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Supplementary Table 1. Details of GWAS summary statistics included in Mendelian randomization analyses

Traits	Consortium	Year	Sample size	population	Web source
Exposure					
Prescription opioid medication use ¹	UKB	2019	318,177	European	https://cnsgenomics.com/content/data
Prescription non-opioid pain medication use ¹	UKB	2019	318,177	European	https://cnsgenomics.com/content/data
Outcome					
Fibromyalgia ²	FinnGen	2023	329,696	European	https://storage.googleapis.com/finngen-public-data-r11/summary_stats/finngen_R11_manifest.tsv
Covariate					
Insomnia ³	UKB	2018	386,533	European	https://ctg.cncr.nl/software/summary_statistics
Anxiety disorders ⁴	ANGST	2016	31,060	European	https://figshare.com/
Major depressive disorder ⁴	PGC	2018	277,614	Majority European	https://figshare.com/

UKB: United Kingdom Biobank; ANGST: Anxiety NeuroGenetics STudy Consortium; PGC: Psychiatric Genomics Consortium.

Supplementary Table 2. Independent Instruments for Prescription Opioid Use: Harmonized Data

CHR	POS	SNP	EA	OA	PAL	F	Prescription opioid use				Fibromyalgia			
							BETA	SE	EAF	P value	BETA	SE	EAF	P value
1	117185103	rs138200696	C	A	FALSE	21.95235	0.198808	0.042431	0.0162	2.80E-06	-0.018216	0.184363	0.004984	0.921293
1	111781489	rs2618039	T	A	TRUE	30.57018	0.061222	0.011073	0.380661	3.20E-08	0.027887	0.02559	0.4595	0.275824
1	31726197	rs945211	G	C	TRUE	21.70739	-0.051379	0.011027	0.383381	3.20E-06	-0.026391	0.026571	0.36292	0.320602
2	221082483	rs138405014	A	G	FALSE	21.01091	-0.217763	0.047507	0.012963	4.60E-06	-0.212615	0.114603	0.012964	0.063562
2	198234182	rs139152977	A	T	TRUE	22.69114	0.163843	0.034395	0.025085	1.90E-06	-0.184372	0.085619	0.02315	0.031286
3	10479853	rs140729888	C	T	FALSE	21.1074	-0.205016	0.044624	0.014589	4.30E-06	0.00642	0.095925	0.018543	0.946639
3	173400185	rs521956	T	C	FALSE	25.21968	-0.0538	0.010713	0.482979	5.10E-07	-0.062854	0.025602	0.44178	0.014087
3	50136751	rs7428430	T	C	FALSE	36.99998	-0.065191	0.010717	0.482569	1.20E-09	-0.066763	0.025509	0.548719	0.008865
3	80430902	rs7631941	T	C	FALSE	20.86816	0.073037	0.015988	0.130947	4.90E-06	0.019315	0.033033	0.182892	0.55873
4	102276925	rs13135092	G	A	FALSE	25.1882	0.098736	0.019673	0.081353	5.20E-07	0.114812	0.099907	0.017412	0.250479
4	139971718	rs1397440	T	C	FALSE	21.50887	-0.053465	0.011528	0.325126	3.50E-06	-0.033677	0.026953	0.339093	0.211499
4	3271055	rs76034781	A	G	FALSE	23.51462	0.098085	0.020227	0.076792	1.20E-06	0.121007	0.050924	0.068308	0.017491
5	152039276	rs11743674	C	G	TRUE	22.07343	0.060548	0.012887	0.222415	2.60E-06	0.040982	0.032946	0.184873	0.213535
6	31281440	rs2253491	A	G	FALSE	25.8764	-0.066951	0.013161	0.208222	3.60E-07	-0.014969	0.034991	0.157859	0.66879
7	2039346	rs56226325	T	C	FALSE	25.29889	-0.074478	0.014807	0.154737	4.90E-07	-0.027494	0.031348	0.208315	0.380442
8	58517451	rs117710046	T	C	FALSE	23.63608	0.209712	0.043135	0.015766	1.20E-06	0.099489	0.070227	0.033849	0.156577
8	138381666	rs1519369	T	C	FALSE	21.24056	-0.053299	0.011565	0.327046	4.00E-06	-0.026056	0.027123	0.336727	0.336719
9	125984333	rs12238134	A	G	FALSE	37.70801	-0.07148	0.01164	0.305094	8.20E-10	-0.00086	0.032216	0.199238	0.978697
9	37213644	rs17487601	A	G	FALSE	24.42004	-0.055459	0.011223	0.356491	7.70E-07	-0.020724	0.028386	0.28261	0.465354
9	78774755	rs7860752	G	A	FALSE	26.00909	0.069464	0.013621	0.192698	3.40E-07	0.041716	0.031335	0.209037	0.1831
10	21501547	rs12357321	A	G	FALSE	29.04654	0.063206	0.011728	0.311848	7.10E-08	-0.032642	0.027894	0.298089	0.241907
10	133139857	rs4258296	C	T	FALSE	24.76303	0.055519	0.011157	0.363464	6.50E-07	-0.011852	0.025672	0.446291	0.644313
11	46098766	rs7110825	C	T	FALSE	22.31481	0.057019	0.01207	0.270232	2.30E-06	0.036486	0.028056	0.291683	0.193438
12	10325113	rs4763505	T	A	TRUE	21.03602	-0.053147	0.011587	0.317492	4.50E-06	0.06638	0.026915	0.347285	0.013652
13	42070569	rs56262049	C	T	FALSE	22.19947	-0.066271	0.014065	0.182332	2.50E-06	-0.006264	0.031688	0.206449	0.843286
13	57678667	rs7319102	G	A	FALSE	22.21949	0.060307	0.012794	0.228749	2.40E-06	0.04803	0.031744	0.203339	0.130267
14	73331535	rs7154623	G	A	FALSE	22.24724	0.064365	0.013646	0.193193	2.40E-06	0.002474	0.029812	0.238302	0.933868
15	86032845	rs113544339	G	T	FALSE	21.46674	-0.165742	0.035772	0.023191	3.60E-06	0.085527	0.0769	0.028751	0.266061
15	41509314	rs2289739	T	G	FALSE	22.62209	0.05427	0.01141	0.343402	2.00E-06	-0.026274	0.026168	0.387573	0.315347
15	75595064	rs75169822	G	A	FALSE	23.39576	0.059168	0.012232	0.262136	1.30E-06	0.013733	0.028062	0.291631	0.624568
16	73066604	rs975376	C	G	TRUE	23.86598	0.07117	0.014568	0.164265	1.00E-06	0.017254	0.030472	0.225195	0.571242
17	45078655	rs59695806	C	T	FALSE	23.80118	0.05741	0.011767	0.294147	1.10E-06	0.054648	0.030618	0.223147	0.07429
20	46044907	rs2297197	G	C	TRUE	24.4425	0.060215	0.012179	0.280804	7.70E-07	0.030618	0.027609	0.308904	0.267447
20	32243354	rs6141277	C	G	TRUE	22.40283	0.052116	0.011011	0.391559	2.20E-06	0.009048	0.02553	0.496529	0.723021
21	41380827	rs73228014	A	G	FALSE	21.37794	0.161016	0.034824	0.024312	3.80E-06	-0.006193	0.097769	0.017418	0.949492

CHR: Chromosome; POS: position; SNP: single nucleotide polymorphism; EA: effect allele; OA: other allele; PAL: palindromic; SE: standard error; EAF: effect allele frequency.

