## Supplementary table 1. Associations of the instrumental SNPs with serum iron and knee osteoarthritis, hip osteoarthritis, total knee replacement, and total hip replacement.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP (GRCh37 position) | Associated potential confounding factors | | Effect allele/  Other allele | Effect allele frequency | SNP & serum iron associations |  | SNP & osteoarthritis associations | | | | | | | |
| Beta (SE) |  | Knee osteoarthritis | | Hip osteoarthritis | | Total knee replacement | | Total hip replacement | |
|  | Beta (SE) | *P* | Beta (SE) | *P* | Beta (SE) | *P* | Beta (SE) | *P* |
| rs2228145 (1:154426970) | interleukin 6; C-reactive protein | | C/A | 0.407 | 0.026 (0.004) |  | -0.005 (0.007) | 0.535 | 0.010 (0.009) | 0.283 | -0.005 (0.012) | 0.659 | 0.019 (0.011) | 0.092 |
| rs35945185 (1:66137239) |  | | A/G | 0.365 | 0.031 (0.004) |  | 0.009 (0.011) | 0.408 | 0.013 (0.013) | 0.338 | 0.005 (0.015) | 0.762 | 0.016 (0.014) | 0.274 |
| rs57659670 (15:45398438) |  | | C/T | 0.075 | -0.042 (0.007) |  | 0.036(0.013) | 0.007 | 0.036 (0.017) | 0.037 | 0.049 (0.023) | 0.035 | 0.019 (0.021) | 0.372 |
| rs77262773 (17:67249711) |  | | T/C | 0.026 | 0.081 (0.014) |  | 0.009 (0.025) | 0.738 | 0.047 (0.032) | 0.145 | 0.017 (0.04) | 0.680 | 0.033 (0.037) | 0.370 |
| rs2005682 (19:35947661) |  | | T/A | 0.305 | -0.029 (0.004) |  | 0.004 (0.008) | 0.597 | -0.004 (0.010) | 0.656 | -0.007 (0.013) | 0.600 | -0.015 (0.012) | 0.214 |
| rs13007705 (2:239069196) |  | | T/C | 0.425 | 0.029 (0.004) |  | 0.010 (0.007) | 0.165 | 0.005 (0.009) | 0.602 | 0.007 (0.012) | 0.599 | -0.001 (0.011) | 0.917 |
| rs855791 (22:37462936) | glycosylated haemoglobin | | A/G | 0.431 | -0.170 (0.005) |  | -0.006 (0.007) | 0.403 | -0.012 (0.009) | 0.205 | -0.008 (0.013) | 0.512 | -0.013 (0.011) | 0.276 |
| rs748587164 (3:133476750)\* |  | | A/T | 0.001 | -0.520 (0.069) |  | - | - | - | - | - | - | - | - |
| rs4854760 (3:133498741) |  | | G/A | 0.313 | 0.053 (0.005) |  | 0.001 (0.007) | 0.933 | 0.001 (0.009) | 0.947 | -0.003 (0.013) | 0.831 | 0.014 (0.012) | 0.236 |
| rs7630745 (3:66427029) |  | | C/T | 0.358 | 0.025 (0.004) |  | 0.001 (0.008) | 0.949 | -0.014 (0.009) | 0.144 | 0.026 (0.013) | 0.044 | -0.009 (0.011) | 0.434 |
| rs9399136 (6:135402339) intergenic | self-reported high cholesterol | | C/T | 0.259 | 0.057 (0.004) |  | -0.018 (0.008) | 0.031 | 0.005 (0.011) | 0.633 | -0.023 (0.014) | 0.101 | 0.009 (0.013) | 0.484 |
| rs1799945 (6:26091179) | glycosylated haemoglobin | | G/C | 0.137 | 0.170 (0.005) |  | 0.007 (0.010) | 0.515 | 0.013 (0.013) | 0.303 | -0.011 (0.017) | 0.513 | 0.017 (0.016) | 0.284 |
| rs1800562 (6:26093141) | glycosylated haemoglobin; low-density lipoprotein; total cholesterol | | A/G | 0.068 | 0.270 (0.008) |  | 0.034 (0.014) | 0.019 | 0.105 (0.018) | 2.9×10-9 | 0.036 (0.024) | 0.132 | 0.101 (0.021) | 1.2×10-6 |
