6200, S621, S6210, S6211, S622, S6220, S6221, S623, S6230, S6231, S624, S6240, S6241, S625, S6250, S6251, S626, S6261, S627, S6270, S6271, S628, S6280, S6281, S72, S720, S7200, S7201, S721, S7210, S7211, S722, S7220, S7221, S723, S72230, S7231, S724, S7240, S7241, S727, S7270, S728, S7280, S729, S7290, S7291, S82, S820, S8200, S8201, S821, S8210, S8211, S822, S8220, S8221, S823, S8231, S824, S8240, S8241, S825, S8250, S8251, S826, S8260, S8261, S827, S8270, S8271, S828, S8280, S8281, S8286, S829, S8290, S8291, S92, S920, S9200, S9201, S921, S9210, S9211, S922, S9220, S9221, S923, S9230, S9231, S924, S9240, S9241, S925, S9250, S9251, S927, S9270, S9271, S929, S9290, S9291; T02, T020, T0200, T021, T0210, T022, T0220, T023, T0230, T0231, T024, T0240, T0241, T025, T0250, T0251, T026, T0260, T027, T0270, T028, T0280, T029, T0290; T08, T08X0, T10, T10X0, T12, T142, T1420; T902,
Fracture*	41270	T911, T912, T921, T922, T931, T932, X5909, Z544

Fracture†	41203	7338, 73381, 73382, 73383, 73384, 73385, 73386, 73387, 73388, 73389; 800, 8000, 8001, 8002, 8003, 801, 8010, 8011, 802, 8020, 8022, 8023, 8024, 8026, 8028, 803, 8030, 8031; 805, 8050, 8052, 8054, 8056, 8058; 806, 8064, 807, 8070, 8072, 8074, 808, 8080, 8082, 8084, 8088, 8089, 809, 8090, 8091;810, 8100, 811, 8110, 812, 8120, 8121, 8122, 8123, 8124, 8125, 813, 8130, 8131, 8132, 8134, 8135, 814,8140, 8141, 815, 8150, 8151, 816, 8160, 8161, 817, 8170; 820, 8200, 8202, 8208, 8210, 8211, 8212; 822, 8220, 8221; 823, 8230, 8231, 8232, 8233, 8240, 8241, 8242, 8244, 8245, 8246, 8247, 8248, 8249, 825, 8250, 8252, 8253, 826, 8260, 8261, 828, 8280, 829, 8290; 905, 9050, 9052, 9053, 9054
Age when attended assessment centre	21003	\
Sex	31	\
Body mass index	21001	\
Smoking status	20116	\
Alcohol consumption frequency	1558	\
Ethnic background	21000	1001, 1002, 1003, 1
Kinship	22021	0
Employment status	6142	\
Education	6138	\
Heel bone mineral density	4105, 3148, 3084	\
Falls in the last year	2296	\
Physical activity	884, 894, 904, 914	\
Cannabis	20453	\
Medication treatments	20003	1140921600, 1141180212, 1140879540, 1140879544, 1140867888, 1140867878, 1141201834, 1140867658, 1140867712, 1140867940, 1140867942, 1140882312, 1140867858, 1140867852, 1140867916
Date of attending assessment center	53	\
Date lost to follow-up	191	\
Date of death	40000	\
Year when the non-cancer illness first diagnosed	20008	\
Date of first in-patient diagnosis based on ICD-9	41263	\
Date of first in-patient diagnosis based on ICD-10	41280	\

Mental and behavioural disorders due to substance misuse*	41270	F10, F100, F101, F102, F103, F104, F105, F106, F107, F108, F109, F11, F110, F111, F112, F113, F114, F115, F117, F119, F12, F120, F121, F122, F123, F125, F128, F129, F13, F130, F131, F132, F133, F134, F139, F14, F140, F141, F142, F145, F149, F15, F150, F151, F152, F153, F155, F158, F159, F16, F161, F162, F163, F165, F167, F168, F169, F17, F170, F171, F172, F173, F174, F177, F179, F18, F181, F182, F185, F189, F19, F190, F191, F192, F193, F194, F195, F198, F199
Schizophrenia, schizotypal and delusional disorders*	41270	F20, F200, F201, F202, F203, F204, F205, F206, F208, F209, F21, F22, F220, F228, F229, F23, F230, F231, F232, F233, F238, F239, F24, F25, F250, F251, F252, F258, F259, F28, F29
Anxiety disorders*	41270	F40, F400, F401, F402, F408, F409, F41, F410, F411, F412, F413, F418, F419
Reaction to severe stress, and adjustment disorders*	41270	F43,F430, F431, F432, F438, F439
Anxiety states†	41203	3000
stress-related disorder†	41203	308, 3089
substance misuse†	41203	291, 2910, 2918, 303, 3039, 305, 3050, 3051, 3059
psychotic disorders†	41203	295, 2953, 2959, 296, 2961, 298, 2982, 2988, 2989

*ICD-10, the International Classification of Diseases, 10th Revisions, †ICD-9, the International Classification of Diseases, 9th Revision.

Supplementary Table 2 The International Classification of Diseases (ICD) codes and self-reported codes for excluded diseases.