Supplementary Table 3. Independent Instruments for Anilides: Harmonized Data

CHR	POS	SNP	EA	OA	PAL	F	Anilides				Fibromyalgia			
							BETA	SE	EAF	P value	BETA	SE	EAF	P value
4	66916395	rs10033431	C	T	FALSE	25.65592	0.037569	0.007417	0.266911	4.10E-07	0.015031	0.030506	0.225218	0.622204
12	57133500	rs11172113	C	T	FALSE	64.66008	-0.053406	0.006642	0.409705	8.90E-16	-0.013484	0.025963	0.399491	0.603508
6	474405	rs11242905	C	T	FALSE	21.14332	0.045169	0.009823	0.127045	4.30E-06	-0.028173	0.036891	0.136795	0.445058
1	154188409	rs12029331	T	C	FALSE	23.47798	0.032173	0.00664	0.415197	1.30E-06	0.042194	0.026128	0.389896	0.106335
15	46024634	rs12438004	C	A	FALSE	27.83504	0.03519	0.00667	0.41891	1.30E-07	-0.016684	0.027451	0.316374	0.543345
1	174465194	rs12568655	A	G	FALSE	37.02729	-0.040732	0.006694	0.388338	1.20E-09	-0.028791	0.02636	0.366984	0.274739
13	58641252	rs1544115	T	C	FALSE	21.1189	0.035023	0.007621	0.246906	4.30E-06	0.046166	0.028218	0.286463	0.101829
11	116025782	rs1648368	T	C	FALSE	22.60683	-0.046745	0.009831	0.12664	2.00E-06	-0.019631	0.036075	0.145103	0.586331
6	31210594	rs17191307	G	T	FALSE	22.41855	0.035463	0.00749	0.253843	2.20E-06	0.012771	0.027368	0.315895	0.640774
4	86319004	rs17449582	T	C	FALSE	25.59528	0.034213	0.006762	0.364194	4.20E-07	0.000158	0.02768	0.305786	0.995442
17	46021601	rs17652520	A	G	FALSE	51.25779	0.05571	0.007781	0.231386	8.10E-13	-0.08888	0.045361	0.088526	0.050066
18	55206086	rs1942262	A	G	FALSE	26.24539	0.036907	0.007204	0.292683	3.00E-07	0.067968	0.029928	0.238986	0.023144
1	156481081	rs2274319	T	C	FALSE	27.62005	0.036021	0.006854	0.348156	1.50E-07	-0.05106	0.025805	0.419407	0.047852
14	72634410	rs2526922	A	G	FALSE	21.53281	-0.030364	0.006543	0.471592	3.50E-06	0.009594	0.025475	0.502458	0.706472
21	18800545	rs2825128	C	A	FALSE	22.68641	0.031356	0.006583	0.446257	1.90E-06	-0.006077	0.026257	0.378439	0.816962
15	74312493	rs2930291	A	G	FALSE	22.10728	-0.032042	0.006815	0.362626	2.60E-06	0.008776	0.028165	0.288361	0.755348
20	32510074	rs293566	C	T	FALSE	25.00599	0.034662	0.006931	0.33269	5.70E-07	0.027312	0.025545	0.466616	0.285003
6	31755003	rs3130486	T	C	FALSE	55.29636	-0.054928	0.007387	0.265164	1.00E-13	0.022195	0.02609	0.388069	0.394944
2	210437903	rs41272663	A	C	FALSE	22.20937	-0.034952	0.007417	0.26235	2.40E-06	-0.022617	0.028775	0.269693	0.431867
4	111381436	rs4356969	C	G	TRUE	23.31609	-0.036262	0.00751	0.264026	1.40E-06	-0.039526	0.031712	0.206754	0.212621
2	233906360	rs4663983	G	A	FALSE	45.30823	-0.055778	0.008286	0.191953	1.70E-11	0.018307	0.034856	0.157411	0.599431
7	67759791	rs4718618	A	G	FALSE	22.00145	0.039548	0.008431	0.185062	2.70E-06	-0.016176	0.028247	0.285018	0.566885
9	13764508	rs4741328	C	T	FALSE	23.74088	-0.033042	0.006781	0.368146	1.10E-06	-0.001509	0.026839	0.347269	0.955168
3	49853534	rs59357103	A	G	FALSE	21.64687	0.040994	0.008811	0.166257	3.30E-06	0.076446	0.043878	0.097528	0.081469
2	216559520	rs62180637	C	T	FALSE	22.76246	-0.031287	0.006558	0.466218	1.80E-06	-0.047314	0.025658	0.440311	0.065173
5	173679222	rs62378567	G	A	FALSE	23.86661	-0.115602	0.023663	0.019365	1.00E-06	0.100514	0.206246	0.004264	0.62601
6	96413600	rs6568392	G	T	FALSE	25.92114	0.040173	0.00789	0.219034	3.60E-07	0.04921	0.032752	0.184226	0.132966
7	136161765	rs73168813	C	G	TRUE	22.49202	0.106267	0.022407	0.02174	2.10E-06	0.009815	0.143582	0.008128	0.945502
9	109757167	rs73531210	T	C	FALSE	22.14014	-0.069919	0.014859	0.05074	2.50E-06	-0.009699	0.042988	0.097206	0.8215
17	72844157	rs73998427	T	C	FALSE	21.90399	0.08754	0.018704	0.031487	2.90E-06	-0.029126	0.054371	0.057438	0.592172
16	54612156	rs74618578	G	A	FALSE	25.41897	-0.103651	0.020559	0.025979	4.60E-07	0.017407	0.104276	0.015697	0.867426
14	92997535	rs75036981	A	G	FALSE	23.18469	0.065923	0.013691	0.061342	1.50E-06	0.04887	0.05734	0.05235	0.394052
2	241531061	rs7567892	T	C	FALSE	31.46067	0.061421	0.01095	0.098818	2.00E-08	-0.006497	0.053615	0.061675	0.903545
13	66362001	rs9571576	C	T	FALSE	23.59808	0.031835	0.006553	0.494235	1.20E-06	0.023321	0.025612	0.535536	0.362529
17	10657732	rs9915717	A	G	FALSE	26.16927	0.041733	0.008158	0.203134	3.10E-07	0.026849	0.030441	0.225725	0.377775
16	5750932	rs9925184	C	T	FALSE	24.32442	0.032846	0.00666	0.435833	8.10E-07	-0.042467	0.025659	0.438045	0.097906

CHR: Chromosome; POS: position; SNP: single nucleotide polymorphism; EA: effect allele; OA: other allele; PAL: palindromic; SE: standard error; EAF: effect allele frequency.

