Supplementary Information:
Genome-wide association study of serum liver enzymes implicates diverse metabolic and liver pathology

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## Supplementary Table 1: Descriptive summary of phenotypes in UK BioBank

| Variable                          | Value    | N         |
|----------------------------------|----------|-----------|
| Female                           | 54%      | 390812    |
| Age (years)                      | 67 (8.0) | 390812    |
| Alanine aminotransferase (U/L)   | 24 (14)  | 390812    |
| Aspartate aminotransferase (U/L) | 24 (11)  | 389565    |
| Alkaline phosphatase (U/L)       | 84 (26)  | 390964    |
| Triglycerides (mmol/L)           | 1.5 (1.0)| 390616    |
| High-density lipoprotein (mmol/L)| 1.5 (0.38)| 358767   |
| Low-density lipoprotein (mmol/L) | 3.7 (0.82)| 321191   |
| Systolic blood pressure (mmHg)   | 145 (19) | 176321    |
| Diastolic blood pressure (mmHg)  | 86 (11)  | 176322    |
| Body mass index (kg/m²)          | 27 (4.8) | 407545    |
| Glucose (mmol/L)                 | 5.1 (1.2)| 358536    |
| Waist-to-hip ratio (cm/cm)       | 0.87 (0.09)| 407545   |

Values are expressed as mean (standard deviation) or percentage.
| Trait                      | UK BioBank | BioBank Japan | Meta-analysis |
|---------------------------|------------|---------------|---------------|
|                           | Lambda_GC | Intercept     | Lambda_GC | Intercept | Lambda_GC |
| Alanine aminotransferase  | 1.44       | 1.26          | 1.13       | 1.02      | 1.03      |
| Aspartate aminotransferase| 1.47       | 1.31          | 1.13       | 1.01      | 1.03      |
| Alkaline phosphatase      | 1.71       | 1.54          | 1.15       | 1.06      | 1.03      |

Genomic control parameters (lambda_GC) and intercept estimates for the UK BioBank, BioBank Japan, and the meta-analysis. Lambda-GC estimates are from METAL and intercept from LDpred.
| CHR:POS | Variant | EA | OA | UK BioBank | BioBank Japan | Gene annotation | Nearest coding genes | P_het | Direction |
|---------|---------|----|----|------------|---------------|------------------|---------------------|-------|-----------|
| 10:101912064 | rs2862954 | T | C | 0.50 | 0.071 | 2.41e-194 | 6.67e-03 | ERLIN1 (e) | 4.34e-25 | ++ |
| 19:19379549 | rs58542926 | T | C | 0.08 | 0.099 | 1.72e-106 | 9.20e-06 | TM6SF2 (e) | 1.64e-08 | ++ |
| 4:146821410 | rs4835265 | A | C | 0.16 | 0.064 | 1.21e-84 | 3.24e-08 | ZNF827 (i) | 1.88e-04 | ++ |
| 11:93870338 | rs7117339 | C | T | 0.88 | 0.071 | 7.00e-80 | 3.45e-05 | PANX1 (i) | 3.81e-06 | ++ |
| 1:16505320 | rs1497406 | G | A | 0.58 | 0.046 | 1.38e-79 | 4.07e-05 | EPHA2, ARHGEF19 (inter) | 3.53e-06 | ++ |
| 19:45411941 | rs429358 | T | C | 0.84 | 0.051 | 7.16e-54 | 1.03e-02 | APOE (e) | 9.12e-06 | ++ |
| 8:9185146 | rs2126259 | T | C | 0.10 | 0.059 | 1.08e-50 | 3.68e-03 | LOC157273 (i) | 7.51e-05 | ++ |
| 22:36545137 | rs132642 | T | A | 0.83 | 0.051 | 7.52e-57 | 1.39e-01 | APOL3 (UTR) | 3.74e-08 | ++ |
| 1:220970028 | rs2642438 | G | A | 0.70 | 0.040 | 1.75e-52 | 1.37e-01 | MARC1 (e) | 1.73e-07 | ++ |
| 1:155106697 | rs12904 | G | A | 0.59 | 0.035 | 7.71e-46 | 7.30e-03 | EFNA1 (UTR) | 1.35e-04 | ++ |
| 10:70985267 | rs2394529 | C | G | 0.70 | 0.036 | 1.19e-42 | 7.17e-02 | LOC101928994 (i) | 1.61e-05 | ++ |
| 2:169834370 | rs72623176 | A | G | 0.04 | 0.047 | 4.92e-14 | 1.22e-02 | ABCB11 (i) | 5.10e-09 | ++ |
| 8:145955007 | rs2467663 | T | C | 0.66 | 0.034 | 3.90e-41 | 1.63e-01 | ZNF251 (i) | 5.77e-06 | ++ |
| 2:227112754 | rs2943654 | T | C | 0.65 | 0.031 | 2.59e-34 | 3.39e-01 | LOC646736, MIR5702 (inter) | 1.20e-05 | ++ |
| 8:10571491 | rs4484649 | C | A | 0.40 | 0.029 | 5.44e-32 | 2.81e-01 | C8orf74, SOX7 (inter) | 4.26e-05 | ++ |
| 2:165557318 | rs6712203 | C | T | 0.63 | 0.028 | 7.71e-29 | 3.62e-01 | COBLL1 (i) | 7.42e-05 | ++ |
| 19:41333284 | rs11878604 | T | C | 0.93 | 0.026 | 2.02e-08 | 6.94e-20 | CYP2T1P, CYP2A6 (inter) | 4.37e-07 | ++ |
| 2:211540507 | rs1047891 | A | C | 0.32 | 0.012 | 7.65e-06 | 6.46e-18 | CPS1 (e) | 3.04e-07 | ++ |
| 1:150479901 | rs1815544 | C | T | 0.60 | 0.024 | 2.22e-22 | 8.47e-01 | TARS2 (UTR) | 7.82e-05 | ++ |
| CHR:POS  | rs56094641 | G     | A     | 1.00e-17 | 0.20 | - 0.002 | 6.54e-01 | FTO (i) | FTO  | 6.80e-05 | +  |
|----------|-----------|-------|-------|----------|------|---------|----------|--------|------|----------|----|