Diseases	Field IDs	Codes
Fracture of bone in neoplastic disease	41270	M907, M9070, M9071, M9072, M9073, M9074, M9075, M9076, M9077, M9078, M9079
Follow-up care involving removal of fracture plate and other internal fixation devices	41270	Z470
	41203	7331, 73313, 73315, 73316
Pathological fracture	41270	M800, M8000, M8001, M8003, M8007, M8008, M801, M8010, M802, M8021, M8028, M804, M8040, M8041, M8046, M8048, M8049, M805, M8050, M8052, M8053, M8055, M8058, M808, M8080, M8081, M8082, M8086, M8088, M8089, M809, M8090, M8091, M8092, M8093, M8094, M8095, M8096, M8097, M8098, M8099, M844, M8440, M8441, M8442, M8443, M8444, M8445, M8446, M8447, M8448, M8449
	20002	1464
Rheumatoid arthritis	41270	M0530, M0531, M0532, M0533, M0534, M0535, M0536, M0537, M0538, M0539, M0580, M0581, M0582, M0583, M0584, M0585, M0586, M058, M0588, M0589, M0590, M0591, M0592, M0593, M0594, M0595, M0596, M0597, M0598, M0599, M0600, M0601, M0602, M0603, M0604, M0605, M0606, M0607, M0608, M0609, M0680, M0681, M0682, M0683, M0684, M0685, M0686, M0687, M0688, M0689, M0690, M0691, M0692, M0693, M0694, M0695, M0696, M0697, M0698, M0699, M0800, M0801, M0802, M0804, M080, M0806, M0807, M0808, M0809
	41203	71400, 71401, 71402, 71403, 71404, 71405, 71406, 71407, 71408, 71409, 71423, 71424
Ulcerative colitis	20002	1463
	41270	K518, K519, M0750, M0751, M0752, M0753, M0754, M0755, M0756, M0757, M0758, M0759, M0920, M0921, M0922, M0923, M0924, M0925, M0926, M0927, M0928, M0929
Multiple sclerosis	20002	1261
	41270	G35
	41203	3409
Crohn's disease	20002	1462
	41270	K50, K500, K501, K508, K509, M074, M0740, M0741, M0742, M0743, M0744, M0745, M0746, M0747, M0748, M0749, M091, M0910, M0911, M0912, M0913, M0914, M0915, M0916, M0917, M0918, M0919
Hyperthyroidism	20002	1225

Lupus erythematosus	41270	E050, E051, E052, E053,,E058, E059, E062
	41203	2424, 2428, 2429, 7753
	41270	L930, L931, L932, M320, M321, M328, M329, M3290
	41203	6954, 7100

Supplementary Table 3 The prevalence of fracture in male, female and pooled samples with or without MDD and the prevalence of MDD in male, female and pooled samples with or without fracture.

		Non-fracture	Fracture	Sum	Prevalence #	P value*		Non-depression	Depression	Sum	Prevalence +	P value*
Female	Depression	4826	1468	6294	23.32%	<0.001	Fracture	20756	1752	22508	7.78%	<0.001
	Non-depression	206113	17542	223655	7.84%		Non-fracture	215446	8785	224231	3.92%	
Male	Depression	3152	754	3906	19.30%	<0.001	Fracture	14564	957	15521	6.17%	<0.001
	Non-depression	182926	12906	195832	6.59%		Non-fracture	184726	5002	189728	2.64%	
Male+Female	Depression	7978	2222	10200	21.78%	<0.001	Fracture	35320	2709	38029	7.12%	<0.001
	Non-depression	389039	30448	419487	7.26%		Non-fracture	400172	13787	413959	3.33%	
Total		397017	32670	429687	7.60%			435492	16496	451988	3.65%	

The prevalence of fracture in samples with or without depression
+ The prevalence of depression in samples with or without fracture
* Chi-square test of the prevalence difference between depression group and non-depression group and the prevalence difference between fracture group and non-fracture group in male, female and pooled samples

Supplementary Table 4 The prevalence of fracture in different age groups with or without MDD and the prevalence of MDD in different age groups with or without fracture.

Age		Non-Fracture	Fracture	Sum	Prevalence#	P value*		Non-depression	Depression	Sum	Prevalence+	P value*
≤44	Depression	724	157	881	17.82%	< 0.001	Fracture	2497	219	2716	8.06%	< 0.001
	Non-depression	39251	2189	41440	5.28%		Non-Fracture	40357	1517	41874	3.62%	
45-59	Depression	3722	977	4699	20.79%	< 0.001	Fracture	14063	1181	15244	7.75%	< 0.001
	Non-depression	181092	12189	193281	6.31%		Non-Fracture	187071	6574	193645	3.39%	
≥60	Depression	3532	1088	4620	23.55%	< 0.001	Fracture	18760	1309	20069	6.52%	< 0.001
	Non-depression	168696	16070	184766	8.70%		Non-Fracture	172744	5696	178440	3.19%	
Total		397017	32670	429687	7.60%			435492	16496	451988	3.65%	

The prevalence of fracture in samples with or without depression
+ The prevalence of depression in samples with or without fracture
* Chi-square test of the prevalence difference between depression group and non-depression group and the prevalence difference between fracture group and non-fracture group in male, female and pooled samples

Supplementary Table 5 The information of 74 lead SNPs for MDD with the risk of fracture.

