**Supplementary Table 1. Summary statistics for DHEAS-associated SNPs using as instrumental variables**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | Chr | EAF | Position | EA | OA | Beta | SE | P | F-statistic |
| rs604126 | 2 | 0.35 | 111943200 | G | A | 0.05 | 0.01 | 1 × 10-8 | 32.7 |
| rs1105977 | 3 | 0.71 | 195929252 | T | C | 0.05 | 0.01 | 1 × 10-8 | 32.8 |
| rs148982377 | 7 | 0.05 | 99075038 | C | T | -0.34 | 0.02 | 2 × 10-60 | 272.4 |
| rs2911280 | 16 | 0.91 | 81591313 | G | A | -0.09 | 0.02 | 2 × 10-8 | 31.3 |

Abbreviations: SNP, single-nucleotide polymorphism; DHEAS, dehydroepiandrosterone sulfate; Chr, chromosome; EAF, effect allele frequency; EA, effect allele; OA, other allele; SE, standard error; P, p value; GWAS, genome-wide association study.

Instrumental variables were selected from a GWAS by Prins BP, et al. **Sci. Rep.** 2017; 7: 11008.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | EA | OA | eBMD | | | FN-BMD | | | LS-BMD | | | Fracture | | |
| Beta | SE | P | Beta | SE | P | Beta | SE | P | Beta | SE | P |
| rs604126 | G | A | 0.007 | 0.002 | 0.003 | 0.003 | 0.008 | 0.68 | 0.006 | 0.009 | 0.47 | -0.001 | 6 × 10-4 | 0.07 |
| rs1105977 | T | C | 5 × 10-4 | 0.002 | 0.86 | -3 × 10-4 | 0.008 | 0.96 | -0.001 | 0.009 | 0.87 | -3 × 10-4 | 6 × 10-4 | 0.57 |
| rs148982377 | C | T | -0.04 | 0.006 | 2 × 10-11 | -0.07 | 0.019 | 4 × 10-4 | -0.11 | 0.022 | 1 × 10-6 | 0.003 | 0.001 | 0.05 |
| rs2911280 | G | A | -0.01 | 0.004 | 0.021 | -0.024 | 0.014 | 0.09 | -0.03 | 0.016 | 0.03 | 0.001 | 0.001 | 0.19 |

**Supplementary Table 2. Summary statistics for association of instrumental variables with BMD and fracture**

Abbreviations: SNP, single-nucleotide polymorphism; EA, effect allele; OA, other allele; BMD, bone mineral density; FN, femoral neck; LS, lumbar spine; eBMD, estimated bone mineral density; SE, standard error, P, p value

Coefficient of determination (R2) of exposure on genetic variants is 0.03. With a one-sided 0.05 α error.

Abbreviations: FGF23, fibroblast growth factor 23; MR, mendelian randomization; SD, standard deviation; eBMD, estimated bone mineral density measured at the heel; LS, lumber spine; FN, femoral neck; baPWV, the brachial-ankle pulse wave velocity; IMT, the intima-media thickness; BP, blood pressure; CAD, coronary artery disease; CARDIoGRAMplusC4D, Coronary Artery Disease Genome-wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics

**Supplementary Table 3. Summary statistics for association of instrumental variables with traits using for multivariable MR**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | EA | OA | Height | | | BMI | | | IGF-1 | | |
| Beta | SE | P | Beta | SE | P | Beta | SE | P |
| rs604126 | G | A | 0.004 | 0.001 | 7 × 10-4 | 0.002 | 0.001 | 0.28 | 0.077 | 0.014 | 4 × 10-8 |
| rs1105977 | T | C | -0.003 | 0.001 | 0.03 | -0.004 | 0.002 | 0.025 | -4 × 10-4 | 0.014 | 0.977 |
| rs148982377 | C | T | 0.031 | 0.003 | 7 × 10-22 | -0.026 | 0.003 | 1 × 10-12 | 0.182 | 0.033 | 4 × 10-8 |
| rs2911280 | G | A | -0.005 | 0.002 | 0.02 | 0.004 | 0.003 | 0.17 | -0.171 | 0.025 | 1 × 10-11 |
| SNP | EA | OA | Testosterone | | | Estradiol | | | SHBG | | |
| Beta | SE | P | Beta | SE | P | Beta | SE | P |
| rs604126 | G | A | -0.001 | 0.007 | 0.886 | -4.715 | 2.673 | 0.077 | -0.199 | 0.068 | 0.003 |
| rs1105977 | T | C | 0.007 | 0.007 | 0.344 | -2.180 | 2.793 | 0.435 | -0.019 | 0.071 | 0.780 |
| rs148982377 | C | T | 0.009 | 0.017 | 0.583 | -18.25 | 6.639 | 0.005 | -0.739 | 0.160 | 4 × 10-6 |
| rs2911280 | G | A | -0.005 | 0.012 | 0.676 | 7.214 | 4.758 | 0.129 | 0.237 | 0.122 | 0.052 |