| rs7385804 (7:100235970) |  | | C/A | 0.371 | -0.057 (0.004) |  | -0.007 (0.007) | 0.327 | -0.020 (0.009) | 0.032 | 0.002 (0.012) | 0.865 | -0.020 (0.011) | 0.084 |
| rs12718598 (7:50428445) |  | | C/T | 0.463 | 0.027 (0.004) |  | 0.002 (0.007) | 0.790 | -2×10-4 (0.012) | 0.987 | 0.006 (0.012) | 0.617 | 0.001 (0.011) | 0.934 |
| SNP, single nucleotide polymorphism; SE, standard error. | | | | | | | | | | | | | | |
|  | |

## Supplementary table 2. Associations of the instrumental SNPs with transferrin saturation and knee osteoarthritis, hip osteoarthritis, total knee replacement, and total hip replacement.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP (GRCh37 position) | Associated potential confounding factors | Effect allele/  Other allele | Effect allele frequency | SNP & serum iron associations |  | SNP & osteoarthritis associations | | | | | | | |
| Beta (SE) |  | Knee osteoarthritis | | Hip osteoarthritis | | Total knee replacement | | Total hip replacement | |
|  | Beta (SE) | *P* | Beta (SE) | *P* | Beta (SE) | *P* | Beta (SE) | *P* |
| rs57659670 (15:45398438) |  | C/T | 0.425 | -0.058 (0.008) |  | 0.036 (0.013) | 0.007 | 0.036 (0.017) | 0.037 | 0.049 (0.023) | 0.035 | 0.019 (0.021) | 0.372 |
| rs2005682 (19:35947661) |  | T/A | 0.259 | -0.032 (0.005) |  | 0.004 (0.008) | 0.597 | -0.004 (0.010) | 0.656 | -0.007 (0.013) | 0.600 | -0.015 (0.012) | 0.214 |
| rs13007705 (2:239069196) |  | T/C | 0.075 | 0.033 (0.005) |  | 0.010 (0.007) | 0.165 | 0.005 (0.009) | 0.602 | 0.007 (0.012) | 0.599 | -0.001 (0.011) | 0.917 |
| rs855791 (22:37462936) | glycosylated haemoglobin | A/G | 0.305 | -0.170 (0.005) |  | -0.006 (0.007) | 0.403 | -0.012 (0.009) | 0.205 | -0.008 (0.013) | 0.512 | -0.013 (0.011) | 0.276 |
| rs748587164 (3:133476750)\* |  | A/T | 0.001 | 0.720 (0.084) |  | - | - | - | - | - | - | - | - |
| rs4854760 (3:133498741) |  | G/A | 0.313 | -0.096 (0.006) |  | 0.001 (0.007) | 0.933 | 0.001 (0.009) | 0.947 | -0.003 (0.013) | 0.831 | 0.014 (0.012) | 0.236 |
| rs3817672 (3:195800811) |  | C/T | 0.440 | 0.026 (0.004) |  | -0.003 (0.007) | 0.651 | 0.006 (0.009) | 0.52 | -0.002 (0.013) | 0.898 | 0.010 (0.011) | 0.348 |
| rs9399136 (6:135402339) | self-reported high cholesterol | C/T | 0.137 | 0.067 (0.005) |  | -0.018 (0.008) | 0.031 | 0.005 (0.011) | 0.633 | -0.023 (0.014) | 0.101 | 0.009 (0.013) | 0.484 |
| rs1799945 (6:26091179) | glycosylated haemoglobin | G/C | 0.068 | 0.210 (0.008) |  | 0.007 (0.010) | 0.515 | 0.013 (0.013) | 0.303 | -0.011 (0.017) | 0.513 | 0.017 (0.016) | 0.284 |
| rs1800562 (6:26093141) | glycosylated haemoglobin; low-density lipoprotein; total cholesterol | A/G | 0.371 | 0.450 (0.013) |  | 0.034 (0.014) | 0.019 | 0.105 (0.018) | 2.9×10-9 | 0.036 (0.024) | 0.132 | 0.101 (0.021) | 1.2×10-6 |