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between UK BioBank and BioBank Japan. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank is shown first, followed by effect in BioBank Japan.
### Supplementary Table 4: Aspartate aminotransferase-altering alleles with heterogeneity between UK BioBank & BioBank Japan

| CHR:POS | Variant | E   | A   | O   | A   | UK BioBank | BioBank Japan | Gene annotation | Nearest coding genes | P_het | Direction |
|---------|---------|-----|-----|-----|-----|------------|---------------|------------------|---------------------|--------|------------|
| 10:101912 | rs28629 | 0.5 | 0.0 | 2.60 | 0.9 | 0.0 | 3.29 | ERLIN1 (e) | ERLIN1 | 1.13 e-09 | ++ |
| 19:193795 | rs58542 | 0.0 | 0.0 | 3.73 | 0.0 | 0.0 | 1.38 | TM6SF2 (e) | TM6SF2 | 2.25 e-04 | ++ |
| 3:5838046 | rs11714 | 0.5 | 0.0 | 2.43 | 0.2 | 0.0 | 2.70 | PXK (i) | PXK | 4.96 e-11 | ++ |
| 1:1651089 | rs36086 | 0.5 | 0.0 | 8.37 | 0.7 | 0.0 | 4.72 | EPHA2, ARHGEF19 (inter) | EPHA2, ARHGEF19 | 8.72 e-05 | ++ |
| 8:8661681 | rs12544 | 0.4 | 0.0 | 1.91 | 0.7 | 0.0 | 1.74 | MFHAS1 (i) | MFHAS1 | 1.13 e-05 | ++ |
| 11:116648 | rs96418 | 0.1 | 0.0 | 8.54 | 0.2 | 0.0 | 1.75 | ZPR1 (UTR) | ZPR1 | 1.42 e-04 | ++ |
| 2:1138410 | rs67342 | 0.6 | 0.0 | 1.11 | 0.9 | 0.0 | 6.98 | IL1F10, IL1RN (inter) | IL1F10, IL1RN | 1.48 e-05 | ++ |
| 10:709852 | rs23945 | 0.7 | 0.0 | 5.40 | 0.1 | 0.0 | 7.28 | LOC101928994 (i) | HKDC1 | 3.69 e-05 | ++ |
| 22:365451 | rs13264 | 0.8 | 0.0 | 9.13 | 0.9 | 0.0 | 7.40 | APOL3 (UTR) | APOL3 | 2.06 e-06 | ++ |
| 1:6614152 | rs19385 | 0.1 | 0.0 | 2.69 | 0.7 | 0.0 | 8.87 | LEPR, PDE4B (inter) | LEPR, PDE4B | 5.30 e-05 | ++ |
| 10:182638 | rs50819 | 0.5 | 0.0 | 1.72 | 0.4 | 0.0 | 1.12 | SLC39A12 (i) | SLC39A12 | 6.81 e-31 | ++ |
| 6:3258260 | rs34656 | 0.3 | 0.0 | 1.86 | 0.4 | 0.0 | 6.04 | HLA-DRB1, HLA-DQA1 (inter) | HLA-DRB1, HLA-DQA1 | 1.44 e-08 | ++ |
| 9:1361418 | rs25190 | 0.8 | 0.0 | 1.34 | 0.7 | 0.0 | 6.32 | ABO (i) | ABO | 9.19 e-06 | ++ |
| 16:587708 | rs11643 | 0.9 | 0.0 | 1.13 | 0.9 | 0.0 | 5.96 | GOT2, AP0PO5 (inter) | GOT2, CDH8 | 3.67 e-13 | ++ |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between UK BioBank and BioBank Japan. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank is shown first, followed by effect in BioBank Japan.
Supplementary Table 5: Alkaline phosphatase-altering alleles with heterogeneity between UK BioBank & BioBank Japan

| CHR:POS | Variant | E  | A  | O  | A  | UK BioBank | BioBank Japan | Gene annotation | Nearest coding genes | P_het | Direction |
|---------|---------|----|----|----|----|------------|---------------|-----------------|---------------------|--------|------------|
| 1:2189506 30  | rs12563 | T  | C  | 0.3 | 1 | 0.1 | 0.1 | 1.59 | E-298 | 0.2 | 0.1 | 2.84 | E-124 | 3.87 | e-11 | ++ |
| 10:653503 186 | rs10822 | G  | A  | 0.4 | 9 | 0.1 | <1e-02 | 300 | 0.4 | 0.0 | 6.35 | E-19 | 2.10 | e-09 | ++ |
| 12:121432 659  | rs97382 | A  | G  | 0.3 | 8 | 0.0 | 0.0 | 1.82 | E-207 | 0.4 | 0.0 | 1.57 | E-06 | 7.05 | e-12 | ++ |
| 2:2773094 26  | rs12603 | T  | C  | 0.3 | 9 | 0.0 | 0.0 | 4.02 | E-146 | 0.5 | 0.0 | 1.12 | E-03 | 1.84 | e-10 | ++ |
| 19:546771 89  | rs8736  | T  | C  | 0.4 | 4 | 0.0 | 0.0 | 4.58 | E-131 | 0.2 | 0.0 | 2.61 | E-04 | 2.67 | e-08 | ++ |
| 11:296255 152  | rs12277 | A  | G  | 0.0 | 5 | 0.1 | 1.25 | E-73 | 0.2 | 0.0 | 2.72 | E-38 | 1.62 | e-05 | ++ |
| 19:193795 49  | rs58542 | C  | T  | 0.9 | 2 | 0.1 | 0.1 | 3.84 | E-136 | 0.9 | 0.0 | 4.92 | E-02 | 1.06 | e-12 | ++ |
| 19:454218 77  | rs48419 | A  | G  | 0.3 | 8 | 0.0 | 0.0 | 4.51 | E-120 | 0.5 | 0.0 | 5.09 | E-04 | 9.65 | e-08 | ++ |
| 11:615923 62  | rs17456 | A  | C  | 0.3 | 5 | 0.0 | 0.0 | 3.57 | E-109 | 0.3 | 0.0 | 7.98 | E-06 | 3.69 | e-05 | ++ |
| 8:1066544 27  | rs66015 | C  | A  | 0.4 | 1 | 0.0 | 0.0 | 6.75 | E-108 | 0.6 | 0.0 | 1.74 | E-02 | 6.34 | e-09 | ++ |
| 2:1698934 37  | rs21610 | G  | A  | 0.4 | 5 | 0.0 | 0.0 | 5.33 | E-94 | 0.2 | 0.0 | 1.14 | E-01 | 2.88 | e-09 | ++ |
| 15:586787 20  | rs26129 | C  | T  | 0.6 | 5 | 0.0 | 1.93 | E-82 | 0.5 | 0.0 | 1.90 | E-02 | 1.32 | e-06 | ++ |
| 4:1000655 59  | rs18007 | T  | G  | 0.3 | 9 | 0.0 | 0.0 | 1.61 | E-78 | 0.1 | 0.0 | 2.58 | E-01 | 1.40 | e-08 | ++ |
| 16:722171 23  | rs72023 | G  | T  | 0.2 | 3 | 0.0 | 0.0 | 1.11 | E-55 | 0.3 | 0.0 | 3.16 | E-01 | 2.50 | e-06 | ++ |
| 1:2089444 738 | rs12137 | A  | T  | 0.9 | 0 | 0.0 | 0.0 | 2.29 | E-35 | 0.9 | 0.0 | 9.86 | E-01 | 1.15 | e-05 | ++ |
| 9:1361404 13  | rs16335 | C  | T  | 0.2 | 7 | 0.1 | <1e-02 | 300 | 0.2 | 0.1 | 1.06 | E-173 | 3.28 | e-22 | ++ |
| 8:9194978 716  | rs13274 | C  | T  | 0.1 | 2 | 0.1 | <1e-02 | 300 | 0.0 | 0.0 | 1.02 | E-06 | 1.81 | e-21 | ++ |
| 8:1265000 761  | rs28601 | C  | G  | 0.5 | 8 | 0.1 | 1.35 | E-286 | 0.8 | 0.0 | 7.51 | E-04 | 2.32 | e-23 | ++ |
| 20:252969 99  | rs60837 | T  | G  | 0.5 | 6 | 0.0 | 0.0 | 1.92 | E-134 | 0.0 | 0.0 | 8.19 | E-03 | 7.68 | e-11 | ++ |
| 14:248719 792  | rs11621 | C  | T  | 0.5 | 5 | 0.0 | 0.0 | 1.17 | E-58 | 0.9 | 0.0 | 5.29 | E-01 | 2.36 | e-07 | ++ |
| Chr:Pos | rsID | SNP | Allele 1 | Allele 2 | EA | OA | Effect Allele Frequency | P_Het | Gene Tag | Direction | Effect in UK BioBank | Effect in BioBank Japan |
|---------|------|-----|----------|----------|----|----|-----------------------|-------|----------|-----------|----------------------|-------------------------|
| 4:6932668 | rs46940 | CT | 0.6 | 8 | 0.0 | 42 | 1.26E-47 | 0.9 | 0.0 | ++ | 1.98E-01 | 5.27E-05 |
| 12:537275 | rs93090 | CT | 0.6 | 9 | 0.0 | 37 | 2.56E-37 | 0.9 | 0.0 | ++ | 8.10E-01 | 1.71E-05 |
| 12:460616 | rs29708 | TA | 0.9 | 0 | 0.0 | 50 | 3.06E-29 | 1.0 | 0.0 | ++ | 8.02E-01 | 3.15E-05 |
| 6:1164181 | rs49461 | AG | 0.4 | 0 | 0.0 | 26 | 1.45E-20 | 0.6 | 0.0 | ++ | 4.67E-01 | 1.06E-04 |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between UK BioBank and BioBank Japan. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank is shown first, followed by effect in BioBank Japan.
| CHR:POS | Variant | EA | OA | BioBank Japan | UK BioBank | Gene annotation | Nearest coding genes |
|---------|---------|----|----|---------------|------------|-----------------|---------------------|
| 12:1135482\-43 | rs1902955 T C | 0.81 | 0.02 | 1.90e-09 | 0.61 | 0.002 | 3.31e-01 | RASAL1 (i) | RASAL1 |
| 6:33860843 | rs1853557 T G | 0.05 | 0.04 | 3.43e-08 | 0.05 | 0.003 | 5.48e-01 | LINC01016 (i) | MLN, GRM4 |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.
Supplementary Table 7: Aspartate aminotransferase-altering alleles:
BioBank Japan only