Supplementary Table 4. Independent Instruments for Anti-inflammatory and antirheumatic products(non-steroids): Harmonized Data

CHR	POS	SNP	EA	OA	PAL	F	Anti-inflammatory and antirheumatic products(non-steroids)				Fibromyalgia			
							BETA	SE	EAF	P value	BETA	SE	EAF	P value
6	31423612	rs114212906	T	C	FALSE	31.79686348	0.092068098	0.016327301	0.0468755	1.70E-08	0.15919	0.044295	0.082001	0.00032578
5	120838771	rs12522598	G	A	FALSE	35.20094753	0.045219532	0.007621602	0.288625	3.00E-09	0.012884	0.026941	0.342658	0.632492
6	30201550	rs2517611	G	A	FALSE	37.99122584	-0.050484305	0.008190532	0.229963	7.10E-10	0.008851	0.039927	0.11654	0.824558
12	57115272	rs3001426	C	T	FALSE	64.37368073	-0.056191782	0.007003514	0.452847	1.00E-15	0.000989	0.025591	0.500582	0.96916
15	74809189	rs34862454	C	T	FALSE	29.97008198	-0.040197316	0.00734261	0.329747	4.40E-08	-0.044758	0.025606	0.44085	0.0804767
4	140022015	rs56166763	C	G	TRUE	32.53143066	-0.040853898	0.007162742	0.368625	1.20E-08	-0.023188	0.026735	0.356358	0.385769
5	150593232	rs6891880	G	A	FALSE	29.74422418	-0.038491819	0.007057721	0.42715	4.90E-08	0.022102	0.025618	0.448896	0.388279

CHR: Chromosome; POS: position; SNP: single nucleotide polymorphism; EA: effect allele; OA: other allele; PAL: palindromic; SE: standard error; EAF: effect allele frequency.

Supplementary Table 5. Independent Instruments for Salicylic Acid and Derivatives: Harmonized Data

CHR	POS	SNP	EA	OA	PAL	F	Salicylic acid and derivatives				Fibromyalgia			
							BETA	SE	EAF	P value	BETA	SE	EAF	P value
1	174478450	rs10218528	A	T	TRUE	25.44728455	-0.0274129	0.008157157	0.368772	4.50E-07	-0.027413	0.026332	0.368772	0.29785
10	3804767	rs10508267	C	G	TRUE	22.00997321	-0.0140475	0.008387159	0.298381	2.70E-06	-0.014048	0.027931	0.298381	0.615006
10	88231148	rs10887793	T	G	FALSE	28.30364837	0.00695225	0.008029935	0.51236	1.00E-07	0.006952	0.025644	0.51236	0.786309
1	53979675	rs11206268	G	A	FALSE	22.37478854	0.0332805	0.015937416	0.0739413	2.20E-06	0.033281	0.048521	0.073941	0.492775
1	233982300	rs113242618	A	G	FALSE	21.59335058	-0.191704	0.033187898	0.00340756	3.40E-06	-0.191704	0.221293	0.003408	0.38633
12	12360936	rs113551213	A	G	FALSE	21.21120099	0.00336374	0.018484725	0.0186803	4.10E-06	0.003364	0.097395	0.01868	0.972449
20	21021728	rs117571676	A	T	TRUE	21.78399422	-0.0991476	0.028544961	0.0327369	3.10E-06	-0.099148	0.071269	0.032737	0.164171
6	160501838	rs117733303	G	A	FALSE	42.04592835	0.0469664	0.028465654	0.010763	8.90E-11	0.046966	0.125054	0.010763	0.707237
18	48974566	rs11874619	C	G	TRUE	21.61165082	0.0390574	0.008310155	0.417775	3.30E-06	0.039057	0.025908	0.417775	0.131675
5	167569461	rs12188010	A	T	TRUE	23.60130178	0.00967845	0.008184145	0.342184	1.20E-06	0.009678	0.026773	0.342184	0.717722
12	67013876	rs12580718	A	G	FALSE	22.382128	-0.00307262	0.008257917	0.448603	2.20E-06	-0.003073	0.025631	0.448603	0.904577
3	170484881	rs13082582	C	G	TRUE	23.59170111	0.0155806	0.008048035	0.422523	1.20E-06	0.015581	0.025934	0.422523	0.547993
22	47441138	rs139696858	A	G	FALSE	23.05088	-0.000176539	0.034201391	0.0201305	1.60E-06	-0.000177	0.091004	0.020131	0.998452
4	20149344	rs1825548	T	A	TRUE	21.30534465	0.0276688	0.011983918	0.167459	3.90E-06	0.027669	0.033951	0.167459	0.415097
9	22076072	rs1831733	C	T	FALSE	32.96400308	-0.00532605	0.007975758	0.383301	9.40E-09	-0.005326	0.026164	0.383301	0.838693
16	58417045	rs185197153	C	A	FALSE	22.12186101	0.110773	0.034696301	0.0158495	2.60E-06	0.110773	0.103181	0.01585	0.283013
6	81900471	rs1931656	A	T	TRUE	21.2879912	0.0186022	0.007992403	0.444513	4.00E-06	0.018602	0.025619	0.444513	0.46777
13	83258474	rs1960743	A	G	FALSE	21.26419108	-0.0372323	0.01271699	0.134144	4.00E-06	-0.037232	0.037624	0.134144	0.32238
6	31359557	rs2523589	T	G	FALSE	31.39391941	-0.0287658	0.007923358	0.50361	2.10E-08	-0.028766	0.025462	0.50361	0.258579
8	125487789	rs28601761	G	C	TRUE	54.84110706	-0.0158631	0.008191943	0.411081	1.30E-13	-0.015863	0.025883	0.411081	0.539956
2	43845437	rs4299376	G	T	FALSE	28.65659567	-0.0135331	0.008459113	0.215856	8.60E-08	-0.013533	0.031173	0.215856	0.664193
13	106178937	rs4995008	A	G	FALSE	21.12904401	0.0207169	0.011761876	0.258744	4.30E-06	0.020717	0.029042	0.258744	0.475636
7	2039346	rs56226325	T	C	FALSE	26.86132395	-0.0274944	0.01093669	0.208315	2.20E-07	-0.027494	0.031348	0.208315	0.380442
1	109278685	rs583104	G	T	FALSE	67.94398016	0.0149427	0.009467476	0.219266	1.70E-16	0.014943	0.030876	0.219266	0.628411
11	70333295	rs59681006	C	T	FALSE	22.87263948	0.00749589	0.011838395	0.134398	1.70E-06	0.007496	0.037228	0.134398	0.840426
9	133279427	rs635634	T	C	FALSE	42.39930942	0.0358817	0.010233878	0.201211	7.40E-11	0.035882	0.031682	0.201211	0.2574
18	70318851	rs7244655	A	G	FALSE	22.3767196	0.0127648	0.009162167	0.279142	2.20E-06	0.012765	0.028452	0.279142	0.653684
19	11080624	rs73015016	A	G	FALSE	60.76465049	0.0235597	0.012271248	0.101063	6.40E-15	0.02356	0.041985	0.101063	0.574701
12	31775248	rs7315004	A	T	TRUE	25.41703357	0.0463966	0.00808484	0.364107	4.60E-07	0.046397	0.026561	0.364107	0.0806752
19	44908822	rs7412	T	C	FALSE	56.76662581	0.0670124	0.014702809	0.0530459	4.90E-14	0.067012	0.05718	0.053046	0.241218
6	160576086	rs74617384	T	A	TRUE	53.40942426	-0.0635929	0.014373422	0.0460565	2.70E-13	-0.063593	0.061393	0.046057	0.300278
8	19963914	rs75278536	G	T	FALSE	27.44787149	-0.00469447	0.012842435	0.0907578	1.60E-07	-0.004694	0.04447	0.090758	0.915927
11	24897384	rs77507211	T	G	FALSE	20.9104423	-0.0183093	0.029851885	0.0541151	4.80E-06	-0.018309	0.056505	0.054115	0.745916
2	2729105	rs896232	T	C	FALSE	23.18223664	-0.0127853	0.008208951	0.289222	1.50E-06	-0.012785	0.028103	0.289222	0.649142
14	42502639	rs950100	A	G	FALSE	21.05631938	0.000742513	0.015582455	0.0505713	4.50E-06	0.000743	0.058167	0.050571	0.989815
22	24201572	rs9612563	C	A	FALSE	21.91791087	-0.0107089	0.017068395	0.0857728	2.80E-06	-0.010709	0.045334	0.085773	0.813262
11	116778201	rs964184	G	C	TRUE	29.76611851	0.0115436	0.011595182	0.145173	4.90E-08	0.011544	0.036184	0.145173	0.749706
21	16156635	rs9982261	A	G	FALSE	21.62289612	0.0276213	0.03761061	0.00885402	3.30E-06	0.027621	0.138716	0.008854	0.842168