| rs7385804 (7:100235970) |  | C/A | 0.431 | -0.062 (0.005) |  | -0.007 (0.007) | 0.327 | -0.020 (0.009) | 0.032 | 0.002 (0.012) | 0.865 | -0.020 (0.011) | 0.084 |
| rs748587164 is not in 1000G reference panel.  SNP, single nucleotide polymorphism; SE, standard error. | | | | | | | | | | | | | |

## Supplementary table 3. Associations of the instrumental SNPs with ferritin and knee osteoarthritis, hip osteoarthritis, total knee replacement, and total hip replacement.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP (GRCh37 position) | Associated potential confounding factors | Effect allele/  Other allele | Effect allele frequency | SNP & serum iron associations |  | SNP & osteoarthritis associations | | | | | | | |
| Beta (SE) |  | Knee osteoarthritis | | Hip osteoarthritis | | Total knee replacement | | Total hip replacement | |
|  | Beta (SE) | *P* | Beta (SE) | *P* | Beta (SE) | *P* | Beta (SE) | *P* |
| rs10801913 (1:116214279) |  | A/G | 0.021 | 0.024 (0.004) |  | 0.004 (0.008) | 0.609 | 0.008 (0.010) | 0.393 | 0.015 (0.013) | 0.258 | 0.024 (0.012) | 0.047 |
| rs6025 (1:169519049) |  | T/C | 0.307 | 0.150 (0.013) |  | 0.026 (0.024) | 0.279 | -0.078 (0.031) | 0.011 | 0.004 (0.041) | 0.919 | -0.110 (0.037) | 0.003 |
| rs551459670 (1:220288690) |  | A/G | 0.028 | 0.140 (0.020) |  | -0.081 (0.061) | 0.181 | -0.041 (0.078) | 0.601 | -0.065 (0.089) | 0.464 | -0.001 (0.085) | 0.99 |
| rs75965181 (1:22584002) | bone mineral density | A/T | 0.011 | -0.120 (0.011) |  | -0.036 (0.027) | 0.191 | -0.027 (0.034) | 0.421 | -0.014 (0.046) | 0.766 | -0.022 (0.042) | 0.598 |
| rs17476364 (10:71094504) | glycosylated haemoglobin; self-reported high cholesterol | C/T | 0.368 | 0.043 (0.006) |  | 0.006 (0.012) | 0.629 | 0.002 (0.015) | 0.897 | -0.003 (0.02) | 0.873 | 0.023 (0.018) | 0.202 |
| rs12419620 (11:2232553) |  | G/T | 0.274 | -0.031 (0.005) |  | 0.002 (0.01) | 0.863 | 0.024 (0.012) | 0.058 | -0.008 (0.017) | 0.635 | 0.023 (0.015) | 0.126 |
| rs12807014 (11:47760078) | trunk fat mass; waist circumference; body mass index | C/T | 0.288 | -0.029 (0.004) |  | -0.016 (0.008) | 0.049 | -0.019 (0.010) | 0.062 | -0.017 (0.014) | 0.214 | -0.023 (0.012) | 0.058 |
| rs4938939 (11:60160838) |  | A/G | 0.002 | 0.022 (0.004) |  | 0.005 (0.008) | 0.490 | -0.006 (0.010) | 0.563 | 0.005 (0.013) | 0.717 | -0.004 (0.012) | 0.721 |
| rs996347 (14:34410892) |  | C/T | 0.003 | 0.049 (0.004) |  | 0.002 (0.007) | 0.751 | 0.007 (0.009) | 0.437 | -0.014 (0.013) | 0.257 | 0.016 (0.012) | 0.174 |
| rs57659670 (15:45398438) |  | C/T | 0.005 | -0.140 (0.008) |  | 0.036 (0.013) | 0.007 | 0.036 (0.017) | 0.037 | 0.049 (0.023) | 0.035 | 0.019 (0.021) | 0.372 |
