

Table S1 Harmonized dataset of two-sample Mendelian randomization for the effect of HDLC on gallstone disease

| SNP | Effect_allele. HDLC | Other_allele. HDLC | Effect_allele. cholelithiasis | Other_allele. cholelithiasis | Beta. HDLC. GLGC | se.HDLC. GLGC | Beta.HDLC. UK.both_ sex | se.HDLC. UK.both_ sex | Beta. cholelithiasis. UK.both_sex | se.cholelithiasis. UK.both_sex | Beta.HDLC. UK.female | se.HDLC. UK.female | Beta. cholelithiasis. UK.female | se.cholelithiasis. UK.female | Beta.HDLC. UK.male | se.HDLC. UK.male | Beta. cholelithiasis. UK.male | se.cholelithiasis. UK.male |
|------------|------------------------|-----------------------|----------------------------------|---------------------------------|------------------------|------------------|-------------------------------|-----------------------------|---|-----------------------------------|-------------------------|-----------------------|---------------------------------------|---------------------------------|-----------------------|---------------------|-------------------------------------|-------------------------------|
| rs10019888 | A | G | A | G | 0.027 | 0.0046 | -0.024569 | 0.0030816 | -7.26E-05 | 0.000544259 | -0.034715 | 0.0046554 | -9.61E-05 | 0.000857473 | -0.018554 | 0.0049851 | -5.51E-05 | 0.00062658 |
| rs10087900 | G | A | G | A | 0.0231 | 0.0036 | -0.019849 | 0.002288 | -0.000521343 | 0.000404392 | -0.028323 | 0.0034534 | -0.000476448 | 0.00063636 | -0.014819 | 0.0037047 | -0.000583383 | 0.00046619 |
| rs10282707 | C | T | C | T | 0.025 | 0.0035 | -0.027124 | 0.0023284 | 0.000726787 | 0.000411672 | -0.029358 | 0.0035179 | 0.000564464 | 0.000648459 | -0.030678 | 0.0037662 | 0.000914013 | 0.000474048 |
| rs103294 | T | C | T | C | 0.0523 | 0.0044 | 0.041711 | 0.0027161 | 0.000948317 | 0.000479954 | 0.050161 | 0.0040937 | 0.00100196 | 0.000754337 | 0.041499 | 0.0044055 | 0.000873819 | 0.000554113 |
| rs10468017 | T | C | T | C | 0.1179 | 0.0038 | 0.10838 | 0.0024851 | -0.000885099 | 0.000440427 | 0.1176 | 0.0037541 | -0.00115257 | 0.000693909 | 0.12259 | 0.0040201 | -0.000569362 | 0.000507018 |
| rs10808546 | T | C | T | C | 0.0409 | 0.0034 | 0.034949 | 0.0022974 | 0.000877439 | 0.000406122 | 0.035385 | 0.0034668 | 0.000957038 | 0.000639104 | 0.041944 | 0.0037211 | 0.000774489 | 0.000468161 |
| rs11045163 | G | A | G | A | 0.0217 | 0.0035 | 0.019082 | 0.0023038 | 0.00049067 | 0.000407293 | 0.021237 | 0.0034735 | 0.000414264 | 0.000640736 | 0.020678 | 0.0037351 | 0.000592278 | 0.000469697 |
| rs11065987 | A | G | A | G | 0.0222 | 0.0035 | -0.022139 | 0.002311 | 0.000583678 | 0.000408387 | -0.022962 | 0.0034865 | 0.000262719 | 0.000642275 | -0.026431 | 0.0037444 | 0.000964345 | 0.000471112 |
| rs11789603 | T | C | T | C | 0.06 | 0.006 | 0.069245 | 0.0036787 | 0.000169102 | 0.000650385 | 0.074592 | 0.0055648 | -0.000119464 | 0.00102518 | 0.078176 | 0.0059425 | 0.000495132 | 0.000748366 |
| rs12286037 | C | T | C | T | 0.1052 | 0.007 | -0.09094 | 0.0045902 | 0.000362853 | 0.000811717 | -0.081006 | 0.0069235 | 0.000214479 | 0.00127631 | -0.12243 | 0.0074384 | 0.000572421 | 0.000936652 |
| rs12328675 | C | T | C | T | 0.0447 | 0.0052 | 0.039477 | 0.0035058 | -0.000341362 | 0.000619658 | 0.048538 | 0.0053081 | 0.000204386 | 0.000978539 | 0.038179 | 0.0056568 | -0.000976654 | 0.000711461 |
| rs12412743 | C | T | C | T | 0.0291 | 0.0045 | -0.026458 | 0.0030509 | 6.13E-05 | 0.000539486 | -0.034187 | 0.0046152 | 0.000410352 | 0.000850685 | -0.023903 | 0.0049279 | -0.000311944 | 0.000620473 |
| rs12740374 | T | G | T | G | 0.0343 | 0.0041 | 0.031133 | 0.0027407 | 0.00050474 | 0.000483859 | 0.033235 | 0.0041444 | 0.000855391 | 0.000762596 | 0.035728 | 0.0044286 | 7.67E-05 | 0.000556804 |
| rs12748152 | C | T | C | T | 0.0506 | 0.0062 | -0.040653 | 0.0041699 | 0.00032059 | 0.000736893 | -0.050556 | 0.0062884 | 0.000273497 | 0.00115858 | -0.038543 | 0.0067591 | 0.000358281 | 0.000850382 |
| rs13099479 | A | G | A | G | 0.036 | 0.0062 | 0.027768 | 0.0040427 | -0.0012673 | 0.00071498 | 0.036523 | 0.0061202 | -0.00104722 | 0.00112844 | 0.02484 | 0.0065238 | -0.00154065 | 0.000821416 |
| rs13107325 | C | T | C | T | 0.0708 | 0.0078 | -0.08196 | 0.0043295 | 0.000669971 | 0.000765675 | -0.081643 | 0.0065678 | -0.000130821 | 0.00121172 | -0.10073 | 0.0069709 | 0.00159418 | 0.000876959 |
| rs1482852 | G | A | G | A | 0.0209 | 0.0035 | 0.018488 | 0.0023328 | 0.00114663 | 0.000412419 | 0.012902 | 0.0035209 | 0.000958583 | 0.000649202 | 0.029087 | 0.0037776 | 0.00136305 | 0.000475268 |
| rs16842 | T | C | T | C | 0.03 | 0.0038 | -0.02903 | 0.0025266 | 0.000158238 | 0.000446445 | -0.034979 | 0.003815 | 0.000450548 | 0.000703229 | -0.029064 | 0.0040898 | -0.000172772 | 0.000514093 |
| rs1689797 | C | A | C | A | 0.0358 | 0.0036 | -0.024297 | 0.0024173 | -0.000176758 | 0.000427003 | -0.021991 | 0.0036485 | -0.000449507 | 0.000672083 | -0.032397 | 0.0039143 | 0.000147899 | 0.000492131 |
| rs16942887 | A | G | A | G | 0.0831 | 0.0051 | 0.060936 | 0.0035695 | -0.000211923 | 0.000630442 | 0.069773 | 0.0053997 | -0.00066389 | 0.000993873 | 0.064501 | 0.0057656 | 0.000332643 | 0.000725292 |
| rs16965220 | A | C | A | C | 0.0219 | 0.0037 | 0.01851 | 0.0024479 | 0.000530008 | 0.000432728 | 0.019179 | 0.003695 | -0.000116729 | 0.000681441 | 0.021828 | 0.0039635 | 0.00129667 | 0.000498438 |
| rs17145738 | T | C | T | C | 0.0408 | 0.0053 | 0.037786 | 0.0034615 | 0.00183169 | 0.000611375 | 0.045269 | 0.0052179 | 0.00215792 | 0.000960796 | 0.037734 | 0.0056136 | 0.00144035 | 0.000705901 |
| rs181360 | T | G | T | G | 0.0376 | 0.0042 | -0.030627 | 0.0028903 | 0.000426229 | 0.000510955 | -0.031452 | 0.0043591 | 0.00050944 | 0.000803646 | -0.036758 | 0.0046844 | 0.000332851 | 0.000589384 |
| rs1883025 | C | T | C | T | 0.0698 | 0.0041 | -0.066763 | 0.0026115 | -0.000343792 | 0.000462011 | -0.085794 | 0.0039423 | 0.000355303 | 0.000727619 | -0.060307 | 0.004228 | -0.00114054 | 0.000532121 |
| rs1942880 | C | T | C | T | 0.0228 | 0.0036 | -0.019857 | 0.0024309 | 0.000383128 | 0.000429707 | -0.023263 | 0.0036668 | 0.00107381 | 0.00067633 | -0.020652 | 0.0039391 | -0.000415617 | 0.000495264 |
| rs1980493 | T | C | T | C | 0.0318 | 0.0048 | -0.030597 | 0.0030163 | 0.00134628 | 0.000533097 | -0.037561 | 0.0045502 | 0.00206857 | 0.000839243 | -0.029706 | 0.0048874 | 0.000500151 | 0.000614288 |
| rs205262 | A | G | A | G | 0.0283 | 0.0039 | -0.025857 | 0.002576 | 0.000603569 | 0.000455124 | -0.02646 | 0.0038919 | 0.000700644 | 0.000717179 | -0.030991 | 0.0041667 | 0.000498031 | 0.000523845 |
| rs2066714 | C | T | C | T | 0.0453 | 0.0071 | 0.045944 | 0.0034121 | -0.000754509 | 0.000602628 | 0.053137 | 0.0051575 | -0.00105045 | 0.00094968 | 0.048347 | 0.0055162 | -0.000404148 | 0.000693557 |
| rs2075650 | A | G | A | G | 0.0554 | 0.0051 | -0.058663 | 0.0032188 | -0.00123164 | 0.000569215 | -0.053986 | 0.0048611 | -0.00176557 | 0.000895899 | -0.077482 | 0.0052088 | -0.000595596 | 0.000656082 |
| rs2240327 | G | A | G | A | 0.0242 | 0.0034 | 0.022584 | 0.0022778 | -0.000693846 | 0.000402631 | 0.026354 | 0.0034389 | -0.00103555 | 0.000633921 | 0.023404 | 0.0036874 | -0.000284464 | 0.000463894 |
| rs2241770 | T | C | T | C | 0.0989 | 0.0057 | -0.11608 | 0.0038461 | -0.000152056 | 0.000680742 | -0.12643 | 0.0058067 | -0.000292793 | 0.00107052 | -0.13048 | 0.0062261 | -1.75E-05 | 0.000785389 |
| rs2292101 | C | T | C | T | 0.0518 | 0.0096 | -0.046017 | 0.006527 | 0.00119825 | 0.00115158 | -0.048302 | 0.0097775 | 0.00040124 | 0.00179869 | -0.053901 | 0.010663 | 0.00213082 | 0.00133933 |
| rs2303975 | A | G | A | G | 0.0279 | 0.0049 | 0.018523 | 0.003621 | 0.000992346 | 0.000640483 | 0.032715 | 0.0054674 | 0.00139052 | 0.0010088 | 0.0069165 | 0.0058609 | 0.000515194 | 0.000737578 |
| rs231492 | G | T | G | T | 0.0433 | 0.0077 | -0.0551 | 0.0041614 | 0.000707353 | 0.000735905 | -0.048309 | 0.0062996 | 0.00195729 | 0.00116086 | -0.075183 | 0.0067162 | -0.000729179 | 0.00084599 |
| rs2454722 | G | A | G | A | 0.0351 | 0.0044 | 0.038045 | 0.0029597 | 0.000237565 | 0.000523185 | 0.046059 | 0.0044771 | 0.000178431 | 0.000825038 | 0.037514 | 0.0047809 | 0.000296971 | 0.000601693 |
| rs3741414 | T | C | T | C | 0.0296 | 0.004 | 0.031959 | 0.0026476 | 7.79E-05 | 0.000468387 | 0.03974 | 0.0039909 | 0.000596539 | 0.000736106 | 0.030386 | 0.0042939 | -0.000534339 | 0.000540798 |