| CHR:POS | Variant | EA | O A | BioBank Japan | UK BioBank | Gene annotation | Nearest coding genes |
|---------|---------|----|-----|---------------|------------|----------------|---------------------|
| 19:41332 | rs118786 | T C | 0.6 1 0.0 3 | 2.14e-14 | 0.9 3 0.007 4 | 1.29e-01 | CYP2T1P, CYP2A6 (inter) | EGLN2, CYP2A6 |
| 7:8017436 | rs139761 | T C | 0.9 5 0.0 8 | 3.45e-14 | 0.9 3 0.007 4 | 1.29e-01 | GNAT3, CD36 (inter) | GNAT3, CD36 |
| 4:7961919 | rs757599 | C A | 0.8 2 0.0 32 | 1.58e-08 | 0.9 3 0.007 4 | 1.29e-01 | LINC01094, BMP2K (inter) | ANXA3, BMP2K |
| 7:5025847 | rs459820 | A T | 0.5 7 0.0 22 | 2.82e-08 | 0.6 9 0.003 5 | 1.93e-01 | C7orf72, IKZF1 (inter) | ZPBP, IKZF1 |
| 12:110069 | rs110675 | G T | 0.9 2 0.0 4 | 3.49e-08 | 0.9 3 0.007 4 | 1.29e-01 | MVK, FAM222A (inter) | MVK, FAM222A |

CHR:POS, chromosome:position. EA, effect allele. O A, other allele. EAF, effect allele frequency. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.
Supplementary Table 8: Alanine aminotransferase-altering alleles with heterogeneity between men and women in UK BioBank

| CHR:POS | Variant | E A | O A | Male E A F Beta P | Female E A F Beta P | Gene annotation | Nearest coding genes | P_het | Direction |
|---------|---------|-----|-----|-------------------|---------------------|------------------|---------------------|-------|-----------|
| 9:11714 6043 | rs7041363 | C   | G   | 0.0 0.0 0.0 51 7 8.19 E-88 | 0.0 0.0 0.0 51 49 3.17 E-51 | AKNA (i) | AKNA | 1.09 E-04 ++ |
| 8:12648 2077 | rs2954021 | A   | G   | 0.0 0.0 0.0 49 7 1.45 E-74 | 0.0 0.0 0.0 49 35 5.05 E-27 | TRIB1, LINC00861 (inter) | TRIB1, FAM84B | 5.45 E-08 ++ |
| 4:14682 1410 | rs4835265 | A   | C   | 0.0 0.0 0.0 16 16 5.41 E-21 | 0.0 0.0 0.0 16 75 1.68 E-64 | ZNF827 (i) | ZNF827 | 3.59 E-05 ++ |
| 1:15510 6697 | rs12904 | G   | A   | 0.0 0.0 0.0 59 19 1.89 E-07 | 0.0 0.0 0.0 59 46 5.12 E-44 | EFNA1 (UTR) | EFNA1 | 4.89 E-07 ++ |
| 10:7098 5267 | rs2394529 | C   | G   | 0.0 0.0 0.0 70 12 1.37 E-03 | 0.0 0.0 0.0 70 55 6.44 E-54 | LOC101928994 (i) | HKDC1 | 3.19 E-13 ++ |
| 16:8049 7341 | rs28650012 | G   | C   | 0.0 0.0 0.0 27 17 1.25 E-05 | 0.0 0.0 0.0 27 41 7.13 E-29 | LOC102724084 (i) | MAF, DYNLRB2 | 9.35 E-05 ++ |
| 16:8398 0529 | rs4782568 | C   | G   | 0.0 0.0 0.0 55 35 2.01 E-23 | 0.0 0.0 0.0 55 15 2.60 E-06 | MLYCD, OSGIN1 (inter) | MLYCD, OSGIN1 | 2.35 E-04 ++ |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between men and women. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank male is shown as effect in men followed by effect in women.
Supplementary Table 9: Aspartate aminotransferase-altering alleles with heterogeneity between men and women in UK BioBank