CHR	BP	SNP	A1	A2	beta_MDD	P_MDD	SE_MDD	beta_fracture	P_fracture	SE_fracture
1	18122009	rs4141983	t	c	0.03	<0.001	0.00	0.00	0.870	0.01
1	49803103	rs35466861	a	g	0.05	<0.001	0.01	0.00	0.880	0.01
1	50559162	rs11579246	a	g	0.05	<0.001	0.01	0.00	0.840	0.01
1	52274078	rs7551758	t	g	-0.03	<0.001	0.00	0.00	0.970	0.01
1	67083671	rs6656912	t	c	-0.03	<0.001	0.00	-0.03	<0.001	0.01
1	72765116	rs2568958	a	g	0.04	<0.001	0.00	0.00	0.930	0.01
1	73664022	rs6424532	a	g	0.03	<0.001	0.00	0.02	0.005	0.01
1	175913828	rs10913112	t	c	-0.03	<0.001	0.00	0.00	0.690	0.01
1	197704717	rs17641524	t	c	-0.03	<0.001	0.01	-0.01	0.160	0.01
2	208049581	rs2111592	a	g	0.03	<0.001	0.00	0.00	0.830	0.01
2	212618440	rs72948506	a	g	0.03	<0.001	0.00	0.00	0.930	0.01
3	49214303	rs9831648	t	g	-0.03	<0.001	0.01	-0.02	0.045	0.01
3	49798864	rs7621797	a	g	0.03	<0.001	0.01	0.02	0.072	0.01
3	61255413	rs843812	a	g	0.02	<0.001	0.00	-0.01	0.270	0.01
3	115977242	rs76954012	a	t	0.04	<0.001	0.01	0.01	0.570	0.01
3	117515519	rs66511648	t	c	-0.03	<0.001	0.00	0.01	0.260	0.01
3	158171455	rs12631196	a	g	0.02	<0.001	0.00	0.00	0.950	0.01
5	87545318	rs3099439	t	c	-0.02	<0.001	0.00	0.00	0.630	0.01
5	103972357	rs30266	a	g	0.04	<0.001	0.00	0.02	0.004	0.01
5	164487555	rs7725715	a	g	0.03	<0.001	0.00	0.00	0.940	0.01
6	25710571	rs68006638	a	g	-0.04	<0.001	0.01	0.01	0.480	0.01
6	26599509	rs45527431	a	g	0.05	<0.001	0.01	-0.01	0.590	0.01
6	26668216	rs62396201	a	g	0.02	<0.001	0.00	0.00	0.560	0.01

6	27197931	rs55658856	a	g	-0.08	<0.001	0.01	-0.02	0.300	0.02
6	27274834	rs56114371	t	c	-0.05	<0.001	0.01	0.00	0.660	0.01
6	27384520	rs6929812	t	c	-0.03	<0.001	0.00	-0.01	0.190	0.01
6	27775674	rs200484	a	g	0.05	<0.001	0.01	0.01	0.340	0.01
6	28326431	rs116406755	a	g	0.04	<0.001	0.01	0.02	0.110	0.01
6	28366151	rs2232423	a	g	0.06	<0.001	0.01	0.00	0.780	0.01
6	28828010	rs116380322	t	c	-0.06	<0.001	0.01	-0.02	0.150	0.01
6	29725013	rs115938232	a	g	-0.06	<0.001	0.01	0.01	0.570	0.01
6	31102618	rs3130566	c	g	0.04	<0.001	0.01	0.00	0.620	0.01
6	31840477	rs501942	t	c	-0.04	<0.001	0.01	0.00	0.920	0.01
6	32577633	rs535777	c	g	-0.04	<0.001	0.01	0.01	0.580	0.01
6	66534041	rs68170059	t	g	-0.03	<0.001	0.01	0.00	0.790	0.01
6	67000001	rs2214123	a	g	0.03	<0.001	0.00	0.00	0.820	0.01
6	142996618	rs2876520	c	g	-0.03	<0.001	0.00	0.00	0.760	0.01
6	165117329	rs9364755	a	g	-0.03	<0.001	0.01	-0.01	0.110	0.01
7	2086814	rs10235664	t	c	0.03	<0.001	0.00	0.01	0.330	0.01
7	12250402	rs3807865	a	g	0.03	<0.001	0.00	0.00	0.720	0.01
7	38724868	rs59082935	t	c	0.04	<0.001	0.01	0.02	0.130	0.01
7	82454404	rs2247523	c	g	-0.02	<0.001	0.00	0.01	0.100	0.01
7	109100414	rs4730387	a	t	0.02	<0.001	0.00	-0.01	0.073	0.01
7	117522956	rs10242758	t	g	0.03	<0.001	0.00	0.02	0.005	0.01
9	11203149	rs1931388	a	g	0.03	<0.001	0.00	0.01	0.059	0.01
9	11522951	rs958538	t	c	0.03	<0.001	0.01	0.00	0.710	0.01
9	17016503	rs263645	a	t	0.03	<0.001	0.00	-0.01	0.083	0.01
9	25235063	rs12057031	t	c	-0.04	<0.001	0.01	0.00	0.810	0.01