| rs3743171 (15:65916527) | body mass index; bone mineral density | T/A | 0.003 | -0.024 (0.004) |  | -0.020 (0.009) | 0.024 | -0.002 (0.011) | 0.888 | -0.021 (0.015) | 0.169 | -0.009 (0.014) | 0.515 |
| rs9921222 (16:375782) | bone mineral density; trunk fat-free mass | C/T | 0.112 | 0.025 (0.004) |  | 0.005 (0.007) | 0.479 | 0.010 (0.009) | 0.292 | 0.001 (0.013) | 0.964 | 0.015 (0.011) | 0.186 |
| rs3747602 (16:4802386) |  | G/T | 0.126 | 0.021 (0.004) |  | -0.008 (0.007) | 0.276 | -0.022 (0.009) | 0.019 | -0.018 (0.013) | 0.157 | -0.027 (0.011) | 0.020 |
| rs34523089 (17:56436109) |  | T/C | 0.446 | 0.069 (0.005) |  | -0.009 (0.010) | 0.350 | -0.001 (0.012) | 0.939 | -0.014 (0.017) | 0.395 | -0.006 (0.015) | 0.700 |
| rs535064984 (17:7020297) | self-reported high cholesterol | C/T | 0.079 | 0.230(0.026) |  | -0.030 (0.055) | 0.589 | 0.060 (0.069) | 0.380 | 0.132 (0.086) | 0.123 | 0.031(0.08) | 0.702 |
| rs1542752 (17:72938100) |  | T/C | 0.323 | 0.034 (0.005) |  | 0.005 (0.01) | 0.649 | 0.020 (0.012) | 0.118 | 0.017 (0.017) | 0.306 | 0.025 (0.015) | 0.098 |
| rs55789050 (17:9793417) | trunk fat mass; body fat mass | T/A | 0.479 | -0.027 (0.004) |  | -0.003 (0.008) | 0.728 | -0.002 (0.010) | 0.852 | -0.020 (0.013) | 0.132 | -0.006 (0.012) | 0.586 |
| rs4808802 (19:18577873) | total cholesterol | C/G | 0.360 | 0.028 (0.004) |  | -0.003 (0.009) | 0.728 | -0.010 (0.011) | 0.385 | -0.009 (0.015) | 0.562 | -0.001 (0.014) | 0.918 |
| rs601338 (19:49206674) | self-reported high cholesterol; total cholesterol; low density lipoprotein | G/A | 0.108 | 0.028 (0.004) |  | 0.015 (0.007) | 0.039 | 0.036 (0.009) | 7.6×10-5 | -0.009 (0.012) | 0.472 | 0.038(0.011) | 4.9×10-4 |
| rs143041401 (19:49550116) |  | A/G | 0.161 | 0.110 (0.013) |  | -0.029 (0.037) | 0.438 | -0.051 (0.043) | 0.240 | 0.076 (0.057) | 0.177 | -0.067 (0.051) | 0.187 |
| rs708686 (19:5840619) |  | T/C | 0.274 | -0.031 (0.004) |  | 0.010 (0.008) | 0.232 | -0.004 (0.010) | 0.726 | 0.035 (0.014) | 0.011 | 0.002 (0.012) | 0.885 |
| rs12693541 (2:190418690) |  | C/T | 0.293 | 0.079 (0.005) |  | -0.014 (0.011) | 0.181 | -0.017 (0.014) | 0.234 | -0.026 (0.019) | 0.164 | -0.021 (0.017) | 0.226 |
| rs1250259 (2:216300482) | low-density lipoprotein; total cholesterol | T/A | 0.007 | -0.024 (0.004) |  | -0.002 (0.008) | 0.761 | -0.007 (0.01) | 0.471 | -0.017 (0.014) | 0.227 | -0.015 (0.012) | 0.213 |
| rs1260326 (2:27730940) | triglycerides; C reactive protein; trunk fat-free mass; total cholesterol; self-reported high cholesterol | T/C | 0.355 | 0.025 (0.004) |  | -0.007 (0.007) | 0.351 | -0.026 (0.009) | 0.006 | -0.031 (0.012) | 0.014 | -0.032 (0.011) | 0.004 |
| rs6757653 (2:29171804) |  | T/C | 0.075 | 0.032 (0.004) |  | 0.016 (0.008) | 0.043 | 0.019 (0.010) | 0.052 | -0.014 (0.013) | 0.286 | 0.018 (0.012) | 0.140 |