CHR: Chromosome; POS: position; SNP: single nucleotide polymorphism; EA: effect allele; OA: other allele; PAL: palindromic; SE: standard error; EAF: effect allele frequency.

Supplementary Table 6. Independent Instruments for Fibromyalgia and Prescription opioid use: Harmonized Data

SNP	EA	OA	Fibromyalgia						Prescription opioid use			
			PAL	F	BETA	SE	EAF	<i>P</i> value	BETA	SE	EAF	<i>P</i> value
rs1112857	C	T	FALSE	23.51682772	0.124468	0.0256666	0.414986	1.23837E-06	0.00709718	0.01125295	0.367083	0.53
rs116875830	T	C	FALSE	22.51043593	-0.640263	0.134948	0.0139187	2.09007E-06	0.010095033	0.026614811	0.0427861	0.7
rs12457428	T	C	FALSE	23.05112554	-0.128443	0.0267525	0.355353	1.57732E-06	1.81336E-05	0.011202702	0.361977	1
rs12659281	A	C	FALSE	20.89879256	-0.157626	0.03448	0.175465	4.84195E-06	-0.008998352	0.014482725	0.163848	0.53
rs12709153	T	C	FALSE	23.62093006	-0.123603	0.025432	0.554786	1.17311E-06	-0.002638458	0.010773131	0.559831	0.81
rs132735	T	G	FALSE	22.17266531	0.125443	0.0266402	0.330019	2.49213E-06	0.005745679	0.012008694	0.27466	0.63
rs17469691	T	C	FALSE	28.86367844	-0.393952	0.0733276	0.0405681	7.76551E-08	-0.010990627	0.021580776	0.0659895	0.61
rs181269261	C	T	FALSE	21.46267178	0.204775	0.0442013	0.0786902	3.60803E-06	-0.010741714	0.027450428	0.0403821	0.7
rs34323745	A	C	FALSE	23.27707765	0.145481	0.0301538	0.216026	1.40252E-06	0.023803086	0.013578659	0.195012	0.08
rs56132815	C	T	FALSE	29.74023045	-0.185963	0.0341	0.183418	4.93992E-08	-0.010228251	0.014860791	0.15845	0.49
rs6135514	C	G	TRUE	27.50015253	-0.160754	0.0306545	0.241869	1.57087E-07	-0.010793898	0.01290487	0.220101	0.4
rs6690293	G	A	FALSE	24.5209774	-0.125664	0.0253771	0.494785	7.35005E-07	0.012095441	0.010786443	0.45097	0.26
rs73203073	T	C	FALSE	24.50035156	0.270618	0.0546727	0.0501359	7.42916E-07	0.006830549	0.020455534	0.0765506	0.74
rs7790414	T	C	FALSE	21.27495318	-0.172604	0.0374211	0.14876	3.97887E-06	-0.024411767	0.014321575	0.168897	0.088
rs77929374	T	C	FALSE	22.08427198	-0.254941	0.0542498	0.0676498	2.60934E-06	-0.033898506	0.022002361	0.0634326	0.12
rs7910831	T	G	FALSE	26.73182748	-0.160908	0.0311217	0.227525	2.33765E-07	0.016220133	0.014710581	0.160147	0.27
rs80335015	C	G	TRUE	21.74957494	0.332848	0.0713708	0.026166	3.1067E-06	-0.039817825	0.027359325	0.0401355	0.15

SNP: single nucleotide polymorphism; EA: effect allele; OA: other allele; PAL: palindromic; SE: standard error; EAF: effect allele frequency.

Supplementary Table 7. Independent Instruments for Fibromyalgia and Anilides: Harmonized Data

