Supplementary Material: Evidence of causal effect of major depression on alcohol dependence: Findings from the Psychiatric Genomics Consortium.

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Supplemental Tables 3

Supplemental Table S1: Listing of 28 Mendelian randomization methods and corresponding variant filtering applied. 3

Supplemental Table S2: Results of the most significant MR approach for each of the MR tests conducted. 4

Supplemental Table S3: Heterogeneity tests conducted with respect to 14 MR tests surviving Bonferroni multiple testing correction. 5

Supplemental Table S4: List of the variants included in the genetic instruments. 6

Supplemental Table S5: Results from 28 MR methods for the 17 causal models tested. 11

S5.1: ACF→AD 11

S5.2: ACF→MD 12

S5.3: ACFe-5→AD 13

S5.4: ACFe-5→MD 14

S5.5: ACQ→AD 15

S5.6: ACQ→MD 16

S5.7: ACQe-5→AD 17

S5.8: ACQe-5→MD 18

S5.9: ADe-5→ACF 19

S5.10: ADe-5→ACQ 20

S5.11: ADe-5→MD 21

S5.12: MDe-5→ACF 22
S5.13: MDe-5→ACQ 23
S5.14: MDe-5→AD 24
S5.15: MD→ACF 25
S5.16: MD→ACQ 26
S5.17: MD→AD 27
Supplemental Table S6: MR-Egger intercept analysis conducted on the 14 findings surviving Bonferroni multiple testing correction. 28
Supplementary Figures 29
Supplemental Figure 1: Distribution of frequency of drinking in the UK Biobank sample. 29
Supplemental Figure S2: Funnel plot (left) and leave-one-out analysis (right) related to the MDe-5 genetic instrument with respect to AD outcome (MDe-5→AD). 30
Supplemental Figure S3: SNP-exposure (AD associations, logOR) and SNP-outcome (MD associations, logOR) coefficients used in the MR analysis. 31
Supplementary Methods 32
Samples 32
Quality checks of UKB alcohol consumption measures 33
Sample Overlap 33
LD score regression analysis 34
Listing of Psychiatric Genomics Consortium Members 35
Major Depressive Disorder Working Group 35
Substance Use Disorder Working Group 43
Acknowledgements 47
References 48

Supplemental Tables

Supplemental Table S1: Listing of 28 Mendelian randomization methods and corresponding variant filtering applied.

	Method	Variant Filtering
1	Egger fixed effects	steiger
2	Egger fixed effects	tophits
3	Egger random effects	steiger
4	Egger random effects	tophits
5	IVW fixed effects	steiger
6	IVW fixed effects	tophits
7	IVW random effects	steiger
8	IVW random effects	tophits
9	Penalised median	steiger
10	Penalised median	tophits
11	Rucker mean (JK)	steiger
12	Rucker mean (JK)	tophits
13	Rucker median (JK)	steiger
14	Rucker median (JK)	tophits
15	Rucker point estimate	steiger
16	Rucker point estimate	tophits
17	Simple median	steiger
18	Simple median	tophits
19	Simple mode	steiger
20	Simple mode	tophits
21	Simple mode (NOME)	steiger
22	Simple mode (NOME)	tophits
23	Weighted median	steiger
24	Weighted median	tophits
25	Weighted mode	steiger
26	Weighted mode	tophits
27	Weighted mode (NOME)	steiger
28	Weighted mode(NOME)	tophits

Note: JK (jackknife); NOME (NO Measurement Error).

Supplemental Table S2: Results of the most significant MR approach for each of the MR tests conducted.

Test	Method	SNPs	Estimate	SE	CI_low	CI_upp	P
1. ACF→AD	Egger	92	-1.967	0.258	-2.473	-1.460	2.51E-11
2. ACF→MD	IVW	96	0.031	0.013	0.006	0.056	0.016
3. ACFe-5→AD	Egger	773	-0.747	0.159	-1.060	-0.435	3.24E-06
4. ACFe-5→MD	IVW	795	0.074	0.008	0.058	0.089	6.50E-20
5. ACQ→AD	IVW	31	0.117	0.012	0.094	0.139	3.81E-11
6. ACQ→MD	IVW	30	0.007	0.001	0.004	0.010	8.06E-05
7. ACQe-5→AD	IVW	385	0.060	0.006	0.048	0.072	7.34E-20
8. ACQe-5→MD	IVW	405	0.008	0.001	0.006	0.009	2.43E-17
9. ADe-5→ACF	Egger	96	-0.055	0.002	-0.059	-0.051	9.11E-48
10. ADe-5→ACQ	IVW	95	0.262	0.013	0.237	0.288	3.26E-36
11. ADe-5→MD	IVW	99	0.006	0.004	-0.001	0.013	0.100
12. MDe-5→ACF	IVW	252	0.024	0.004	0.016	0.032	1.27E-08
13. MDe-5→ACQ	IVW	251	0.306	0.062	0.185	0.428	1.46E-06
14. MDe-5→ADe-5	IVW	259	0.280	0.056	0.169	0.390	1.29E-06
15. MD→ACF	IVW	36	0.053	0.008	0.038	0.068	4.06E-08
16. MD→ACQ	Egger	36	-4.773	0.534	-5.820	-3.726	1.93E-10
17. MD→AD	Rucker median (JK)	40	0.277	0.104	0.038	0.470	0.01

Note: IVW (inverse variance-weighted); JK (jackknife).

Supplemental Table S3: Heterogeneity tests conducted with respect to 14 MR tests surviving Bonferroni multiple testing correction.

Test	Maximum likelihood			MR Egger			IVW			Heterogeneity (P>0.05)
	Q	df	P	Q	df	P	Q	df	P	
ACF→AD	152.4	91	5.87E-05	120.0	90	0.019	151.0	91	7.88E-05	violated
ACFe-5→AD	875.7	772	0.005	864.3	771	0.011	875.0	772	0.006	violated
ACFe-5→MD	1707.1	794	8.72E-69	1702.7	793	1.94E-68	1707.1	794	8.73E-69	violated
ACQ→AD	45.8	30	0.033	36.0	29	0.175	45.2	30	0.037	violated
ACQ→MD	102.1	29	4.48E-10	99.2	28	6.91E-10	98.8	29	1.53E-09	violated
ACQE-5→AD	433.7	384	0.040	425.8	383	0.065	435.3	384	0.036	violated
ACQE-5→MD	957.4	404	6.83E-47	943.5	403	2.46E-45	957.3	404	6.89E-47	violated
ADe-5→ACF	813.6	95	1.4E-114	797.1	94	7E-112	838.4	95	2.3E-119	violated
ADe-5→ACQ	628.3	94	5.91E-80	636.5	93	6.51E-82	643.3	94	9.62E-83	violated
MD→ACF	182.7	35	6.84E-22	184.0	34	1.67E-22	178.8	35	3.31E-21	violated
MD→ACQ	143.1	35	4.99E-15	126.1	34	1.63E-12	139.6	35	1.99E-14	violated
MDe-5→ACF	817.3	251	3.73E-61	813.9	250	6.62E-61	815.1	251	8.11E-61	violated
MDe-5→ACQ	625.1	250	4.68E-34	616.3	249	4.22E-33	623.2	250	8.28E-34	violated
MDe-5→AD	282.6	258	0.140	282.2	257	0.134	282.3	258	0.143	pass

Note: MR=Mendelian Randomization; Q=the weighted sum of squared differences between individual effects and the pooled effect across variants, with the weights being those used in the pooling method; IVW=inverse variance weighted method; df=degrees of freedom. A statistically significant Q test suggests the presence of heterogeneity due to pleiotropy or other causes.

Supplemental Table S4: List of the variants included in the genetic instruments.
GWS: genetic variants with p < 5E-8; e-5: additional suggestive variants (p<1E-5).

	GWS	e-5
MD GWS n=36 e-5 n=259	rs12552;rs1432639;rs8025231;rs12129573;rs12958048;rs247910;rs6905391;rs61867293;rs915057;rs11135349;rs1806153;rs4904738;rs7430565;rs10149470;rs34215985;rs11682175;rs10959913;rs2005864;rs4869056;rs8063603;rs116755193;rs5758265;rs7856424;rs17727765;rs7198928;rs2389016;rs4261101;rs62099069;rs11663393;rs1354115;rs1226412;rs7200826;rs4143229;rs10950398;rs9402472;rs4074723;rs9427672;rs159963;rs11643192;rs56015757	rs2102341;rs9869821;rs56887639;rs41278104;rs4526442;rs12202410;rs7649917;rs2267983;rs11674333;rs2332571;rs143099908;rs58235352;rs4242470;rs913930;rs2509805;rs77087420;rs7771570;rs12966052;rs9592461;rs7659414;rs73102900;rs141769277;rs574593;rs10131621;rs10913112;rs28567442;rs9355502;rs55993664;rs2237517;rs4660091;rs17229439;rs62188629;rs11140773;rs13112458;rs1518367;rs548886;rs326783;rs12440728;rs28684628;rs10895718;rs6471081;rs7017108;rs4870062;rs174594;rs75903747;rs2514218;rs618190;rs281279;rs13296641;rs71639293;rs13012596;rs79631004;rs1945095;rs1548461;rs7566887;rs7580862;rs6063085;rs142091199;rs3734537;rs7288411;rs2730146;rs75344947;rs17058066;rs7118275;rs13414769;rs1403175;rs1542919;rs11866581;rs191117454;rs12194348;rs9363467;rs6676085;rs3806843;rs4645169;rs12667890;rs7543975;rs2316896;rs73104582;rs115888694;rs4741037;rs2576241;rs12923444;rs10780141;rs13032969;rs2085224;rs113689582;rs9663959;rs386906;rs2412137;rs7558022;rs77115380;rs72652244;rs1965662;rs35445561;rs55977891;rs60101897;rs7130926;rs13213510;rs75801343;rs58141521;rs182589382;rs10818400;rs16851266;rs11718931;rs67253370;rs9541811;rs80315381;rs415551;rs12882789;rs75965579;rs372519;rs141729694;rs67436663;rs10193609;rs11649444;rs1484144;rs10164955;rs6549268;rs11697370;rs79146560;rs751;rs2956287;rs7084559;rs4799949;rs7318041;rs62450957;rs78459865;rs115452;rs7248751;rs11590808;rs12353994;rs117763335;rs8044997;rs74004011;rs117901488;rs7727592;rs4757899;rs1526565;rs6848655;rs16890282;rs17792983;rs11205624;rs451162;rs1551281;rs73080460;rs78732941;rs112754009;rs11060415;rs9939201;rs62568191;rs7144406;rs11867618;rs58671397;rs80054962;rs7805525;rs11749656;rs61915164;rs75712664;rs4550100;rs946121;rs72932364;rs62142905;rs2332700;rs4650228;rs272822;rs9825208;rs11945373;rs7808633;rs2906681;rs117466029;rs6058826;rs4417256;rs622726;rs6009347;rs1848322;rs188208805;rs12414918;rs35733856;rs7096162;rs7603111;rs7685163;rs142270618;rs9359139;rs4478545;rs10023969;rs114810615;rs7942337;rs12541504;rs62510219;rs3955150;rs2842586;rs58587963;rs7294775;rs17747401;rs55942359;rs111998295;rs9859955;rs150508916;rs12325768;rs16840705;rs57867301;rs12252016;rs73257781;rs12209889;rs7862197;rs12673908;rs59427701;rs6715781;rs8094639;rs72805045;rs62296782;rs1488400;rs11659932;rs6722247;rs11065340;rs16855545;rs74978286;rs11172371;rs12767338
AD e-5 n=96	-	rs1229984;rs9571413;rs17028896;rs79171978;rs10789062;rs579837;rs111312143;rs1028427;rs13296886;rs77694582;rs8088633;rs147909804;rs2006682;rs870089;rs78323057;rs7240201;rs5768156;rs187025437;rs10191160;rs56328486;rs2970614;rs7823585;rs697958;rs4615888;rs1730735;rs28360848;rs2160261;rs2206569;rs73186506;rs143900286;rs7712550;rs1415133;rs2757859;rs10198090;rs4233;rs72768646;rs1375349;rs117677392;rs9566204;rs7591637;rs3849554;rs3853252;rs13384037;rs79229737;rs1875144;rs1838821;rs1409313;rs34407172;rs757488;rs114993002;rs13206208;rs56403843;rs12904039;rs77324299;rs2115417;rs968079;rs116020305;rs62459100;rs35979784;rs6935819;rs277827;rs7695188;rs11223625;rs59367695;r