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | EA | OA | Falls | | | Grip strength | | | Physical activity | | |
| Beta | SE | P | Beta | SE | P | Beta | SE | P |
| rs604126 | G | A | 4 × 10-5 | 0.001 | 0.97 | 0.002 | 0.001 | 0.20 | -0.006 | 0.004 | 0.16 |
| rs1105977 | T | C | -1 × 10-4 | 0.001 | 0.88 | -3 × 10-4 | 0.001 | 0.81 | 0.010 | 0.004 | 0.021 |
| rs148982377 | C | T | -0.003 | 0.003 | 0.26 | 0.014 | 0.003 | 1 × 10-4 | 0.007 | 0.010 | 0.50 |
| rs2911280 | G | A | 5 × 10-4 | 0.002 | 0.80 | 9 × 10-5 | 0.002 | 0.97 | -0.007 | 0.007 | 0.32  Abbreviations: SNP, single-nucleotide polymorphism; EA, effect allele; OA, other allele; BMI, body mass index; SHBG, sex hormone- binging globulin; SE, standard error, P, p value |

**Supplementary Table 4. Summary statistics for DHEAS-associated SNPs using as instrumental variables in men and women**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Men | SNP | Chr | EAF | Position | EA | OA | Beta | SE | P | F-statistic |
| rs12648421 | 4 | 0.108 | 21096616 | A | G | -0.099 | 0.019 | 4 × 10-7 | 25.4 |
| rs36155566 | 6 | 0.820 | 119198146 | C | T | 0.089 | 0.016 | 4 × 10-7 | 30.1 |
| rs45446698 | 7 | 0.035 | 99332948 | G | T | -0.341 | 0.035 | 4 × 10-22 | 94.5 |
| rs615567 | 13 | 0.387 | 22319209 | T | A | -0.071 | 0.012 | 2 × 10-8 | 31.1 |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Women | SNP | Chr | EAF | Position | EA | OA | Beta | SE | P | F-statistic |
| rs77533229 | 2 | 0.021 | 43479683 | A | G | -0.425 | 0.060 | 1 × 10-12 | 27.3 |
| rs117978821 | 7 | 0.030 | 99107775 | C | T | -0.297 | 0.047 | 2 × 10-10 | 25.9 |
| rs615567 | 13 | 0.400 | 22319209 | T | A | -0.085 | 0.016 | 1 × 10-7 | 49.8 |
| rs7181230 | 15 | 0.368 | 40360741 | G | A | 0.085 | 0.016 | 3 × 10-7 | 40.0 |
| rs2547231 | 19  Abbreviations: SNP, single-nucleotide polymorphism; DHEAS, dehydroepiandrosterone sulfate; Chr, chromosome; EAF, effect allele frequency; EA, effect allele; OA, other allele; SE, standard error; P, p value.  Instrumental variables were selected from a GWAS by Pott J, et al. **J. Clin. Endocrinol. Metab**. 2019; 104(11): 5008-23. | 0.826 | 48385057 | A | C | 0.143 | 0.021 | 1 × 10-11 | 46.3 |