9	36999369	rs7030813	t	c	0.02	<0.001	0.00	-0.01	0.047	0.01
9	37182655	rs62535714	a	g	0.03	<0.001	0.01	-0.01	0.380	0.01
9	119731359	rs2418449	t	c	0.03	<0.001	0.00	-0.01	0.320	0.01
10	106551929	rs971527	t	c	0.03	<0.001	0.01	0.01	0.061	0.01
10	106610839	rs1021363	a	g	0.03	<0.001	0.00	0.01	0.140	0.01
11	61471678	rs198457	t	c	-0.03	<0.001	0.01	0.01	0.180	0.01
11	88748162	rs10501696	a	g	0.03	<0.001	0.00	0.00	0.610	0.01
11	113283459	rs6277	a	g	-0.02	<0.001	0.00	0.01	0.050	0.01
11	113365084	rs4936275	t	c	0.03	<0.001	0.00	0.00	0.970	0.01
12	52352301	rs61914045	a	g	0.03	<0.001	0.01	0.01	0.240	0.01
13	31790053	rs9529218	t	c	-0.03	<0.001	0.01	0.00	0.920	0.01
13	53860655	rs9536381	t	c	0.03	<0.001	0.00	0.00	0.920	0.01
13	80921519	rs508502	t	c	-0.03	<0.001	0.00	0.00	0.480	0.01
14	42097937	rs1950829	a	g	0.03	<0.001	0.00	-0.01	0.180	0.01
14	75125540	rs7152906	t	c	-0.03	<0.001	0.00	0.00	0.970	0.01
14	103997525	rs754287	a	t	-0.03	<0.001	0.00	-0.02	0.003	0.01
15	88945878	rs28541419	c	g	0.03	<0.001	0.01	0.00	0.590	0.01
16	13800430	rs12919291	c	g	0.03	<0.001	0.01	0.02	0.003	0.01
18	35155910	rs4799949	t	c	-0.03	<0.001	0.00	0.00	0.740	0.01
18	50776391	rs17410557	t	c	-0.03	<0.001	0.00	-0.01	0.130	0.01
18	52474170	rs8093506	a	g	0.03	<0.001	0.01	0.03	<0.001	0.01
18	52757346	rs9953930	t	c	0.03	<0.001	0.01	0.01	0.560	0.01
18	53099012	rs12967143	c	g	-0.03	<0.001	0.00	-0.01	0.370	0.01
18	53207207	rs1452787	a	g	-0.03	<0.001	0.00	0.00	0.900	0.01
18	77580712	rs7241572	a	g	0.03	<0.001	0.01	0.01	0.230	0.01

20	44692598	rs13037326	t	c	0.03	<0.001	0.00	0.00	0.650	0.01

Supplementary Table 6 Baseline characteristics of participants and comparison between individuals with and without MDD and fracture.

Baseline characteristic	Overall (N=429,687)	Whether participants with depression or not		P value	Overall (N=451,988)	Whether participants with fracture or not		P value
		NO (N=419,487)	Yes (N=10,200)			NO (N=413,959)	Yes (N=38,029)	
sex =1 (%)	199738 (46.50)	195832 (46.70)	3906 (38.30)	<0.001	205249 (45.40)	189728 (45.80)	15521 (40.80)	<0.001
Ref_Age (mean (SD))	58.82 (11.44)	58.70 (11.44)	63.62 (10.41)	<0.001	58.44 (11.38)	58.30 (11.37)	59.93 (11.43)	<0.001
BMI (mean (SD))	27.34 (4.72)	27.31 (4.68)	28.78 (5.88)	<0.001	27.36 (4.74)	27.36 (4.72)	27.31 (4.88)	0.054
Employment status =1 (%)	249462 (58.20)	245399 (58.70)	4063 (40.00)	<0.001	261371 (58.00)	242867 (58.80)	18504 (48.80)	<0.001
Education =1 (%)	352085 (83.10)	344667 (83.30)	7418 (74.20)	<0.001	369846 (83.00)	340576 (83.40)	29270 (78.40)	<0.001
Smoking =1 (%)	194302 (45.40)	188643 (45.10)	5659 (55.80)	<0.001	204948 (45.50)	186841 (45.30)	18107 (47.80)	<0.001
Alcohol =1 (%)	402021 (93.60)	393266 (93.80)	8755 (86.10)	<0.001	422282 (93.50)	387351 (93.60)	34931 (92.00)	<0.001
Medication =1 (%)	14267 (3.30)	11404 (2.70)	2863 (28.10)	<0.001	16164 (3.60)	14459 (3.50)	1705 (4.50)	<0.001
Physical activity =1 (%)	299229 (69.60)	293149 (69.90)	6080 (59.60)	<0.001	313528 (69.40)	287730 (69.50)	25798 (67.80)	<0.001
Sleep duration (mean (SD))	7.12 (1.22)	7.13 (1.20)	7.08 (1.87)	<0.001	7.12 (1.23)	7.13 (1.21)	7.07 (1.39)	<0.001
Grip strength (mean (SD))	32.14 (11.19)	32.23 (11.19)	28.39 (10.77)	<0.001	31.88 (11.26)	32.06 (11.22)	29.92 (11.54)	<0.001
Falls =1 (%)	81007 (18.90)	77570 (18.50)	3437 (33.90)	<0.001	87403 (19.40)	76506 (18.50)	10897 (28.70)	<0.001
BMD (mean (SD))	0.54 (0.14)	0.54 (0.14)	0.53 (0.14)	<0.001	0.54 (0.14)	0.55 (0.14)	0.50 (0.13)	<0.001
Cannabis =1 (%)	30938 (22.00)	30395 (22.00)	543 (24.10)	0.016	32683 (22.00)	30185 (21.90)	2498 (23.30)	0.001
Fracture =1 (%)	32670 (7.60)	30448 (7.30)	2222 (21.80)	<0.001	38029 (8.40)	0 (0.00)	38029 (100.00)	<0.001
Depression =1 (%)	10200 (2.40)	0 (0.00)	10200 (100.00)	<0.001	16496 (3.60)	13787 (3.30)	2709 (7.10)	<0.001