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ACF GWS n=92 e-5 n=795	rs1229984;rs1260326;rs11940694;rs2726036;rs187977087;rs1302808;rs1893659;rs58905411;rs35105141;rs13135092;rs11787216;rs9372625;rs2764740;rs33705;rs11039429;rs362307;rs838145;rs473098;rs11640961;rs62244890;rs9814516;rs113011189;rs138993217;rs1078345;rs62466318;rs748919;rs4726481;rs1788030;rs8614;rs12674337;rs461599;rs17486305;rs61873510;rs7330939;rs10188314;rs6567160;rs1421085;rs13102973;rs6030200;rs1228589;rs117799466;rs13390019;rs2717063;rs6962304;rs139816136;rs9349379;rs2159935;rs73050128;rs650558;rs9905730;rs9906502;rs2453875;rs11864886;rs118188698;rs13263946;rs11999622;rs79616692;rs2193098;rs4241258;rs4417025;rs12930744;rs1515591;rs4739105;rs13178443;rs2746025;rs4135294;rs72768626;rs2244598;rs262240;rs12153855;rs6949878;rs9923768;rs11700855;rs780569;rs6699175;rs62339673;rs72892910;rs489062;rs6750325;rs34092348;rs34473884;rs10165161;rs2111861;rs10510130;rs28622224;rs71651683;rs118134876;rs7143137;rs2450038;rs9403297;rs3809827	rs4242715;rs13334375;rs773116;rs1666658;rs7514579;rs13020444;rs9829192;rs72946169;rs2333020;rs6977819;rs1727332;rs4822482;rs10454798;rs10029093;rs17662759;rs4982052;rs17698314;rs2525570;rs7948028;rs7253767;rs28787109;rs6497931;rs11072479;rs518425;rs1592676;rs186347;rs7206833;rs13152711;rs4800204;rs78621285;rs67174000;rs7305229;rs8030809;rs17411201;rs2280334;rs61907308;rs77082783;rs71658797;rs801733;rs920990;rs10278679;rs4883583;rs6810396;rs113569731;rs62477431;rs7970350;rs12139282;rs35073053;rs9959195;rs10893172;rs17185470;rs73168402;rs7919624;rs147913309;rs9649581;rs9313379;rs4877154;rs62135521;rs201438;rs2586462;rs10792669;rs2007761;rs56194430;rs7973103;rs1558426;rs17097556;rs76723380;rs4844948;rs4912532;rs28609675;rs13021035;rs13334065;rs34805485;rs59188188;rs205430;rs4908678;rs150338262;rs34494851;rs4822219;rs9607821;rs185799410;rs3857984;rs10274474;rs613872;rs322776;rs10741228;rs2256042;rs73543300;rs13024996;rs3802134;rs7298932;rs6079439;rs4103350;rs4729573;rs919740;rs12594415;rs17033014;rs146016966;rs2423617;rs7131312;rs11707909;rs550942;rs150620544;rs533143;rs6993770;rs9564398;rs34132475;rs35277691;rs138014720;rs2055581;rs576811;rs74424378;rs565078;rs113695602;rs1605676;rs55834548;rs62032512;rs803223;rs74679146;rs80101850;rs11886864;rs12203592;rs10860227;rs116899184;rs6129084;rs34811474;rs4757589;rs74439139;rs147212529;rs4412427;rs62037863;rs76225816;rs874296;rs9690021;rs17127898;rs2238660;rs2274794;rs2387577;rs28657372;rs4749973;rs6876760;rs7566798;rs8049649;rs11176488;rs113929582;rs11737516;rs11932400;rs13139006;rs68024891;rs8021044;rs194847;rs878650;rs10819272;rs12339878;rs12428363;rs531385;rs7599739;rs911475;rs997467;rs10516441;rs10881995;rs12620112;rs1730142;rs55950970;rs6892188;rs9925015;rs10846422;rs184890270;rs6427160;rs10064927;rs10812220;rs113902570;rs11646721;rs117513075;rs117386364;rs1862205;rs2321871;rs4728701;rs67822265;rs1453027;rs1133822;rs145898511;rs17762018;rs1957891;rs75426915;rs7873013;rs9818981;rs77056814;rs12436192;rs12657131;rs116538582;rs7527242;rs10281159;rs61781392;rs2305656;rs72610002;rs13413257;rs1363119;rs4289073;rs4734113;rs10848575;rs168866;rs9806536;rs1905239;rs35205260;rs76376012;rs77371894;rs10259230;rs11060461;rs149726000;rs7932314;rs8105087;rs9295295;rs11548200;rs142151294;rs565522;rs62271373;rs62576216;rs7197830;rs13096270;rs191050839;rs2608842;rs4798996;rs1158620;rs17214836;rs17648701;rs62149419;rs10830706;rs13354106;rs56328909;rs8133767;rs11070032;rs188810925;rs35505101;rs741300;rs1540687;rs35485971;rs11127264;rs1541456;rs718765;rs72664387;rs78225463;rs825586;rs13248791;rs72633596;rs28847576;rs4742659;rs10616;rs12192387;rs1286254;rs183848312;rs140894866;rs75743445;rs5770872;rs12640626;rs189869162;rs13021454;rs61825452;rs1762777;rs1022666;rs112819214;rs76201730;rs2618615;rs4491284;rs59762781;rs75973672;rs16977123;rs2244460;rs72711443;rs7780801;rs9394656;rs10847019;rs12576516;rs2286975;rs11030578;rs75336816;rs1083337;rs11705838;rs11750012;rs190661793;rs1835366;rs10010043;rs10777337;rs10796098;rs60127739;rs8176510;rs9880967;rs1766167;rs1999

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ACQ GWS n=31 e-5 n=405	rs1229984;rs28712821;rs1260326;rs13107325;rs1302808;rs11604680;rs528301;rs4309187;rs109536;rs7688435;rs11030084;rs13066050;rs17884691;rs6690101;rs62135525;rs2424645;rs61873510;rs7908206;rs34908430;rs13413953;rs56094641;rs2117760;rs4743012;rs190963713;rs9822731;rs4938236;rs59129513;rs11180333;rs1596178;rs858518	rs9517948;rs3756291;rs117917416;rs2413941;rs884300;rs7928223;rs11640031;rs12124523;rs28450941;rs17747233;rs751527;rs974883;rs7831595;rs7080385;rs11860773;rs2533273;rs28929474;rs2789517;rs3811038;rs7132908;rs2201246;rs2756186;rs4759272;rs2111223;rs34060476;rs7119188;rs35529543;rs4480324;rs56073641;rs114328297;rs1921059;rs158609;rs12714026;rs10960629;rs76771389;rs7539883;rs4696055;rs818014;rs828867;rs174568;rs5757905;rs13167181;rs1380358;rs11678525;rs1266182;rs314743;rs12955111;rs529563;rs113443718;rs4582621;rs62312644;rs7009797;rs5026696;rs28450747;rs3829229;rs6944446;rs7871715;rs12786124;rs1819341;rs368565;rs75772932;rs112709686;rs12337051;rs12692050;rs13361473;rs2107903;rs2882321;rs6722461;rs7144180;rs4756104;rs6683303;rs77123275;rs147711594;rs72811598;rs10975579;rs61776651;rs2567387;rs750396;rs12141953;rs4899268;rs7631586;rs9607812;rs10822145;rs11112972;rs7830638;rs140859990;rs17780429;rs2632526;rs440619;rs79652094;rs62333032;rs7483281;rs75265557;rs79227398;rs113942174;rs2068650;rs78423589;rs113239280;rs245568;rs6562616;rs739625;rs12532031;rs3741212;rs2199841;rs73922180;rs925974;rs11634907;rs17177078;rs72960115;rs9947816;rs10123172;rs77535478;rs1055129;rs11917151;rs10151802;rs7087041;rs79006794;rs7654978;rs13035558;rs147865473;rs1910091;rs4671383;rs79346805;rs11589105;rs13207840;rs291550;rs3905155;rs13098920;rs391957;rs1862054;rs78322172;rs10742977;rs113121679;rs11580207;rs2048121;rs2955256;rs4719223;rs11605042;rs7190081;rs7080200;rs7630012;rs2627088;rs2145596;rs1543442;rs8074036;rs1492791;rs2624562;rs55932213;rs111880612;rs147465378;rs3906093;rs9469907;rs141719031;rs11683493;rs143978198;rs112480981;rs11739041;rs273628;rs11648249;rs61999908;rs77178067;rs2195580;rs2214540;rs2013212;rs67486429;rs12413410;rs13296299;rs6943920;rs80137311;rs10903967;rs13357015;rs1884326;rs1528350;rs2274793;rs59824845;rs7557477;rs76045244;rs429150;rs150575801;rs3112887;rs35572189;rs35753830;rs72729664;rs72910144;rs10421783;rs11054854;rs1834373;rs1873341;rs2735313;rs4630770;rs116276044;rs139855233;rs140430387;rs148754536;rs2017500;rs2311435;rs1230163;rs2554671;rs6086808;rs9349379;rs138864321;rs45536631;rs72648451;rs76829797;rs7700874;rs10798945;rs223496;rs2278464;rs2621288;rs273116;rs72752040;rs7553325;rs7687139;rs846012;rs9403215;rs9533742;rs139716206;rs2227827;rs60816887;rs6136465;rs75393236;rs79949859;rs9904617;rs9972882;rs1536260;rs2798221;rs59286975;rs6949073;rs12123775;rs1409767;rs17552417;rs57229705;rs75564661;rs7668470;rs113672126;rs1284442;rs2406231;rs75907151;rs9881842;rs12968939;rs469999;rs55881639;rs73102047;rs7540635;rs10226149;rs10786218;rs12534200;rs1398540

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Supplemental Table S5: Results from 28 MR methods for the 17 causal models tested.