**Supplementary Table 5. Summary statistics for association of instrumental variables with BMD in men and women**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Men | | | | | | Women | | | | | |
| SNP | EA | OA | eBMD | | | SNP | EA | OA | eBMD | | |
| Beta | SE | P | Beta | SE | P |
| rs12648421 | A | G | 0.008 | 0.006 | 0.232 | rs77533229 | A | G | -4 × 10-4 | 0.012 | 0.968 |
| rs36155566 | C | T | 0.005 | 0.005 | 0.305 | rs117978821 | C | T | -0.071 | 0.012 | 2 × 10-9 |
| rs45446698 | G | T | -0.015 | 0.011 | 0.158 | rs615567 | T | A | -0.001 | 0.004 | 0.656 |
| rs615567 | T | A | 0.011 | 0.004 | 0.015 | rs7181230 | A | G | -0.003 | 0.004 | 0.358 |
|  | | | | | | rs2547231 | C | A | -0.007 | 0.005 | 0.156 |

Abbreviations: SNP, single-nucleotide polymorphism; EA, effect allele; OA, other allele; eBMD, estimated bone mineral density; SE, standard error, P, p value

**Supplementary Table 6. The functional grades of RegulomeDB**

|  |  |
| --- | --- |
| Category | Description |
| Likely to affect binding and linked to expression of a gene target | |
| 1a | eQTL + TF binding + matched TF motif + matched DNase footprint + DNase peak |
| 1b | eQTL + TF binding + any motif + DNase footprint + DNase peak |
| 1c | eQTL + TF binding + matched TF motif + DNase peak |
| 1d | eQTL + TF binding + any motif + DNase peak |
| 1e | eQTL + TF binding + matched TF motif |
| 1f | eQTL + TF binding/DNase peak |
| Likely to affect binding |  |
| 2a | TF binding + matched TF motif + matched DNase footprint + DNase peak |
| 2b | TF binding + any motif + DNase footprint + DNase peak |
| 2c | TF binding + matched TF motif + DNase peak |
| Less likely to affect binding |  |
| 3a | TF binding + any motif + DNase peak |
| 3b | TF binding + matched TF motif |
| Minimal binding evidence |  |
| 4 | TF binding + DNase peak |
| 5 | TF binding or DNase peak |
| 6 | Motif hit |
| 7 | No evidence |

Abbreviations: SNP, single-nucleotide polymorphism; eQTL, expression quantitative trait loci; TF, transcription factor

This table was based on Boyle AP, et al. **Genome. Res.** 2012;22(9):1790-1797.

**Supplementary Table 7. MR-Egger analysis for association of DHEAS with BMD and fracture**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Method | eBMD | | | FN-BMD | | | LS-BMD | | | Fracture | | |
| Estimate | 95%CI | P | Estimate | 95%CI | P | Estimate | 95%CI | P | Estimate | 95%CI | P |
| MR-Egger | 0.134 | 0.072–0.195 | 0.050 | 0.241 | 0.103–0.378 | 0.074 | 0.376 | 0.217–0.536 | 0.043 | 0.992 | 0.981–1.003 | 0.295 |
| MR-Egger intercept | -0.002 | | 0.592 | -0.008 | | 0.356 | -0.013 | | 0.251 | 0.0004 | | 0.28 |

Abbreviations: MR, Mendelian randomization; SNP, single-nucleotide polymorphism; EA, effect allele; OA, other allele; BMD, bone mineral density; FN, femoral neck; LS, lumbar spine; eBMD, estimated bone mineral density; P, p value