| rs6029148 (20:39124408) |  | A/G | 0.191 | 0.046 (0.006) |  | 0.012 (0.014) | 0.385 | 0.051 (0.018) | 0.004 | 0.060 (0.024) | 0.011 | 0.058 (0.021) | 0.006 |
| rs855791 (22:37462936) | glycosylated haemoglobin | A/G | 0.492 | -0.044 (0.003) |  | -0.006 (0.007) | 0.403 | -0.012 (0.009) | 0.205 | -0.008 (0.013) | 0.512 | -0.013 (0.011) | 0.276 |
| rs1131262 (3:133941320) |  | T/C | 0.368 | -0.032 (0.005) |  | -0.014 (0.011) | 0.185 | -0.018 (0.014) | 0.203 | -0.013 (0.018) | 0.489 | -0.046 (0.017) | 0.007 |
| rs762752083 (3:52536039)\* |  | T/G | 0.006 | 0.350 (0.046) |  | - | - | - | - | - | - | - | - |
| rs750717575 (3:52536725)\* |  | A/G | 0.333 | 0.240 (0.041) |  | - | - | - | - | - | - | - | - |
| rs745795585 (3:52539395)\* |  | A/G | 0.153 | 0.290 (0.031) |  | - | - | - | - | - | - | - | - |
| rs34216132 (3:52727675) |  | C/G | 0.258 | 0.170 (0.028) |  | 0.073 (0.07) | 0.297 | 0.093 (0.084) | 0.268 | 0.133 (0.110) | 0.227 | 0.136 (0.101) | 0.180 |
| rs1799945 (6:26091179) | glycosylated haemoglobin | G/C | 0.218 | 0.059 (0.005) |  | 0.007 (0.01) | 0.515 | 0.013 (0.013) | 0.303 | -0.011 (0.017) | 0.513 | 0.017 (0.016) | 0.284 |
| rs1800562 (6:26093141) | glycosylated haemoglobin; low-density lipoprotein; total cholesterol | A/G | 0.484 | 0.130 (0.008) |  | 0.034 (0.014) | 0.019 | 0.105 (0.018) | 2.9×10-9 | 0.036 (0.024) | 0.132 | 0.101 (0.021) | 1.2×10-6 |
| rs36184164 (6:43781092) |  | G/T | 0.016 | 0.036 (0.005) |  | 0.001 (0.013) | 0.925 | -0.006 (0.016) | 0.695 | -0.007 (0.019) | 0.705 | -0.007 (0.017) | 0.691 |
| rs2529440 (7:30511794) |  | T/C | 0.071 | -0.035 (0.003) |  | 0.002 (0.007) | 0.794 | 0.010 (0.009) | 0.291 | 0.009 (0.012) | 0.486 | 0.008 (0.011) | 0.498 |
| rs4841429 (8:10568529) | bone mineral density | G/A | 0.119 | 0.060 (0.006) |  | -0.009 (0.013) | 0.527 | -0.011 (0.017) | 0.544 | -0.017 (0.023) | 0.475 | -0.012 (0.021) | 0.552 |
| rs2954029 (8:126490972) | triglycerides; total cholesterol; low-density lipoprotein; high-density lipoprotein; trunk fat mass | T/A | 0.137 | -0.024 (0.003) |  | -0.004 (0.007) | 0.555 | -0.011 (0.009) | 0.214 | 0.006 (0.012) | 0.64 | -0.010 (0.011) | 0.369 |
| rs13253974 (8:23377910) |  | A/G | 0.068 | 0.024 (0.004) |  | -0.002 (0.008) | 0.833 | -0.007 (0.01) | 0.477 | 0.028 (0.013) | 0.033 | -0.011 (0.012) | 0.33 |
| rs7865362 (9:33117965) |  | T/C | 0.161 | 0.025 (0.004) |  | -0.001 (0.007) | 0.913 | 0.021 (0.009) | 0.027 | -0.003 (0.013) | 0.819 | 0.022 (0.011) | 0.057 |
| rs745795585, rs762752083, and rs750717575 are not in 1000G reference panel.  SNP, single nucleotide polymorphism; SE, standard error. | | | | | | | | | | | | | |  | 0.431 |

