**Supplementary materials**

**Mendelian randomization study of circulating lipids and biliary tract cancer among East Asians**

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Table S1. The genetic instruments used in Mendelian analysis for high-density lipoprotein cholesterol.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | CHR | position | Nearest genes# | effect\_allele | other\_allele | beta.exposure | se.exposure | beta.outcome | se.outcome |
| rs1011685 | 8 | 19830769 | *LPL* | T | C | 0.1664 | 0.0131 | 0.112749 | 0.115902 |
| rs1109166 | 16 | 67977382 | *PSKH1,CTRL,PSMB10,LCAT,SLC12A4* | T | C | -0.0749 | 0.0118 | -0.12981 | 0.107547 |
| rs11216126 | 11 | 116617240 | *BUD13* | A | C | -0.117 | 0.0091 | 0.025548 | 0.106533 |
| rs12708980 | 16 | 57012379 | *CETP* | T | G | 0.1536 | 0.0115 | 0.173321 | 0.150063 |
| rs1532085 | 15 | 58683366 |  | A | G | 0.1152 | 0.0092 | 0.07156 | 0.077981 |
| rs17138358 | 7 | 17920253 | *SNX13* | C | G | -0.042 | 0.0077 | -0.01327 | 0.077489 |
| rs17519093 | 11 | 116629905 | *BUD13,ZPR1* | A | G | 0.1152 | 0.015 | 0.123932 | 0.18698 |
| rs17821274 | 15 | 58684478 |  | T | C | -0.0547 | 0.0079 | 0.088185 | 0.079001 |
| rs1800588 | 15 | 58723675 | *LIPC,LOC101928694* | T | C | 0.137 | 0.0099 | -0.01673 | 0.076804 |
| rs1883023 | 9 | 107564846 | *ABCA1* | T | C | -0.061 | 0.008 | -0.07773 | 0.078256 |
| rs1883025 | 9 | 107664301 | *ABCA1* | T | C | -0.0983 | 0.0091 | 0.106465 | 0.085198 |
| rs1943973 | 18 | 47179516 |  | A | G | 0.082 | 0.0103 | -0.06237 | 0.107398 |
| rs1973688 | 15 | 58582540 |  | T | C | -0.087 | 0.0098 | -0.14503 | 0.097418 |
| rs2000813 | 18 | 47093864 | *LIPG* | T | C | 0.0543 | 0.0097 | 0.046731 | 0.088444 |
| rs2144300 | 1 | 230294916 | *GALNT2* | T | C | 0.0564 | 0.0104 | -0.06927 | 0.098234 |
| rs2297400 | 9 | 107599481 | *ABCA1* | T | C | -0.065 | 0.0088 | 0.036517 | 0.079708 |
| rs3760782 | 19 | 11346550 | *DOCK6,C19orf80* | T | C | -0.0676 | 0.0107 | -0.11545 | 0.089654 |
| rs3764261 | 16 | 56993324 | *HERPUD1,CETP* | A | C | 0.262 | 0.0141 | 0.078876 | 0.094707 |
| rs3786247 | 18 | 47118923 | *LIPG* | T | G | -0.0957 | 0.0102 | 0.110171 | 0.077015 |
| rs4420638 | 19 | 45422946 | *TOMM40,APOE,APOC1,APOC1P1* | A | G | 0.1129 | 0.0132 | 0.10342 | 0.143481 |
| rs445925 | 19 | 45415640 | *TOMM40,APOE,APOC1,APOC1P1* | A | G | 0.1197 | 0.0207 | -0.28181 | 0.154736 |
| rs4821116 | 22 | 21973319 | *UBE2L3,YDJC,CCDC116* | T | C | -0.0444 | 0.008 | 0.020328 | 0.080262 |
| rs6124760 | 20 | 44581453 | *PCIF1,ZNF335* | C | G | 0.1043 | 0.0168 | 0.019221 | 0.161578 |
| rs651821 | 11 | 116662579 | *BUD13,ZPR1,APOA5* | T | C | 0.1888 | 0.0102 | 0.200154 | 0.082798 |
| rs7115583 | 11 | 116784376 | *SIK3* | T | G | 0.0784 | 0.0115 | 0.105511 | 0.118701 |
| rs8034802 | 15 | 58724792 | *LIPC,LOC101928694* | A | T | 0.0824 | 0.0094 | -0.02033 | 0.081995 |

#: flanking distance (in kB) on each side was 20. NA denotes no gene was available.