BMD, bone mineral density; BMI, body mass index.

Supplementary Table 7 The results of genetic correlation and cross-trait analysis between MDD and fracture.

Method	**rg**	**se**	**z**	**P value**	**h2_obs**	**h2_obs_se**	**h2_int**	**h2_int_se**	**gcov_int**	**gcov_int_se**	
linkage disequilibrium score regeression	0.21	0.03	7.09	1.36E-12	0.08	3.10E-03	0.99	0.01	0.02	0.01	
	nc1@p9, mean (std)	**nc2@p9, mean (std)**	**nc12@p9, mean (std)**	**nc@p9, mean (std)**	**rho_beta, mean (std)**	**rg, mean (std)**	**fraction_concordant_within_shared, mean (std)**	**π_1, mean (std)**	**π_2, mean (std)**	**π_{12}, mean (std)**	**dice, mean (std)**
MiXeR	11428 (579)	203 (80)	866 (94)	12294 (565)	0.96 (0.04)	0.23 (0.02)	0.92 (0.04)	4E-03 (1.82E-04)	6.37E-05 (2.50E-05)	2.71E-04 (2.94E-05)	12.97% (1.45%)

rg = genetic correlation, se = standard error of rg, P value= p-value for rg, gcov_int, gcov_int_se = cross-trait LD Score regression intercept and standard error.
nc1@p9, nc2@p9, and nc12@p9 = the number of causal variants for trait1, trait2 and both, respectively; nc@p9 = number of trait-influencing variants specific to MDD; rho_beta = the correlation of effect sizes within the shared polygenic component; rg = genetic correlation; concordant_fraction = the proportion of shared variants with concordant direction of effect in both traits on all shared variants; π_1, π_2, and π_{12} = polygenicity of trait1, trait2 and both, respectively.

Supplementary Table 8 Distinct genomic loci shared between MDD and fracture at conjunctional false discovery rate (conjFDR)<0.05.

locusnum	snpid	geneid	chrnum	chrpos	zscore_MDD	zscore_fracture	conjfdr_MDD_fracture	pval_MDD	pval_fracture
1	rs7554101	SGIP1	1	67156472	-4.99	-4.31	0.008	<0.001	<0.001
2	rs310749	PPARG	3	12273768	-3.67	3.79	0.048	<0.001	<0.001
3	rs10217595	FAM120AOS	9	96180891	4.23	4.11	0.017	<0.001	<0.001
4	rs2311117	RAB27B	18	52473793	-5.18	-3.81	0.042	<0.001	<0.001

Supplementary Table 9 The results of SMR analyses for the expression of *SGIP1* (ENSG00000118473) with MDD and fracture in spinal cord (cervical) and muscle (gastrocnemius).

Trait	Tissue	topSNP	A1	A2	Freq	b_GWAS	se_GWAS	p_GWAS	b_eQTL	se_eQTL	p_eQTL	b_SMR	se_SMR	p_SMR	p_HEIDI
MDD	spinal cord (cervical)	rs6680364	A	G	0.44	0.02	0.00	<0.001	0.45	0.08	<0.001	0.05	0.01	<0.001	0.785
Fracture	spinal cord (cervical)	rs6680364	A	G	0.44	0.02	0.01	<0.001	0.45	0.08	<0.001	0.05	0.02	0.004	0.055
MDD	muscle (gastrocnemius)	rs11208920	A	C	0.44	0.02	0.00	<0.001	0.28	0.03	<0.001	0.08	0.02	<0.001	0.090
Fracture	muscle (gastrocnemius)	rs11208920	A	C	0.44	0.02	0.01	0.001	0.28	0.03	<0.001	0.08	0.03	0.002	0.194