| CHR:POS | Variant | EA | OA | Male | Female | Gene annotation | Nearest coding genes | P_het | Direction |
|---------|---------|----|----|------|--------|-----------------|----------------------|-------|-----------|
| 1:155106 | rs1290 4 | G 59 | A 0 | 0.01 4 | 8.98E-05 | 0.04 8.16E-34 | EFNA1 (UTR) | 3.07E-06 | ++ |
| 11:11664 | rs9641 84 | G 13 | C 0.06 3 | 5.74E-33 | 0.02 2.69E-06 | ZPR1 (UTR) | 3.47E-07 | ++ |
| 10:70985 | rs2394 529 | C 70 | G 0.00 71 | 6.93E-02 | 0.04 2.69E-35 | LOC101928 994 (i) | 5.12E-10 | ++ |
| 4:774166 | rs1250 0824 | A 35 | G 0.02 9 | 9.59E-15 | 0.00 9.53E-02 | SHROOM3 (i) | 4.00E-05 | ++ |
| 19:55824 | rs7246 479 | G 51 | T 0.00 2 | 5.82E-01 | 0.02 3.02E-13 | TMEM150B (e) | 6.53E-05 | ++ |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between men and women. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank male is shown as effect in men followed by effect in women.
Supplementary Table 10: Alkaline phosphatase-altering alleles with heterogeneity between men and women in UK BioBank

| CHR:POS | Variant | EA | OA | Male | Female | Gene annotation | Nearest coding genes | P_het | Direction |
|---------|---------|----|----|------|--------|-----------------|----------------------|-------|-----------|
| 19:1937 9549 | rs58542926 | C | T | 0.1 | 0.1 | 3.35E-96 | 3.27E-42 | TM6SF2 (e) | 1.52E-08 | ++ |
| 9:13614 0462 | rs1633513 | C | T | 0.1 | 0.1 | 9.70E-205 | 1.00E-162 | ABO (i) | 1.75E-05 | ++ |
| 19:4916 4952 | rs281392 | A | G | 0.1 | 0.1 | 2.40E-164 | 3.00E-117 | NTN5 (e) | 6.07E-06 | ++ |
| 8:12650 0031 | rs28601761 | C | G | 0.1 | 0.1 | 1.80E-204 | 4.23E-88 | TRIB1, LINC00861 (inter) | TRIB1, FAM84B | 7.47E-17 | ++ |
| 20:2529 6970 | rs6083799 | T | G | 0.0 | 0.0 | 2.35E-90 | 3.68E-45 | ABHD12 (i) | ABHD12 | 6.77E-07 | ++ |
| 4:69326 683 | rs4694077 | C | T | 0.0 | 0.0 | 2.09E-38 | 6.23E-11 | Tmprss11E (i) | Tmprss11E | 4.13E-06 | ++ |
| 6:25783 315 | rs39236036 | T | C | 0.0 | 0.0 | 7.19E-25 | 3.72E-06 | SLC17A1 (UTR) | SLC17A1 | 7.14E-05 | ++ |
| 5:88364 958 | rs6886306 | T | C | 0.0 | 0.0 | 6.88E-22 | 3.14E-05 | MEF2C-AS1 (i) | MEF2C, CETN3 | 1.48E-04 | ++ |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. P_het, P value for heterogeneity between men and women. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region. Direction: + indicates that the variant increases the liver enzyme while - indicates that the variant decreases the liver enzyme. Direction of effect in UK BioBank male is shown as effect in men followed by effect in women.
| Variant | Trait                                                                 | E | O | A | EA | Beta | P       | Gene annotation |
|---------|-----------------------------------------------------------------------|---|---|---|----|------|---------|----------------|
| rs1277  | E78 Disorders of lipoprotein metabolism and other lipidaemias         | A | G | 0.8 | 0.01 | 1.22e-55 | PSRC1 (d) |
| 930     | I10 Essential (primary) hypertension                                  | G | A | 0.5 | 0.004 | 3.44e-08 | PKN2-AS1 (i) |
| rs1277  | I20 Angina pectoris                                                   | A | G | 0.8 | 0.004 | 2.46e-17 | PSRC1 (d) |
| 930     | I21 Acute myocardial infarction                                       | A | G | 0.8 | 0.002 | 2.06e-09 | PSRC1 (d) |
| rs1277  | I25 Chronic ischaemic heart disease                                  | A | G | 0.8 | 0.005 | 4.30e-25 | PSRC1 (d) |
| 930     | K42 Umbilical hernia                                                 | A | C | 0.5 | 0.001 | 2.04e-13 | LOC102723886 (i) |
| rs6712  | E11 Non-insulin-dependent diabetes mellitus                          | C | T | 0.7 | 0.003 | 1.51e-13 | COBLL1 (i) |
| 203     | K80 Cholelithiasis                                                   | C | G | 0.0 | 0.026 | 7.59e-257 | ABCG8 (e) |
| rs1188  | E11 Non-insulin-dependent diabetes mellitus                          | C | G | 0.0 | 0.004 | 5.93e-34 | ABCG8 (e) |
| 7534    | K82 Other diseases of gallbladder                                    | C | G | 0.0 | 0.003 | 1.92e-35 | ABCG8 (e) |
| rs1188  | K83 Other diseases of biliary tract                                  | C | G | 0.0 | 0.002 | 4.36e-14 | ABCG8 (e) |
| 7534    | I10 Essential (primary) hypertension                                 | T | G | 0.7 | 0.005 | 1.02e-08 | MSL2, PCCB (inter) |
| rs6450  | K80 Cholelithiasis                                                   | C | G | 0.0 | 0.004 | 3.51e-11 | TM4SF1-AS1, TM4SF4 (inter) |
| 40      | E11 Non-insulin-dependent diabetes mellitus                          | A | G | 0.9 | 0.002 | 1.07e-08 | LINCO1948, C5orf67 (inter) |
| rs1468  | K80 Cholelithiasis                                                   | T | C | 0.8 | 0.003 | 2.60e-13 | ABCB4 (i) |
| 615     | E78 Disorders of lipoprotein metabolism and other lipidaemias         | A | G | 0.4 | 0.006 | 8.90e-35 | TRIB1, LINCO00861 (inter) |
| rs2954  | E10 Essential (primary) hypertension                                 | C | A | 0.4 | 0.005 | 2.98e-13 | C8orf74, SOX7 (inter) |
| 021     | I25 Chronic ischaemic heart disease                                  | A | G | 0.8 | 0.002 | 3.74e-09 | TRIB1, LINCO00861 (inter) |
| rs6876  | E78 Disorders of lipoprotein metabolism and other lipidaemias         | G | A | 0.3 | 0.003 | 2.00e-08 | ABO (i) |
| 21      | I26 Pulmonary embolism                                               | G | A | 0.3 | 0.002 | 3.71e-42 | ABO (i) |
| rs6876  | I80 Phlebitis and thrombophlebitis                                   | G | A | 0.3 | 0.003 | 4.15e-62 | ABO (i) |
| 21      | I84 Haemorrhoids                                                     | G | A | 0.3 | 0.004 | 1.63e-15 | ABO (i) |
| rs6876  | K57 Diverticular disease of intestine                                | G | A | 0.3 | 0.003 | 2.73e-13 | ABO (i) |
| 21      | M79 Other soft tissue disorders, not elsewhere classified             | G | A | 0.3 | 0.002 | 4.19e-10 | ABO (i) |
| rs1051 713 | K80 Cholelithiasis | C  | T  | 0.8 | 0.003 | 1.23e-14 | ALOX5 (i) |
|-----------|-------------------|----|----|-----|--------|----------|-----------|
| rs4766 462 | E03 Other hypothyroidism | A  | T  | 0.6 | 0.002 | 1.35e-10 | SH2B3 (i) |
| rs4766 462 | I10 Essential (primary) hypertension | A  | T  | 0.6 | 0.005 | 1.07e-10 | SH2B3 (i) |
| rs8648 99 | I83 Varicose veins of lower extremities | G  | A  | 0.5 | 0.002 | 2.38e-09 | ATF1, TMPRSS12 (inter) |
| rs1106 1602 | M16 Coxarthrosis [arthrosis of hip] | T  | G  | 0.5 | 0.001 | 1.80e-08 | MLXIP (i) |
| rs5609 4641 | E11 Non-insulin-dependent diabetes mellitus | G  | A  | 0.3 | 0.004 | 6.85e-26 | FTO (i) |
| rs5609 4641 | E66 Obesity | G  | A  | 0.3 | 0.004 | 3.00e-33 | FTO (i) |
| rs5609 4641 | I10 Essential (primary) hypertension | G  | A  | 0.3 | 0.004 | 9.48e-11 | FTO (i) |
| rs1713 8478 | K80 Cholelithiasis | C  | A  | 0.8 | 0.003 | 4.72e-08 | HNF1B (i) |
| rs4293 58 | G30-G32 Other degenerative diseases of the nervous system | T  | C  | 0.8 | 0.002 | 4.15e-54 | APOE (e) |
| rs5854 2926 | E78 Disorders of lipoprotein metabolism and other lipidaemias | T  | C  | 0.0 | 0.008 | 9.56e-17 | TM6SF2 (e) |
| rs4293 58 | E78 Disorders of lipoprotein metabolism and other lipidaemias | T  | C  | 0.8 | 0.014 | 1.81e-74 | APOE (e) |
| rs4293 58 | F05 Delirium, not induced by alcohol and other psychoactive substances | T  | C  | 0.8 | 0.000 | 1.86e-12 | APOE (e) |
| rs4293 58 | I20 Angina pectoris | T  | C  | 0.8 | 0.004 | 1.12e-15 | APOE (e) |
| rs4293 58 | I21 Acute myocardial infarction | T  | C  | 0.8 | 0.002 | 7.00e-10 | APOE (e) |
| rs4293 58 | I25 Chronic ischaemic heart disease | T  | C  | 0.8 | 0.005 | 2.49e-19 | APOE (e) |
| rs5854 2926 | K76 Other diseases of liver | T  | C  | 0.0 | 0.002 | 8.23e-09 | TM6SF2 (e) |
| rs7599 | K80 Cholelithiasis | A  | G  | 0.3 | 0.002 | 6.85e-09 | TMEM147 (UTR) |
| rs7384 09 | I85 Oesophageal varices | G  | C  | 0.2 | 0.000 | 2.97e-14 | PNPLA3 (e) |
| rs7384 09 | K70 Alcoholic liver disease | G  | C  | 0.2 | 0.000 | 1.98e-14 | PNPLA3 (e) |
| rs7384 09 | K74 Fibrosis and cirrhosis of liver | G  | C  | 0.2 | 0.000 | 2.25e-11 | PNPLA3 (e) |
| rs7384 09 | K76 Other diseases of liver | G  | C  | 0.2 | 0.002 | 4.77e-22 | PNPLA3 (e) |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. Traits are represented as International Classification of Diseases code followed by disease name. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.
## Supplementary Table 12: Phenome-wide association studies of aspartate aminotransferase-increasing alleles