## Supplementary table 4. Associations of the instrumental SNPs with total iron-binding capacity and knee osteoarthritis, hip osteoarthritis, total knee replacement, and total hip replacement.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP (GRCh37 position) | Associated potential confounding factors\* | Effect allele/  Other allele | Effect allele frequency | SNP & serum iron associations\* |  | SNP & osteoarthritis associations | | | | | | | |
| Beta (SE) |  | Knee osteoarthritis | | Hip osteoarthritis | | Total knee replacement | | Total hip replacement | |
|  | Beta (SE) | *P* | Beta (SE) | *P* | Beta (SE) | *P* | Beta (SE) | *P* |
| rs6025 (1:169519049) |  | T/C | 0.028 | -0.093 (0.018) |  | 0.026 (0.024) | 0.279 | -0.078 (0.031) | 0.011 | 0.004 (0.041) | 0.919 | -0.110 (0.037) | 0.003 |
| rs174546 (11:61569830) |  | T/C | 0.335 | 0.046 (0.005) |  | -0.008 (0.007) | 0.267 | -0.012 (0.009) | 0.21 | -0.001 (0.012) | 0.934 | 0.007 (0.011) | 0.531 |
| rs17580 (14:94847262) |  | A/T | 0.259 | 0.076 (0.012) |  | -0.013 (0.019) | 0.495 | -0.034 (0.025) | 0.172 | -0.065 (0.031) | 0.039 | -0.038 (0.028) | 0.18 |
| rs57659670 (15:45398438) |  | C/T | 0.038 | 0.077 (0.009) |  | 0.036 (0.013) | 0.007 | 0.036 (0.017) | 0.037 | 0.049 (0.023) | 0.035 | 0.019 (0.021) | 0.372 |
| rs112727702 (19:50091204) |  | T/G | 0.075 | 0.043 (0.006) |  | -0.007 (0.011) | 0.531 | -0.029 (0.014) | 0.035 | -0.006 (0.017) | 0.715 | -0.037 (0.015) | 0.015 |
| rs12693541 (2:190418690) |  | C/T | 0.232 | -0.048 (0.007) |  | -0.014 (0.011) | 0.181 | -0.017 (0.014) | 0.234 | -0.026 (0.019) | 0.164 | -0.021 (0.017) | 0.226 |
| rs1132274 (20:17596155) |  | A/C | 0.168 | 0.036 (0.006) |  | 0.015 (0.01) | 0.145 | 0.009 (0.013) | 0.508 | 0.028 (0.017) | 0.104 | -0.001 (0.016) | 0.965 |
| rs855791 (22:37462936) | glycosylated haemoglobin | A/G | 0.119 | 0.026 (0.005) |  | -0.006 (0.007) | 0.403 | -0.012 (0.009) | 0.205 | -0.008 (0.013) | 0.512 | -0.013 (0.011) | 0.276 |
| rs4854760 (3:133498741) |  | G/A | 0.001 | 0.340 (0.008) |  | 0.001 (0.007) | 0.933 | 0.001 (0.009) | 0.947 | -0.003 (0.013) | 0.831 | 0.014 (0.012) | 0.236 |
| rs3817672 (3:195800811) |  | C/T | 0.313 | -0.031 (0.005) |  | -0.003 (0.007) | 0.651 | 0.006 (0.009) | 0.52 | -0.002 (0.013) | 0.898 | 0.010 (0.011) | 0.348 |
| rs59950280 (4:3452345) |  | A/G | 0.440 | 0.033 (0.005) |  | -0.011 (0.008) | 0.182 | -0.019 (0.01) | 0.05 | -0.037 (0.013) | 0.005 | -0.027 (0.012) | 0.022 |
| rs9399136 (6:135402339) | self-reported high cholesterol | C/T | 0.137 | -0.033 (0.005) |  | -0.018 (0.008) | 0.031 | 0.005 (0.011) | 0.633 | -0.023 (0.014) | 0.101 | 0.009 (0.013) | 0.484 |
| rs1799945 (6:26091179) | glycosylated haemoglobin | G/C | 0.068 | -0.120 (0.008) |  | 0.007 (0.01) | 0.515 | 0.013 (0.013) | 0.303 | -0.011 (0.017) | 0.513 | 0.017 (0.016) | 0.284 |
| rs1800562 (6:26093141) | glycosylated haemoglobin; low-density lipoprotein; total cholesterol | A/G | 0.214 | -0.450 (0.010) |  | 0.034 (0.014) | 0.019 | 0.105 (0.018) | 2.9×10-9 | 0.036 (0.024) | 0.132 | 0.101 (0.021) | 1.2×10-6 |