SNP	EA	OA	Fibromyalgia						Prescription anilides use			
			PAL	F	BETA	SE	EAF	<i>P</i> value	BETA	SE	EAF	<i>P</i> value
rs1112857	C	T	FALSE	23.51683	0.124468	0.025667	0.414986	1.23837E-06	-0.01425	0.006845	`	0.037
rs116875830	T	C	FALSE	22.51044	-0.640263	0.134948	0.013919	2.09007E-06	-0.018116	0.016262	0.042361	0.27
rs12457428	T	C	FALSE	23.05113	-0.128443	0.026753	0.355353	1.57732E-06	-0.01422	0.00683	0.360493	0.037
rs12659281	A	C	FALSE	20.89879	-0.157626	0.03448	0.175465	4.84195E-06	-0.003977	0.008786	0.165208	0.65
rs12709153	T	C	FALSE	23.62093	-0.123603	0.025432	0.554786	1.17311E-06	0.003055	0.006572	0.561493	0.64
rs132735	T	G	FALSE	22.17267	0.125443	0.02664	0.330019	2.49213E-06	0.003293	0.007303	0.275715	0.65
rs17469691	T	C	FALSE	28.86368	-0.393952	0.073328	0.040568	7.76551E-08	0.012732	0.013069	0.066626	0.33
rs181269261	C	T	FALSE	21.46267	0.204775	0.044201	0.07869	3.60803E-06	0.011767	0.016751	0.039899	0.48
rs34323745	A	C	FALSE	23.27708	0.145481	0.030154	0.216026	1.40252E-06	0.004127	0.00827	0.194791	0.62
rs56132815	C	T	FALSE	29.74023	-0.185963	0.0341	0.183418	4.93992E-08	-0.004916	0.00901	0.158553	0.59
rs6135514	C	G	TRUE	27.50015	-0.160754	0.030655	0.241869	1.57087E-07	-0.008472	0.007854	0.220092	0.28
rs6690293	G	A	FALSE	24.52098	-0.125664	0.025377	0.494785	7.35005E-07	0.014365	0.006566	0.451675	0.029
rs73203073	T	C	FALSE	24.50035	0.270618	0.054673	0.050136	7.42916E-07	-0.006419	0.012482	0.076158	0.61
rs7790414	T	C	FALSE	21.27495	-0.172604	0.037421	0.14876	3.97887E-06	-0.000725	0.008731	0.168142	0.93
rs77929374	T	C	FALSE	22.08427	-0.254941	0.05425	0.06765	2.60934E-06	0.014272	0.013344	0.063978	0.28
rs7910831	T	G	FALSE	26.73183	-0.160908	0.031122	0.227525	2.33765E-07	-0.004268	0.008966	0.159358	0.63
rs80335015	C	G	TRUE	21.74957	0.332848	0.071371	0.026166	3.1067E-06	0.005828	0.016564	0.040598	0.72

SNP: single nucleotide polymorphism; EA: effect allele; OA: other allele; PAL: palindromic; SE: standard error; EAF: effect allele frequency.

Supplementary Table 8. Independent Instruments for Fibromyalgia and Anti-inflammatory and antirheumatic products: Harmonized Data

SNP	EA	OA	PAL	F	Fibromyalgia		EAF	<i>P</i> value	Prescription anti-inflammatory and antirheumatic products use			
					BETA	SE			BETA	SE	EAF	<i>P</i> value
rs1112857	C	T	FALSE	23.51683	0.124468	0.025667	0.414986	1.24E-06	-0.01757438	0.00723569	0.365694	0.015
rs116875830	T	C	FALSE	22.51044	-0.640263	0.134948	0.013919	2.09E-06	-0.00772408	0.01706245	0.0428624	0.65
rs12457428	T	C	FALSE	23.05113	-0.128443	0.026753	0.355353	1.58E-06	-0.01278043	0.00721537	0.362124	0.077
rs12659281	A	C	FALSE	20.89879	-0.157626	0.03448	0.175465	4.84E-06	0.01520685	0.0092838	0.165552	0.1
rs12709153	T	C	FALSE	23.62093	-0.123603	0.025432	0.554786	1.17E-06	0.009084178	0.00695581	0.56169	0.19
rs132735	T	G	FALSE	22.17267	0.125443	0.02664	0.330019	2.49E-06	0.006764955	0.00771152	0.276781	0.38
rs17469691	T	C	FALSE	28.86368	-0.393952	0.073328	0.040568	7.77E-08	0.015987316	0.01380506	0.0667214	0.25
rs181269261	C	T	FALSE	21.46267	0.204775	0.044201	0.07869	3.61E-06	-0.00301909	0.01774415	0.0397219	0.86
rs34323745	A	C	FALSE	23.27708	0.145481	0.030154	0.216026	1.4E-06	-0.00780612	0.00874496	0.194351	0.37
rs56132815	C	T	FALSE	29.74023	-0.185963	0.0341	0.183418	4.94E-08	-0.00258245	0.00955322	0.158693	0.79
rs6135514	C	G	TRUE	27.50015	-0.160754	0.030655	0.241869	1.57E-07	-0.01444686	0.00831171	0.2203	0.082
rs6690293	G	A	FALSE	24.52098	-0.125664	0.025377	0.494785	7.35E-07	0.00432823	0.00693254	0.451038	0.53
rs73203073	T	C	FALSE	24.50035	0.270618	0.054673	0.050136	7.43E-07	0.011048713	0.01319433	0.0762388	0.4
rs7790414	T	C	FALSE	21.27495	-0.172604	0.037421	0.14876	3.98E-06	0.001546597	0.00922357	0.168353	0.87
rs77929374	T	C	FALSE	22.08427	-0.254941	0.05425	0.06765	2.61E-06	0.007361514	0.01406366	0.0646	0.6
rs7910831	T	G	FALSE	26.73183	-0.160908	0.031122	0.227525	2.34E-07	-0.01552409	0.0095018	0.159211	0.1
rs80335015	C	G	TRUE	21.74957	0.332848	0.071371	0.026166	3.11E-06	-0.00808648	0.01748229	0.0406881	0.64

NSAIDs: non-steroids; SNP: single nucleotide polymorphism; EA: effect allele; OA: other allele; PAL: palindromic; SE: standard error; EAF: effect allele frequency.

Supplementary Table 9. Independent Instruments for Fibromyalgia: Harmonized Data

SNP	EA	OA	PAL	F	Fibromyalgia				Prescription salicylic acid and derivatives use			
					BETA	SE	EAF	P value	BETA	SE	EAF	P value
rs1112857	C	T	FALSE	23.51683	0.124468	0.025667	0.414986	1.24E-06	-0.007773	0.00828911	0.3658	0.35
rs116875830	T	C	FALSE	22.51044	-0.640263	0.134948	0.013919	2.09E-06	0.0155226	0.0195772	0.0429466	0.43
rs12457428	T	C	FALSE	23.05113	-0.128443	0.026753	0.355353	1.58E-06	-0.011408	0.00825885	0.360612	0.17
rs12659281	A	C	FALSE	20.89879	-0.157626	0.03448	0.175465	4.84E-06	-0.006621	0.01067817	0.164419	0.54
rs12709153	T	C	FALSE	23.62093	-0.123603	0.025432	0.554786	1.17E-06	0.0134351	0.00796449	0.56207	0.092
rs132735	T	G	FALSE	22.17267	0.125443	0.02664	0.330019	2.49E-06	0.0044156	0.00883642	0.275866	0.62
rs17469691	T	C	FALSE	28.86368	-0.393952	0.073328	0.040568	7.77E-08	0.0040916	0.01584021	0.0666369	0.8
rs181269261	C	T	FALSE	21.46267	0.204775	0.044201	0.07869	3.61E-06	0.0148297	0.0201862	0.0404619	0.46
rs34323745	A	C	FALSE	23.27708	0.145481	0.030154	0.216026	1.40E-06	0.0058277	0.01003006	0.195106	0.56
rs56132815	C	T	FALSE	29.74023	-0.185963	0.0341	0.183418	4.94E-08	0.0090652	0.01094756	0.158407	0.41
rs6135514	C	G	TRUE	27.50015	-0.160754	0.030655	0.241869	1.57E-07	-0.016513	0.0095324	0.219984	0.083
rs6690293	G	A	FALSE	24.52098	-0.125664	0.025377	0.494785	7.35E-07	-0.006289	0.00794748	0.450073	0.43
rs73203073	T	C	FALSE	24.50035	0.270618	0.054673	0.050136	7.43E-07	0.0154241	0.01503761	0.0767983	0.31
rs7790414	T	C	FALSE	21.27495	-0.172604	0.037421	0.14876	3.98E-06	-0.007789	0.01061805	0.167784	0.46
rs77929374	T	C	FALSE	22.08427	-0.254941	0.05425	0.06765	2.61E-06	0.0056416	0.016158	0.0641728	0.73
rs7910831	T	G	FALSE	26.73183	-0.160908	0.031122	0.227525	2.34E-07	-0.016356	0.01086466	0.158931	0.13
rs80335015	C	G	TRUE	21.74957	0.332848	0.071371	0.026166	3.11E-06	0.0096046	0.01999091	0.0408847	0.63