Table S1 (continued)

Table S1 (continued)

| SNP | Effect_allele. HDLC | Other_allele. HDLC | Effect_allele. cholelithiasis | Other_allele. cholelithiasis | Beta. HDLC. GLGC | se.HDLC. GLGC | Beta.HDLC. UK.both_ sex | se.HDLC. UK.both_ sex | Beta. cholelithiasis. UK.both_sex | se.cholelithiasis. UK.both_sex | Beta.HDLC. UK.female | se.HDLC. UK.female | Beta. cholelithiasis. UK.female | se.cholelithiasis. UK.female | Beta.HDLC. UK.male | se.HDLC. UK.male | Beta. cholelithiasis. UK.male | se.cholelithiasis. UK.male |
|-----------|------------------------|-----------------------|----------------------------------|---------------------------------|------------------------|------------------|-------------------------------|-----------------------------|---|-----------------------------------|-------------------------|-----------------------|---------------------------------------|---------------------------------|-----------------------|---------------------|-------------------------------------|-------------------------------|
| rs3822072 | G | A | G | A | 0.0251 | 0.0034 | -0.020892 | 0.0022873 | -0.000547031 | 0.000404405 | -0.032495 | 0.0034498 | -0.000753746 | 0.000636198 | -0.012518 | 0.0037068 | -0.000309604 | 0.000466362 |
| rs3936511 | A | G | A | G | 0.0308 | 0.0046 | -0.032082 | 0.0029097 | 1.49E-05 | 0.000514443 | -0.036609 | 0.0043998 | 0.000816183 | 0.000810473 | -0.034176 | 0.0047019 | -0.000909622 | 0.000592267 |
| rs3996352 | G | A | G | A | 0.0296 | 0.0034 | 0.031122 | 0.0022795 | -0.000192975 | 0.000402853 | 0.047545 | 0.0034368 | -0.00020572 | 0.000633745 | 0.019497 | 0.0036955 | -0.000184879 | 0.000464588 |
| rs4148005 | T | G | T | G | 0.0283 | 0.0036 | -0.019184 | 0.0024502 | 0.000435196 | 0.000432995 | -0.01781 | 0.0036933 | 0.000209067 | 0.00068067 | -0.024835 | 0.003974 | 0.000679715 | 0.000499772 |
| rs4379922 | C | T | C | T | 0.0247 | 0.0036 | 0.023015 | 0.002354 | 0.000162479 | 0.000416097 | 0.026514 | 0.0035527 | 0.000424889 | 0.000655176 | 0.024443 | 0.0038123 | -0.000133338 | 0.000479361 |
| rs4465830 | A | G | A | G | 0.0597 | 0.0044 | -0.063308 | 0.0029151 | -3.90E-05 | 0.000515737 | -0.089434 | 0.0044006 | -0.000913932 | 0.000811933 | -0.04797 | 0.0047193 | 0.00097863 | 0.000594252 |
| rs4660293 | A | G | A | G | 0.0353 | 0.004 | -0.042216 | 0.0026858 | 0.000535331 | 0.000475122 | -0.044915 | 0.0040525 | 0.00083609 | 0.000747465 | -0.048655 | 0.004351 | 0.00019015 | 0.000547905 |
| rs4693156 | C | T | C | T | 0.0197 | 0.0035 | 0.018287 | 0.0023456 | 0.000672762 | 0.000414675 | 0.01854 | 0.0035355 | 0.00109012 | 0.000651904 | 0.021868 | 0.0038044 | 0.000209851 | 0.000478607 |
| rs4917014 | G | T | G | T | 0.0222 | 0.0036 | 0.015987 | 0.0024464 | 0.000571274 | 0.000432391 | 0.023043 | 0.0036929 | 0.000711575 | 0.000680578 | 0.011132 | 0.0039611 | 0.000393549 | 0.000498339 |
| rs492571 | T | C | T | C | 0.0663 | 0.009 | -0.041743 | 0.0057213 | 0.00165069 | 0.00101379 | -0.055287 | 0.0086328 | 0.00250382 | 0.00159507 | -0.035456 | 0.0092682 | 0.000686533 | 0.00116901 |
| rs4976033 | A | G | A | G | 0.0215 | 0.0037 | -0.012458 | 0.0023529 | 3.14E-05 | 0.000415844 | -0.013915 | 0.0035493 | -8.81E-05 | 0.000654178 | -0.013889 | 0.0038128 | 0.000164054 | 0.000479573 |
| rs499974 | C | A | C | A | 0.0263 | 0.0044 | -0.034754 | 0.0031368 | 0.000300973 | 0.00055427 | -0.041732 | 0.0047234 | 0.00139133 | 0.000870287 | -0.034605 | 0.005093 | -0.000991572 | 0.00064061 |
| rs593245 | T | C | T | C | 0.0208 | 0.0038 | 0.011161 | 0.0022914 | -0.000774433 | 0.000404684 | 0.010439 | 0.0034596 | -0.00134566 | 0.000636862 | 0.015217 | 0.0037093 | -0.000108883 | 0.000466501 |
| rs6031587 | C | T | C | T | 0.0488 | 0.0074 | -0.053726 | 0.0044944 | 0.0024202 | 0.000794043 | -0.055242 | 0.0067878 | 0.00323551 | 0.00125154 | -0.063941 | 0.007273 | 0.00150084 | 0.000913702 |
| rs633695 | G | A | G | A | 0.0885 | 0.0054 | 0.08496 | 0.0025125 | 0.00018662 | 0.000444804 | 0.096275 | 0.0037915 | -6.37E-05 | 0.000700218 | 0.09127 | 0.0040694 | 0.000460859 | 0.000512553 |
| rs676210 | A | G | A | G | 0.066 | 0.004 | 0.062039 | 0.0028222 | 0.00100913 | 0.000498922 | 0.069442 | 0.0042593 | 0.00184087 | 0.000785546 | 0.067623 | 0.0045704 | 3.36E-05 | 0.000574798 |
| rs6898870 | G | A | G | A | 0.0298 | 0.0055 | -0.01429 | 0.0025919 | 0.000240486 | 0.000458097 | -0.0095124 | 0.0039115 | 0.000688626 | 0.000721016 | -0.022652 | 0.004198 | -0.000262966 | 0.000527988 |
| rs7306660 | G | A | G | A | 0.0345 | 0.0036 | -0.024604 | 0.0023791 | -0.000182522 | 0.000420403 | -0.031831 | 0.0035973 | -0.000482376 | 0.000662445 | -0.022059 | 0.0038447 | 0.000169924 | 0.000483891 |
| rs737337 | T | C | T | C | 0.0565 | 0.0061 | -0.054572 | 0.0042869 | 0.000133182 | 0.000757782 | -0.055705 | 0.0064962 | 0.000495735 | 0.001197 | -0.065365 | 0.006911 | -0.000313668 | 0.000869817 |
| rs765548 | T | C | T | C | 0.1065 | 0.0038 | 0.11913 | 0.0025771 | -0.000526262 | 0.000456974 | 0.11678 | 0.0038985 | -0.00096185 | 0.000719632 | 0.14903 | 0.0041619 | -5.01E-05 | 0.000526385 |
| rs884366 | G | A | G | A | 0.0199 | 0.0037 | -0.018314 | 0.002464 | -0.000461024 | 0.000435496 | -0.024642 | 0.0037191 | -0.000617263 | 0.000685308 | -0.014953 | 0.00399 | -0.000273676 | 0.000502051 |
| rs9457931 | A | G | A | G | 0.0552 | 0.0073 | -0.030468 | 0.0048529 | -0.00103053 | 0.000857578 | -0.02809 | 0.0073404 | -0.00214183 | 0.00135002 | -0.040419 | 0.0078393 | 0.000236768 | 0.000988209 |
| rs998584 | C | A | C | A | 0.026 | 0.0038 | -0.033179 | 0.0022835 | 5.98E-05 | 0.000403569 | -0.034788 | 0.0034501 | -0.000359708 | 0.000635668 | -0.039329 | 0.0036933 | 0.000559874 | 0.00046473 |

Female: women specify participants in the UK Biobank; male: men specify participants in the UK Biobank. Beta, regression coefficient; se, standard error; HDLC, high-density lipoprotein cholesterol; both_sex, combined sex participants in the UK Biobank; GLGC, Global Lipids Genetics Consortium; SNP, single-nucleotide polymorphism.