| Variant | Trait                                                      | E | A | EA | O   | A   | F   | Beta | P        | Gene annotation |
|---------|------------------------------------------------------------|---|---|----|-----|-----|-----|------|---------|-----------------|
| rs100243| I10 Essential (primary) hypertension                       | G | A | 0.5| 0.004| 6   | 1   | 3.44e-08 | PKN2-AS1 (i)    |
| 6       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs654769| E11 Non-insulin-dependent diabetes mellitus                | G | A | 0.4| 0.002| 7   | 2   | 4.53e-08 | GCKR (i)        |
| 2       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs294365| E11 Non-insulin-dependent diabetes mellitus                | T | C | 0.7| 0.003| 1   | 7   | 4.25e-18 | LOC646736, MIR5702 (inter) |
| 4       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs654769| E78 Disorders of lipoprotein metabolism and other lipidaemias | G | A | 0.4| 0.004| 7   | 1   | 2.46e-13 | GCKR (i)        |
| 2       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs654769| K80 Cholelithiasis                                         | G | A | 0.4| 0.002| 7   | 4   | 4.74e-10 | GCKR (i)        |
| 2       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs654769| M10 Gout                                                   | G | A | 0.4| 0.001| 7   | 2   | 6.31e-11 | GCKR (i)        |
| 2       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs259497| I10 Essential (primary) hypertension                       | C | G | 0.5| 0.003| 5   | 2   | 1.66e-10 | C5orf56 (i)     |
| 3       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs689424| J45 Asthma                                                  | A | G | 0.8| 0.005| 9   | 5   | 4.41e-09 | VN1R10P, ZNF204P (inter) |
| 9       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs132125| E03 Other hypothyroidism                                   | A | G | 0.8| 0.003| 9   | 4   | 8.80e-10 | VN1R10P, ZNF204P (inter) |
| 62      |                                                             |   |   |    |      |     |     |      |         |                 |
| rs132125| E05 Thyrotoxicosis [hyperthyroidism]                       | A | G | 0.8| 0.001| 9   | 3   | 5.10e-10 | VN1R10P, ZNF204P (inter) |
| 62      |                                                             |   |   |    |      |     |     |      |         |                 |
| rs132125| E10 Insulin-dependent diabetes mellitus                    | A | G | 0.8| 0.001| 9   | 5   | 4.41e-09 | VN1R10P, ZNF204P (inter) |
| 62      |                                                             |   |   |    |      |     |     |      |         |                 |
| rs691631| I83 Varicose veins of lower extremities                   | T | A | 0.5| -    | 2   | 0.001| 3.86e-08 | MIR588, RSPO3 (inter) |
| 8       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs132125| K40 Inguinal hernia                                        | A | G | 0.8| 0.003| 9   | 5   | 1.65e-09 | VN1R10P, ZNF204P (inter) |
| 62      |                                                             |   |   |    |      |     |     |      |         |                 |
| rs937247| K40 Inguinal hernia                                        | T | C | 0.3| 0.002| 5   | 3   | 1.36e-08 | RFX6, VGLL2 (inter) |
| 5       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs132125| K90 Intestinal malabsorption                               | A | G | 0.8| 0.005| 9   | 5   | 6.94e-15 | VN1R10P, ZNF204P (inter) |
| 62      |                                                             |   |   |    |      |     |     |      |         |                 |
| rs132125| N40 Hyperplasia of prostate                                | A | G | 0.8| 0.007| 9   | 7   | 5.15e-13 | VN1R10P, ZNF204P (inter) |
| 62      |                                                             |   |   |    |      |     |     |      |         |                 |
| rs295402| E78 Disorders of lipoprotein metabolism and other lipidaemias | T | A | 0.5| 0.006| 2   | 8   | 6.26e-34 | TRIB1, LINC00861 (inter) |
| 7       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs125449| I10 Essential (primary) hypertension                       | G | C | 0.5| 0.004| 3   | 7   | 2.16e-10 | MFHAS1 (i)      |
| 92      |                                                             |   |   |    |      |     |     |      |         |                 |
| rs484143| I10 Essential (primary) hypertension                       | C | A | 0.4| 0.006| 8   | 1   | 3.73e-16 | LOC102723313 (i) |
| 6       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs295402| I25 Chronic ischaemic heart disease                       | T | A | 0.5| 0.002| 2   | 8   | 2.28e-09 | TRIB1, LINC00861 (inter) |
| 7       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs113895| K80 Cholelithiasian                                        | T | C | 0.5| 0.002| 9   | 5   | 5.94e-10 | SDCBP (i)       |
| 159     |                                                             |   |   |    |      |     |     |      |         |                 |
| rs180097| E78 Disorders of lipoprotein metabolism and other lipidaemias | C | G | 0.8| 0.005| 5   | 2   | 1.08e-09 | ABCA1 (UTR)    |
| 8       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs251909| E78 Disorders of lipoprotein metabolism and other lipidaemias | C | T | 0.7| 0.005| 7   | 9   | 2.63e-15 | ABO (i)         |
| 3       |                                                             |   |   |    |      |     |     |      |         |                 |
| rs251909| I26 Pulmonary embolism                                    | C | T | 0.7| 0.003| 9   | 7   | 2.29e-19 | ABO (i)         |
| SNP          | Trait Description                                                                 | Chr | Pos | Minor Allele | Major Allele | P   | OR (95% CI)       | Gene Tags          |
|--------------|------------------------------------------------------------------------------------|-----|-----|--------------|--------------|-----|------------------|--------------------|
| rs251909     | I80 Phlebitis and thrombophlebitis                                                  | C   | T   | 0.7          | 0.3          | 0.004 | 3.52e-57         | ABO (i)            |
| rs251909     | I84 Haemorrhoids                                                                  | C   | T   | 0.7          | 0.3          | 0.003 | 6.03e-09         | ABO (i)            |
| rs251909     | K57 Diverticular disease of intestine                                               | C   | T   | 0.7          | 0.3          | 0.003 | 2.51e-08         | ABO (i)            |
| rs251909     | M79 Other soft tissue disorders, not elsewhere classified                           | C   | T   | 0.7          | 0.3          | 0.002 | 7.57e-10         | ABO (i)            |
| rs964184     | E78 Disorders of lipoprotein metabolism and other lipidaemias                      | G   | C   | 0.1          | 0.9          | 0.009 | 1.00e-31         | ZPR1 (UTR)         |
| rs705699     | E03 Other hypothyroidism                                                           | G   | A   | 0.6          | 0.4          | 0.002 | 1.57e-09         | RAB5B (i)          |
| rs705699     | J33 Nasal polyp                                                                   | G   | A   | 0.6          | 0.4          | 0.001 | 4.13e-08         | RAB5B (i)          |
| rs705699     | J45 Asthma                                                                         | G   | A   | 0.6          | 0.4          | 0.003 | 5.48e-10         | RAB5B (i)          |
| rs217184     | E78 Disorders of lipoprotein metabolism and other lipidaemias                      | T   | C   | 0.8          | 0.2          | 0.003 | 3.83e-08         | HPR (i)            |