S5.1: ACF→AD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	92	-1.967	0.258	-2.473	-1.460	2.51E-11
2	Egger fixed effects - tophits	92	-1.967	0.258	-2.473	-1.460	2.51E-11
3	Egger random effects - steiger	92	-1.967	0.344	-2.641	-1.292	1.42E-07
4	Egger random effects - tophits	92	-1.967	0.344	-2.641	-1.292	1.42E-07
5	IVW fixed effects - steiger	92	-0.398	0.091	-0.576	-0.221	2.96E-05
6	IVW fixed effects - tophits	92	-0.398	0.091	-0.576	-0.221	2.96E-05
7	IVW random effects - steiger	92	-0.398	0.152	-0.696	-0.100	0.010
8	IVW random effects - tophits	92	-0.398	0.152	-0.696	-0.100	0.010
9	Penalised median - steiger	92	-0.119	0.195	-0.502	0.263	0.541
10	Penalised median - tophits	92	-0.119	0.205	-0.520	0.282	0.560
11	Rucker mean (JK) - steiger	92	-1.448	0.985	0.482	-3.379	0.145
12	Rucker mean (JK) - tophits	92	-1.502	0.965	0.389	-3.393	0.123
13	Rucker median (JK) - steiger	92	-1.902	0.752	-2.635	0.056	0.013
14	Rucker median (JK) - tophits	92	-1.932	0.698	-2.603	0.059	0.007
15	Rucker point estimate - steiger	92	-1.967	0.344	-2.641	-1.292	1.42E-07
16	Rucker point estimate - tophits	92	-1.967	0.344	-2.641	-1.292	1.42E-07
17	Simple median - steiger	92	-0.051	0.187	-0.417	0.315	0.784
18	Simple median - tophits	92	-0.051	0.186	-0.417	0.314	0.783
19	Simple mode - steiger	92	-0.153	0.533	-1.198	0.892	0.774
20	Simple mode - tophits	92	-0.153	0.480	-1.093	0.787	0.750
21	Simple mode (NOME) - steiger	92	-0.153	0.479	-1.092	0.785	0.749
22	Simple mode (NOME) - tophits	92	-0.153	0.543	-1.218	0.911	0.778
23	Weighted median - steiger	92	-0.199	0.202	-0.595	0.197	0.324
24	Weighted median - tophits	92	-0.199	0.195	-0.582	0.183	0.307
25	Weighted mode - steiger	92	-0.242	0.410	-1.046	0.562	0.557
26	Weighted mode - tophits	92	-0.242	0.402	-1.031	0.547	0.549
27	Weighted mode (NOME) - steiger	92	-0.242	0.423	-1.070	0.586	0.568
28	Weighted mode (NOME) - tophits	92	-0.242	0.398	-1.022	0.538	0.545

S5.2: ACF→MD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	96	-0.004	0.029	-0.060	0.052	0.879
2	Egger fixed effects - tophits	96	-0.004	0.029	-0.060	0.052	0.879
3	Egger random effects - steiger	96	-0.004	0.094	-0.190	0.181	0.963
4	Egger random effects - tophits	96	-0.004	0.094	-0.190	0.181	0.963
5	IVW fixed effects - steiger	96	0.031	0.013	0.006	0.056	0.016
6	IVW fixed effects - tophits	96	0.031	0.013	0.006	0.056	0.016
7	IVW random effects - steiger	96	0.031	0.042	-0.050	0.113	0.455
8	IVW random effects - tophits	96	0.031	0.042	-0.050	0.113	0.455
9	Penalised median - steiger	96	-0.007	0.048	-0.102	0.088	0.883
10	Penalised median - tophits	96	-0.007	0.045	-0.096	0.081	0.875
11	Rucker mean (JK) - steiger	96	0.020	0.079	0.174	-0.135	0.802
12	Rucker mean (JK) - tophits	96	0.018	0.077	0.170	-0.134	0.816
13	Rucker median (JK) - steiger	96	0.018	0.046	-0.148	0.199	0.697
14	Rucker median (JK) - tophits	96	0.019	0.045	-0.153	0.178	0.682
15	Rucker point estimate - steiger	96	0.031	0.042	-0.050	0.113	0.455
16	Rucker point estimate - tophits	96	0.031	0.042	-0.050	0.113	0.455
17	Simple median - steiger	96	0.080	0.044	-0.006	0.166	0.070
18	Simple median - tophits	96	0.080	0.043	-0.005	0.164	0.064
19	Simple mode - steiger	96	0.092	0.095	-0.094	0.279	0.333
20	Simple mode - tophits	96	0.092	0.096	-0.096	0.281	0.338
21	Simple mode (NOME) - steiger	96	0.092	0.092	-0.089	0.274	0.320
22	Simple mode (NOME) - tophits	96	0.092	0.098	-0.100	0.285	0.350
23	Weighted median - steiger	96	-0.007	0.046	-0.097	0.084	0.883
24	Weighted median - tophits	96	-0.007	0.046	-0.097	0.083	0.882
25	Weighted mode - steiger	96	-0.004	0.045	-0.092	0.084	0.927
26	Weighted mode - tophits	96	-0.004	0.044	-0.091	0.083	0.926
27	Weighted mode (NOME) - steiger	96	-0.004	0.044	-0.090	0.082	0.925
28	Weighted mode (NOME) - tophits	96	-0.004	0.048	-0.098	0.090	0.932

S5.3: ACFe-5→AD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	773	-0.747	0.159	-1.060	-0.435	3.24E-06
2	Egger fixed effects - tophits	773	-0.747	0.159	-1.060	-0.435	3.24E-06
3	Egger random effects - steiger	773	-0.747	0.179	-1.098	-0.397	3.21E-05
4	Egger random effects - tophits	773	-0.747	0.179	-1.098	-0.397	3.21E-05
5	IVW fixed effects - steiger	773	-0.202	0.054	-0.308	-0.096	1.92E-04
6	IVW fixed effects - tophits	773	-0.202	0.054	-0.308	-0.096	1.92E-04
7	IVW random effects - steiger	773	-0.202	0.061	-0.322	-0.082	0.001
8	IVW random effects - tophits	773	-0.202	0.061	-0.322	-0.082	0.001
9	Penalised median - steiger	773	-0.117	0.094	-0.302	0.068	0.214
10	Penalised median - tophits	773	-0.117	0.093	-0.299	0.065	0.207
11	Rucker mean (JK) - steiger	773	-0.611	0.462	0.295	-1.517	0.187
12	Rucker mean (JK) - tophits	773	-0.602	0.455	0.290	-1.494	0.186
13	Rucker median (JK) - steiger	773	-0.643	0.671	-1.509	-0.043	0.339
14	Rucker median (JK) - tophits	773	-0.619	0.656	-1.475	-0.048	0.346
15	Rucker point estimate - steiger	773	-0.747	0.179	-1.098	-0.397	3.21E-05
16	Rucker point estimate - tophits	773	-0.747	0.179	-1.098	-0.397	3.21E-05
17	Simple median - steiger	773	-0.128	0.091	-0.308	0.051	0.160
18	Simple median - tophits	773	-0.128	0.089	-0.304	0.047	0.151
19	Simple mode - steiger	773	-0.069	0.362	-0.778	0.640	0.848
20	Simple mode - tophits	773	-0.069	0.361	-0.776	0.638	0.848
21	Simple mode (NOME) - steiger	773	-0.069	0.368	-0.790	0.651	0.850
22	Simple mode (NOME) - tophits	773	-0.069	0.376	-0.805	0.667	0.854
23	Weighted median - steiger	773	-0.144	0.096	-0.332	0.044	0.133
24	Weighted median - tophits	773	-0.144	0.095	-0.330	0.042	0.128
25	Weighted mode - steiger	773	-0.032	0.276	-0.572	0.509	0.909
26	Weighted mode - tophits	773	-0.032	0.249	-0.520	0.457	0.899
27	Weighted mode (NOME) - steiger	773	-0.032	0.294	-0.608	0.545	0.915
28	Weighted mode (NOME) - tophits	773	-0.032	0.273	-0.567	0.504	0.908

S5.4: ACFe-5→MD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	795	-0.001	0.021	-0.042	0.041	0.980
2	Egger fixed effects - tophits	795	-0.001	0.021	-0.042	0.041	0.980
3	Egger random effects - steiger	795	-0.001	0.046	-0.090	0.089	0.991
4	Egger random effects - tophits	795	-0.001	0.046	-0.090	0.089	0.991
5	IVW fixed effects - steiger	795	0.074	0.008	0.058	0.089	6.50E-20
6	IVW fixed effects - tophits	795	0.074	0.008	0.058	0.089	6.50E-20
7	IVW random effects - steiger	795	0.074	0.017	0.041	0.107	1.48E-05
8	IVW random effects - tophits	795	0.074	0.017	0.041	0.107	1.48E-05
9	Penalised median - steiger	795	0.055	0.021	0.014	0.097	0.009
10	Penalised median - tophits	795	0.055	0.022	0.013	0.098	0.011
11	Rucker mean (JK) - steiger	795	0.010	0.052	0.112	-0.093	0.851
12	Rucker mean (JK) - tophits	795	0.008	0.053	0.111	-0.096	0.885
13	Rucker median (JK) - steiger	795	4.51E-04	0.059	-0.089	0.098	0.994
14	Rucker median (JK) - tophits	795	-0.002	0.057	-0.088	0.097	0.966
15	Rucker point estimate - steiger	795	-0.001	0.046	-0.090	0.089	0.991
16	Rucker point estimate - tophits	795	-0.001	0.046	-0.090	0.089	0.991
17	Simple median - steiger	795	0.077	0.019	0.039	0.115	6.41E-05
18	Simple median - tophits	795	0.077	0.018	0.041	0.113	2.80E-05
19	Simple mode - steiger	795	0.076	0.082	-0.084	0.236	0.353
20	Simple mode - tophits	795	0.076	0.083	-0.088	0.239	0.364
21	Simple mode (NOME) - steiger	795	0.076	0.085	-0.091	0.242	0.373
22	Simple mode (NOME) - tophits	795	0.076	0.079	-0.078	0.230	0.336
23	Weighted median - steiger	795	0.055	0.021	0.014	0.097	0.009
24	Weighted median - tophits	795	0.055	0.021	0.013	0.097	0.010
25	Weighted mode - steiger	795	0.030	0.045	-0.059	0.120	0.503
26	Weighted mode - tophits	795	0.030	0.042	-0.052	0.112	0.467
27	Weighted mode (NOME) - steiger	795	0.046	0.044	-0.040	0.132	0.299
28	Weighted mode (NOME) - tophits	795	0.046	0.044	-0.041	0.132	0.301