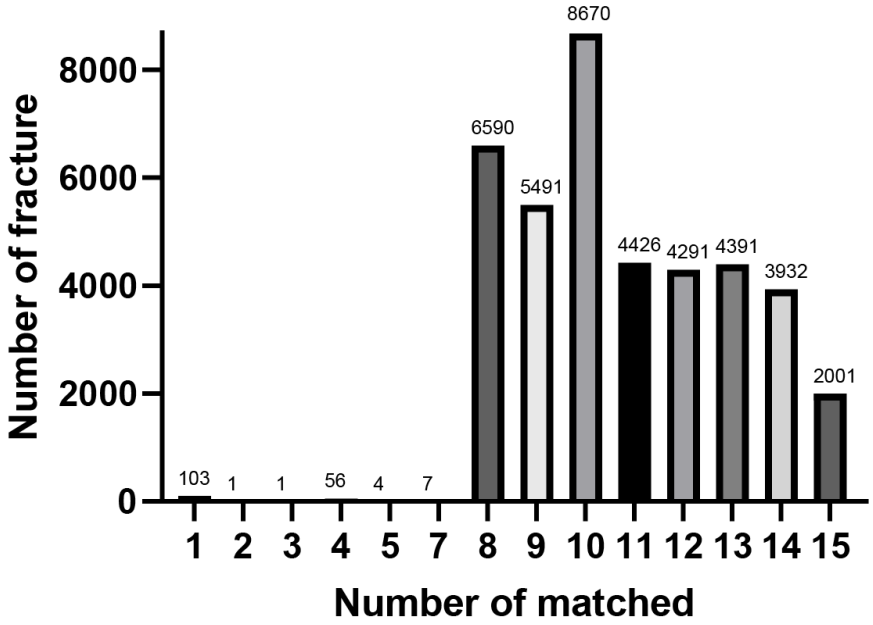
Supplementary Table 10 The general biological functions of 53 genes.

Ensg	entrezID	symbol	hgnc_symbol	OMIM	uniprotID	DrugBank
ENSG00000184588	5142	PDE4B	PDE4B	600127	Q07343	DB00131:DB00201:DB00277:DB00651:DB00806:DB00824:DB01088:DB01113:DB01412:DB01427:DB01647:DB01656:DB01791:DB01954:DB01959:DB02660:DB03349:DB03606:DB03807:DB03849:DB04149:DB04530:DB05219:DB05266:DB05676:DB06909:DB08299
ENSG00000118473	84251	SGIP1	SGIP1	611540	Q9BQI5	NA
ENSG00000152760	200132	TCTEX1D1	TCTEX1D1	NA	Q8N7M0	NA
ENSG00000152763	79819	WDR78	WDR78	NA	Q5VTH9	NA
ENSG00000198160	57708	MIER1	MIER1	616848	Q8N108	NA
ENSG00000116704	23169	SLC35D1	SLC35D1	610804	Q9NTN3	NA
ENSG00000162594	149233	IL23R	IL23R	607562	Q5VWK5	NA
ENSG00000081985	3595	IL12RB2	IL12RB2	601642	Q99665	NA
ENSG00000142864	26135	SERBP1	SERBP1	607378	Q8NC51	NA
ENSG00000116717	1647	GADD45A	GADD45A	126335	P24522	NA
ENSG00000134046	8932	MBD2	MBD2	603547	Q9UBB5	NA
ENSG00000101751	11201	POLI	POLI	605252	Q9UNA4	NA
ENSG00000166845	162681	C18orf54	C18orf54	613258	Q8IYD9	NA
ENSG00000264350	1E+08	SNRPGP2	SNRPGP2	NA	NA	NA
ENSG00000041353	5874	RAB27B	RAB27B	603869	O00194	NA
ENSG00000196628	6925	TCF4	TCF4	602272	P15884	NA
ENSG00000197548	10533	ATG7	ATG7	608760	O95352	NA
ENSG00000144560	9686	VGLL4	VGLL4	NA	Q14135	NA
ENSG00000144559	132001	TAMM41	TAMM41	614948	Q96BW9	NA
ENSG00000157152	6854	SYN2	SYN2	600755	NA	NA
ENSG00000226642	1E+08	ACTG1P12	ACTG1P12	NA	NA	NA