Table S2. The genetic instruments used in Mendelian analysis for low-density lipoprotein cholesterol.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | CHR | Position | Nearest genes# | effect\_allele | other\_allele | beta.exposure | se.exposure | beta.outcome | se.outcome |
| rs10119 | 19 | 45406673 | *PVRL2,TOMM40,APOE,APOC1* | A | G | 0.2063 | 0.019 | -0.23501 | 0.127425 |
| rs10172650 | 2 | 21205457 | *APOB* | A | G | -0.0945 | 0.012 | 0.004845 | 0.120422 |
| rs12117661 | 1 | 55487346 | *BSND,PCSK9* | C | G | 0.0764 | 0.0141 | 0.115547 | 0.133346 |
| rs12610605 | 19 | 45370838 | *PVRL2* | A | G | 0.0495 | 0.0088 | 0.010751 | 0.076884 |
| rs12916 | 5 | 74656539 | *HMGCR,COL4A3BP* | T | C | -0.0793 | 0.0082 | -0.06848 | 0.076846 |
| rs12918956 | 16 | 72224335 | *PMFBP1* | T | C | 0.0503 | 0.0087 | -0.01473 | 0.077593 |
| rs174533 | 11 | 61549025 | *MYRF,TMEM258,MIR611,FEN1,FADS1* | A | G | -0.0602 | 0.0104 | -0.10152 | 0.0789 |
| rs1799955 | 13 | 32929232 | *BRCA2* | A | G | 0.0517 | 0.0087 | 0.017321 | 0.076968 |
| rs1865063 | 19 | 11341029 | *DOCK6,C19orf80* | T | C | -0.0549 | 0.0095 | -0.11334 | 0.08946 |
| rs2738452 | 19 | 11229218 | *LDLR,MIR6886* | A | G | -0.0734 | 0.0116 | -0.02992 | 0.115503 |
| rs2738464 | 19 | 11242307 | *LDLR,MIR6886,SPC24* | C | G | 0.0957 | 0.012 | 0.140272 | 0.082853 |
| rs2980869 | 8 | 126488250 |  | T | C | -0.0503 | 0.0084 | -0.06524 | 0.076824 |
| rs445925 | 19 | 45415640 | *TOMM40,APOE,APOC1,APOC1P1* | A | G | -0.5219 | 0.0214 | -0.28181 | 0.154736 |
| rs505151 | 1 | 55529187 | *PCSK9,USP24* | A | G | -0.104 | 0.0184 | 0.138774 | 0.182896 |
| rs5744651 | 5 | 74871997 | *POLK* | A | G | 0.1367 | 0.0228 | 0.230642 | 0.166838 |
| rs579459 | 9 | 136154168 | *ABO* | T | C | -0.0568 | 0.0096 | 0.144194 | 0.085974 |
| rs588245 | 2 | 21270057 | *APOB* | A | G | 0.074 | 0.0132 | 0.205052 | 0.137286 |
| rs599839 | 1 | 109822166 | *CELSR2,PSRC1,MYBPHL* | A | G | 0.1877 | 0.0162 | -0.03768 | 0.144532 |
| rs8051431 | 16 | 72015251 | *PKD1L3* | C | G | 0.0753 | 0.0093 | -0.06694 | 0.084031 |

#: flanking distance (in kB) on each side was 20. NA denotes no gene was available.