S5.5: ACQ→AD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	31	0.196	0.025	0.146	0.245	1.50E-08
2	Egger fixed effects - tophits	31	0.196	0.025	0.146	0.245	1.50E-08
3	Egger random effects - steiger	31	0.196	0.031	0.134	0.257	7.97E-07
4	Egger random effects - tophits	31	0.196	0.031	0.134	0.257	7.97E-07
5	IVW fixed effects - steiger	31	0.117	0.012	0.094	0.139	3.81E-11
6	IVW fixed effects - tophits	31	0.117	0.012	0.094	0.139	3.81E-11
7	IVW random effects - steiger	31	0.117	0.018	0.081	0.152	3.79E-07
8	IVW random effects - tophits	31	0.117	0.018	0.081	0.152	3.79E-07
9	Penalised median - steiger	31	0.085	0.024	0.038	0.133	4.53E-04
10	Penalised median - tophits	31	0.085	0.024	0.037	0.133	4.83E-04
11	Rucker mean (JK) - steiger	31	0.148	0.058	0.262	0.035	0.016
12	Rucker mean (JK) - tophits	31	0.149	0.058	0.263	0.034	0.016
13	Rucker median (JK) - steiger	31	0.136	0.083	0.060	0.230	0.113
14	Rucker median (JK) - tophits	31	0.139	0.085	0.062	0.231	0.112
15	Rucker point estimate - steiger	31	0.196	0.025	0.146	0.245	1.50E-08
16	Rucker point estimate - tophits	31	0.196	0.025	0.146	0.245	1.50E-08
17	Simple median - steiger	31	0.092	0.025	0.042	0.142	2.97E-04
18	Simple median - tophits	31	0.092	0.026	0.041	0.142	3.48E-04
19	Simple mode - steiger	31	0.110	0.053	0.006	0.214	0.048
20	Simple mode - tophits	31	0.110	0.050	0.011	0.208	0.037
21	Simple mode (NOME) - steiger	31	0.110	0.053	0.005	0.214	0.049
22	Simple mode (NOME) - tophits	31	0.110	0.055	0.003	0.217	0.054
23	Weighted median - steiger	31	0.129	0.026	0.077	0.181	1.05E-06
24	Weighted median - tophits	31	0.129	0.026	0.078	0.180	8.40E-07
25	Weighted mode - steiger	31	0.052	0.058	-0.061	0.165	0.373
26	Weighted mode - tophits	31	0.052	0.056	-0.059	0.163	0.364
27	Weighted mode (NOME) - steiger	31	0.206	0.044	0.121	0.291	4.98E-05
28	Weighted mode (NOME) - tophits	31	0.206	0.044	0.120	0.292	5.73E-05

S5.6: ACQ→MD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	30	-1.68E-04	0.003	-0.005	0.005	0.948
2	Egger fixed effects - tophits	30	-1.68E-04	0.003	-0.005	0.005	0.948
3	Egger random effects - steiger	30	-1.68E-04	0.009	-0.018	0.018	0.985
4	Egger random effects - tophits	30	-1.68E-04	0.009	-0.018	0.018	0.985
5	IVW fixed effects - steiger	30	0.007	0.001	0.004	0.010	8.06E-05
6	IVW fixed effects - tophits	30	0.007	0.001	0.004	0.010	8.06E-05
7	IVW random effects - steiger	30	0.007	0.005	-0.003	0.017	0.204
8	IVW random effects - tophits	30	0.007	0.005	-0.003	0.017	0.204
9	Penalised median - steiger	30	0.002	0.004	-0.007	0.010	0.721
10	Penalised median - tophits	30	0.002	0.004	-0.007	0.010	0.709
11	Rucker mean (JK) - steiger	30	0.002	0.010	0.023	-0.018	0.816
12	Rucker mean (JK) - tophits	30	0.003	0.010	0.022	-0.017	0.799
13	Rucker median (JK) - steiger	30	0.002	0.006	-0.020	0.021	0.688
14	Rucker median (JK) - tophits	30	0.002	0.006	-0.019	0.022	0.704
15	Rucker point estimate - steiger	30	0.007	0.005	-0.003	0.017	0.204
16	Rucker point estimate - tophits	30	0.007	0.005	-0.003	0.017	0.204
17	Simple median - steiger	30	0.011	0.006	-2.72E-04	0.022	0.056
18	Simple median - tophits	30	0.011	0.005	2.45E-05	0.021	0.049
19	Simple mode - steiger	30	0.012	0.011	-0.009	0.034	0.275
20	Simple mode - tophits	30	0.012	0.010	-0.008	0.033	0.257
21	Simple mode (NOME) - steiger	30	0.012	0.012	-0.011	0.035	0.308
22	Simple mode (NOME) - tophits	30	0.012	0.012	-0.010	0.035	0.301
23	Weighted median - steiger	30	0.002	0.004	-0.006	0.010	0.653
24	Weighted median - tophits	30	0.002	0.004	-0.007	0.011	0.662
25	Weighted mode - steiger	30	0.001	0.004	-0.007	0.010	0.753
26	Weighted mode - tophits	30	0.001	0.004	-0.006	0.009	0.718
27	Weighted mode (NOME) - steiger	30	0.002	0.004	-0.006	0.010	0.652
28	Weighted mode (NOME) - tophits	30	0.002	0.004	-0.006	0.010	0.649

S5.7: ACQe-5→AD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	385	0.115	0.017	0.081	0.149	8.77E-11
2	Egger fixed effects - tophits	385	0.115	0.017	0.081	0.149	8.77E-11
3	Egger random effects - steiger	385	0.115	0.019	0.078	0.153	4.51E-09
4	Egger random effects - tophits	385	0.115	0.019	0.078	0.153	4.51E-09
5	IVW fixed effects - steiger	385	0.060	0.006	0.048	0.072	7.34E-20
6	IVW fixed effects - tophits	385	0.060	0.006	0.048	0.072	7.34E-20
7	IVW random effects - steiger	385	0.060	0.007	0.046	0.074	4.63E-16
8	IVW random effects - tophits	385	0.060	0.007	0.046	0.074	4.63E-16
9	Penalised median - steiger	385	0.045	0.011	0.024	0.066	1.92E-05
10	Penalised median - tophits	385	0.045	0.011	0.024	0.066	3.78E-05
11	Rucker mean (JK) - steiger	385	0.091	0.044	0.177	0.004	0.040
12	Rucker mean (JK) - tophits	385	0.090	0.043	0.174	0.006	0.035
13	Rucker median (JK) - steiger	385	0.066	0.030	0.042	0.174	0.029
14	Rucker median (JK) - tophits	385	0.067	0.034	0.040	0.168	0.048
15	Rucker point estimate - steiger	385	0.115	0.017	0.081	0.149	8.77E-11
16	Rucker point estimate - tophits	385	0.115	0.017	0.081	0.149	8.77E-11
17	Simple median - steiger	385	0.050	0.010	0.031	0.070	5.35E-07
18	Simple median - tophits	385	0.050	0.010	0.031	0.070	3.37E-07
19	Simple mode - steiger	385	0.035	0.040	-0.043	0.113	0.378
20	Simple mode - tophits	385	0.035	0.038	-0.039	0.109	0.355
21	Simple mode (NOME) - steiger	385	0.035	0.039	-0.041	0.111	0.366
22	Simple mode (NOME) - tophits	385	0.035	0.039	-0.042	0.112	0.372
23	Weighted median - steiger	385	0.056	0.010	0.036	0.076	3.49E-08
24	Weighted median - tophits	385	0.056	0.011	0.035	0.077	1.85E-07
25	Weighted mode - steiger	385	0.035	0.040	-0.044	0.114	0.384
26	Weighted mode - tophits	385	0.035	0.040	-0.044	0.114	0.387
27	Weighted mode (NOME) - steiger	385	0.035	0.047	-0.057	0.127	0.454
28	Weighted mode (NOME) - tophits	385	0.035	0.046	-0.054	0.124	0.442

S5.8: ACQe-5→MD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	405	-0.005	0.002	-0.009	-3.26E-04	0.035
2	Egger fixed effects - tophits	405	-0.005	0.002	-0.009	-3.26E-04	0.035
3	Egger random effects - steiger	405	-0.005	0.005	-0.014	0.005	0.367
4	Egger random effects - tophits	405	-0.005	0.005	-0.014	0.005	0.367
5	IVW fixed effects - steiger	405	0.008	0.001	0.006	0.009	2.43E-17
6	IVW fixed effects - tophits	405	0.008	0.001	0.006	0.009	2.43E-17
7	IVW random effects - steiger	405	0.008	0.002	0.004	0.011	2.16E-04
8	IVW random effects - tophits	405	0.008	0.002	0.004	0.011	2.16E-04
9	Penalised median - steiger	405	0.001	0.003	-0.005	0.007	0.759
10	Penalised median - tophits	405	0.001	0.003	-0.005	0.007	0.760
11	Rucker mean (JK) - steiger	405	-0.005	0.005	0.005	-0.015	0.339
12	Rucker mean (JK) - tophits	405	-0.005	0.005	0.005	-0.015	0.305
13	Rucker median (JK) - steiger	405	-0.004	0.004	-0.016	0.007	0.270
14	Rucker median (JK) - tophits	405	-0.005	0.004	-0.017	0.006	0.253
15	Rucker point estimate - steiger	405	-0.005	0.005	-0.014	0.005	0.367
16	Rucker point estimate - tophits	405	-0.005	0.005	-0.014	0.005	0.367
17	Simple median - steiger	405	0.005	0.002	0.001	0.010	0.015
18	Simple median - tophits	405	0.005	0.002	0.001	0.010	0.014
19	Simple mode - steiger	405	-0.005	0.009	-0.022	0.012	0.577
20	Simple mode - tophits	405	-0.005	0.008	-0.020	0.011	0.533
21	Simple mode (NOME) - steiger	405	-0.005	0.008	-0.021	0.011	0.558
22	Simple mode (NOME) - tophits	405	-0.005	0.009	-0.022	0.012	0.573
23	Weighted median - steiger	405	0.001	0.003	-0.004	0.007	0.611
24	Weighted median - tophits	405	0.001	0.003	-0.004	0.007	0.625
25	Weighted mode - steiger	405	3.99E-04	0.004	-0.008	0.009	0.924
26	Weighted mode - tophits	405	3.99E-04	0.004	-0.007	0.008	0.918
27	Weighted mode (NOME) - steiger	405	3.99E-04	0.004	-0.008	0.008	0.922
28	Weighted mode (NOME) - tophits	405	3.99E-04	0.004	-0.008	0.008	0.922