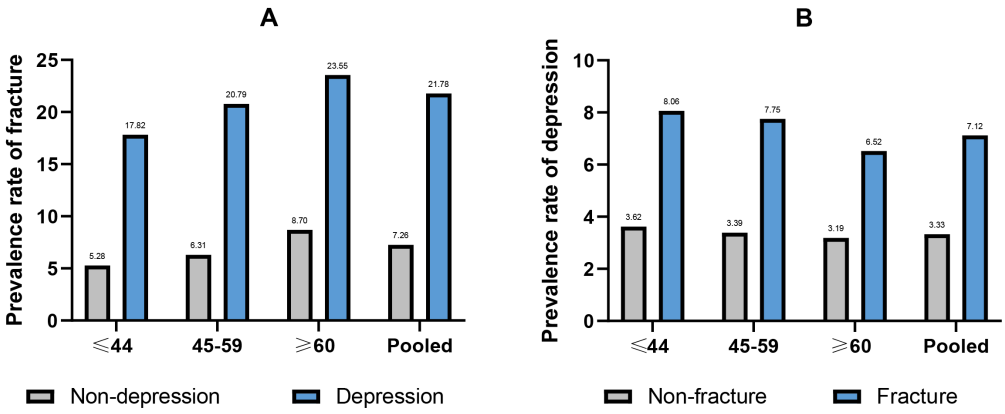
ENSG00000132170	5468	PPARG	PPARG	601487	P37231	DB00132:DB00159:DB00197:DB00244:DB00313:DB00328:DB00412:DB00573:DB00731:DB00795:DB00912:DB00966:DB01014:DB01039:DB01050:DB01067:DB01118:DB01132:DB01252:DB01393:DB02266:DB02709:DB02746:DB03600:DB03756:DB04224:DB04270:DB04689:DB04971:DB05187:DB05490:DB05854:DB06510:DB06521:DB06533:DB06536:DB06908:DB06926:DB07053:DB07111:DB07172:DB07208:DB07209:DB07302:DB07509:DB07675:DB07723:DB07724:DB07842:DB07863:DB08121:DB08302:DB08402:DB08435:DB08560:DB08604:DB08760:DB08915:DB09006:DB09061:DB09198:DB09201:DB09213:DB11133:DB11672:DB11811:DB12007:DB12662:DB13873:DB13961:DB14009:DB14011:DB14034:DB14635
ENSG00000154743	80746	TSEN2	TSEN2	608753	Q8NCE0	NA
ENSG00000075975	23609	MKRN2	MKRN2	608426	Q9H000	NA
ENSG00000132155	5894	RAF1	RAF1	164760	P04049	DB00398:DB04973:DB05190:DB05268:DB08862:DB08896:DB08912:DB12010
ENSG00000233252	106480793	CRIP1P1	CRIP1P1	NA	NA	NA
ENSG00000088726	55287	TMEM40	TMEM40	NA	Q8WWA1	NA
ENSG00000144712	23066	CAND2	CAND2	610403	O75155	NA
ENSG00000144713	6161	RPL32	RPL32	NA	P62910	NA
ENSG00000144711	9922	IQSEC1	IQSEC1	610166	Q6DN90	NA
ENSG00000188312	401541	CENPP	CENPP	611505	Q6IPU0	NA
ENSG00000127080	64768	IPPK	IPPK	NA	Q9H8X2	NA
ENSG00000185963	23299	BICD2	BICD2	609797	Q8TD16	NA
ENSG00000187984	138649	ANKRD19P	ANKRD19P	NA	NA	NA
ENSG00000127081	83744	ZNF484	ZNF484	NA	Q5JVG2	NA
ENSG00000127084	89846	FGD3	FGD3	617554	Q5JSP0	NA
ENSG00000157303	203328	SUSD3	SUSD3	616429	Q96L08	NA
ENSG00000165233	84270	C9orf89	C9orf89	617726	NA	NA
ENSG00000131669	4814	NINJ1	NINJ1	602062	Q92982	NA
ENSG00000165238	65268	WNK2	WNK2	606249	Q9Y3S1	NA
ENSG00000204352	445577	C9orf129	C9orf129	NA	Q5T035	NA
ENSG00000227603	NA	RP11-165J3.6	NA	NA	NA	NA

ENSG00000188938	158293	FAM120AOS	FAM120AOS	NA	Q5T036	NA
ENSG00000048828	23196	FAM120A	FAM120A	612265	Q9NZB2	NA
ENSG00000197724	5253	PHF2	PHF2	604351	O75151	NA
ENSG00000158079	138639	PTPDC1	PTPDC1	NA	A2A3K4	NA
ENSG00000269946	NA	RP11-2B6.3	NA	NA	NA	NA
ENSG00000269929	NA	RP11-2B6.2	NA	NA	NA	NA
ENSG00000230262	158257	MIRLET7DHG	MIRLET7DHG	NA	NA	NA
ENSG00000199133	406886	MIRLET7D	MIRLET7D	612145	NA	NA
ENSG00000175787	169841	ZNF169	ZNF169	603404	Q14929	NA
ENSG00000232063	100132077	RP11-307E17.8	LOC100132077	NA	NA	NA
ENSG00000148110	84641	HIATL1	HIATL1	NA	Q5SR56	NA

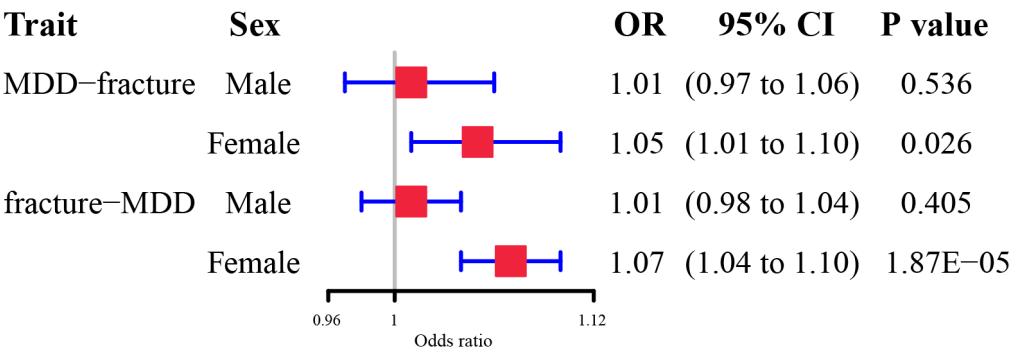
Supplementary Fig.1 The matching information of 39 965 patients with fracture.