Table S2 Harmonized dataset of two-sample Mendelian randomization for the effect of triglycerides on gallstone disease

| SNP | Effect_allele.TG | Other_allele.TG | Effect_allele.cholelithiasis | Other_allele.cholelithiasis | Beta.TG.GLGC | se.TG.GLGC | Beta.TG.UK.both_sex | se.TG.UK.both_sex | Beta.cholelithiasis.UK.both_sex | se.cholelithiasis.UK.both_sex | beta.TG.UK.female | se.TG.UK.female | Beta.cholelithiasis.UK.female | se.cholelithiasis.UK.female | Beta.TG.UK.male | se.TG.UK.male | Beta.cholelithiasis.UK.male | se.cholelithiasis.UK.male |
|------------|------------------|-----------------|------------------------------|-----------------------------|--------------|------------|---------------------|-------------------|---------------------------------|-------------------------------|-------------------|-----------------|-------------------------------|-----------------------------|-----------------|---------------|-----------------------------|---------------------------|
| rs10401969 | T | C | T | C | 0.121 | 0.0065 | -0.099379 | 0.004362 | 0.000531676 | 0.000757307 | -0.081062 | 0.0059918 | 0.000677146 | 0.00119054 | -0.12459 | 0.0066721 | 0.000352387 | 0.000874068 |
| rs10501321 | T | C | T | C | 0.0216 | 0.0035 | -0.022928 | 0.0024759 | -0.000163473 | 0.000429506 | -0.01843 | 0.0034044 | -0.000667665 | 0.000676072 | -0.028831 | 0.0037829 | 0.000420815 | 0.000494989 |
| rs10513688 | A | G | A | G | 0.0306 | 0.0056 | 0.026017 | 0.0039316 | 0.000435703 | 0.000681974 | 0.030092 | 0.0053987 | 0.00128954 | 0.0010726 | 0.022901 | 0.0060162 | -0.000566674 | 0.000786683 |
| rs10861661 | C | A | C | A | 0.0227 | 0.0041 | 0.017942 | 0.0026883 | -0.000534271 | 0.000465992 | 0.018454 | 0.0037052 | -0.000934354 | 0.000735365 | 0.018255 | 0.0040961 | -7.43E-05 | 0.000535473 |
| rs11057408 | G | T | G | T | 0.0258 | 0.0035 | -0.027928 | 0.0024585 | 0.00080572 | 0.000426334 | -0.036305 | 0.0033829 | 0.000819368 | 0.000671797 | -0.019988 | 0.0037529 | 0.000782971 | 0.000490722 |
| rs11613352 | C | T | C | T | 0.028 | 0.0039 | -0.028067 | 0.0027009 | 3.94E-05 | 0.000468681 | -0.024369 | 0.0037081 | 0.000595823 | 0.000736497 | -0.033686 | 0.0041339 | -0.000616153 | 0.000541195 |
| rs11820504 | C | T | C | T | 0.0604 | 0.0044 | 0.067505 | 0.0030573 | -0.000344427 | 0.000530629 | 0.067433 | 0.0042069 | -0.00124828 | 0.000836081 | 0.071214 | 0.0046671 | 0.00070735 | 0.000610834 |
| rs1211644 | T | C | T | C | 0.0298 | 0.0053 | -0.018736 | 0.0026331 | -0.000367478 | 0.000456761 | -0.022972 | 0.0036146 | 9.34E-05 | 0.000717743 | -0.014913 | 0.0040309 | -0.000896656 | 0.000527453 |
| rs12412743 | T | C | T | C | 0.0238 | 0.0044 | 0.016102 | 0.0031102 | 6.13E-05 | 0.000539486 | 0.020078 | 0.004284 | 0.000410352 | 0.000850685 | 0.012433 | 0.0047423 | -0.000311944 | 0.000620473 |
| rs12602912 | T | C | T | C | 0.0241 | 0.0041 | 0.024129 | 0.0029281 | 0.000861337 | 0.000507722 | 0.02429 | 0.0040251 | 0.00114964 | 0.000798995 | 0.025239 | 0.004475 | 0.000526359 | 0.000585278 |
| rs12676857 | C | T | C | T | 0.0332 | 0.0046 | 0.034976 | 0.0032805 | -0.000191865 | 0.000569072 | 0.034155 | 0.0045156 | -0.000860148 | 0.000896461 | 0.037763 | 0.005006 | 0.000592019 | 0.000655234 |
| rs12679834 | T | C | T | C | 0.1647 | 0.0054 | -0.19636 | 0.0038337 | -0.000528781 | 0.00066743 | -0.19469 | 0.0052721 | -0.00042999 | 0.00105041 | -0.20839 | 0.005856 | -0.00065831 | 0.00076932 |
| rs12748152 | T | C | T | C | 0.0372 | 0.0059 | 0.03194 | 0.0042467 | 0.00032059 | 0.000736893 | 0.038854 | 0.0058283 | 0.000273497 | 0.00115858 | 0.025615 | 0.0065025 | 0.000358281 | 0.000850382 |
| rs13389219 | C | T | C | T | 0.0271 | 0.0034 | -0.036997 | 0.0023726 | -0.000116974 | 0.000411854 | -0.04787 | 0.0032599 | -0.000536492 | 0.00064811 | -0.026814 | 0.0036278 | 0.000361418 | 0.000474785 |
| rs17513135 | T | C | T | C | 0.022 | 0.0039 | 0.024565 | 0.0027687 | 0.000510905 | 0.000480194 | 0.026677 | 0.0038053 | 0.00083464 | 0.000755593 | 0.023434 | 0.0042321 | 0.000143022 | 0.000553625 |
| rs1883025 | C | T | C | T | 0.0219 | 0.004 | -0.018986 | 0.0026639 | -0.000343792 | 0.000462011 | -0.020669 | 0.0036642 | 0.000355303 | 0.000727619 | -0.018101 | 0.0040685 | -0.00114054 | 0.000532121 |
| rs2068888 | G | A | G | A | 0.0241 | 0.0034 | -0.030814 | 0.0023294 | -0.00025375 | 0.0004042 | -0.029817 | 0.0032021 | -0.000834351 | 0.000636154 | -0.033404 | 0.00356 | 0.000408101 | 0.0004659 |
| rs2251830 | C | A | C | A | 0.0236 | 0.0036 | -0.015452 | 0.0023336 | 0.000589998 | 0.000404861 | -0.013688 | 0.0032093 | 0.0012169 | 0.000637593 | -0.01801 | 0.0035647 | -0.000133357 | 0.000466312 |
| rs2954022 | C | A | C | A | 0.078 | 0.0033 | -0.090137 | 0.0023214 | 0.000900101 | 0.000403401 | -0.084837 | 0.0031927 | 0.00114037 | 0.00063514 | -0.10078 | 0.0035455 | 0.000608082 | 0.000464755 |
| rs3198697 | C | T | C | T | 0.0198 | 0.0034 | -0.024684 | 0.0023557 | -0.000241451 | 0.00040874 | -0.024553 | 0.0032349 | -0.000751999 | 0.00064245 | -0.026186 | 0.0036047 | 0.000359952 | 0.000471847 |
| rs3760627 | C | T | C | T | 0.0189 | 0.0034 | 0.017197 | 0.0023288 | 0.000233052 | 0.00040373 | 0.019613 | 0.0031986 | -3.11E-05 | 0.000634864 | 0.0154 | 0.0035628 | 0.000551836 | 0.000465839 |
| rs4587594 | G | A | G | A | 0.0694 | 0.0035 | -0.080107 | 0.0024238 | 0.000102297 | 0.000421031 | -0.073549 | 0.0033358 | 0.000441091 | 0.000663321 | -0.091551 | 0.0036991 | -0.000297538 | 0.000484708 |
| rs4719841 | G | A | G | A | 0.0232 | 0.0034 | 0.025629 | 0.0025073 | 0.000594046 | 0.000435049 | 0.028861 | 0.0034524 | 0.000963709 | 0.000685656 | 0.023324 | 0.0038244 | 0.000169229 | 0.000500641 |
| rs4804311 | A | G | A | G | 0.0392 | 0.006 | -0.046466 | 0.0042414 | -8.35E-05 | 0.000735884 | -0.046614 | 0.0058369 | 0.000520112 | 0.0011595 | -0.048459 | 0.0064737 | -0.000761766 | 0.000847068 |
| rs492571 | C | T | C | T | 0.0799 | 0.0088 | 0.073756 | 0.0058373 | 0.00165069 | 0.00101379 | 0.084051 | 0.0080265 | 0.00250382 | 0.00159507 | 0.066444 | 0.0089185 | 0.000686533 | 0.00116901 |
| rs676210 | G | A | G | A | 0.0733 | 0.0039 | -0.076578 | 0.0028741 | 0.00100913 | 0.000498922 | -0.081252 | 0.0039517 | 0.00184087 | 0.000785546 | -0.07514 | 0.0043912 | 3.36E-05 | 0.000574798 |
| rs6831256 | G | A | G | A | 0.0258 | 0.0035 | 0.023806 | 0.0023498 | 6.48E-05 | 0.000407496 | 0.028335 | 0.0032282 | -0.00049967 | 0.000640974 | 0.019968 | 0.0035935 | 0.000731536 | 0.000469998 |
| rs6995541 | G | A | G | A | 0.0265 | 0.0037 | 0.025804 | 0.0025704 | -0.000214148 | 0.000445768 | 0.02417 | 0.0035297 | -0.000275463 | 0.000700783 | 0.028887 | 0.003933 | -0.000144023 | 0.000514479 |
| rs714052 | A | G | A | G | 0.1084 | 0.005 | -0.1244 | 0.0035021 | 0.00153531 | 0.000608615 | -0.13325 | 0.0048061 | 0.00200846 | 0.000956506 | -0.12092 | 0.0053626 | 0.000969708 | 0.000702674 |
| rs7205804 | G | A | G | A | 0.0367 | 0.0034 | -0.03117 | 0.0023377 | 3.35E-06 | 0.000405544 | -0.028914 | 0.0032099 | -0.0004044 | 0.000637442 | -0.035323 | 0.0035774 | 0.000483926 | 0.000468141 |
| rs72555385 | G | A | G | A | 0.0749 | 0.0124 | 0.066648 | 0.0054047 | 1.50E-05 | 0.000936889 | 0.068328 | 0.0074473 | 0.000395581 | 0.0014783 | 0.068451 | 0.0082374 | -0.000427318 | 0.00107671 |
| rs749671 | G | A | G | A | 0.0211 | 0.0034 | -0.014732 | 0.0024009 | -0.000561806 | 0.000416539 | -0.021209 | 0.0032991 | -0.000570191 | 0.000655261 | -0.0082727 | 0.0036709 | -0.000550313 | 0.000480381 |
| rs8077889 | C | A | C | A | 0.0252 | 0.0042 | 0.017051 | 0.0028315 | 8.93E-05 | 0.000491272 | 0.017457 | 0.0038934 | 0.000344642 | 0.00077296 | 0.017435 | 0.0043261 | -0.000204843 | 0.000566464 |
| rs9686661 | T | C | T | C | 0.0379 | 0.0044 | 0.044983 | 0.0029181 | -0.000227378 | 0.000506298 | 0.054406 | 0.0040172 | 0.000319563 | 0.000797755 | 0.036792 | 0.004452 | -0.0008637 | 0.000582803 |
| rs998584 | A | C | A | C | 0.0293 | 0.0037 | 0.03985 | 0.0023261 | 5.98E-05 | 0.000403569 | 0.042217 | 0.0032007 | -0.000359708 | 0.000635668 | 0.039566 | 0.0035507 | 0.000559874 | 0.00046473 |

Female: women specify participants in the UK Biobank; male: men specify participants in the UK Biobank. Beta, regression coefficient; se, standard error; TG, triglycerides; both_sex, combined sex participants in the UK Biobank; GLGC, Global Lipids Genetics Consortium; SNP, single-nucleotide polymorphism.