S5.9: ADe-5→ACF

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	96	-0.055	0.002	-0.059	-0.051	9.11E-48
2	Egger fixed effects - tophits	96	-0.055	0.002	-0.059	-0.051	9.11E-48
3	Egger random effects - steiger	96	-0.055	0.016	-0.087	-0.023	0.001
4	Egger random effects - tophits	96	-0.055	0.016	-0.087	-0.023	0.001
5	IVW fixed effects - steiger	96	-0.020	0.001	-0.021	-0.018	6.55E-39
6	IVW fixed effects - tophits	96	-0.020	0.001	-0.021	-0.018	6.55E-39
7	IVW random effects - steiger	96	-0.020	0.008	-0.035	-0.004	0.016
8	IVW random effects - tophits	96	-0.020	0.008	-0.035	-0.004	0.016
9	Penalised median - steiger	96	-0.005	0.004	-0.013	0.003	0.251
10	Penalised median - tophits	96	-0.005	0.004	-0.013	0.004	0.259
11	Rucker mean (JK) - steiger	96	-0.049	0.040	0.030	-0.129	0.226
12	Rucker mean (JK) - tophits	96	-0.050	0.042	0.031	-0.132	0.231
13	Rucker median (JK) - steiger	96	-0.051	0.055	-0.143	-4.77E-04	0.357
14	Rucker median (JK) - tophits	96	-0.050	0.057	-0.141	-4.16E-04	0.382
15	Rucker point estimate - steiger	96	-0.055	0.016	-0.087	-0.023	0.001
16	Rucker point estimate - tophits	96	-0.055	0.016	-0.087	-0.023	0.001
17	Simple median - steiger	96	-0.007	0.004	-0.015	0.001	0.089
18	Simple median - tophits	96	-0.007	0.004	-0.015	0.001	0.095
19	Simple mode - steiger	96	-0.011	0.010	-0.032	0.010	0.295
20	Simple mode - tophits	96	-0.011	0.011	-0.032	0.010	0.300
21	Simple mode (NOME) - steiger	96	-0.011	0.011	-0.032	0.010	0.304
22	Simple mode (NOME) - tophits	96	-0.011	0.010	-0.031	0.009	0.284
23	Weighted median - steiger	96	-0.005	0.004	-0.013	0.003	0.238
24	Weighted median - tophits	96	-0.005	0.004	-0.013	0.003	0.238
25	Weighted mode - steiger	96	-0.005	0.009	-0.023	0.013	0.599
26	Weighted mode - tophits	96	-0.005	0.009	-0.022	0.012	0.582
27	Weighted mode (NOME) - steiger	96	-0.006	0.010	-0.025	0.013	0.539
28	Weighted mode (NOME) - tophits	96	-0.006	0.009	-0.024	0.012	0.526

S5.10: ADe-5→ACQ

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	95	0.496	0.027	0.442	0.549	3.22E-32
2	Egger fixed effects - tophits	95	0.496	0.027	0.442	0.549	3.22E-32
3	Egger random effects - steiger	95	0.496	0.187	0.128	0.863	0.010
4	Egger random effects - tophits	95	0.496	0.187	0.128	0.863	0.010
5	IVW fixed effects - steiger	95	0.262	0.013	0.237	0.288	3.26E-36
6	IVW fixed effects - tophits	95	0.262	0.013	0.237	0.288	3.26E-36
7	IVW random effects - steiger	95	0.262	0.089	0.088	0.437	0.004
8	IVW random effects - tophits	95	0.262	0.089	0.088	0.437	0.004
9	Penalised median - steiger	95	0.111	0.051	0.010	0.212	0.031
10	Penalised median - tophits	95	0.111	0.051	0.011	0.211	0.030
11	Rucker mean (JK) - steiger	95	0.501	0.427	1.339	-0.337	0.244
12	Rucker mean (JK) - tophits	95	0.496	0.418	1.315	-0.322	0.238
13	Rucker median (JK) - steiger	95	0.469	0.500	-0.087	1.498	0.351
14	Rucker median (JK) - tophits	95	0.471	0.498	-0.090	1.418	0.347
15	Rucker point estimate - steiger	95	0.496	0.187	0.128	0.863	0.010
16	Rucker point estimate - tophits	95	0.496	0.187	0.128	0.863	0.010
17	Simple median - steiger	95	0.130	0.053	0.027	0.233	0.013
18	Simple median - tophits	95	0.130	0.051	0.031	0.230	0.010
19	Simple mode - steiger	95	0.136	0.124	-0.107	0.379	0.276
20	Simple mode - tophits	95	0.136	0.126	-0.111	0.383	0.285
21	Simple mode (NOME) - steiger	95	0.136	0.132	-0.123	0.395	0.307
22	Simple mode (NOME) - tophits	95	0.136	0.132	-0.123	0.395	0.307
23	Weighted median - steiger	95	0.111	0.051	0.011	0.211	0.030
24	Weighted median - tophits	95	0.111	0.052	0.009	0.213	0.033
25	Weighted mode - steiger	95	0.124	0.109	-0.089	0.337	0.256
26	Weighted mode - tophits	95	0.124	0.113	-0.097	0.345	0.274
27	Weighted mode (NOME) - steiger	95	0.136	0.114	-0.088	0.359	0.237
28	Weighted mode (NOME) - tophits	95	0.136	0.122	-0.102	0.374	0.267

S5.11: ADe-5→MD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	99	-0.008	0.008	-0.024	0.008	0.330
2	Egger fixed effects - tophits	99	-0.008	0.008	-0.024	0.008	0.330
3	Egger random effects - steiger	99	-0.008	0.011	-0.030	0.014	0.489
4	Egger random effects - tophits	99	-0.008	0.011	-0.030	0.014	0.489
5	IVW fixed effects - steiger	99	0.006	0.004	-0.001	0.013	0.100
6	IVW fixed effects - tophits	99	0.006	0.004	-0.001	0.013	0.100
7	IVW random effects - steiger	99	0.006	0.005	-0.004	0.016	0.246
8	IVW random effects - tophits	99	0.006	0.005	-0.004	0.016	0.246
9	Penalised median - steiger	99	0.003	0.007	-0.010	0.017	0.648
10	Penalised median - tophits	99	0.003	0.007	-0.010	0.016	0.636
11	Rucker mean (JK) - steiger	99	-0.003	0.013	0.022	-0.027	0.828
12	Rucker mean (JK) - tophits	99	-0.003	0.012	0.021	-0.027	0.807
13	Rucker median (JK) - steiger	99	0.002	0.012	-0.029	0.015	0.885
14	Rucker median (JK) - tophits	99	0.001	0.012	-0.029	0.014	0.909
15	Rucker point estimate - steiger	99	0.006	0.005	-0.004	0.016	0.246
16	Rucker point estimate - tophits	99	0.006	0.005	-0.004	0.016	0.246
17	Simple median - steiger	99	0.004	0.007	-0.010	0.017	0.601
18	Simple median - tophits	99	0.004	0.007	-0.010	0.017	0.598
19	Simple mode - steiger	99	-0.002	0.016	-0.035	0.030	0.892
20	Simple mode - tophits	99	-0.002	0.016	-0.034	0.029	0.890
21	Simple mode (NOME) - steiger	99	-0.002	0.018	-0.037	0.033	0.900
22	Simple mode (NOME) - tophits	99	-0.002	0.017	-0.036	0.031	0.897
23	Weighted median - steiger	99	0.003	0.007	-0.010	0.016	0.633
24	Weighted median - tophits	99	0.003	0.007	-0.010	0.016	0.633
25	Weighted mode - steiger	99	-0.003	0.014	-0.031	0.024	0.808
26	Weighted mode - tophits	99	-0.003	0.014	-0.030	0.023	0.801
27	Weighted mode (NOME) - steiger	99	-0.003	0.015	-0.033	0.026	0.820
28	Weighted mode (NOME) - tophits	99	-0.003	0.015	-0.032	0.026	0.816

S5.12: MDe-5→ACF

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	252	-0.009	0.010	-0.028	0.010	0.347
2	Egger fixed effects - tophits	252	-0.009	0.010	-0.028	0.010	0.347
3	Egger random effects - steiger	252	-0.009	0.031	-0.071	0.053	0.772
4	Egger random effects - tophits	252	-0.009	0.031	-0.071	0.053	0.772
5	IVW fixed effects - steiger	252	0.024	0.004	0.016	0.032	1.27E-08
6	IVW fixed effects - tophits	252	0.024	0.004	0.016	0.032	1.27E-08
7	IVW random effects - steiger	252	0.024	0.013	-0.002	0.050	0.072
8	IVW random effects - tophits	252	0.024	0.013	-0.002	0.050	0.072
9	Penalised median - steiger	252	0.004	0.017	-0.030	0.037	0.834
10	Penalised median - tophits	252	0.004	0.018	-0.031	0.038	0.837
11	Rucker mean (JK) - steiger	252	0.001	0.026	0.051	-0.050	0.984
12	Rucker mean (JK) - tophits	252	-0.001	0.026	0.051	-0.053	0.971
13	Rucker median (JK) - steiger	252	0.001	0.029	-0.047	0.046	0.966
14	Rucker median (JK) - tophits	252	-0.002	0.030	-0.051	0.043	0.946
15	Rucker point estimate - steiger	252	-0.009	0.031	-0.071	0.053	0.772
16	Rucker point estimate - tophits	252	-0.009	0.031	-0.071	0.053	0.772
17	Simple median - steiger	252	0.037	0.013	0.012	0.062	0.004
18	Simple median - tophits	252	0.037	0.013	0.011	0.062	0.004
19	Simple mode - steiger	252	0.040	0.044	-0.046	0.127	0.358
20	Simple mode - tophits	252	0.040	0.044	-0.045	0.126	0.355
21	Simple mode (NOME) - steiger	252	0.040	0.046	-0.049	0.130	0.378
22	Simple mode (NOME) - tophits	252	0.040	0.047	-0.053	0.134	0.395
23	Weighted median - steiger	252	0.004	0.017	-0.029	0.037	0.804
24	Weighted median - tophits	252	0.004	0.016	-0.028	0.036	0.801
25	Weighted mode - steiger	252	0.001	0.019	-0.037	0.038	0.963
26	Weighted mode - tophits	252	0.001	0.018	-0.034	0.036	0.960
27	Weighted mode (NOME) - steiger	252	0.001	0.019	-0.037	0.038	0.963
28	Weighted mode (NOME) - tophits	252	0.001	0.020	-0.038	0.040	0.964

S5.13: MDe-5→ACQ

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	251	-0.494	0.177	-0.842	-0.147	0.006
2	Egger fixed effects - tophits	251	-0.494	0.177	-0.842	-0.147	0.006
3	Egger random effects - steiger	251	-0.494	0.438	-1.354	0.365	0.261
4	Egger random effects - tophits	251	-0.494	0.438	-1.354	0.365	0.261
5	IVW fixed effects - steiger	251	0.306	0.062	0.185	0.428	1.46E-06
6	IVW fixed effects - tophits	251	0.306	0.062	0.185	0.428	1.46E-06
7	IVW random effects - steiger	251	0.306	0.155	0.002	0.611	0.050
8	IVW random effects - tophits	251	0.306	0.155	0.002	0.611	0.050
9	Penalised median - steiger	251	0.137	0.176	-0.207	0.481	0.436
10	Penalised median - tophits	251	0.137	0.163	-0.183	0.457	0.402
11	Rucker mean (JK) - steiger	251	-0.534	0.503	0.451	-1.519	0.289
12	Rucker mean (JK) - tophits	251	-0.466	0.496	0.505	-1.437	0.348
13	Rucker median (JK) - steiger	251	-0.535	0.427	-1.556	0.389	0.212
14	Rucker median (JK) - tophits	251	-0.458	0.471	-1.473	0.411	0.333
15	Rucker point estimate - steiger	251	-0.494	0.438	-1.354	0.365	0.261
16	Rucker point estimate - tophits	251	-0.494	0.438	-1.354	0.365	0.261
17	Simple median - steiger	251	0.249	0.161	-0.066	0.564	0.122
18	Simple median - tophits	251	0.249	0.160	-0.066	0.563	0.121
19	Simple mode - steiger	251	-0.474	0.543	-1.539	0.590	0.383
20	Simple mode - tophits	251	-0.474	0.570	-1.592	0.643	0.406
21	Simple mode (NOME) - steiger	251	-0.474	0.596	-1.642	0.693	0.426
22	Simple mode (NOME) - tophits	251	-0.474	0.546	-1.544	0.595	0.385
23	Weighted median - steiger	251	0.183	0.171	-0.152	0.518	0.284
24	Weighted median - tophits	251	0.183	0.166	-0.143	0.509	0.271
25	Weighted mode - steiger	251	0.259	0.431	-0.587	1.104	0.549
26	Weighted mode - tophits	251	0.259	0.455	-0.634	1.151	0.570
27	Weighted mode (NOME) - steiger	251	0.336	0.460	-0.565	1.237	0.465
28	Weighted mode (NOME) - tophits	251	0.336	0.458	-0.562	1.234	0.464