| rs171384     | K80 Cholelithias                                                                  | C   | A   | 0.8          | 0.2          | 0.003 | 4.72e-08         | HNF1B (i)          |
| rs585429     | E78 Disorders of lipoprotein metabolism and other lipidaemias                      | T   | C   | 0.0          | 0.5          | 0.008 | 9.56e-17         | TM6SF2 (e)         |
| rs439401     | E78 Disorders of lipoprotein metabolism and other lipidaemias                      | C   | T   | 0.5          | 0.5          | 0.004 | 3.36e-15         | APOE, APOC1 (inter) |
| rs118827     | E78 Disorders of lipoprotein metabolism and other lipidaemias                      | T   | A   | 0.4          | 0.6          | 0.003 | 7.62e-12         | RASIP1 (i)         |
| rs118827     | I10 Essential (primary) hypertension                                               | T   | A   | 0.4          | 0.6          | 0.004 | 5.56e-10         | RASIP1 (i)         |
| rs585429     | K76 Other diseases of liver                                                        | T   | C   | 0.0          | 0.5          | 0.002 | 8.23e-09         | TM6SF2 (e)         |
| rs118827     | K80 Cholelithias                                                                  | T   | A   | 0.4          | 0.6          | 0.002 | 3.12e-14         | RASIP1 (i)         |
| rs738409     | I85 Oesophageal varices                                                           | G   | C   | 0.2          | 0.8          | 0.000 | 2.97e-14         | PNPLA3 (e)         |
| rs738409     | K70 Alcoholic liver disease                                                        | G   | C   | 0.2          | 0.8          | 0.000 | 1.98e-14         | PNPLA3 (e)         |
| rs738409     | K74 Fibrosis and cirrhosis of liver                                               | G   | C   | 0.2          | 0.8          | 0.000 | 2.25e-11         | PNPLA3 (e)         |
| rs738409     | K74 Other diseases of liver                                                        | G   | C   | 0.2          | 0.8          | 0.002 | 4.77e-22         | PNPLA3 (e)         |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. Traits are represented as International Classification of Diseases code followed by disease name. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.
| Variant | Trait | Trait Description | E | A | O | Beta | P    | Gene annotation |
|---------|-------|-------------------|---|---|---|------|------|-----------------|
| rs12603 26 | E11 | Non-insulin-dependent diabetes mellitus | T | C | A | 0.4 | - | 1.88e-10 | GCKR (e) |
| rs12603 26 | E78 | Disorders of lipoprotein metabolism and other lipidaemias | T | C | A | 0.4 | - | 3.09e-17 | GCKR (e) |
| rs12603 26 | K80 | Cholelithiasis | T | C | A | 0.4 | - | 9.37e-12 | GCKR (e) |
| rs12603 26 | M10 | Gout | T | C | A | 0.7 | - | 2.81e-14 | GCKR (e) |
| rs68733 9 | I10 | Essential (primary) hypertension | T | C | A | 0.7 | - | 2.38e-08 | MSL2, PCCB (inter) |
| rs68733 9 | I21 | Acute myocardial infarction | T | C | A | 0.7 | - | 2.38e-08 | MSL2, PCCB (inter) |
| rs12633 863 | K80 | Cholelithiasis | A | G | A | 0.5 | - | 2.82e-18 | TM4SF4 (i) |
| rs22908 46 | K80 | Cholelithiasis | T | C | A | 0.7 | - | 1.16e-21 | LRBA (e) |
| rs27281 02 | M10 | Gout | T | C | A | 0.7 | - | 9.96e-24 | PKD2 (i) |
| rs3923 | E83 | Disorders of mineral metabolism | T | C | A | 0.7 | - | 8.38e-52 | VN1R10P, ZNF204P (inter) |
| rs69122 83 | I10 | Essential (primary) hypertension | A | G | A | 0.5 | - | 8.04e-10 | ZNF318, ABCC10 (inter) |
| rs3923 | K90 | Intestinal malabsorption | T | C | A | 0.4 | - | 6.60e-23 | SLC17A1 (UTR) |
| rs76428 4 | K90 | Intestinal malabsorption | G | A | A | 0.5 | - | 2.96e-25 | VN1R10P, ZNF204P (inter) |
| rs28601 761 | E78 | Disorders of lipoprotein metabolism and other lipidaemias | G | A | C | 0.6 | - | 4.43e-40 | TRIB1, LINC00861 (inter) |
| rs66015 27 | I10 | Essential (primary) hypertension | C | A | A | 0.4 | - | 4.15e-15 | PINX1 (i) |
| rs28601 761 | I25 | Chronic ischaemic heart disease | C | G | A | 0.6 | - | 1.03e-11 | TRIB1, LINC00861 (inter) |
| rs16335 13 | I80 | Phlebitis and thrombophlebitis | C | T | A | 0.2 | - | 1.38e-15 | ABO (i) |
| rs10900 229 | K80 | Cholelithiasis | C | T | A | 0.7 | - | 2.13e-17 | ZFAND4 (i) |
| rs10822 186 | K80 | Cholelithiasis | G | A | A | 0.4 | - | 9.47e-09 | REEP3 (i) |
| rs17456 6 | J45 | Asthma | G | A | A | 0.3 | - | 9.23e-09 | FADS2 (i) |
| rs17456 6 | J45 | Asthma | G | A | A | 0.3 | - | 7.15e-09 | FADS2 (i) |
| rs20739 50 | E03 | Other hypothyroidism | C | T | A | 0.7 | - | 6.98e-11 | ATXN2 (i) |
| rs20739 50 | I10 | Essential (primary) hypertension | C | T | A | 0.7 | - | 3.28e-11 | ATXN2 (i) |
| rs97382 26 | I25 | Chronic ischaemic heart disease | A | G | A | 0.4 | - | 8.11e-10 | HNF1A (i) |
| SNP    | Trait                                                                 |Chr:Pos | Effect Allele | Effect Allele Frequency | p-Value | Gene Tags |
|--------|----------------------------------------------------------------------|--------|---------------|-------------------------|---------|-----------|
| rs97382 26 | K80 Cholelithiasis                                                   | A      | G             | 0.4                     | 0.002   | 7         | HNF1A (i) |
| rs29415 05  | J45 Asthma                                                           | A      | G             | 0.3                     | 0.003   | 2         | PGAP3 (i) |
| rs58542 926 | E78 Disorders of lipoprotein metabolism and other lipidaemias      | C      | T             | 0.9                     | 0.008   | 8         | TM6SF2 (e) |
| rs58542 926 | K76 Other diseases of liver                                         | C      | T             | 0.9                     | 0.002   | 1         | TM6SF2 (e) |
| rs60887 30  | C44 Other malignant neoplasms of skin                               | C      | G             | 0.5                     | 0.002   | 7         | EDEM2 (i) |
| rs17216 707 | N20 Calculus of kidney and ureter                                   | C      | T             | 0.1                     | 0.001   | 8         | BCAS1, CYP24A1 (inter) |
| rs28368 82  | K51 Ulcerative colitis                                              | G      | A             | 0.7                     | 0.001   | 7         | LINC01700, PSMG1 (inter) |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. Traits are represented as International Classification of Diseases code followed by disease name. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.
| Trait                  | GCP | GCP Z score | Rho  | Rho Z score | Heritability of metabolic trait (Z score) | Heritability of liver enzyme (Z score) |
|------------------------|-----|-------------|------|-------------|----------------------------------------|--------------------------------------|
| Triglycerides          | 0.65| 2.86        | 0.18 | 1.04        | 10.08                                  | 12.71                                |
| High-density lipoprotein | 0.53| 2.25        | -0.31| -5.61       | 9.26                                   | 12.72                                |
| Body mass index        | 0.65| 2.48        | 0.40 | 6.05        | 26.27                                  | 12.71                                |
| Waist-hip-ratio        | 0.09| 0.72        | 0.13 | 0.94        | 19.63                                  | 12.71                                |
| Fasting glucose        | -0.26| -1.51      | 0.19 | 3.22        | 8.10                                   | 12.71                                |
| Systolic blood pressure| -0.20| -0.93       | 0.32 | 4.16        | 23.09                                  | 12.71                                |
| Diastolic blood pressure| -0.19| -0.90      | 0.29 | 3.57        | 22.83                                  | 12.71                                |