Table S3 Harmonized dataset of two-sample Mendelian randomization for the effect of liver fat content on gallstone disease

| SNP | Effect_allele.NAFLD | Other_allele.NAFLD | Effect_allele.cholelithiasis | Other_allele.cholelithiasis | Beta.Hep_steatosis.GOLD | se.Hep_steatosis.GOLD | Beta.NAFLD.AGES | se.NAFLD.AGES | Beta.cholelithiasis.UK | se.cholelithiasis.UK |
|-----------|---------------------|--------------------|------------------------------|-----------------------------|-------------------------|-----------------------|-----------------|---------------|------------------------|----------------------|
| rs2228603 | T | C | T | C | 0.238 | 0.035 | 0.184 | 0.053 | 0.000486059 | 0.000761385 |
| rs738409 | G | C | G | C | 0.261 | 0.021 | 0.232 | 0.032 | -0.00220539 | 0.000488266 |

Beta, regression coefficient; se, standard error; Hep_steatosis, hepatic steatosis; NAFLD, non-alcoholic fatty liver disease; GOLD, Genetics of Obesity-related Liver Disease; AGES, Old Order Amish, Age, Gene/Environment Susceptibility-Reykjavik study; UK, the UK Biobank cohort; SNP, single-nucleotide polymorphism.

Table S4 Harmonized dataset of two-sample Mendelian randomization for the effect of LDLC on gallstone disease

| SNP | Effect_allele.LDLC | Other_allele.LDLC | Effect_allele.cholelithiasis | Other_allele.cholelithiasis | Beta.LDLC.GLGC | se.LDLC.GLGC | Beta.LDLC.UK.both_sex | se.LDLC.UK.both_sex | Beta.cholelithiasis.UK.both_sex | se.cholelithiasis.UK.both_sex | Beta.LDLC.UK.female | se.LDLC.UK.female | Beta.cholelithiasis.UK.female | se.cholelithiasis.UK.female | Beta.LDLC.UK.male | se.LDLC.UK.male | Beta.cholelithiasis.UK.male | se.cholelithiasis.UK.male |
|-------------|--------------------|-------------------|------------------------------|-----------------------------|----------------|--------------|-----------------------|---------------------|---------------------------------|-------------------------------|---------------------|-------------------|-------------------------------|-----------------------------|-------------------|-----------------|-----------------------------|---------------------------|
| rs10195252 | T | C | T | C | 0.0238 | 0.0039 | -0.013394 | 0.0023987 | -0.000272351 | 0.000410046 | -0.020526 | 0.0032665 | -0.000676653 | 0.00064565 | -0.0054446 | 0.0035642 | 0.000187234 | 0.000472377 |
| rs10947332 | A | G | A | G | 0.0504 | 0.0056 | 0.045433 | 0.0036141 | -0.00103338 | 0.000618097 | 0.052541 | 0.0049035 | -0.00162052 | 0.000969445 | 0.037786 | 0.0053934 | -0.000339619 | 0.000715308 |
| rs11065987 | A | G | A | G | 0.0269 | 0.0038 | -0.025275 | 0.0023896 | 0.000583678 | 0.000408387 | -0.023866 | 0.0032515 | 0.000262719 | 0.000642275 | -0.027153 | 0.0035541 | 0.000964345 | 0.000471112 |
| rs112201728 | T | C | T | C | 0.0675 | 0.0104 | 0.054991 | 0.0046338 | -0.00049049 | 0.000791708 | 0.070652 | 0.0062946 | -0.000968118 | 0.00124287 | 0.037466 | 0.0069049 | 9.24E-05 | 0.000915277 |
| rs11220462 | A | G | A | G | 0.059 | 0.0059 | 0.040434 | 0.0034608 | 0.000382179 | 0.000591849 | 0.034022 | 0.0047092 | -0.000150584 | 0.000930674 | 0.048587 | 0.0051467 | 0.00100583 | 0.000682857 |
| rs11563251 | T | C | T | C | 0.0345 | 0.0062 | 0.020104 | 0.0037514 | -0.00221903 | 0.000641197 | 0.02591 | 0.0051005 | -0.00226225 | 0.00100781 | 0.014109 | 0.0055843 | -0.00214888 | 0.000740229 |
| rs11591147 | G | T | G | T | 0.497 | 0.018 | -0.34847 | 0.0088975 | 0.000179825 | 0.00152518 | -0.35623 | 0.012134 | -0.00168225 | 0.00240308 | -0.34543 | 0.013199 | 0.00232818 | 0.00175572 |
| rs117733303 | G | A | G | A | 0.1551 | 0.022 | 0.08793 | 0.0087077 | -0.00290238 | 0.00148804 | 0.11606 | 0.01186 | -0.00579976 | 0.0023381 | 0.057819 | 0.012936 | 0.000528062 | 0.00171848 |
| rs12670798 | C | T | C | T | 0.0344 | 0.0043 | 0.027899 | 0.0027261 | -0.000217255 | 0.00046577 | 0.033656 | 0.0037087 | -0.000366807 | 0.000732217 | 0.021685 | 0.0040551 | -4.48E-05 | 0.000537575 |
| rs12721109 | G | A | G | A | 0.4462 | 0.0183 | -0.34087 | 0.0073581 | 0.00139244 | 0.00126199 | -0.39975 | 0.010015 | 1.42E-05 | 0.00198811 | -0.28031 | 0.010936 | 0.00299465 | 0.00145294 |
| rs12740374 | G | T | G | T | 0.161 | 0.0044 | -0.1181 | 0.0028258 | 0.00050474 | 0.000483859 | -0.11046 | 0.0038552 | 0.000855391 | 0.000762596 | -0.1284 | 0.0041897 | 7.67E-05 | 0.000556804 |
| rs12748152 | T | C | T | C | 0.0499 | 0.0066 | 0.011806 | 0.0043104 | 0.00032059 | 0.000736893 | 0.014833 | 0.0058594 | 0.000273497 | 0.00115858 | 0.0084685 | 0.0064182 | 0.000358281 | 0.000850382 |
| rs13315871 | G | A | G | A | 0.0344 | 0.0063 | -0.028708 | 0.0041849 | 0.000264737 | 0.000714333 | -0.030069 | 0.0057161 | 0.000529921 | 0.00112772 | -0.027495 | 0.0061965 | -4.79E-05 | 0.000820422 |
| rs1367117 | A | G | A | G | 0.1186 | 0.004 | 0.082043 | 0.002482 | -0.000916447 | 0.00042493 | 0.090315 | 0.0033736 | -0.00103018 | 0.00066779 | 0.073846 | 0.0036957 | -0.000788718 | 0.00049064 |
| rs1408272 | T | G | T | G | 0.052 | 0.0083 | -0.049188 | 0.0043406 | -0.000373132 | 0.000742093 | -0.047485 | 0.0059054 | -0.00111693 | 0.00116646 | -0.051789 | 0.0064568 | 0.000485838 | 0.000856649 |
| rs1535 | A | G | A | G | 0.0529 | 0.0038 | -0.031219 | 0.0024717 | 0.00154735 | 0.000422381 | -0.034077 | 0.0033695 | 0.00234594 | 0.000665549 | -0.028335 | 0.0036682 | 0.00059189 | 0.000486185 |
| rs1564348 | C | T | C | T | 0.0481 | 0.005 | 0.033276 | 0.0031276 | -0.000148865 | 0.000534696 | 0.045218 | 0.0042561 | -0.000394528 | 0.000840901 | 0.020036 | 0.004651 | 0.000142107 | 0.000616883 |
| rs17508045 | T | C | T | C | 0.0488 | 0.0066 | -0.034993 | 0.0041561 | -0.000161859 | 0.000710633 | -0.034394 | 0.0056778 | -0.0012224 | 0.00112213 | -0.03658 | 0.0061527 | 0.00105585 | 0.000815972 |
| rs17789218 | T | C | T | C | 0.0241 | 0.0043 | -0.017218 | 0.0027435 | 0.000874905 | 0.000468761 | -0.018567 | 0.0037303 | 0.00102662 | 0.000736761 | -0.015758 | 0.0040838 | 0.000681001 | 0.000541161 |
| rs1883025 | C | T | C | T | 0.0296 | 0.0044 | -0.023862 | 0.0027037 | -0.000343792 | 0.000462011 | -0.026426 | 0.003683 | 0.000355303 | 0.000727619 | -0.021399 | 0.0040159 | -0.00114054 | 0.000532121 |
| rs2000999 | A | G | A | G | 0.065 | 0.0046 | 0.049659 | 0.0030082 | 0.000454092 | 0.000514194 | 0.05644 | 0.0040938 | 0.000161443 | 0.000808948 | 0.042614 | 0.0044732 | 0.000786531 | 0.000592952 |
| rs2228603 | C | T | C | T | 0.104 | 0.0072 | -0.089614 | 0.0044515 | 0.000486059 | 0.000761385 | -0.064558 | 0.006073 | 0.00127081 | 0.00119989 | -0.11934 | 0.0065997 | -0.000420847 | 0.000876243 |
| rs2294261 | A | C | A | C | 0.0333 | 0.0037 | -0.015909 | 0.0023592 | -1.39E-05 | 0.000403073 | -0.018899 | 0.0032122 | -0.000333387 | 0.000634297 | -0.012747 | 0.0035061 | 0.000339558 | 0.000464675 |
| rs247616 | C | T | C | T | 0.0547 | 0.0041 | -0.033836 | 0.002514 | -2.34E-05 | 0.000429705 | -0.048311 | 0.0034232 | -0.00018878 | 0.000676377 | -0.017415 | 0.0037353 | 0.000185386 | 0.000495214 |
| rs2737252 | G | A | G | A | 0.0314 | 0.0041 | -0.02164 | 0.0026124 | -0.000297307 | 0.000446345 | -0.023404 | 0.0035551 | -0.00125157 | 0.00070213 | -0.01971 | 0.0038845 | 0.000802905 | 0.000514755 |
| rs2738459 | A | C | A | C | 0.0532 | 0.0058 | -0.022332 | 0.0023663 | 0.000186694 | 0.00040444 | -0.024775 | 0.0032208 | 0.000628625 | 0.000636198 | -0.019809 | 0.003518 | -0.000321547 | 0.000466456 |
| rs2965157 | T | C | T | C | 0.1886 | 0.0112 | -0.21328 | 0.0069524 | 0.000127013 | 0.00118835 | -0.24636 | 0.0094533 | -0.000234755 | 0.00186807 | -0.17918 | 0.010347 | 0.000541374 | 0.00137164 |
| rs314253 | T | C | T | C | 0.0242 | 0.0038 | -0.015604 | 0.0024627 | 0.000766988 | 0.000420855 | -0.011216 | 0.0033562 | 0.000821382 | 0.00066297 | -0.020912 | 0.0036559 | 0.000713611 | 0.000484559 |
| rs3780181 | A | G | A | G | 0.0445 | 0.0074 | -0.028533 | 0.0047333 | 0.000987286 | 0.000808958 | -0.031248 | 0.0064404 | 0.00134956 | 0.00127159 | -0.026345 | 0.00704 | 0.000538136 | 0.000933809 |
| rs6016373 | A | G | A | G | 0.0349 | 0.0037 | -0.025221 | 0.00244 | -2.77E-06 | 0.00041701 | -0.027803 | 0.0033196 | 0.000232035 | 0.000656048 | -0.022765 | 0.0036293 | -0.00028023 | 0.000480878 |