S5.14: MDe-5→AD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	259	0.070	0.191	-0.305	0.445	0.715
2	Egger fixed effects - tophits	259	0.070	0.191	-0.305	0.445	0.715
3	Egger random effects - steiger	259	0.070	0.210	-0.342	0.482	0.739
4	Egger random effects - tophits	259	0.070	0.210	-0.342	0.482	0.739
5	IVW fixed effects - steiger	259	0.280	0.056	0.169	0.390	1.29E-06
6	IVW fixed effects - tophits	259	0.280	0.056	0.169	0.390	1.29E-06
7	IVW random effects - steiger	259	0.280	0.062	0.158	0.401	9.64E-06
8	IVW random effects - tophits	259	0.280	0.062	0.158	0.401	9.64E-06
9	Penalised median - steiger	259	0.220	0.093	0.038	0.402	0.018
10	Penalised median - tophits	259	0.220	0.093	0.037	0.403	0.018
11	Rucker mean (JK) - steiger	259	0.266	0.100	0.462	0.070	0.008
12	Rucker mean (JK) - tophits	259	0.267	0.104	0.471	0.063	0.011
13	Rucker median (JK) - steiger	259	0.274	0.065	-0.077	0.408	3.27E-05
14	Rucker median (JK) - tophits	259	0.280	0.068	-0.090	0.408	4.95E-05
15	Rucker point estimate - steiger	259	0.280	0.056	0.169	0.390	1.29E-06
16	Rucker point estimate - tophits	259	0.280	0.056	0.169	0.390	1.29E-06
17	Simple median - steiger	259	0.301	0.091	0.123	0.479	9.36E-04
18	Simple median - tophits	259	0.301	0.088	0.127	0.474	6.79E-04
19	Simple mode - steiger	259	0.272	0.282	-0.281	0.824	0.336
20	Simple mode - tophits	259	0.272	0.303	-0.323	0.866	0.371
21	Simple mode (NOME) - steiger	259	0.272	0.286	-0.289	0.832	0.343
22	Simple mode (NOME) - tophits	259	0.272	0.316	-0.347	0.890	0.390
23	Weighted median - steiger	259	0.220	0.093	0.037	0.403	0.018
24	Weighted median - tophits	259	0.220	0.091	0.042	0.398	0.016
25	Weighted mode - steiger	259	0.122	0.202	-0.273	0.518	0.545
26	Weighted mode - tophits	259	0.122	0.219	-0.307	0.551	0.577
27	Weighted mode (NOME) - steiger	259	0.122	0.229	-0.326	0.570	0.593
28	Weighted mode (NOME) - tophits	259	0.122	0.241	-0.351	0.595	0.613

S5.15: MD→ACF

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	36	0.032	0.035	-0.037	0.100	0.373
2	Egger fixed effects - tophits	36	0.032	0.035	-0.037	0.100	0.373
3	Egger random effects - steiger	36	0.032	0.190	-0.340	0.403	0.868
4	Egger random effects - tophits	36	0.032	0.190	-0.340	0.403	0.868
5	IVW fixed effects - steiger	36	0.053	0.008	0.038	0.068	4.06E-08
6	IVW fixed effects - tophits	36	0.053	0.008	0.038	0.068	4.06E-08
7	IVW random effects - steiger	36	0.053	0.040	-0.025	0.131	0.193
8	IVW random effects - tophits	36	0.053	0.040	-0.025	0.131	0.193
9	Penalised median - steiger	36	0.028	0.031	-0.034	0.089	0.374
10	Penalised median - tophits	36	0.028	0.032	-0.035	0.091	0.387
11	Rucker mean (JK) - steiger	36	0.078	0.187	0.444	-0.289	0.681
12	Rucker mean (JK) - tophits	36	0.071	0.180	0.424	-0.282	0.696
13	Rucker median (JK) - steiger	36	0.050	0.064	-0.193	0.616	0.444
14	Rucker median (JK) - tophits	36	0.048	0.065	-0.196	0.559	0.464
15	Rucker point estimate - steiger	36	0.053	0.040	-0.025	0.131	0.193
16	Rucker point estimate - tophits	36	0.053	0.040	-0.025	0.131	0.193
17	Simple median - steiger	36	0.045	0.031	-0.015	0.106	0.144
18	Simple median - tophits	36	0.045	0.032	-0.017	0.108	0.154
19	Simple mode - steiger	36	0.081	0.070	-0.056	0.218	0.256
20	Simple mode - tophits	36	0.081	0.066	-0.048	0.210	0.226
21	Simple mode (NOME) - steiger	36	0.081	0.073	-0.062	0.224	0.275
22	Simple mode (NOME) - tophits	36	0.081	0.068	-0.052	0.214	0.241
23	Weighted median - steiger	36	0.033	0.032	-0.029	0.096	0.293
24	Weighted median - tophits	36	0.033	0.031	-0.027	0.094	0.278
25	Weighted mode - steiger	36	0.043	0.059	-0.073	0.159	0.469
26	Weighted mode - tophits	36	0.043	0.056	-0.067	0.153	0.446
27	Weighted mode (NOME) - steiger	36	0.053	0.073	-0.090	0.196	0.474
28	Weighted mode (NOME) - tophits	36	0.053	0.067	-0.079	0.184	0.437

S5.16: MD→ACQ

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	36	-4.773	0.534	-5.820	-3.726	1.93E-10
2	Egger fixed effects - tophits	36	-4.773	0.534	-5.820	-3.726	1.93E-10
3	Egger random effects - steiger	36	-4.773	1.982	-8.658	-0.888	0.022
4	Egger random effects - tophits	36	-4.773	1.982	-8.658	-0.888	0.022
5	IVW fixed effects - steiger	36	-0.565	0.109	-0.778	-0.352	8.82E-06
6	IVW fixed effects - tophits	36	-0.565	0.109	-0.778	-0.352	8.82E-06
7	IVW random effects - steiger	36	-0.565	0.446	-1.439	0.309	0.214
8	IVW random effects - tophits	36	-0.565	0.446	-1.439	0.309	0.214
9	Penalised median - steiger	36	-1.118	0.370	-1.843	-0.393	0.002
10	Penalised median - tophits	36	-1.118	0.383	-1.868	-0.368	0.003
11	Rucker mean (JK) - steiger	36	-5.141	2.626	0.005	-10.287	0.058
12	Rucker mean (JK) - tophits	36	-5.339	2.660	-0.126	-10.552	0.052
13	Rucker median (JK) - steiger	36	-4.739	2.236	-10.764	-0.537	0.041
14	Rucker median (JK) - tophits	36	-4.887	2.276	-11.274	-0.692	0.039
15	Rucker point estimate - steiger	36	-4.773	1.982	-8.658	-0.888	0.022
16	Rucker point estimate - tophits	36	-4.773	1.982	-8.658	-0.888	0.022
17	Simple median - steiger	36	-0.971	0.376	-1.707	-0.235	0.010
18	Simple median - tophits	36	-0.971	0.370	-1.696	-0.246	0.009
19	Simple mode - steiger	36	-1.507	0.677	-2.833	-0.181	0.032
20	Simple mode - tophits	36	-1.507	0.682	-2.843	-0.171	0.034
21	Simple mode (NOME) - steiger	36	-1.507	0.683	-2.846	-0.168	0.034
22	Simple mode (NOME) - tophits	36	-1.507	0.696	-2.871	-0.143	0.037
23	Weighted median - steiger	36	-0.986	0.372	-1.715	-0.256	0.008
24	Weighted median - tophits	36	-0.986	0.367	-1.705	-0.266	0.007
25	Weighted mode - steiger	36	-1.287	0.583	-2.430	-0.144	0.034
26	Weighted mode - tophits	36	-1.287	0.586	-2.435	-0.139	0.035
27	Weighted mode (NOME) - steiger	36	-1.350	0.674	-2.672	-0.028	0.053
28	Weighted mode (NOME) - tophits	36	-1.350	0.622	-2.569	-0.131	0.037

S5.17: MD→AD

	Method - Filtering	SNPs	Estimate	SE	CI_low	CI_upp	P
1	Egger fixed effects - steiger	40	-0.357	0.846	-2.016	1.301	0.675
2	Egger fixed effects - tophits	40	-0.357	0.846	-2.016	1.301	0.675
3	Egger random effects - steiger	40	-0.357	0.699	-1.727	1.012	0.612
4	Egger random effects - tophits	40	-0.357	0.699	-1.727	1.012	0.612
5	IVW fixed effects - steiger	40	0.274	0.138	0.004	0.544	0.054
6	IVW fixed effects - tophits	40	0.274	0.138	0.004	0.544	0.054
7	IVW random effects - steiger	40	0.274	0.113	0.052	0.496	0.021
8	IVW random effects - tophits	40	0.274	0.113	0.052	0.496	0.021
9	Penalised median - steiger	40	0.264	0.178	-0.085	0.613	0.138
10	Penalised median - tophits	40	0.264	0.179	-0.087	0.615	0.140
11	Rucker mean (JK) - steiger	40	0.279	0.106	0.487	0.070	0.012
12	Rucker mean (JK) - tophits	40	0.270	0.108	0.481	0.059	0.016
13	Rucker median (JK) - steiger	40	0.281	0.108	0.060	0.480	0.013
14	Rucker median (JK) - tophits	40	0.277	0.104	0.038	0.470	0.011
15	Rucker point estimate - steiger	40	0.274	0.138	0.004	0.544	0.054
16	Rucker point estimate - tophits	40	0.274	0.138	0.004	0.544	0.054
17	Simple median - steiger	40	0.309	0.175	-0.034	0.653	0.078
18	Simple median - tophits	40	0.309	0.168	-0.021	0.639	0.066
19	Simple mode - steiger	40	0.526	0.392	-0.241	1.294	0.187
20	Simple mode - tophits	40	0.526	0.399	-0.257	1.309	0.195
21	Simple mode (NOME) - steiger	40	0.526	0.372	-0.202	1.255	0.165
22	Simple mode (NOME) - tophits	40	0.526	0.367	-0.193	1.246	0.160
23	Weighted median - steiger	40	0.263	0.173	-0.076	0.602	0.129
24	Weighted median - tophits	40	0.263	0.175	-0.080	0.605	0.132
25	Weighted mode - steiger	40	0.289	0.347	-0.392	0.969	0.411
26	Weighted mode - tophits	40	0.289	0.360	-0.418	0.995	0.428
27	Weighted mode (NOME) - steiger	40	0.310	0.333	-0.342	0.962	0.357
28	Weighted mode (NOME) - tophits	40	0.310	0.349	-0.375	0.995	0.380