Table S3. The genetic instruments used in Mendelian analysis for total cholesterol.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | CHR | Position | Nearest genes# | effect\_allele | other\_allele | beta.exposure | se.exposure | beta.outcome | se.outcome |
| rs10119 | 19 | 45406673 | *PVRL2,TOMM40,APOE,APOC1* | A | G | 0.1357 | 0.0189 | -0.23501 | 0.127425 |
| rs10172650 | 2 | 21205457 | *APOB* | A | G | -0.0973 | 0.012 | 0.004845 | 0.120422 |
| rs12916 | 5 | 74656539 | *HMGCR,COL4A3BP* | T | C | -0.0794 | 0.0081 | -0.06848 | 0.076846 |
| rs12918956 | 16 | 72224335 | *PMFBP1* | T | C | 0.0513 | 0.0087 | -0.01473 | 0.077593 |
| rs1532085 | 15 | 58683366 |  | A | G | 0.0588 | 0.0099 | 0.07156 | 0.077981 |
| rs17122278 | 11 | 118449370 | *IFT46,ARCN1* | A | G | -0.0469 | 0.0088 | -0.00938 | 0.077496 |
| rs174533 | 11 | 61549025 | *MYRF,TMEM258,MIR611,FEN1,FADS1* | A | G | -0.0549 | 0.0103 | -0.10152 | 0.0789 |
| rs1800774 | 16 | 57015545 | *CETP* | T | C | -0.0688 | 0.0125 | -0.19464 | 0.156448 |
| rs1865063 | 19 | 11341029 | *DOCK6,C19orf80* | T | C | -0.0775 | 0.0095 | -0.11334 | 0.08946 |
| rs1883025 | 9 | 107664301 | *ABCA1* | T | C | -0.0735 | 0.0096 | 0.106465 | 0.085198 |
| rs2070895 | 15 | 58723939 | *LIPC,LOC101928694* | A | G | 0.0757 | 0.0108 | -0.01236 | 0.076917 |
| rs2297400 | 9 | 107599481 | *ABCA1* | T | C | -0.0577 | 0.0093 | 0.036517 | 0.079708 |
| rs2738452 | 19 | 11229218 | *LDLR,MIR6886* | A | G | -0.0688 | 0.0116 | -0.02992 | 0.115503 |
| rs2738464 | 19 | 11242307 | *LDLR,MIR6886,SPC24* | C | G | 0.0827 | 0.0119 | 0.140272 | 0.082853 |
| rs2980869 | 8 | 126488250 |  | T | C | -0.0705 | 0.0084 | -0.06524 | 0.076824 |
| rs3764261 | 16 | 56993324 | *HERPUD1,CETP* | A | C | 0.0809 | 0.0148 | 0.078876 | 0.094707 |
| rs579459 | 9 | 136154168 | *ABO* | T | C | -0.0588 | 0.0096 | 0.144194 | 0.085974 |
| rs599839 | 1 | 109822166 | *CELSR2,PSRC1,MYBPHL* | A | G | 0.1684 | 0.0161 | -0.03768 | 0.144532 |
| rs7192750 | 16 | 72014782 | *PKD1L3* | T | C | -0.0683 | 0.0092 | 0.067094 | 0.084043 |
| rs7254892 | 19 | 45389596 | *PVRL2,TOMM40,APOE* | A | G | -0.3981 | 0.0264 | -0.35756 | 0.201697 |
| rs7776054 | 6 | 135418916 |  | A | G | 0.0598 | 0.0093 | 0.131965 | 0.080583 |
| rs780092 | 2 | 27743154 | *GCKR* | A | G | 0.0526 | 0.0087 | 0.017496 | 0.084062 |
| rs9958734 | 18 | 47118398 | *LIPG* | T | C | -0.0919 | 0.0111 | 0.0929 | 0.077236 |

#: flanking distance (in kB) on each side was 20. NA denotes no gene was available.