Table S4 (continued)

Table S4 (continued)

| SNP | Effect_allele.LDLC | Other_allele.LDLC | Effect_allele.cholelithiasis | Other_allele.cholelithiasis | Beta.LDLC.GLGC | se.LDLC.GLGC | Beta.LDLC.UK.both_sex | se.LDLC.UK.both_sex | Beta.cholelithiasis.UK.both_sex | se.cholelithiasis.UK.both_sex | Beta.LDLC.UK.female | se.LDLC.UK.female | Beta.cholelithiasis.UK.female | se.cholelithiasis.UK.female | Beta.LDLC.UK.male | se.LDLC.UK.male | Beta.cholelithiasis.UK.male | se.cholelithiasis.UK.male |
|------------|--------------------|-------------------|------------------------------|-----------------------------|----------------|--------------|-----------------------|---------------------|---------------------------------|-------------------------------|---------------------|-------------------|-------------------------------|-----------------------------|-------------------|-----------------|-----------------------------|---------------------------|
| rs6065311 | C | T | C | T | 0.0417 | 0.0036 | 0.025124 | 0.002359 | 0.000696426 | 0.000403162 | 0.032556 | 0.0032076 | 0.000362603 | 0.000633656 | 0.017005 | 0.0035111 | 0.00108216 | 0.000465439 |
| rs6511720 | G | T | G | T | 0.2209 | 0.0061 | -0.17743 | 0.0036249 | 0.000599792 | 0.000621574 | -0.19144 | 0.0049372 | 0.000671822 | 0.000978832 | -0.1636 | 0.0053846 | 0.00049627 | 0.000715964 |
| rs7254892 | G | A | G | A | 0.4853 | 0.0119 | -0.41887 | 0.0067697 | 0.00432116 | 0.00116263 | -0.47472 | 0.009186 | 0.00459571 | 0.00182796 | -0.36281 | 0.010097 | 0.00399961 | 0.00134174 |
| rs72902576 | T | G | T | G | 0.0933 | 0.0133 | -0.078918 | 0.0057713 | 0.00167103 | 0.000986164 | -0.069228 | 0.0078601 | 0.00254732 | 0.00155134 | -0.090445 | 0.0085744 | 0.000638709 | 0.00113732 |
| rs75687619 | T | G | T | G | 0.1735 | 0.0161 | 0.17049 | 0.0073867 | -0.00209175 | 0.00126301 | 0.19452 | 0.010078 | -0.00224586 | 0.00198751 | 0.14514 | 0.010952 | -0.00194031 | 0.00145597 |
| rs7640978 | C | T | C | T | 0.0392 | 0.0069 | -0.034954 | 0.0041269 | -0.00120938 | 0.000705535 | -0.033924 | 0.0056148 | -0.000792659 | 0.00110907 | -0.036144 | 0.0061386 | -0.00169213 | 0.000814354 |
| rs7703051 | A | C | A | C | 0.0727 | 0.0037 | 0.060545 | 0.0024289 | 0.000143863 | 0.000415435 | 0.067811 | 0.0033086 | 0.000158891 | 0.000654207 | 0.052838 | 0.0036078 | 0.000133409 | 0.000478544 |
| rs7832643 | T | G | T | G | 0.0339 | 0.0038 | 0.014503 | 0.0024071 | 0.000220301 | 0.000411442 | 0.015922 | 0.0032755 | 0.000598461 | 0.000647207 | 0.012999 | 0.0035799 | -0.000230316 | 0.000474536 |
| rs8017377 | A | G | A | G | 0.0303 | 0.0038 | 0.01645 | 0.0023544 | 0.000473956 | 0.000402363 | 0.019541 | 0.0032063 | 0.00101748 | 0.00063331 | 0.013177 | 0.0034984 | -0.000138684 | 0.000463735 |
| rs868943 | G | A | G | A | 0.0264 | 0.0037 | -0.01454 | 0.0023801 | 0.000358961 | 0.000406662 | -0.014653 | 0.0032438 | 0.000502691 | 0.000640549 | -0.01473 | 0.0035334 | 0.000181818 | 0.000468303 |
| rs9875338 | G | A | G | A | 0.027 | 0.0037 | -0.015745 | 0.0024036 | -0.000307445 | 0.000410629 | -0.015721 | 0.0032718 | -0.00072233 | 0.000646093 | -0.016053 | 0.0035732 | 0.000181854 | 0.000473454 |

Female: women specify participants in the UK Biobank; male: men specify participants in the UK Biobank. Beta, regression coefficient; se, standard error; LDLC, low density lipoprotein cholesterol; both_sex, combined sex participants in the UK Biobank; GLGC, Global Lipids Genetics Consortium; SNP, single-nucleotide polymorphism.

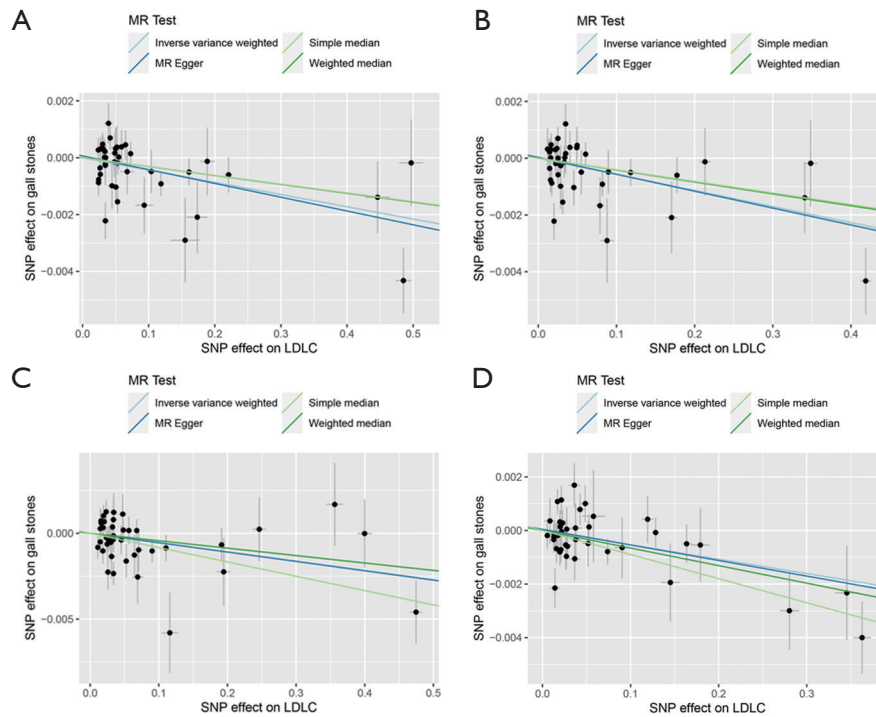


Figure S1 Comparison of the causal estimates between LDLC and gallstone disease from the various MR methods as sensitivity analysis. (A) Comparison of the two-sample MR analysis causal estimates between LDLC and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Comparison of the one-sample MR analysis causal estimates between LDLC and gallstone disease from the UK Biobank cohort. (C) Comparison of the one-sample MR analysis causal estimates between LDLC and gallstone disease from women-specific populations in the UK Biobank cohort. (D) Comparison of the one-sample MR analysis causal estimates between LDLC and gallstone disease from men-specific populations in the UK Biobank cohort. SNP, single-nucleotide polymorphism; MR, Mendelian randomization; LDLC, low-density lipoprotein cholesterol.

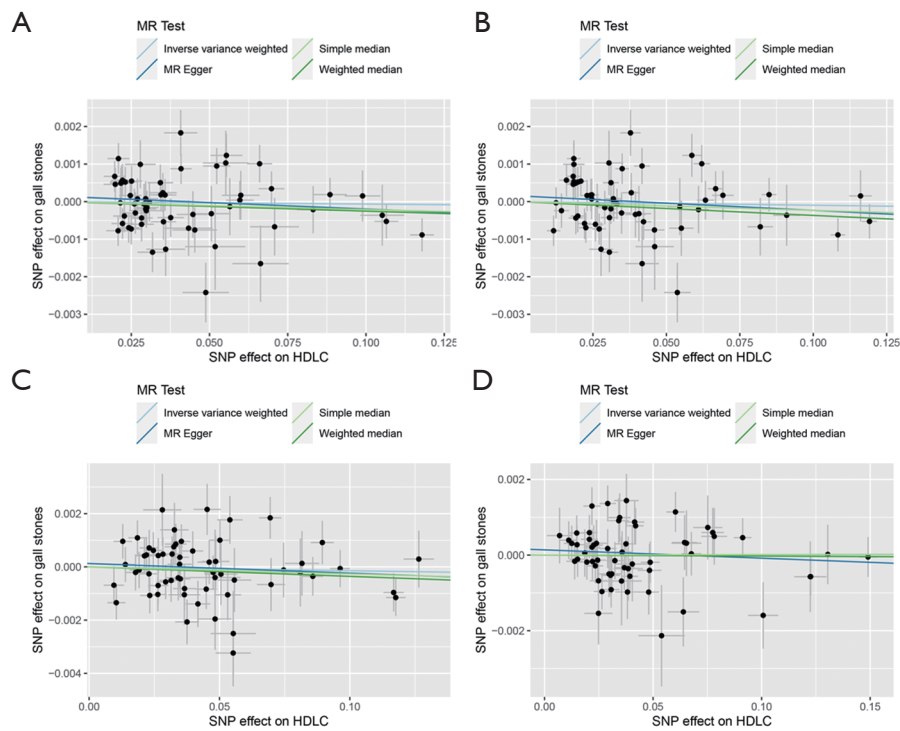


Figure S2 Comparison of the causal estimates between HDLC and gallstone disease from the various MR methods as sensitivity analysis. (A) Comparison of the two-sample MR analysis causal estimates between HDLC and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Comparison of the one-sample MR analysis causal estimates between HDLC and gallstone disease from the UK Biobank cohort. (C) Comparison of the one-sample MR analysis causal estimates between HDLC and gallstone disease from women-specific populations in the UK Biobank cohort. (D) Comparison of the one-sample MR analysis causal estimates between HDLC and gallstone disease from men-specific populations in the UK Biobank cohort. SNP, single-nucleotide polymorphism; MR, Mendelian randomization; HDLC, high-density lipoprotein cholesterol.