GCP, genetic causality proportion. Significantly positive GCP implies that the metabolic trait is causal for the liver enzyme, and negative GCP implies that the liver enzyme is causal for the metabolic trait. Rho represents the estimated genetic correlation between the liver enzyme and the metabolic trait. SE, standard error.
Supplementary Table 15: Latent causal variable analysis of aspartate aminotransferase and metabolic traits

| Trait                  | GCP    | GCP Z score | Rho   | Rho Z score | Heritability of metabolic trait (Z score) | Heritability of liver enzyme (Z score) |
|------------------------|--------|-------------|-------|-------------|------------------------------------------|----------------------------------------|
| Triglycerides          | 0.24   | 0.76        | 0.02  | 0.10        | 10.08                                    | 11.69                                  |
| High-density lipoprotein| 0.34   | 1.78        | -0.02 | -0.34       | 9.26                                     | 11.69                                  |
| Body mass index        | 0.37   | 0.97        | 0.17  | 1.87        | 26.27                                    | 11.69                                  |
| Waist-hip-ratio        | 0.22   | 0.50        | 0.01  | 0.10        | 19.65                                    | 11.70                                  |
| Fasting glucose        | 0.24   | 0.71        | -0.01 | -0.10       | 8.10                                     | 11.69                                  |
| Systolic blood pressure| -0.46  | -2.07       | 0.24  | 2.65        | 23.09                                    | 11.69                                  |
| Diastolic blood pressure| -0.41 | -1.87       | 0.19  | 1.98        | 22.83                                    | 11.69                                  |