SNP: single nucleotide polymorphism; EA: effect allele; OA: other allele; PAL: palindromic; SE: standard error; EAF: effect allele frequency.

Supplementary Table 10. Two-sample MR results of causal relationships between prescription pain medications use and fibromyalgia

Exposure	Outcome	Method	N SNP	OR (95%CI)	P value	heterogeneity		horizontal pleiotropy			MR PRESSO	
						Q	Q- <i>P</i> value	Egger Intercept	SE	<i>P</i> value	Outlier	<i>P</i> value
Prescription opioid use	Fibromyalgia	Inverse variance weighted	27	1.42(1.17,1.72)	3.55E-04	28.63	0.33	0.01	0.02	0.72	NA	0.37
		MR Egger		1.28(0.72,2.27)	0.40	28.48	0.29					
		Weighted median		1.40(1.07,1.83)	0.01							
Anti-inflammatory and antirheumatic products(non-steroids)		Inverse variance weighted	6	1.67(0.82,3.41)	0.16	12.21	0.03	-0.10	0.06	0.17	NA	0.06
		MR Egger		10.85(1.12,105.45)	0.11	7.17	0.13					
		Weighted median		1.17(0.61,2.23)	0.64							
Salicylic acid and derivatives		Inverse variance weighted	26	0.93(0.74,1.16)	0.51	9.79	1.00	0.01	0.02	0.67	NA	1.00
		MR Egger		0.82(0.46,1.47)	0.52	9.60	1.00					
		Weighted median		0.88(0.64,1.19)	0.40							
Anilide	Inverse variance weighted	34	1.15(0.88,1.51)	0.31	37.96	0.25	0.03	0.02	0.17	NA	0.26	
	MR Egger		0.56(0.20,1.56)	0.28	35.71	0.30						
	Weighted median		1.09(0.75,1.58)	0.64								
Fibromyalgia	Prescription opioid use	Inverse variance weighted	15	1.03(0.99,1.07)	0.21	11.45	0.65	0.00	0.01	0.67	NA	0.66
		MR Egger		1.01(0.93,1.10)	0.85	11.26	0.59					
		Weighted median		1.03(0.97,1.08)	0.37							
	Anti-inflammatory and antirheumatic products(non-steroids)	Inverse variance weighted	15	1.00(0.96,1.02)	0.57	20.24	0.12	0.00	0.01	0.58	NA	0.58
		MR Egger		1.01(0.94,1.08)	0.81	19.75	0.10					
		Weighted median		1.00(0.96,1.03)	0.81							
	Salicylic acid and derivatives	Inverse variance weighted	15	1.01(0.98,1.03)	0.70	12.98	0.53	0.01	0.01	0.40	NA	0.69
		MR Egger		0.98(0.92,1.04)	0.57	12.24	0.51					
		Weighted median		0.99(0.95,1.03)	0.60							
Anilide	Inverse variance weighted	15	1.00(0.97,1.03)	0.90	18.93	0.17	0.00	0.01	0.59	NA	0.91	
	MR Egger		1.01(0.95,1.08)	0.67	18.49	0.14						
	Weighted median		1.03(0.99,1.06)	0.14								

SNP: single nucleotide polymorphism; SE: standard error; NA: not applicable; Q: Cochran’s Q statistic.

Supplementary Table 11. Two-sample MR results of causal relationships for prescription opioid use, major depressive disorder and fibromyalgia

Exposure	Outcome	Methods	N SNP	BETA	SE	<i>P</i> value	lo_ci	up_ci	OR	OR_lci95	OR_uci95
MDD	Fibromyalgia	MR Egger	32	-0.170744961	0.35661545	0.635557301	-0.869711243	0.528221322	0.843036554	0.419072542	1.69591314
MDD	Fibromyalgia	Weighted median	32	0.385528711	0.143235076	0.007111437	0.104787963	0.666269459	1.470391528	1.110475123	1.946960539
MDD	Fibromyalgia	Inverse variance weighted	32	0.333330092	0.102172549	0.001104641	0.133071896	0.533588289	1.395607902	1.142332124	1.705039519
MDD	Fibromyalgia	Simple mode	32	0.596219896	0.29293623	0.05044407	0.022064886	1.170374906	1.815244003	1.022310116	3.223200809
MDD	Fibromyalgia	Weighted mode	32	0.581956282	0.313385949	0.072836048	-0.032280177	1.196192741	1.789535846	0.968235267	3.307500412
POU	MDD	MR Egger	26	0.157684872	0.126135179	0.223306241	-0.089540079	0.404909823	1.170797185	0.914351618	1.499167303
POU	MDD	Weighted median	26	0.167918362	0.051505979	0.001113446	0.066966643	0.268870082	1.182840042	1.06925981	1.308485134
POU	MDD	Inverse variance weighted	26	0.135578611	0.040750296	0.00087768	0.055708031	0.215449191	1.145199218	1.057288943	1.240418957
POU	MDD	Simple mode	26	0.198195452	0.106410406	0.074317174	-0.010368944	0.406759849	1.219200666	0.989684629	1.501943368
POU	MDD	Weighted mode	26	0.193189432	0.101920687	0.06964629	-0.006575115	0.39295398	1.213112574	0.993446454	1.481350216

POU: prescription opioid use; MDD: major depressive disorder; SNP: single nucleotide polymorphism; SE: standard error; lo_ci: lower confidence interval; up_ci: upper confidence interval; OR: odds ratio; lci95: lower 95% confidence interval; uci95: upper 95% confidence interval

Supplementary Table 12. Two-sample MR results of causal relationships for prescription opioid use, insomnia and fibromyalgia