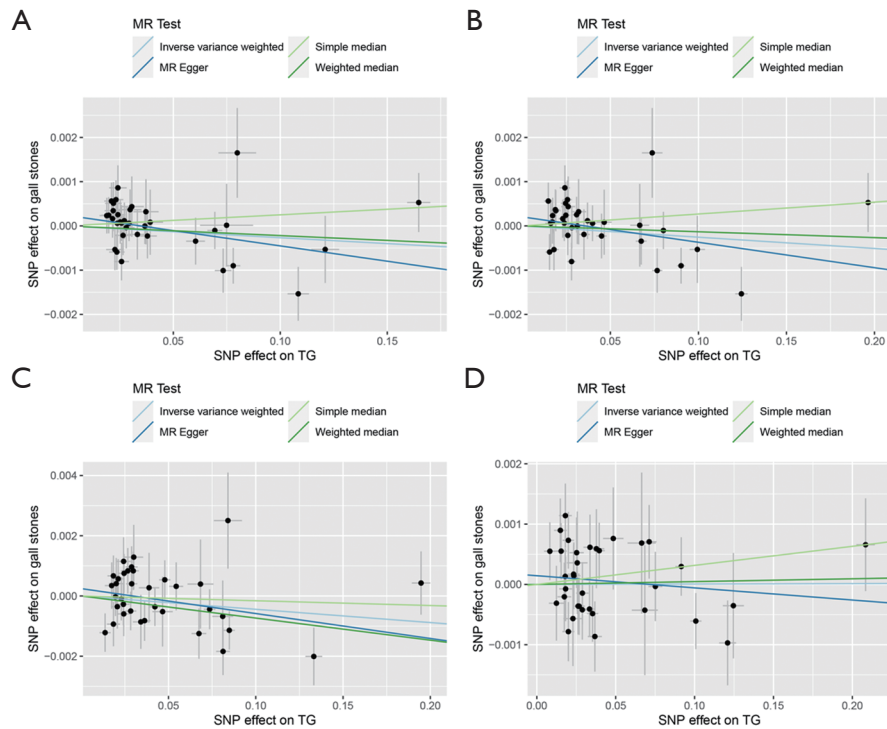


Figure S3 Comparison of the causal estimates between TGs and gallstone disease from the various MR methods as sensitivity analysis. (A) Comparison of the two-sample MR analysis causal estimates between TGs and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Comparison of the one-sample MR analysis causal estimates between TGs and gallstone disease from the UK Biobank cohort. (C) Comparison of the one-sample MR analysis causal estimates between TGs and gallstone disease from women-specific populations in the UK Biobank cohort. (D) Comparison of the one-sample MR analysis causal estimates between TGs and gallstone disease from men-specific populations in the UK Biobank cohort. SNP, single-nucleotide polymorphism; MR, Mendelian randomization; TG, triglyceride.

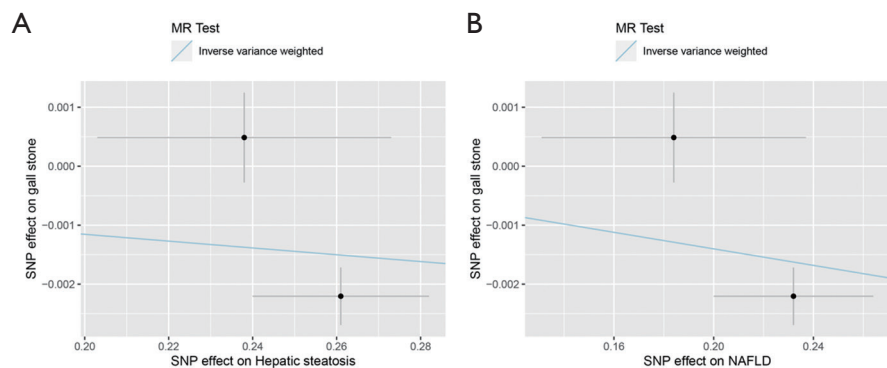


Figure S4 Comparison of the causal estimates between liver fat content and gallstone disease from the various MR methods as sensitivity analysis. (A) Comparison of the two-sample MR analysis causal estimates between hepatic steatosis and gallstone disease from the Genetics of Obesity-related Liver Disease and the UK Biobank cohort. (B) Comparison of the one-sample MR analysis causal estimates between non-alcoholic fatty liver disease and gallstone disease from the Old Order Amish, Age, Gene/Environment Susceptibility-Reykjavik study and the UK Biobank cohort. SNP, single-nucleotide polymorphism; MR, Mendelian randomization; NAFLD, non-alcoholic fatty liver disease.

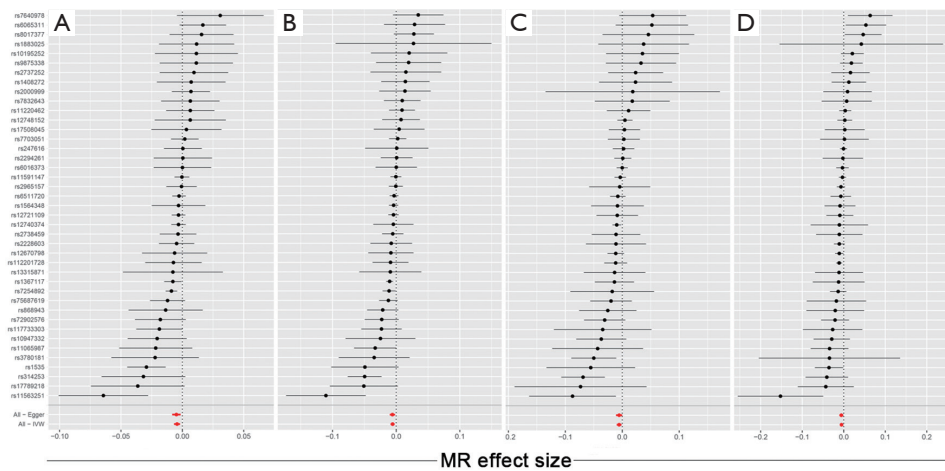


Figure S5 Forest plot of variant specific inverse variance estimates for causal association between LDLC and gallstone disease. (A) Variant specific inverse variance estimates for causal association between LDLC and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Variant specific inverse variance estimates for causal association between LDLC and gallstone disease from the UK Biobank cohort. (C) Variant specific inverse variance estimates for causal association between LDLC and gallstone disease from women-specific populations in the UK Biobank cohort. (D) Variant specific inverse variance estimates for causal association between LDLC and gallstone disease from men-specific populations in the UK Biobank cohort. IVW, inverse variance-weighting; LDLC, low-density lipoprotein cholesterol; MR, Mendelian randomization.

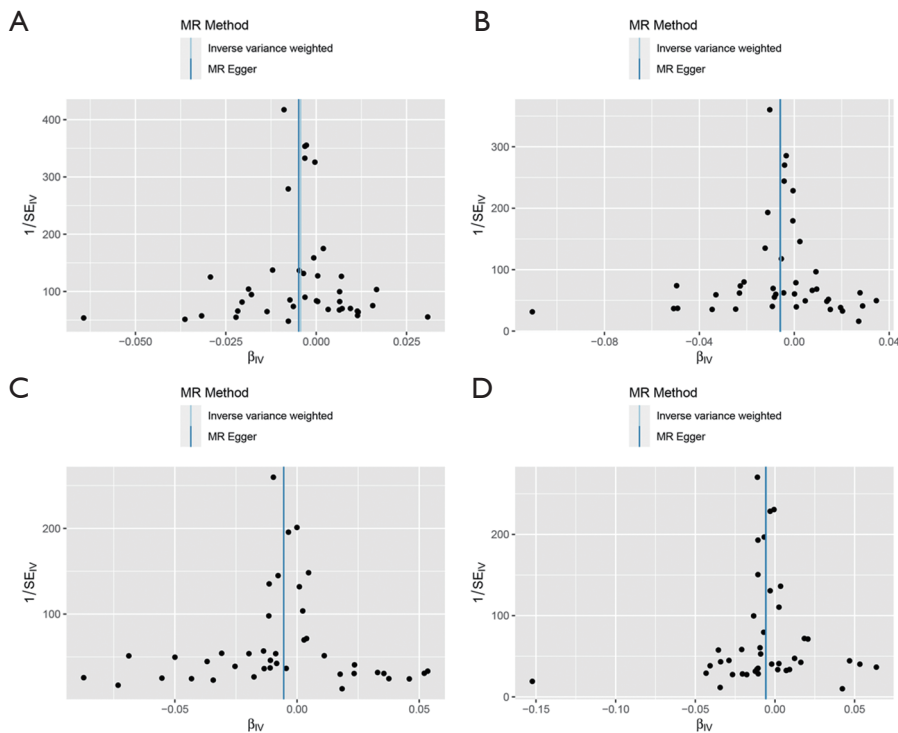


Figure S6 Funnel plot of causal association between LDLC and gallstone disease. (A) Funnel plot for causal association between LDLC and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Funnel plot for causal association between LDLC and gallstone disease from the UK Biobank cohort. (C) Funnel plot for causal association between LDLC and gallstone disease from women-specific populations in the UK Biobank cohort. (D) Funnel plot for causal association between LDLC and gallstone disease from men-specific populations in the UK Biobank cohort. LDLC, low-density lipoprotein cholesterol; MR, Mendelian randomization; SE, standard error.

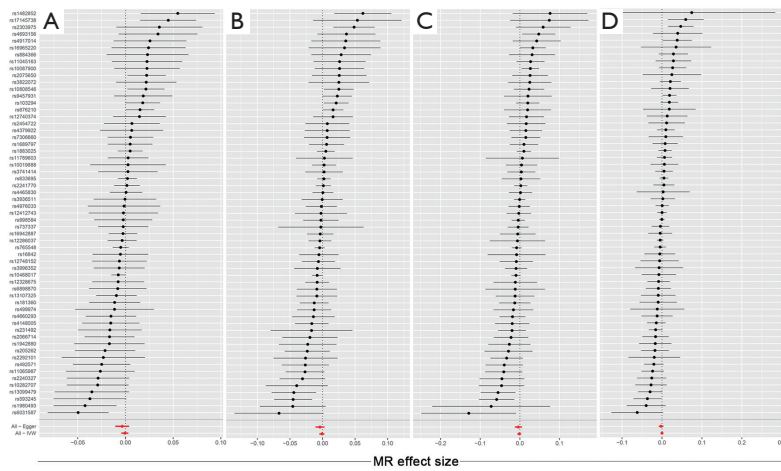


Figure S7 Forest plot of variant specific inverse variance estimates for causal association between HDLC and gallstone disease. (A) Variant specific inverse variance estimates for causal association between HDLC and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Variant specific inverse variance estimates for causal association between HDLC and gallstone disease from the UK Biobank cohort. (C) Variant specific inverse variance estimates for causal association between HDLC and gallstone disease from women-specific populations in the UK Biobank cohort. (D) Variant specific inverse variance estimates for causal association between HDLC and gallstone disease from men-specific populations in the UK Biobank cohort. HDLC, high-density lipoprotein cholesterol; IVW, inverse variance-weighting; MR, Mendelian randomization.