| rs1495743 (8:18273300) |  | G/C | 0.354 | -0.043 (0.006) |  | -1×10-4 (0.015) | 0.078 | -0.019 (0.011) | 0.078 | -0.020 (0.015) | 0.160 | -0.032 (0.013) | 0.017 |
| SNP, single nucleotide polymorphism; SE, standard error. | | | | | | | | | | | | | |  | 0.431 |

## Supplementary table 5. Leave-one-out analysis of the causal association between the four systemic iron status biomarkers with conservative instruments and hip osteoarthritis & total hip replacement.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Iron biomarkers | SNP (leave out) | Hip osteoarthritis | | Total hip replacement | |
| OR (95% CI) | *P* value\* | OR (95% CI) | *P* value\* |
| Serum iron | rs1800562 | 1.06 (0.98, 1.16) | 0.154 | 1.08 (0.97, 1.20) | 0.159 |
| rs855791 | 1.27 (1.15, 1.40) | **<0.001** | 1.28 (1.14, 1.44) | **<0.001** |
| rs1799945 | 1.20 (1.11, 1.30) | **<0.001** | 1.22 (1.10, 1.34) | **<0.001** |
| rs57659670 | 1.18 (1.10, 1.27) | **<0.001** | 1.20 (1.10, 1.30) | **<0.001** |
| Transferrin saturation | rs1800562 | 1.06 (0.98, 1.14) | 0.183 | 1.07 (0.97, 1.18) | 0.164 |
| rs855791 | 1.19 (1.12, 1.27) | **<0.001** | 1.19 (1.11, 1.29) | **<0.001** |
| rs1799945 | 1.18 (1.11, 1.26) | **<0.001** | 1.19 (1.10, 1.28) | **<0.001** |
| rs57659670 | 1.17 (1.10, 1.23) | **<0.001** | 1.17 (1.09, 1.25) | **<0.001** |
| Ferritin | rs1800562 | 0.94 (0.78, 1.14) | 0.544 | 1.03 (0.82, 1.30) | 0.791 |
| rs855791 | 1.25 (1.06, 1.47) | **0.009** | 1.34 (1.10, 1.63) | **0.004** |
| rs1799945 | 1.25 (1.07, 1.48) | **0.006** | 1.34 (1.10, 1.63) | **0.004** |
| rs57659670 | 1.75 (1.43, 2.13) | **<0.001** | 1.76 (1.39, 2.23) | **<0.001** |
| Total iron-binding capacity | rs1800562 | 0.97 (0.81, 1.16) | 0.727 | 0.91 (0.73, 1.13) | 0.399 |
| rs855791 | 0.82 (0.76, 0.88) | **<0.001** | 0.82 (0.75, 0.89) | **<0.001** |
| rs1799945 | 0.81 (0.75, 0.87) | **<0.001** | 0.81 (0.74, 0.88) | **<0.001** |
| rs57659670 | 0.80 (0.75, 0.86) | **<0.001** | 0.80 (0.74, 0.88) | **<0.001** |
| \* Bolded *P* values indicate statistical significance (<0.012).  IVW, inverse variance weighted; OR, odds ratio; CI: compatibility/confidence interval. | | | | | |
| Supplementary table 6. Associations of the instrumental SNPs with four systemic iron status biomarkers and knee osteoarthritis and hip osteoarthritis in the 2019 osteoarthritis genome-wide association study dataset.  