Exposure	Outcome	Methods	N SNP	BETA	SE	<i>P</i> value	lo_ci	up_ci	OR	OR_lci95	OR_uci95
POU	Insomnia	MR Egger	26	0.124772176	0.083956818	0.150259589	-0.039783187	0.289327539	1.132890324	0.960997773	1.335529095
POU	Insomnia	Weighted median	26	0.130592374	0.032131059	4.82E-05	0.067615498	0.19356925	1.139503195	1.06995383	1.213573423
POU	Insomnia	Inverse variance weighted	26	0.124384281	0.027261323	5.05E-06	0.070952088	0.177816475	1.132450967	1.073529789	1.194606061
POU	Insomnia	Simple mode	26	0.136662746	0.076053596	0.0844440063	-0.012402301	0.285727793	1.146441441	0.98767429	1.330730172
POU	Insomnia	Weighted mode	26	0.127932357	0.066950661	0.067556812	-0.003290938	0.259155652	1.136476126	0.996714471	1.295835489
Insomnia	Fibromyalgia	MR Egger	71	-0.451439953	0.447020935	0.31607853	-1.327600986	0.42472108	0.636710658	0.265112508	1.529163846
Insomnia	Fibromyalgia	Weighted median	71	0.327373594	0.169256178	0.05308978	-0.004368514	0.659115703	1.387319675	0.995641014	1.933082159
Insomnia	Fibromyalgia	Inverse variance weighted	71	0.337723955	0.132134782	0.010591202	0.078739783	0.596708128	1.401753503	1.081922751	1.81613048
Insomnia	Fibromyalgia	Simple mode	71	0.281293508	0.431335567	0.516443129	-0.564124203	1.126711219	1.324842399	0.568858133	3.085492288
Insomnia	Fibromyalgia	Weighted mode	71	0.214877326	0.337369774	0.526254936	-0.44636743	0.876122082	1.239709807	0.639948592	2.401568539

POU: prescription opioid use; SNP: single nucleotide polymorphism; SE: standard error; lo_ci: lower confidence interval; up_ci: upper confidence interval; or: odds ratio; lci95: lower 95% confidence interval; uci95: upper 95% confidence interval

Supplementary Table 13. Estimates of the effect of prescription opioid use on fibromyalgia mediated by major depressive disorder and insomnia

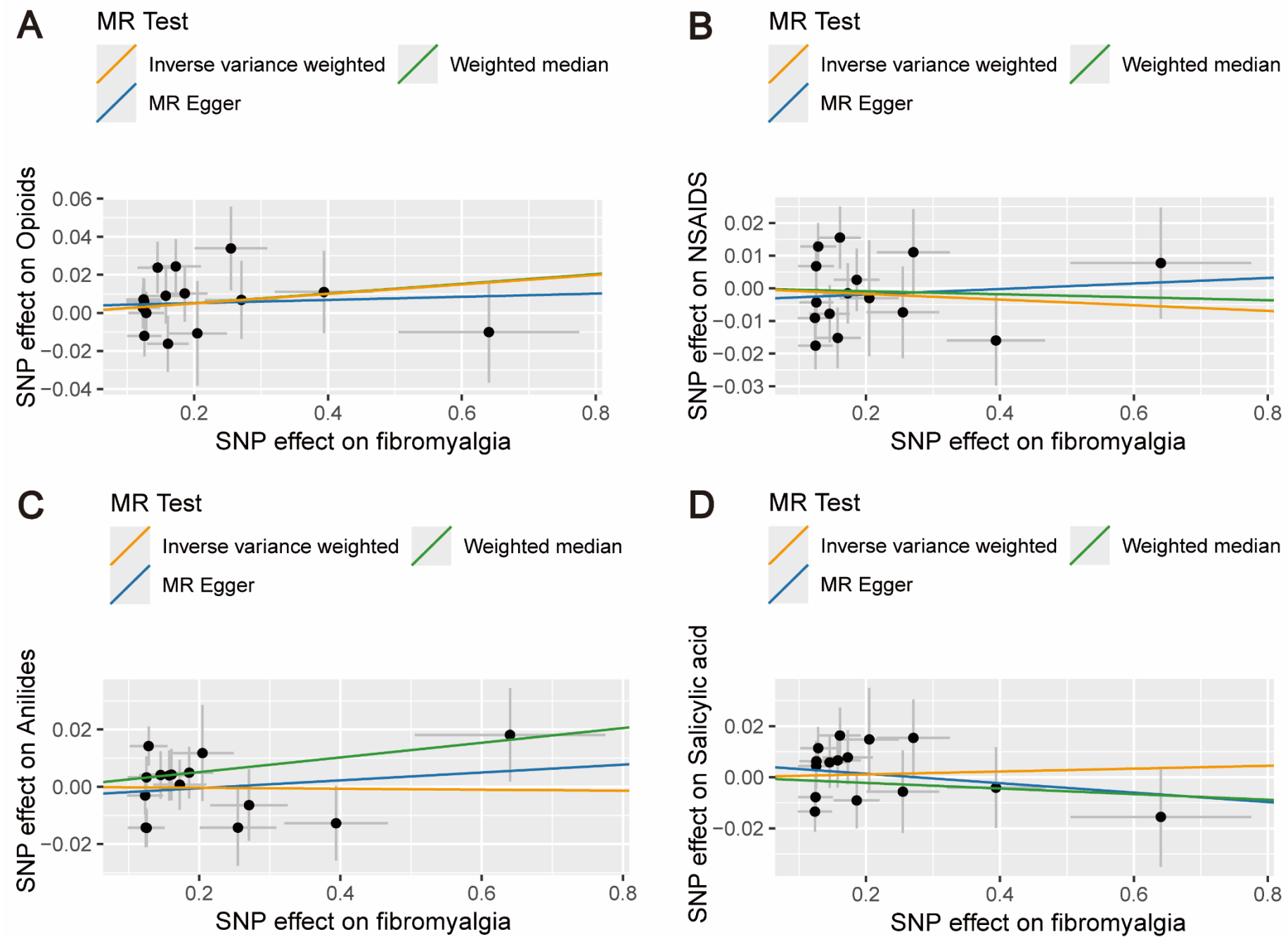
Exposures	Mediator	Outcome	Proportion mediated	Mediating effect	<i>P</i> value
POU	MDD	Fibromyalgia	0.129733452	0.045192431	0.190252
POU	Insomnia	Fibromyalgia	0.120590651	0.042007552	0.347917

POU: prescription opioid use; MDD: major depressive disorder.

