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

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# **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 |
| MDGWS n=36e-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 |
| ADe-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;rs12130986;rs138113771;rs117423246;rs77857549;rs1069713;rs72774745;rs7780507;rs75454767;rs12294621;rs115905625;rs117237067;rs7708547;rs2344350;rs7230303;rs4932479;rs17685204;rs6790555;rs11905918;rs117292932;rs116498276;rs34440275;rs7805762;rs1729435;rs80284955;rs2478836;rs9616088;rs17762082;rs58333289;rs62001835;rs419742;rs140551998;rs2211257;rs56287425;rs4673119;rs10209092 |
| ACFGWS n=92e-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;rs1999124;rs9586550;rs10860862;rs10876200;rs6534293;rs9611883;rs149204679;rs6102221;rs1004478;rs8049975;rs12619698;rs140030075;rs2224873;rs112782399;rs117198910;rs1668145;rs36058267;rs75911910;rs117933573;rs10190125;rs17577546;rs12786237;rs62177355;rs76358731;rs11609860;rs11712750;rs139604081;rs62439319;rs295018;rs34880628;rs10189857;rs2844333;rs28828150;rs72696774;rs74601167;rs985553;rs12337009;rs34853711;rs77518705;rs9564692;rs6864478;rs8015745;rs9544000;rs10787760;rs112972431;rs117274283;rs16835292;rs956752;rs1401955;rs16966646;rs142965466;rs2283460;rs73277969;rs3024629;rs35010655;rs3922824;rs45504492;rs78685194;rs10032667;rs73187733;rs1784862;rs56186469;rs13170975;rs1431558;rs13111060;rs2309241;rs2944776;rs4884859;rs71494763;rs117117913;rs12121490;rs1870998;rs2410001;rs2852045;rs34737940;rs71565748;rs76793233;rs10937101;rs11173335;rs112635299;rs1174687;rs12245197;rs13120213;rs17310025;rs34896720;rs4801850;rs4812700;rs56228311;rs62182135;rs76749787;rs78509406;rs846012;rs10184004;rs10507758;rs10773974;rs10793986;rs11768020;rs11790082;rs13169322;rs2276966;rs35820211;rs4092465;rs62019905;rs6853599;rs7311803;rs7592564;rs79203683;rs35886351;rs36053727;rs62159870;rs6723854;rs7158551;rs7444051;rs7875010;rs11662970;rs11688135;rs13146322;rs141261452;rs145334515;rs1483796;rs153060;rs1981098;rs28409011;rs59927996;rs61499730;rs7561278;rs7594388;rs76183880;rs76354419;rs957523;rs11673889;rs139931532;rs141976463;rs145806557;rs150565883;rs17018664;rs17034081;rs2307273;rs34135807;rs4851300;rs73073894;rs7357754;rs75168584;rs867987;rs1202288;rs12127199;rs17088197;rs2074388;rs35120418;rs4812492;rs6937144;rs7511006;rs76907224;rs7731540;rs9819832;rs11993084;rs12453682;rs13307443;rs144364889;rs149048491;rs1793811;rs2322834;rs4936644;rs60745358;rs60791078;rs74498418;rs7862119;rs111694597;rs11741952;rs12718064;rs1393065;rs1585524;rs1891196;rs356465;rs55905351;rs76825908;rs114546625;rs116212148;rs12194193;rs1966859;rs2971016;rs4732788;rs57057505;rs7332134;rs7789946;rs11106114;rs1119248;rs11589269;rs117555837;rs13020754;rs16981755;rs34480849;rs347675;rs4236892;rs4772811;rs72896573;rs766476;rs78672418;rs9949235;rs11221547;rs117034637;rs12466127;rs17716086;rs2914860;rs35005836;rs366684;rs3845865;rs58740162;rs6485475;rs1001939;rs10460192;rs116581473;rs117123482;rs13147207;rs314961;rs4760029;rs6919440;rs9343;rs10739773;rs117588436;rs12703359;rs17397728;rs28733079;rs389877;rs6013500;rs74615678;rs8107051;rs9546474;rs10245705;rs11688502;rs16991213;rs17049738;rs17083734;rs28693968;rs73088494;rs74531417;rs75229149;rs112779396;rs11674460;rs11775