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Iron biomarkers | Instrument set (number of instruments) | Analysis method | Knee osteoarthritis | | Hip osteoarthritis | | | OR (95% CI) | *P* value\* | OR (95% CI) | *P* value\* | | Serum iron | Liberal instruments (14) | IVW | 1.04 (0.96, 1.13) | 0.309 | 1.15 (1.01, 1.30) | **0.037** | | Weighted median | 1.06 (0.97, 1.16) | 0.174 | 1.04 (0.91, 1.19) | 0.533 | | MR-Egger | 1.06 (0.95, 1.20) | 0.298 | 1.22 (1.01, 1.47) | **0.042** | | Sensitivity instruments (12) | IVW | 1.07 (0.99, 1.16) | 0.059 | 1.15 (1.00, 1.32) | **0.049** | | Weighted median | 1.07 (0.98, 1.16) | 0.148 | 1.04 (0.91, 1.19) | 0.515 | | MR-Egger | 1.11 (0.99, 1.24) | 0.065 | 1.23 (1.00, 1.51) | **0.049** | | Conservative instruments (4) | IVW | 1.09 (0.98, 1.22) | 0.115 | 1.15 (0.90, 1.47) | 0.248 | | Weighted median | 1.07 (0.98, 1.16) | 0.111 | 1.04 (0.91, 1.19) | 0.538 | | Transferrin saturation | Liberal instruments (10) | IVW | 1.05 (0.98, 1.12) | 0.175 | 1.15 (1.05, 1.26) | **0.002** | | Weighted median | 1.09 (1.02, 1.16) | **0.010** | 1.14 (1.02, 1.29) | **0.023** | | MR-Egger | 1.07 (0.97, 1.18) | 0.194 | 1.20 (1.06, 1.37) | **0.005** | | Sensitivity instruments (8) | IVW | 1.05 (0.99, 1.12) | 0.096 | 1.16 (1.05, 1.27) | **0.002** | | Weighted median | 1.09 (1.02, 1.16) | **0.010** | 1.15 (1.02, 1.30) | **0.018** | | MR-Egger | 1.06 (0.96, 1.17) | 0.225 | 1.20 (1.05, 1.37) | **0.009** | | Conservative instruments (4) | IVW | 1.05 (0.95, 1.16) | 0.366 | 1.15 (0.99, 1.35) | 0.075 | | Weighted median | 1.07 (1.01, 1.14) | 0.034 | 1.13 (1.03, 1.25) | **0.013** | | Ferritin | Liberal instruments (37) | IVW | 0.96 (0.86, 1.08) | 0.495 | 1.12 (0.94, 1.33) | 0.189 | | Weighted median | 0.90 (0.77, 1.05) | 0.172 | 1.11 (0.92, 1.32) | 0.275 | | MR-Egger | 0.89 (0.72, 1.09) | 0.258 | 1.16 (0.84, 1.60) | 0.362 | | Sensitivity instruments (33) | IVW | 0.92 (0.81, 1.06) | 0.241 | 1.08 (0.88, 1.32) | 0.467 | | Weighted median | 0.87 (0.73, 1.02) | 0.086 | 0.99 (0.82, 1.22) | 0.992 | | MR-Egger | 0.92 (0.71, 1.18) | 0.504 | 1.27 (0.88, 1.83) | 0.208 | | Conservative instruments (4) | IVW | 0.99 (0.72, 1.36) | 0.951 | 1.32 (0.77, 2.27) | 0.308 | | Weighted median | 0.99 (0.79, 1.27) | 0.985 | 0.98 (0.73, 1.33) | 0.911 | | Total iron-binding capacity | Liberal instruments (15) | IVW | 0.96 (0.91, 1.02) | 0.201 | 0.90 (0.82, 0.98) | **0.013** | | Weighted median | 0.96 (0.91, 1.00) | 0.074 | 0.94 (0.86, 1.03) | 0.181 | | MR-Egger | 0.95 (0.88, 1.02) | 0.150 | 0.88 (0.79, 0.99) | **0.031** | | Sensitivity instruments (33) | IVW | 0.96 (0.91, 1.02) | 0.164 | 0.90 (0.82, 0.98) | **0.015** | | Weighted median | 0.96 (0.91, 1.00) | 0.071 | 0.94 (0.86, 1.03) | 0.179 | | MR-Egger | 0.96 (0.89, 1.03) | 0.202 | 0.89 (0.79, 0.99) | **0.043** | | Conservative instruments (4) | IVW | 0.95 (0.83, 1.08) | 0.402 | 0.79 (0.71, 0.88) | **<0.001** | | Weighted median | 0.94 (0.87, 1.01) | 0.076 | 0.79 (0.72, 0.86) | **<0.001** | | \* Bolded *P* values indicate value of <0.05.  IVW, inverse variance weighted; OR, odds ratio; CI: compatibility/confidence interval. | | | | | | | | | | | | | |