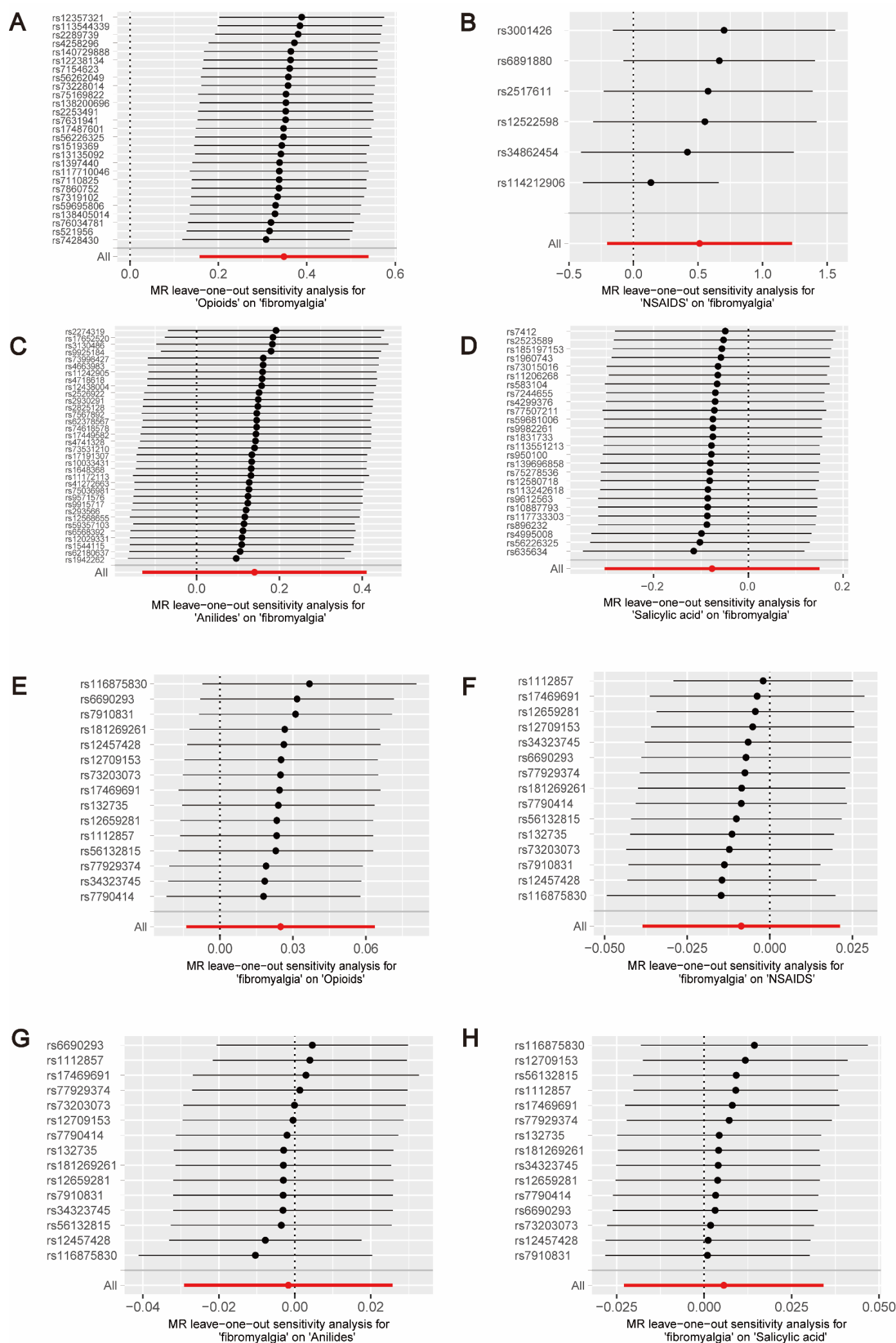
Supplementary Table 14. Two-sample MR results of causal relationships between prescription opioid use and anxiety disorders

Exposure	Outcome	Methods	N SNP	BETA	SE	<i>P</i> value	lo_ci	up_ci	OR	OR_lci95	OR_uci95
POU	Anxiety disorders	MR Egger	20	-0.36996738	0.785904122	0.643470951	-1.910339459	1.170404698	0.690756862	0.148030128	3.223296836
POU	Anxiety disorders	Weighted median	20	-0.0256311	0.162200456	0.874440143	-0.343543994	0.292281793	0.974694588	0.709252278	1.339480421
POU	Anxiety disorders	Inverse variance weighted	20	0.009107327	0.116654475	0.937771603	-0.219535444	0.237750099	1.009148925	0.802891699	1.268392181
POU	Anxiety disorders	Simple mode	20	-0.128370143	0.311794674	0.685156689	-0.739487704	0.482747419	0.879527768	0.477358402	1.620520541
POU	Anxiety disorders	Weighted mode	20	-0.107545894	0.279596076	0.704770263	-0.655554202	0.440462414	0.898035307	0.519154266	1.553425378

POU: prescription opioid use; SNP: single nucleotide polymorphism; SE: standard error; lo_ci: lower confidence interval; up_ci: upper confidence interval; or: odds ratio; lci95: lower 95% confidence interval; uci95: upper 95% confidence interval



Supplementary Figure 1. Scatter plots of the causal effect of fibromyalgia on pain medication use. (A) Scatter plots of the causal effect of fibromyalgia on Opioids; (B) Scatter plots of the causal effect of fibromyalgia on Anti-inflammatory and antirheumatic products(non-steroids); (C) Scatter plots of the causal effect of fibromyalgia on Anilides; (D) Scatter plots of the causal effect of fibromyalgia on Salicylic acid.



Supplementary Figure 2. Leave-one-out analysis of IVW estimates between prescription pain medication use and fibromyalgia. (A) Leave-one-out analysis for Opioids on fibromyalgia; (B) Leave-one-out analysis for Anti-inflammatory and antirheumatic products(non-steroids) on fibromyalgia; (C) Leave-one-out analysis for Anilides on fibromyalgia; (D) Leave-one-out analysis for Salicylic acid on fibromyalgia; (E) Leave-one-out analysis for fibromyalgia on Opioids; (F) Leave-one-out analysis for fibromyalgia on Anti-inflammatory and antirheumatic products(non-steroids); (G) Leave-one-out analysis for fibromyalgia on Anilides; (H) Leave-one-out analysis for fibromyalgia on Salicylic acid.

Supplementary Method 1

We performed mediation Mendelian randomization (Mediation MR) analysis to assess the proportion of the effect of prescription opioid use on fibromyalgia that was mediated by depressive disorder, anxiety and insomnia. First, we obtained the genetic association estimates for the effect of the exposure on the mediator (β_{XZ}) and the effect of the mediator on the outcome (β_{ZY}). The total effect (β_{all}) was the direct estimate of the exposure on the outcome. The mediation effect was calculated as $\beta_{XZ} \times \beta_{ZY}$, representing the indirect effect of the exposure on the outcome via the mediator. The direct effect was calculated as $\beta_{all} - \beta_{XZ} \times \beta_{ZY}$, representing the effect of the exposure on the outcome not through the mediator. Proportion mediated was Calculated as $\beta_{XZ} \times \beta_{ZY} / \beta_{all}$, quantifying the proportion of the total effect mediated by the mediator.

To test the statistical significance of the mediation effect, we employed the product of coefficients method and performed the Sobel test. The standard error (SE) of the mediation effect was calculated using the delta method with the following formula: $S = (\beta_{XZ}^2 \times SE_{ZY}^2 + \beta_{ZY}^2 \times SE_{XZ}^2)^{1/2}$ where SE_{XZ} and SE_{ZY} are the standard errors of the estimates β_{XZ} and β_{ZY} , respectively. Based on this, the Z-statistic was computed ($Z = \beta_{XZ} \times \beta_{ZY} / SE$), and a two-sided P-value was derived.

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