949;rs11805391;rs11971487;rs12145004;rs12250380;rs2660824;rs4744264;rs6480771;rs76749014;rs116896093;rs2862996;rs3101409;rs34650286;rs62535504;rs72886368;rs76050430;rs7616192;rs78903711;rs12491347;rs147839860;rs181817998;rs2399023;rs35031736;rs35438744;rs61908948;rs948656;rs9611007;rs113439251;rs12622374;rs1475259;rs61784580;rs67142644;rs7038598;rs113209907;rs138567114;rs145028172;rs146768419;rs4833353;rs12283755;rs12449895;rs13007283;rs13398888;rs2585593;rs2854045;rs31082;rs34416524;rs62130412;rs62135171;rs634985;rs9845894;rs10795036;rs10936697;rs12711964;rs13433863;rs1476161;rs35464261;rs648044;rs8060733;rs118062442;rs141711348;rs2498034;rs2586895;rs4702635;rs62055084;rs76052955;rs879854;rs9519183;rs1416160;rs2253023;rs2357023;rs41270859;rs7225157;rs9345501;rs1469883;rs1809931;rs181308633;rs1851911;rs191251423;rs2830420;rs56368241;rs57688343;rs12167058;rs145250558;rs4533324;rs4546951;rs56319762;rs6436165;rs71193760;rs75311157;rs953120;rs1845295;rs2126642;rs2683206;rs71463381;rs117543392;rs2604321;rs4973430;rs56270168;rs60654199;rs6517139;rs7619783;rs9872904;rs11782346;rs13166413;rs17058952;rs8061067;rs11671255;rs2880768;rs45527334;rs6733138;rs67864638;rs77189738;rs10148864;rs10253794;rs11889901;rs34351747;rs72705581;rs112401820;rs185695806;rs76361844;rs35288079;rs560650;rs59247870;rs6837215;rs7374149;rs78848836;rs112214303;rs12985737;rs217536;rs2206751;rs2381641;rs2876453;rs4446382;rs7834078;rs7950166;rs9357723;rs9784763;rs9940216;rs117384726;rs17430740;rs4718887;rs61278557;rs66994942;rs12054057;rs144230577;rs1521754;rs1906675;rs35868739;rs6884797;rs6961762;rs72687577;rs138034490;rs2107969;rs28412070;rs547667;rs7000542;rs716064;rs72945224;rs7659104;rs849402;rs10990975;rs1347872;rs16853589;rs77149260;rs10254599;rs10742057;rs115695800;rs117286906;rs16882459;rs1808366;rs1887771;rs2837984;rs35486269;rs35574173;rs56186782;rs606151;rs6859485 |
| ACQGWS n=31e-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;rs139854039;rs2045386;rs72833896;rs117237359;rs12693975;rs633314;rs7659621;rs7710699;rs80105397;rs9379850;rs11590627;rs117590151;rs2327440;rs727879;rs12470839;rs17484355;rs56275045;rs55750330;rs7307912;rs117324897;rs142500578;rs10474277;rs143431269;rs9826014;rs117597649;rs12273687;rs1589977;rs1592269;rs2834081;rs4426170;rs58790004;rs6668225;rs7656565;rs10188267;rs111307142;rs1423903;rs284933;rs4140445;rs74488554;rs9309394;rs1467664;rs2545799;rs451276;rs4834397;rs6754723;rs73859938;rs17062232;rs2383378;rs6721107;rs67348902;rs7338687;rs2717789;rs34346764;rs35206901;rs116906779;rs16990831;rs17153120;rs17574146;rs3823057;rs79734662;rs9891699;rs2278342;rs231333;rs2749418;rs6953992;rs117984133;rs17223037;rs17268607;rs7219016;rs10008793;rs117032571;rs572591;rs71600496;rs9311399;rs13138252;rs140070614;rs3876032;rs4631807;rs7026534;rs827102;rs965013;rs117733513;rs11859542;rs12026735;rs1958604;rs3093310;rs74537816;rs10264306;rs12449282;rs17607000;rs72710779;rs113958283;rs117512186;rs13235943;rs204402;rs2439272;rs34319416;rs67008508;rs74650977;rs1329195;rs6720452;rs1199575;rs1211507;rs12378980;rs3914188;rs10413482;rs10761602;rs117572024;rs4726915;rs115226268;rs1377549;rs17225380;rs7544083;rs7816871;rs12317467;rs12673790;rs139850812;rs143166223;rs2163336;rs2851485;rs74514433;rs76443550;rs1335788;rs1948833;rs4897289;rs150722160;rs16839634;rs61960513 |