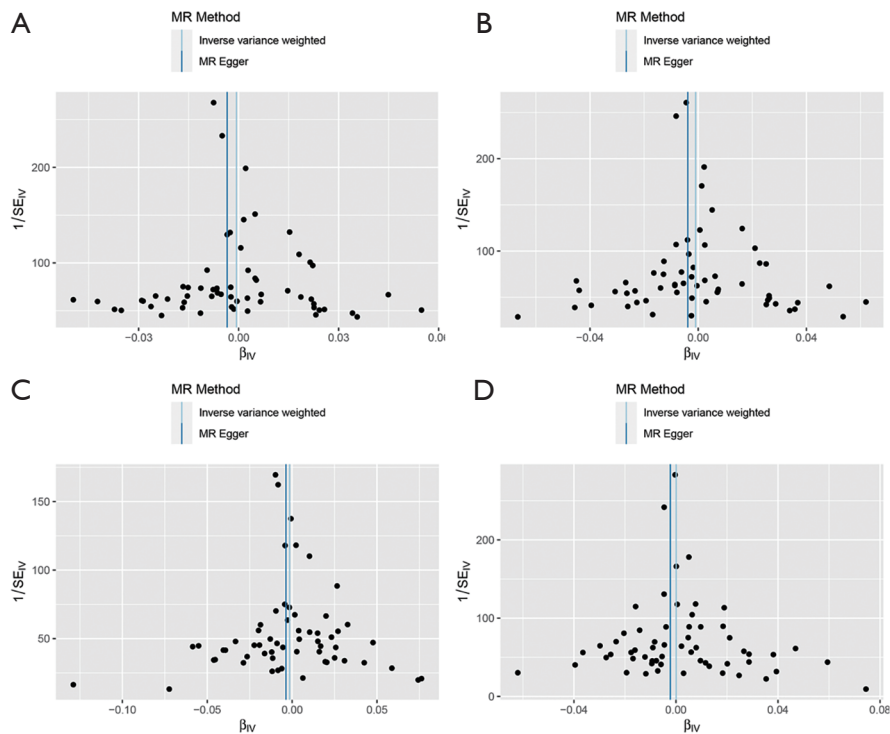


Figure S8 Funnel plot of causal association between HDLC and gallstone disease. (A) Funnel plot for causal association between HDLC and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Funnel plot for causal association between HDLC and gallstone disease from the UK Biobank cohort. (C) Funnel plot for causal association between HDLC and gallstone disease from women-specific populations in the UK Biobank cohort. (D) Funnel plot for causal association between HDLC and gallstone disease from men-specific populations in the UK Biobank cohort. HDLC, high-density lipoprotein cholesterol; MR, Mendelian randomization; SE, standard error.

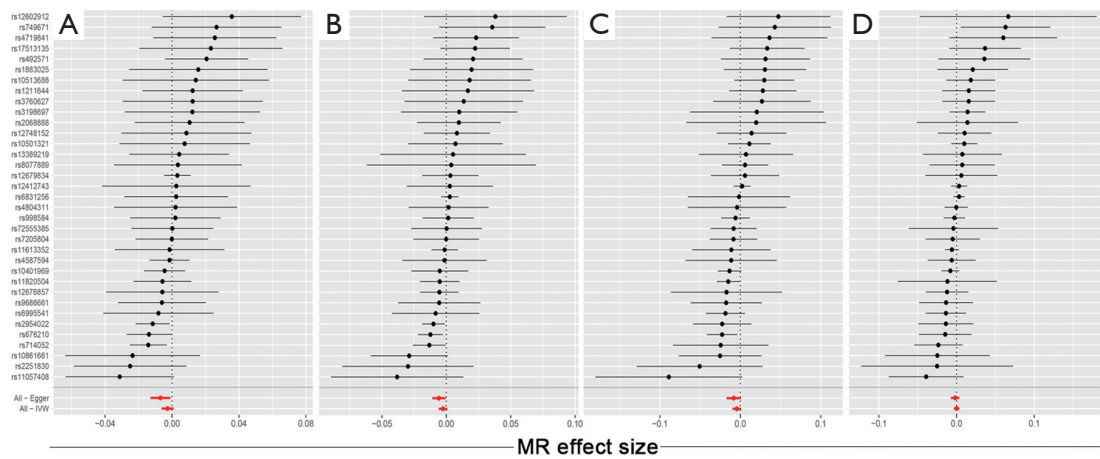


Figure S9 Forest plot of variant specific inverse variance estimates for causal association between triglycerides and gallstone disease. (A) Variant specific inverse variance estimates for causal association between triglycerides and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Variant specific inverse variance estimates for causal association between triglycerides and gallstone disease from the UK Biobank cohort. (C) Variant specific inverse variance estimates for causal association between triglycerides and gallstone disease from women-specific populations in the UK Biobank cohort. (D) Variant specific inverse variance estimates for causal association between triglycerides and gallstone disease from men-specific populations in the UK Biobank cohort. IVW, inverse variance-weighting; MR, Mendelian randomization.

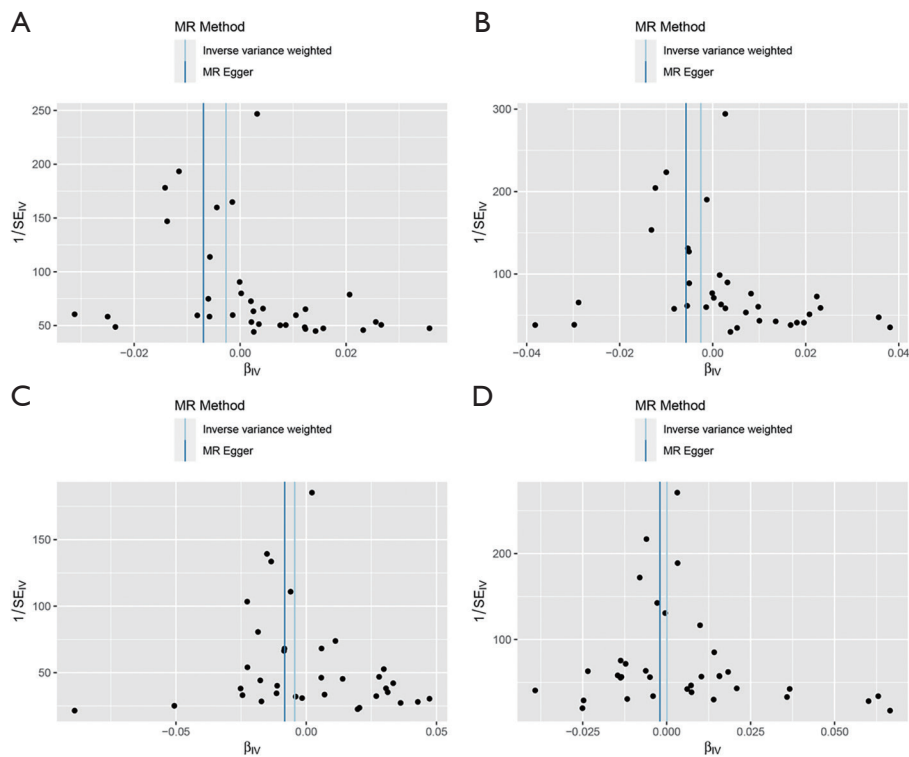


Figure S10 Funnel plot of causal association between triglycerides and gallstone disease. (A) Funnel plot for causal association between triglycerides and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Funnel plot for causal association between triglycerides and gallstone disease from the UK Biobank cohort. (C) Funnel plot for causal association between triglycerides and gallstone disease from women-specific populations in the UK Biobank cohort. (D) Funnel plot for causal association between triglycerides and gallstone disease from men-specific populations in the UK Biobank cohort. MR, Mendelian randomization; SE, standard error.

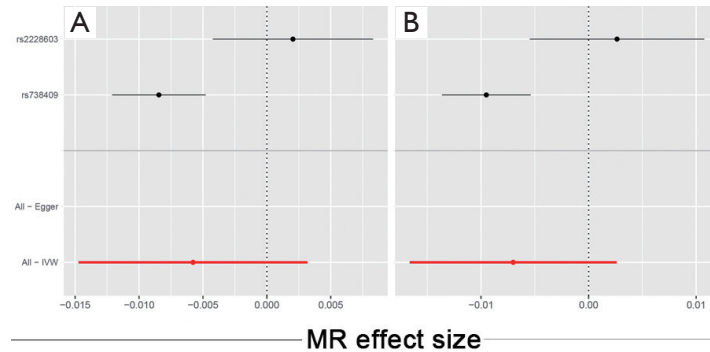


Figure S11 Forest plot of variant specific inverse variance estimates for causal association between liver fat content and gallstone disease. (A) Variant specific inverse variance estimates for causal association between hepatic steatosis and gallstone disease from the Genetics of Obesity-related Liver Disease and the UK Biobank cohort. (B) Variant specific inverse variance estimates for causal association between non-alcoholic fatty liver disease and gallstone disease from the Old Order Amish, Age, Gene/Environment Susceptibility-Reykjavik study and the UK Biobank cohort. IVW, inverse variance-weighting; MR, Mendelian randomization.

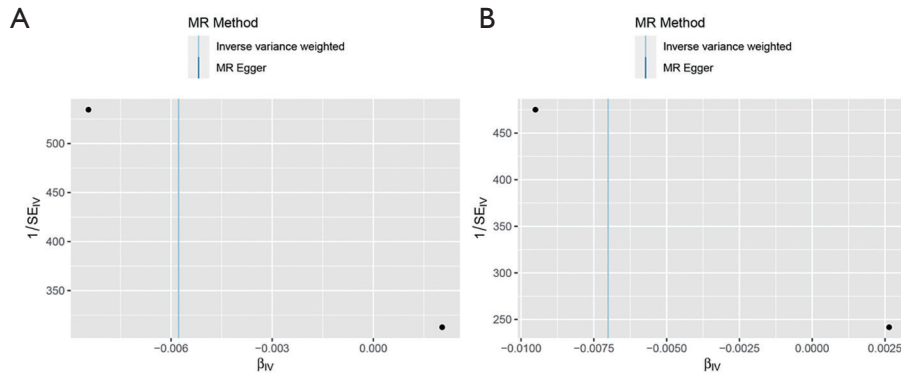


Figure S12 Funnel plot of causal association between liver fat content and gallstone disease. (A) Funnel plot for causal association between hepatic steatosis and gallstone disease from the Genetics of Obesity-related Liver Disease and the UK Biobank cohort. (B) Funnel plot for causal association between non-alcoholic fatty liver disease and gallstone disease from the Old Order Amish, Age, Gene/Environment Susceptibility-Reykjavik study and the UK Biobank cohort. MR, Mendelian randomization; SE, standard error.