GCP, genetic causality proportion. Significantly positive GCP implies that the metabolic trait is causal for the liver enzyme, and negative GCP implies that the liver enzyme is causal for the metabolic trait. Rho represents the estimated genetic correlation between the liver enzyme and the metabolic trait. SE, standard error.
## Supplementary Table 16: Latent causal variable analysis of alkaline phosphatase and metabolic traits

| Trait                        | GCP  | GCP Z score | Rho  | Rho Z score | Heritability of metabolic trait (Z score) | Heritability of liver enzyme (Z score) |
|------------------------------|------|-------------|------|-------------|------------------------------------------|----------------------------------------|
| Triglycerides                | 0.38 | 1.08        | -0.04| -0.20       | 10.08                                    | 6.53                                   |
| High-density lipoprotein     | 0.20 | 1.06        | -0.08| -1.44       | 9.26                                     | 6.53                                   |
| Body mass index              | 0.29 | 0.64        | 0.21 | 1.83        | 26.27                                    | 6.53                                   |
| Waist-hip-ratio              | -0.57| -2.15       | -0.09| -0.55       | 19.63                                    | 6.53                                   |
| Fasting glucose              | -0.07| -0.09       | 0.07 | 1.07        | 8.10                                     | 6.53                                   |
| Systolic blood pressure      | -0.01| -0.02       | 0.24 | 2.19        | 23.09                                    | 6.55                                   |
| Diastolic blood pressure     | -0.01| -0.02       | 0.25 | 2.20        | 22.83                                    | 6.55                                   |

GCP, genetic causality proportion. Significantly positive GCP implies that the metabolic trait is causal for the liver enzyme, and negative GCP implies that the liver enzyme is causal for the metabolic trait. Rho represents the estimated genetic correlation between the liver enzyme and the metabolic trait. SE, standard error.
Supplementary Table 17: Effect of all liver enzyme-increasing alleles on primary biliary cholangitis

| CHR:POS     | Variant   | EA   | OA   | EAF | Beta | P             | Proxy  | R2  | Gene annotation |
|-------------|-----------|------|------|-----|------|---------------|--------|-----|-----------------|
| 3:161823590 | rs17236494| C (T) | A (C) | 0.21| -0.26| 5.31E-05      | rs4679904 | 0.85 | ARF7            |
| 4:103947120 | rs223454  | A (A) | G (C) | 0.51| -0.21| 7.66E-05      | rs223420 | 0.98 | UBE2D3P         |
| 4:103797685 | rs179195  | T (A) | C (G) | 0.47| -0.22| 2.19E-05      | rs228614 | 0.85 | MANBA           |

CHR:POS, chromosome:position. EA, effect allele. OA, other allele. EAF, effect allele frequency. When liver enzyme-increasing variants were not themselves available, proxy variants were used. EA and OA of proxy variants are shown in parentheses. Gene tags: (e) exonic, (i) intronic, (u) upstream, (d) downstream, (inter) intergenic, (UTR) untranslated region.
Supplementary Table 18: Effects of polygenic risk scores on cirrhosis and hepatic steatosis in Michigan Genomics Initiative

| Liver enzyme               | Cirrhosis       | Hepatic steatosis |   |
|---------------------------|-----------------|-------------------|---|
|                           | Odds ratio      | P value           | Odds ratio | P value |
| Alanine aminotransferase  | 1.23 (1.17-1.30)| 5.10E-15          | 1.17 (1.14-1.21) | 9.60E-28 |
| Asparate aminotransferase | 1.10 (1.04-1.16)| 5.10E-04          | 1.08 (1.05-1.11) | 3.80E-08 |
| Alkaline phosphatase      | 1.05 (0.99-1.10)| 8.60E-02          | 1.02 (0.99-1.05) | 1.20E-01 |

Effect of each rank unit of polygenic risk score for a specific liver enzyme on cirrhosis and hepatic steatosis. Effects are represented as odds ratio (95% confidence interval).
Supplementary Figure 1: Quantile-quantile plots

(A) Quantile-quantile plots for genetic variants affecting (A) alanine aminotransferase (ALT), (B) aspartate aminotransferase (AST), or (C) alkaline phosphatase (ALP).
Supplementary Figure 2: Effects of liver enzyme-increasing variants on metabolic traits.

(A-C) Associations between metabolic traits and variants increasing (A) alanine aminotransferase (ALT), (B) aspartate aminotransferase (AST), or (C) alkaline phosphatase (ALP). For all panels, only genome wide-significant associations (p < 5 x 10^{-8}) are shown. Red indicates that the liver enzyme-increasing allele increases the trait, while blue indicates that it decreases it. Larger circles indicate lower p value. Data are from genome-wide association studies in UK Biobank. Green highlighting indicates variants that affect the liver enzymes themselves.
Supplementary Figure 3: Effects of liver enzyme-increasing variants on serum/plasma metabolites.

Associations between variants associated with alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) and serum/plasma metabolites. Data on associations between genetic variants and serum/plasma metabolite concentrations are from 17. Red indicates that the liver enzyme-increasing allele increases metabolite concentration, blue that it decreases it, and white that there is no significant association. A Bonferroni correction for 123 metabolites and 378 genetic variants (p < 1.1 x 10^-6 or |Z| > 4.88) was used. Hierarchical clustering of genetic variants was performed using Z scores for variant-metabolite associations as a distance metric. * rs58542926-C (TM6SF2) had opposite directions on ALT and ALP.
Supplementary Figure 4: Associations between aspartate aminotransferase polygenic risk score and cirrhosis and steatosis.

(A-B) Association between percentile of aspartate aminotransferase polygenic risk score on (A) cirrhosis or (B) steatosis. All results are depicted as odds ratios for cirrhosis or steatosis relative to individuals in the 0-10th percentile of polygenic risk score, adjusted for sex, age, age$^2$, and principal components 1-10.
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