## 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](https://paperpile.com/c/ZqdkLD/PW92)

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](https://paperpile.com/c/ZqdkLD/bKPa)

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](https://paperpile.com/c/ZqdkLD/r3olI) 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](https://paperpile.com/c/ZqdkLD/Tg94D%2BeaH6Q%2BzZenH) 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](https://paperpile.com/c/ZqdkLD/uEDAz)

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](https://paperpile.com/c/ZqdkLD/xofo) 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](https://paperpile.com/c/ZqdkLD/Ic1gW) 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](https://paperpile.com/c/ZqdkLD/oClPh) To quantify potential bias from GWAS summary statistics due to overlapping samples, we used LambdaMeta implemented in GEnetic Analysis Repository (GEAR).[11](https://paperpile.com/c/ZqdkLD/JSLby) 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 (h2-SNP) was estimated using LD-Score Regression analysis.[9](https://paperpile.com/c/ZqdkLD/Ic1gW) 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](https://paperpile.com/c/ZqdkLD/Ic1gW) 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 h2-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 h2-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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# **Acknowledgements**

The Psychiatric Genomics Consortium (PGC): We are deeply indebted to the investigators who comprise the PGC, and to the hundreds of thousands of subjects who have shared their life experiences with PGC investigators. The PGC has received major funding from the National Institute of Mental Health and the National Institute on Drug Abuse (PGC3: U01 MH109528 and U01 MH109532, PGC2: U01 MH094421, PGC1:U01MH085520). The Substance Use Disorders Working Group of the Psychiatric Genomics Consortium (PGC-SUD) is supported by funds from NIDA and NIMH to MH109532 and, previously, with analyst support from NIAAA to U01AA008401 (COGA). We gratefully acknowledge the contributing studies and the participants in those studies without whom this effort would not be possible. For a full list of acknowledgements of all individual cohorts included in the PGC-SUD and PGC-MD groups, please see the original publications.

Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org) hosted by SURFsara, which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003) along with a supplement from the Dutch Brain Foundation and the VU University Amsterdam.

Renato Polimanti was supported by a Young Investigator Grant from the American Foundation for Suicide Prevention. Roseann E. Peterson was supported by National Institutes of Health K01 grant MH113848. Nathan A. Gillespie was supported by National Institutes of Health R00 grant R00DA023549.

This paper represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.This work was conducted using the UK Biobank Resource (application number 25331).

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QIMR (MD): We thank the twins and their families for their willing participation in our studies. NG Martin is supported by the National Health and Medical Research Council, Australia (941177, 971232, 3399450 and 443011). QIMR (AD): Supported by NIH grants AA07535, AA07728, AA13320, AA13321, AA14041, AA11998, AA17688, DA012854, DA019951; by grants from the Australian National Health and Medical Research Council (241944, 339462, 389927, 389875, 389891, 389892, 389938, 442915, 442981, 496739, 552485, 552498); by grants from the Australian Research Council (A7960034, A79906588, A79801419, DP0770096, DP0212016, DP0343921); and by the FP-5 GenomEUtwin Project (QLG2-CT-2002-01254). GWAS genotyping at CIDR was supported by a grant to the late Richard Todd, PhD, MD, former PI of grant AA13320 and a key contributor to research described in this manuscript. S.E.M., D.R.N., A.F.M., M.A.R.F., S.M., D.L.D., and G.W.M. are supported by the National Health and Medical Research Council (NHMRC) Fellowship Scheme. We acknowledge the contributions of project investigator Alexandre Todorov, PhD at Washington University. We also thank Dixie Statham, Ann Eldridge, Marlene Grace, Kerrie McAloney (sample collection); Lisa Bowdler, Steven Crooks (DNA processing); David Smyth, Harry Beeby, and Daniel Park (IT support) at Queensland Institute of Medical Research, Brisbane Australia. Last, but not least, we thank the twins and their families for their participation.

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