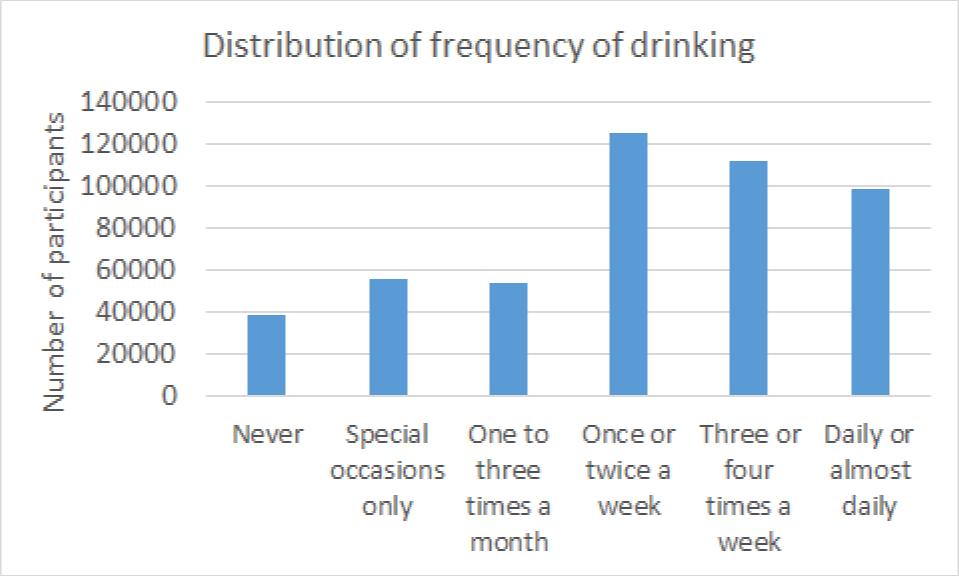
Supplemental Table S6: MR-Egger intercept analysis conducted on the 14 findings surviving Bonferroni multiple testing correction.

Test	MR-Egger Estimate			MR-Egger Intercept			MR-Egger Intercept (P > 0.1)
	Beta	SE	P	Intercept	SE	P	
ACF→AD	-0.75	0.18	3.21E-05	0.043	0.009	3.36E-06	violated
ACFe-5→AD	-0.001	0.09	0.991	0.011	0.003	0.001	violated
ACFe-5→MD	0.12	0.02	4.51E-09	0.002	0.001	0.081	violated
ACQ→AD	-0.005	0.01	0.367	-0.033	0.011	0.006	violated
ACQ→MD	0.2	0.04	7.97E-07	0.003	0.003	0.354	pass
ACQe-5→AD	<0.001	<0.01	0.985	-0.014	0.004	0.002	violated
ACQe-5→MD	-1.97	0.37	1.42E-07	0.003	0.001	0.009	violated
ADe-5→ACF	-0.05	0.02	0.001	0.007	0.003	0.017	violated
ADe-5→ACQ	0.5	0.19	0.010	-0.046	0.032	0.161	pass
MD→ACF	-0.01	0.03	0.772	0.001	0.006	0.908	pass
MD→ACQ	-0.49	0.44	0.261	0.142	0.065	0.037	violated
MDe-5→ACF	0.07	0.21	0.739	0.001	0.001	0.247	pass
MDe-5→ACQ	0.03	0.18	0.868	0.027	0.014	0.052	violated
MDe-5→AD	-4.77	2.08	0.022	0.007	0.006	0.297	pass

Note: Abbreviations: ACF, alcohol consumption frequency; ACQ, alcohol consumption quantity; AD, alcohol dependence; MD, major depression. An intercept significantly different from zero suggests directional pleiotropy.

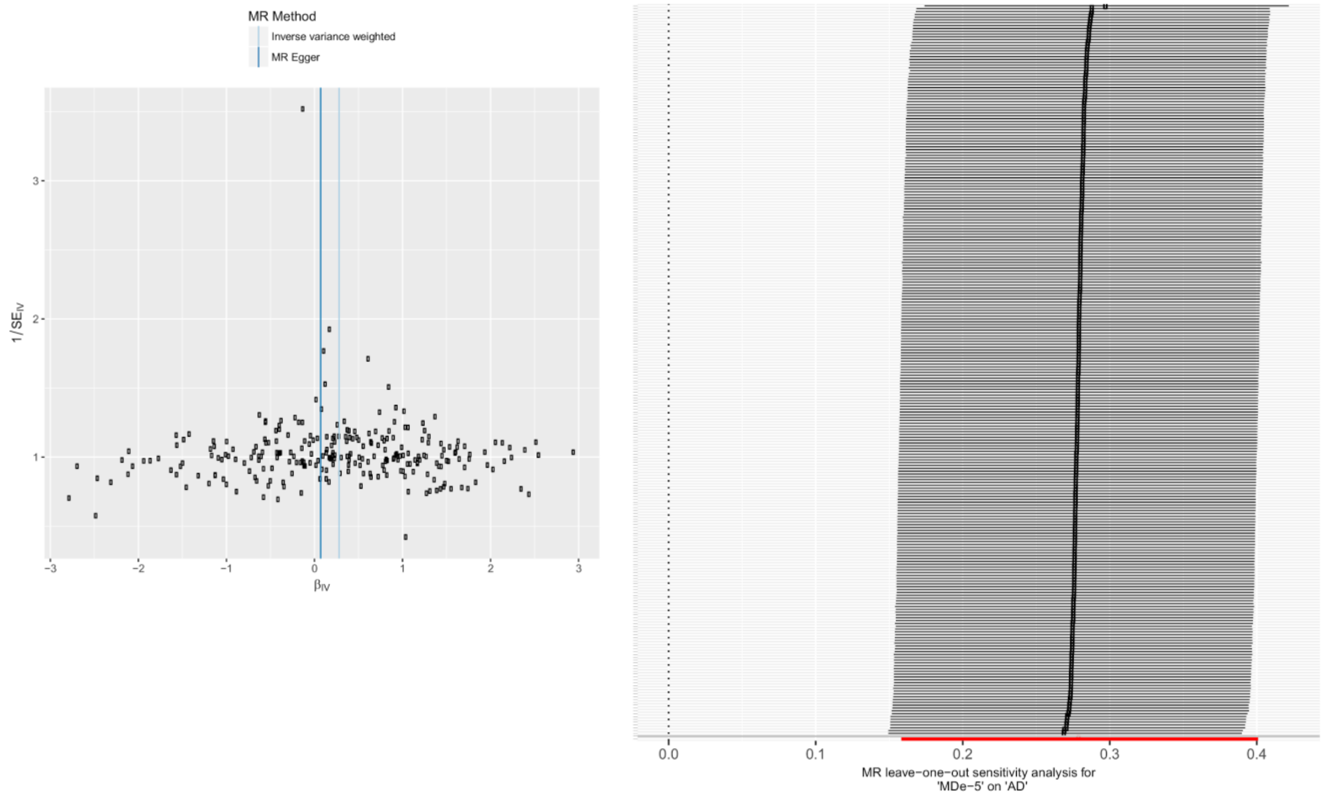
Supplementary Figures

Supplemental Figure 1: Distribution of frequency of drinking in the UK Biobank sample.



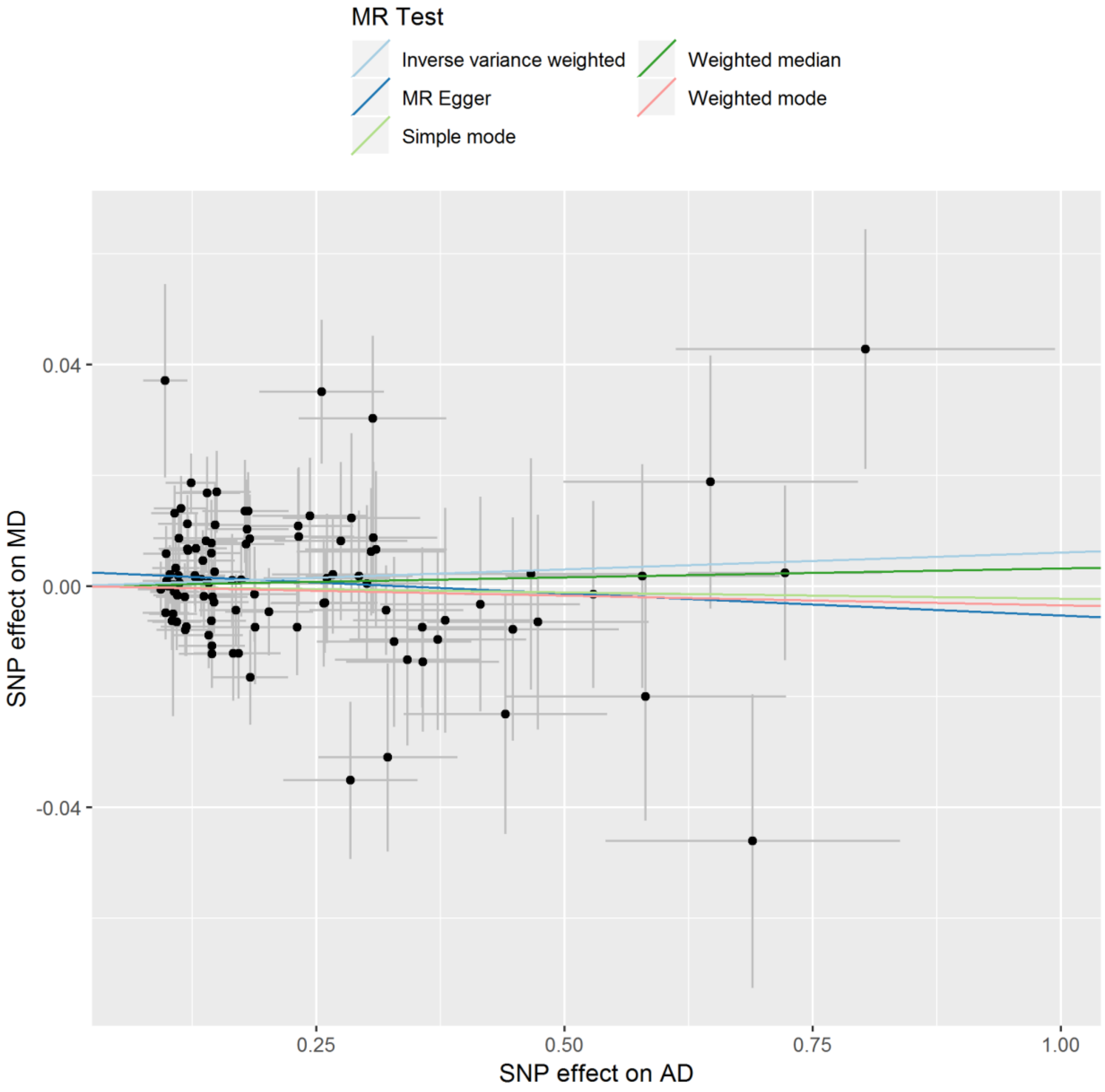
Note: in the original UK Biobank scoring, scores ranged from 1 (daily or almost daily) to 6 (never). In our analyses, scores were recoded to ensure that higher scores represented more frequent drinking.