Table S5 Mendelian randomization estimations showing the effect of lipid profiles on GSD in combined sex

| Exposure | Methods | Odds ratio ^a | 95% CI | P value | Ph | Q-statistics |
|---------------|---------------------------------|-------------------------|----------------|----------|----------|--------------|
| LDLC | IVW | 0.994 | 0.991 0.997 | 4.15E-04 | 1.03E-02 | 63.5 |
| | MR-Egger | 0.994 | 0.990 0.998 | 7.03E-03 | 7.98E-03 | 63.4 |
| | Weighted median | 0.996 | 0.992 1.000 | 3.70E-02 | - | - |
| | Simple median | 0.996 | 0.991 1.001 | 1.02E-01 | - | - |
| | MR-Egger intercept ^b | 0.0001 | -0.0002 0.0003 | 8.32E-01 | - | - |
| HDLC | IVW | 0.999 | 0.995 1.003 | 6.25E-01 | 2.91E-04 | 102.4 |
| | MR-Egger | 0.996 | 0.989 1.003 | 2.71E-01 | 3.26E-04 | 100.6 |
| | Weighted median | 0.996 | 0.992 1.001 | 1.21E-01 | - | - |
| | Simple median | 0.998 | 0.993 1.003 | 3.67E-01 | - | - |
| | MR-Egger intercept ^b | 0.0002 | -0.0001 0.0004 | 3.16E-01 | - | - |
| Triglycerides | IVW | 0.997 | 0.994 1.001 | 1.30E-01 | 3.87E-01 | 35.7 |
| | MR-Egger | 0.994 | 0.989 0.999 | 3.52E-02 | 4.55E-01 | 33.2 |
| | Weighted median | 0.999 | 0.993 1.004 | 6.36E-01 | - | - |
| | Simple median | 1.003 | 0.996 1.009 | 4.29E-01 | - | - |
| | MR-Egger intercept ^b | 0.0001 | -0.0001 0.0005 | 1.25E-01 | - | - |

^a, odds ratio per 1 SD increase; ^b, regression coefficient (95% CI). CI, confidence interval; GSD, gallstone disease; IVW, inverse variance-weighting; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; MR, Mendelian randomization; Ph, P value for heterogeneity; SD, standard deviation.

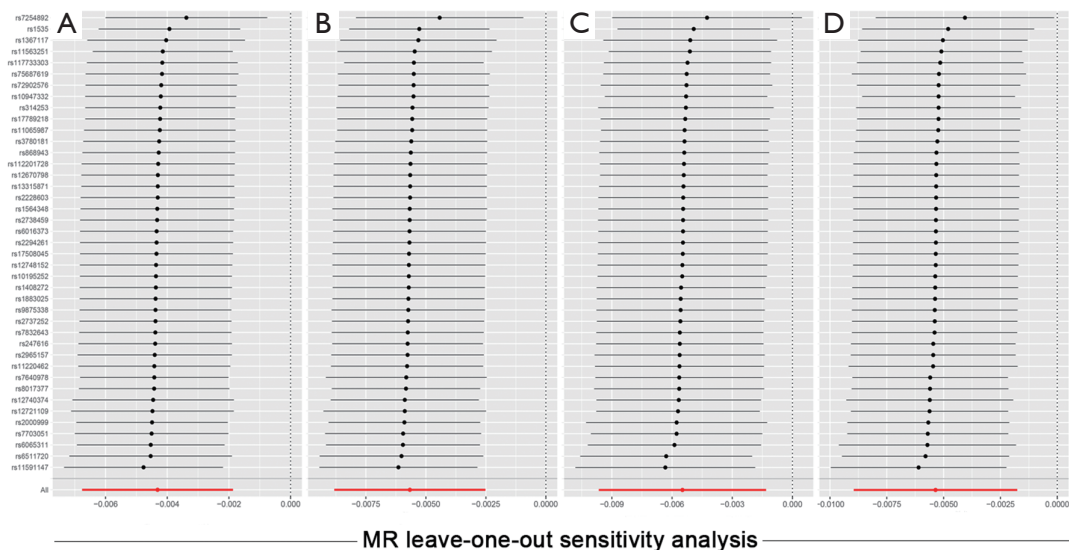


Figure S13 Leave-one-out plot to assess if a single variant is driving the association between LDLC and gallstone disease. (A) Leave-one-out plot to assess the two-sample MR causal estimation between LDLC and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Leave-one-out plot to assess the one-sample MR analysis causal estimation between LDLC and gallstone disease from the UK Biobank cohort. (C) Leave-one-out plot to assess the one-sample MR analysis causal estimation between LDLC and gallstone disease from women-specific populations in the UK Biobank cohort. (D) Leave-one-out plot to assess the one-sample MR analysis causal estimation between LDLC and gallstone disease from men-specific populations in the UK Biobank cohort. MR, Mendelian randomization; LDLC, low-density lipoprotein cholesterol.

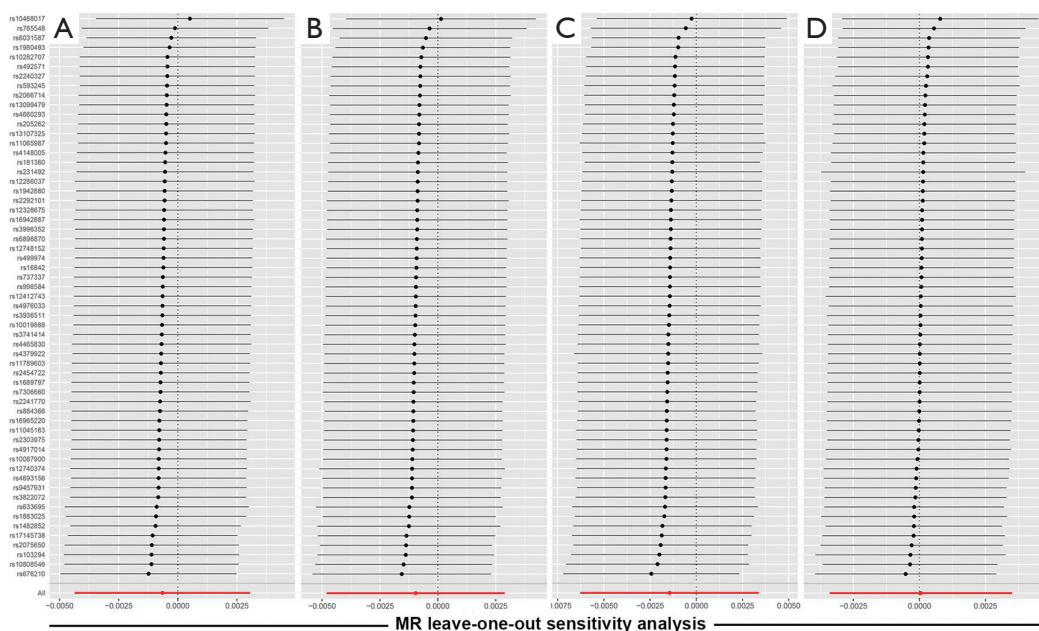


Figure S14 Leave-one-out plot to assess if a single variant is driving the association between HDLC and gallstone disease. (A) Leave-one-out plot to assess the two-sample MR causal estimation between HDLC and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Leave-one-out plot to assess the one-sample MR analysis causal estimation between HDLC and gallstone disease from the UK Biobank cohort. (C) Leave-one-out plot to assess the one-sample MR analysis causal estimation between HDLC and gallstone disease from women-specify populations in the UK Biobank cohort. (D) Leave-one-out plot to assess the one-sample MR analysis causal estimation between HDLC and gallstone disease from men-specify populations in the UK Biobank cohort. MR, Mendelian randomization; HDLC, high-density lipoprotein cholesterol.

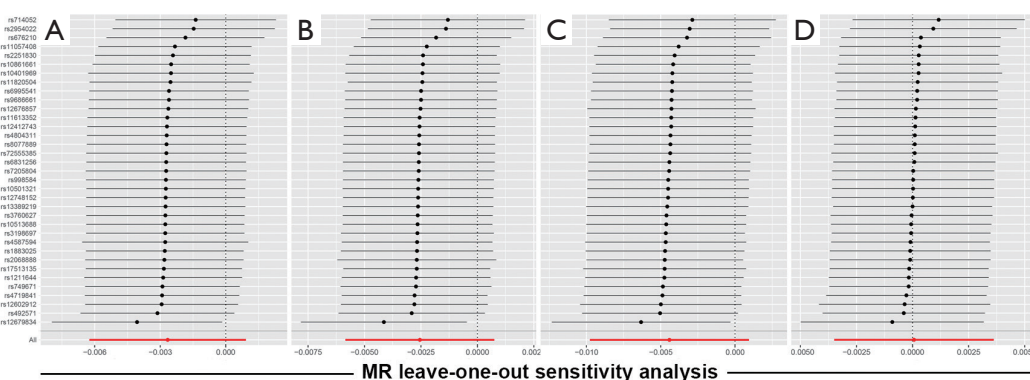


Figure S15 Leave-one-out plot to assess if a single variant is driving the association between triglycerides and gallstone disease. (A) Leave-one-out plot to assess the two-sample MR causal estimation between triglycerides and gallstone disease from the Global Lipids Genetics Consortium and the UK Biobank cohort. (B) Leave-one-out plot to assess the one-sample MR analysis causal estimation between triglycerides and gallstone disease from the UK Biobank cohort. (C) Leave-one-out plot to assess the one-sample MR analysis causal estimation between triglycerides and gallstone disease from women-specify populations in the UK Biobank cohort. (D) Leave-one-out plot to assess the one-sample MR analysis causal estimation between triglycerides and gallstone disease from men-specify populations in the UK Biobank cohort. MR, Mendelian randomization.

Table S6 Multivariable mendelian randomization estimations showing the effect of plasma lipid profiles on GSD

| Exposure | Odds ratio ^a | 95% CI | P value | |
|----------------------------|-------------------------|--------|---------|----------|
| LDL-cholesterol | | | | |
| Two-sample MR ^b | 1.001 | 1.000 | 1.003 | 1.18E-01 |
| Combined ^c | 0.993 | 0.990 | 0.996 | 0.00E+00 |
| Men ^c | 0.995 | 0.991 | 0.998 | 1.00E-03 |
| Women ^c | 0.992 | 0.989 | 0.996 | 0.00E+00 |
| HDL-cholesterol | | | | |
| Two-sample MR ^b | 0.998 | 0.995 | 1.001 | 2.18E-01 |
| Combined ^c | 0.998 | 0.996 | 1.001 | 1.30E-01 |
| Men ^c | 1.001 | 0.999 | 1.004 | 3.36E-01 |
| Women ^c | 0.996 | 0.993 | 0.999 | 1.30E-02 |
| Triglycerides | | | | |
| Two-sample MR ^b | 1.005 | 1.001 | 1.008 | 1.20E-02 |
| Combined ^c | 0.999 | 0.996 | 1.002 | 6.28E-01 |
| Men ^c | 1.002 | 0.999 | 1.005 | 2.60E-01 |
| Women ^c | 0.998 | 0.993 | 1.002 | 2.88E-01 |

^a, odds ratio per 1 SD increase; ^b, two-sample MR between GLGC and UK Biobank; ^c, one-sample MR in UK Biobank. CI, confidence interval; GLGC, Global Lipids Genetics Consortium; GSD, gallstone disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MR, Mendelian randomization; SD, standard deviation.