Supplementary Fig.2 The prevalence rate in different age groups. Panel A: the prevalence rate for fracture with or without major depressive disorder (MDD). Panel B: the prevalence rate for MDD with or without fracture.

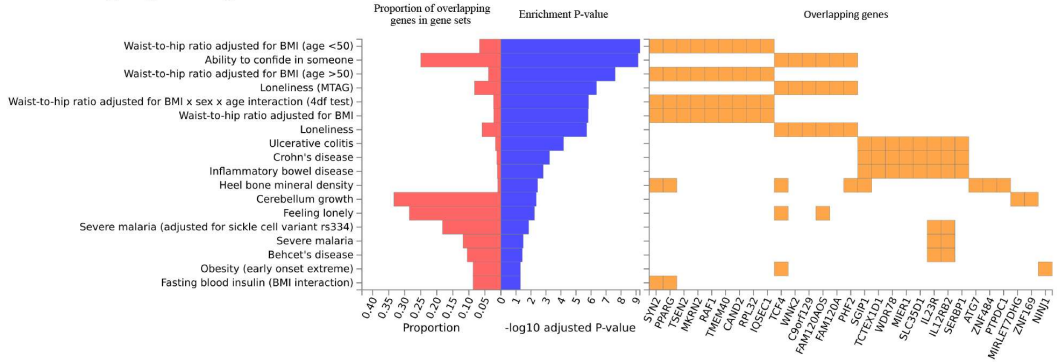


Supplementary Fig.3 The association of genetically predicted major depressive disorder (MDD) with fracture and vice versa in male and female.

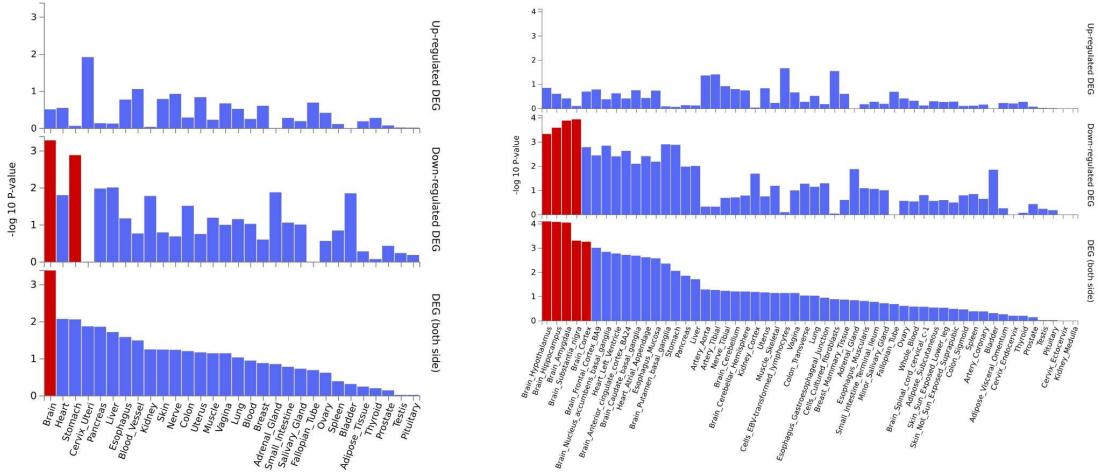
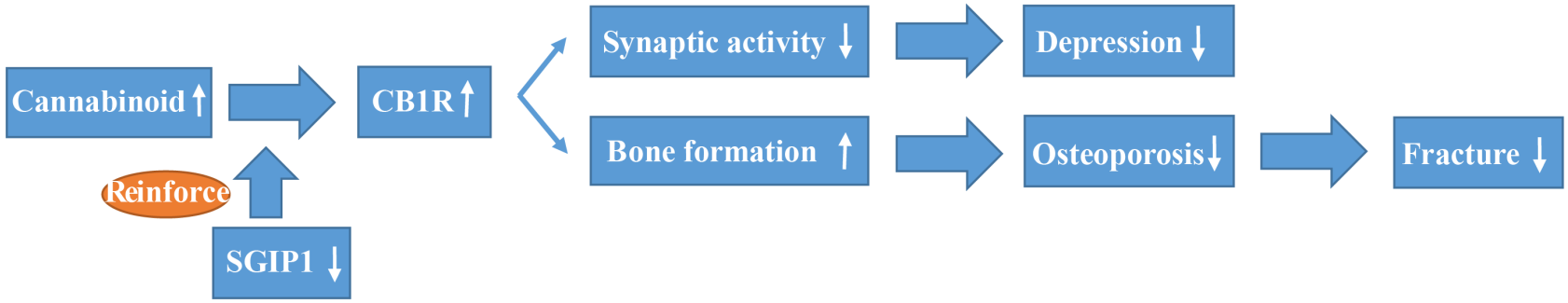


Supplementary Fig.4 The annotation of genetic association with FUMA.

A. GWAS catalog reported genes



B. Tissue specificity (DEG)



Supplementary Fig.5 A simple illustration of the assumptive mechanism: the potential implication of the *SGIP1* gene in the pathology of major depressive disorder (MDD) and fracture.