Supplemental Figure S2: Funnel plot (left) and leave-one-out analysis (right) related to the MDe-5 genetic instrument with respect to AD outcome (MDe-5→AD).
Funnel plot reports the contribution of each variant (effect size on the x-axis, 1/SE on the y-axis) to MR estimate (solid lines; light-blue for Inverse Variance Weighted (IVW), blue for MR-Egger). Leave-one-out plot report the MR estimate (IVW) excluding one variant at a time from the genetic instrument.



Abbreviations: ACF, alcohol consumption frequency; ACQ, alcohol consumption quantity; AD, alcohol dependence; MD, major depression; IVW, Inverse Variance Weighted.

Supplemental Figure S3: SNP-exposure (AD associations, logOR) and SNP-outcome (MD associations, logOR) coefficients used in the MR analysis.
Error bars (95% CIs) are reported for each association.



Supplementary Methods

Samples

1. Major depression (MD)[1]

MD summary association data were obtained from the latest GWAS meta-analysis including 135,458 MD cases and 344,901 controls from the MD working group of the PGC (PGC-MDD2), which included 7 cohorts: (1) 29 samples of European-ancestry with MD-cases required to meet international consensus criteria (DSM-IV, ICD-9, or ICD-10) for a lifetime diagnosis of MD established using structured diagnostic instruments from assessments by trained interviewers, clinician-administered checklists, or medical record review and controls in most samples were screened for the absence of lifetime MD (22/29 samples), and randomly selected from the population; (2) Generation Scotland employed direct interviews; (3) iPSYCH (Denmark) used national treatment registers; (4) deCODE (Iceland) used national treatment registers and direct interviews; (5) GERA used Kaiser-Permanente treatment records (CA, US); (6) UK Biobank combined self-reported MD symptoms and/or treatment for MD by a medical professional; and (7) 23andMe used self-report of treatment for MD by a medical professional. All controls included in datasets 2-7 were screened for the absence of MD.

2. Alcohol Dependence (AD)[2]

AD summary association data from unrelated subjects of European descent (10,206 cases; 28,480 controls) were obtained from GWAS meta-analysis of 14 cohorts conducted by the PGC Substance Use Disorder Workgroup. Detailed descriptions of the AD samples have been previously reported. In brief, AD was defined as meeting criteria for a DSM-IV (or DSM-IIIR in one instance) diagnosis of AD and with the exception of three cohorts with population-based controls (n=7,015), all controls were screened for AD. Individuals with no history of drinking alcohol and those meeting criteria for DSM-IV alcohol abuse were additionally excluded as controls where applicable (i.e., where these data were available).

3. UK Biobank (UKB) - alcohol consumption quantity and frequency

The UK Biobank cohort consists of 502,000 middle-aged (40-69 years) individuals recruited from the United Kingdom. The UK Biobank records extensive (n>2000) phenotypes of the participants ranging from anthropometric traits, to disease status, to lifestyle behaviors.

Information on alcohol intake was obtained through various self-report questionnaires. Frequency of consumption (AC-Frequency) was assessed in 501,718 participants (UKB field IDs: 1558) with the item “About how often do you drink alcohol?”. Frequency was originally assessed at a scale ranging from 1 (daily or almost daily) to 6 (never), but was reverse coded so that a lower score represented less frequent drinking. Supplementary Figure 3 shows the distribution in the UKB population. In those who drink at least once or twice a week, information on quantity of consumption (AC-Quantity) was assessed (n=348,039). AC-Quantity was assessed based on the average weekly alcohol intake for five general classes: red wine (field ID: 1568), champagne plus white wine (field ID: 1578), spirits (field ID: 1598), beer plus cider intake (field ID: 1558), and fortified wine (field ID: 1608). The following item was used: “In an average WEEK, how many servings of {class of alcohol} would you drink?”.

For a complete description of the UKB genotype curation, please see the report by Ong and colleagues.[3] All participants provided informed written consent, the study was approved by the National Research Ethics Service Committee North West – Haydock, and all study procedures were performed in accordance with the World Medical Association Declaration of Helsinki ethical principles for medical research. In brief, approximately 488,000 participants were genotyped and on custom-designed Affymetrix UK BiLEVE Axiom or UK Biobank Axiom arrays (Affymetrix Santa Clara, USA), which produced a combined total of 805,426 markers in the released data. Following standard quality control (QC) the dataset was phased and ~96M genotypes were imputed using Haplotype Reference Consortium (HRC) and UK10K haplotype resources.[4–6] Due to the UKB's reported QC issues with non-HRC SNPs, we retained only the ~40M HRC SNPs for analysis. In light of a large number of related individuals in the UKB cohort, the GWAS was performed using BOLT-LMM which is a linear mixed model framework that explicitly models the genetic relatedness within the sample.[7]

Among the 487,409 individuals who passed initial genotyping QC, 409,694 participants had white-British ancestry, based on self-reported ethnicity and genetic principal components. To maximize our effective sample size, we also included UKB participants if their self-reported ancestry was not white-British (this includes a substantial number of individuals reporting their ancestry as "Irish" or "any other white background") but their first two genetic principal components fell within the region of those that are classified white-British in the n = 409,694 set. We identified 438,870 individuals for this study who are genetically similar to those of white-British ancestry. After exclusion of ethnic outliers, we included 438,308 participants in the AC-Frequency and 307,098 participants in the AC-Quantity GWAS.

Quality checks of UKB alcohol consumption measures

To combine the different classes of alcohol, we followed the procedures developed by Clarke et al.,[8] although a few minor changes were made. In contrast to Clarke et al., we excluded outliers using sex-specific norms and we did not include weight as a covariate in our analysis. To calculate the total units of alcohol, the number of reported drinks was multiplied with a factor depending on the class of alcohol. The factors were 1.67 (red wine and champagne/white wine), 2.3 (beer), 1 (spirit), and 2.25 (fortified wine). We subsequently identified outliers as those who score >5 SD above the average. Outliers were determined in males and females separately. After exclusion of outliers, the mean level of AC-Quantity was 19.90 units (SD=16.26). As expected, the mean level of AC-Quantity was higher in males (mean=25.16; SD=18.72) compared to females (mean=14.42; SD=10.76). Next, we performed a regression analysis including AC-Quantity as the dependent variable and age and sex as predictors. The residuals were used as the outcome measure in genetic association analyses.

Sample Overlap

Among the samples included in the MD and AD GWAS, three cohorts (of 22 AD cohorts and 35 MD cohorts) were present in both analyses and some individuals from these cohorts may overlap. LD score regression is not biased by sample overlap.[9] Simulations on two-sample MR methods demonstrated that the relative bias (which may be toward a null direction) with 50% sample overlap was 5% and with 30% sample overlap was 3%.[10] To quantify potential bias from GWAS summary statistics due to overlapping samples, we used LambdaMeta implemented in GEnetic Analysis Repository (GEAR).[11] Under the null hypothesis, LambdaMeta is 1 when no "sample-overlap" effect is affecting the pair of summary statistics. When the summary statistics are affected by sample overlap, LambdaMeta < 1; when there are technical differences, LambdaMeta > 1. LambdaMeta between MD and AD GWAS was 1.0021, suggesting results should not be significantly biased due to sample overlap.

LD score regression analysis

The proportion of variance in phenotypic liability that could be explained by the aggregated effect of all SNPs (h^{2-}SNP) was estimated using LD-Score Regression analysis.[9] The method is based on the premise that an estimated SNP effect-size includes effects of all SNPs in linkage disequilibrium (LD) with that SNP. A SNP that tags many other SNPs will have a higher probability of tagging a causal genetic variant compared to a SNP that tags few other SNPs. The LD score measures the amount of genetic variation tagged by a SNP within a specific population. Accordingly, assuming a trait with a polygenic architecture, SNPs with a higher LD-score have on average stronger effect sizes than SNPs with lower LD-scores. When regressing the effect size from the association analysis against the LD score for each SNP, the slope of the regression line provides an estimate of the proportion of variance accounted for by all SNPs included in the estimation of LD scores.[9] For this analysis, we included in the regression 1,217,311 SNPs that were present in the HapMap 3 reference panel. Analyses were performed using pre-computed LD scores based on 1000 Genomes Project reference data on individuals of European ancestry (available for download at https://data.broadinstitute.org/alkesgroup/LDSCORE/). The h^2-SNP estimates for the two binary traits were converted to the liability scale, using sample prevalence of 0.159 for AD and 0.15 for MD. It should be noted that h^2-SNP estimates may be slightly underestimated since summary statistics were derived from a linear mixed model analysis (BOLT-LMM) and mixed models may change the expected behavior of the mean chi-square.

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Sarah E Medland 28
Divya Mehta 2, 75
Christel M Middeldorp 10, 76, 77
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Wouter J Peyrot 19
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Jorge A Quiroz 88
Per Qvist 7, 8, 9
John P Rice 89
Brien P. Riley 17
Margarita Rivera 27, 90
Saira Saeed Mirza 36
Robert Schoevers 91
Eva C Schulte 92, 93
Ling Shen 61
Jianxin Shi 94
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Grant C B Sinnamon 97
Johannes H Smit 19
Daniel J Smith 98
Hreinn Stefansson 99
Stacy Steinberg 99
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Henning Teismann 101
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Wesley Thompson 9, 53, 103, 104
Pippa A Thomson 105
Thorgeir E Thorgeirsson 99
Matthew Traylor 106
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Vassily Trubetskoy 4
André G Uitterlinden 107
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Peter M Visscher 1, 2
Yunpeng Wang 9, 53, 104
Bradley T. Webb 111
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Jürgen Wellmann 101
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Hualin S Xi 112
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Volker Arolt 114
Bernhard T Baune 14
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Sven Cichon 34, 46, 115, 116
Udo Dannlowski 114
EJC de Geus 10, 117
J Raymond DePaulo 49

Enrico Domenici 118
Katharina Domschke 119
Tõnu Esko 5, 78
Hans J Grabe 109
Steven P Hamilton 120
Caroline Hayward 121
Andrew C Heath 89
Kenneth S Kendler 17
Stefan Kloiber 58, 122, 123
Glyn Lewis 124
Qingqin S Li 125
Susanne Lucae 58
Pamela AF Madden 89
Patrik K Magnusson 22
Nicholas G Martin 28
Andrew M McIntosh 11, 33
Andres Metspalu 78, 126
Ole Mors 9, 127
Preben Bo Mortensen 8, 9, 12, 13
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Thomas G Schulze 47, 93, 133, 134, 135
Jordan W Smoller 38, 39, 40
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