Table S4. The genetic instruments used in Mendelian analysis for triglyceride.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | CHR | Position | Nearest genes# | effect\_allele | other\_allele | beta.exposure | se.exposure | beta.outcome | se.outcome |
| rs1077834 | 15 | 58723479 | *LIPC,LOC101928694* | T | C | -0.0843 | 0.0116 | 0.013713 | 0.077345 |
| rs11216206 | 11 | 1.17E+08 | *SIK3* | C | G | 0.0804 | 0.0105 | -0.18362 | 0.086535 |
| rs13233571 | 7 | 72971231 | *BCL7B,TBL2* | T | C | -0.1189 | 0.0141 | -0.0957 | 0.12851 |
| rs157582 | 19 | 45396219 | *PVRL2,TOMM40,APOE* | T | C | 0.1073 | 0.0168 | -0.13534 | 0.089198 |
| rs17482753 | 8 | 19832646 | *LPL* | T | G | -0.154 | 0.0144 | 0.113639 | 0.115885 |
| rs2001945 | 8 | 1.26E+08 |  | C | G | -0.0647 | 0.0087 | 0.019545 | 0.077868 |
| rs662799 | 11 | 1.17E+08 | *BUD13,ZPR1,APOA5* | A | G | -0.2825 | 0.0116 | 0.20139 | 0.082968 |
| rs7164909 | 15 | 58686754 |  | T | C | -0.0638 | 0.0111 | -0.00599 | 0.086438 |
| rs780094 | 2 | 27741237 | *GCKR* | T | C | 0.1047 | 0.0087 | -0.01964 | 0.077378 |
| rs995000 | 1 | 63107526 | *DOCK7* | T | C | -0.0801 | 0.0109 | 0.099126 | 0.110095 |

#: flanking distance (in kB) on each side was 20. NA denotes no gene was available.

Table S5. Association of biliary tract cancer with levels of circulating lipids according to different methods.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | HDL | LDL | CHL | TRG |
| Inverse variance weighted |  |  |  |
|  *β* (se; *P* value) | -0.012 (0.007; 0.123) | -0.001 (0.008; 0.915) | -0.0001 (0.008; 0.989) | 0.001 (0.009; 0.936) |
|  Q statistics (*P* value)  | 2.77 (0.948) | 8.28 (0.407) | 8.19 (0.415) | 4.31 (0.828) |
| MR-egger |  |  |  |  |
| *β* (se; *P* value) | -0.027 (0.032; 0.423) | -0.001 (0.035; 0.987) | 0.024 (0.035; 0.512) | 0.007 (0.037; 0.849) |
|  Q statistics (*P* value)  | 3.02 (0.963) | 8.28 (0.506) | 8.70 (0.465) | 4.34 (0.887) |
|  Intercept (*P* value) | 0.007 (0.636) | -0.0001 (0.993) | -0.011 (0.499) | -0.003 (0.860) |
| Weighted median |  |  |  |  |
| *β* (se; *P* value) | -0.012 (0.013; 0.414) | -0.003 (0.017; 0.856) | -0.007 (0.015; 0.670) | 0.010 (0.017; 0.585) |
| Weighted mode |  |  |  |  |
| *β* (se; *P* value) | -0.011 (0.010; 0.285) | -0.002 (0.011; 0.856) | -0.001 (0.011; 0.908) | 0.006 (0.011; 0.606) |

HDL, high density lipoprotein; LDL, low density lipoprotein; CHL, cholesterol; TRG, triglyceride.

Figure S1. The forest plot of leave-one-out analysis for high-density lipoprotein cholesterol.



Figure S2. The forest plot of leave-one-out analysis for low-density lipoprotein cholesterol.



Figure S3. The forest plot of leave-one-out analysis for total cholesterol.



Figure S4. The forest plot of leave-one-out analysis for triglyceride.



Figure S5. Results of pairwise multivariable Mendelian randomization analysis.



Figure S6. Results of multivariable Mendelian randomization analysis.