**Supplementary Table 8. Leave-one-out analysis for associations DHEAS with BMD and fracture**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | | Remove rs604126 | | | Remove rs1105977 | | | Remove rs148982377 | | | Remove rs2911280 | | |
| Estimate | 95%CI | P | Estimate | 95%CI | P | Estimate | 95%CI | P | Estimate | 95%CI | P |
| BMD | eBMD | 0.116 | 0.081-0.158 | 7 × 10-7 | 0.129 | 0.096-1.163 | 2 × 10-14 | 0.100 | 0.014-0.187 | 0.024 | 0.119 | 0.070-0.168 | 2 × 10-6 |
| FN-BMD | 0.193 | 0.092-0.294 | 1 × 10-4 | 0.198 | 0.098-0.299 | 1 × 10-4 | 0.114 | -0.069-0.298 | 0.221 | 0.172 | 0.071-0.273 | 8 × 10-4 |
| LS-BMD | 0.299 | 0.150-0.447 | 7 × 10-5 | 0.312 | 0.196-0.429 | 1 × 10-7 | 0.174 | -0.065-0.413 | 0.154 | 0.272 | 0.117-0.428 | 5 × 10-4 |
|  | | OR | 95%CI | P | OR | 95%CI | P | OR | 95%CI | P | OR | 95%CI | P |
| Fracture | | 0.990 | 0.982-0.998 | 0.019 | 0.988 | 0.980-0.996 | 0.006 | 0.983 | 0.968-0.998 | 0.033 | 0.989 | 0.981-0.997 | 0.012 |

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; eBMD, estimated bone mineral density; LS, lumbar spine; FN, femoral neck; OR, odds ratio; CI, confidence interval; P, p value

**Supplementary Table 9. MR analysis for associations DHEAS with BMD in men and women**

Abbreviations: MR, Mendelian randomization; DHEAS, dehydroepiandrosterone sulfate; eBMD, estimated bone mineral density; CI, confidence interval; P, p value; IVW, inverse-variance-weighted; MR-PRESSO, Mendelian randomization-pleiotropy residual sum and outlier

MR-PRESSO analysis for association of DHEAS with eBMD could not have been performed, since the number of instrumental variables was too small to run analysis.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Method | eBMD -Men- | | | eBMD -Women- | | | |
| Estimate | 95%CI | P | Estimate | | 95%CI | P |
| IVW | 0.069 | 0.021 – 0.118 | 0.004 | 0.064 | | -0.020 – 0.150 | 0.136 |
| Cochran’s Q | 2.389 | | 0.495 | 24.847 | | | 5 × 10-5 |
| Weighted-median | 0.055 | 0.0002 – 0.111 | 0.049 | 0.025 | | -0.019 – 0.071 | 0.268 |
| MR-Egger | 0.022 | -0.065 – 0.110 | 0.669 | 0.082 | | -0.094 – 0.260 | 0.428 |
| MR-Egger intercept | 0.007 | | 0.332 | -0.003 | | | 0.827 |
| MR-PRESSO |  | |  | 0.043 | 0.025 – 0.060 | | 0.043 |

**Supplementary Table 10. Functional assessment for candidate SNPs of DHEAS GAWS using FUMA**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| SNP | loci/ lead SNP | r2 | Nearest gene | Position | CADD score | RegulomeDB score |
| rs7567444 | 2q13 /  rs604126 | 0.619 | ACOXL:AC096670.3 | ncRNA\_intronic | 2.3 | 7 |
| rs2015454 | 0.614 | ACOXL:AC096670.3 | ncRNA\_intronic | 0.86 | NA |
| rs4848393 | 0.621 | BCL2L11 | intronic | 8.712 | 4 |
| rs11378324 | 0.613 | BCL2L11 | intronic | 8.521 | NA |
| rs2241845 | 0.624 | BCL2L11 | intronic | 7.372 | NA |
| rs2241843 | 0.623 | BCL2L11 | intronic | **10.25** | NA |
| rs59854799 | 0.618 | BCL2L11 | intronic | 6.03 | NA |
| rs6758181 | 0.610 | BCL2L11 | intronic | 5.061 | 5 |
| rs4849417 | 0.602 | BCL2L11 | intronic | 0.029 | 6 |
| rs6746608 | 0.611 | BCL2L11 | intronic | 3.52 | NA |
| rs6750599 | 0.610 | BCL2L11 | intronic | 2.411 | **1f** |
| rs10204044 | 0.609 | BCL2L11 | intronic | 0.626 | 7 |
| rs13396983 | 0.610 | BCL2L11 | intronic | 1.903 | 6 |
| rs1980045 | 0.607 | BCL2L11 | intronic | 2.054 | 6 |
| rs1877331 | 0.615 | BCL2L11 | intronic | 3.838 | NA |
| rs6542334 | 2q13 /  rs604126 | 0.615 | BCL2L11 | intronic | 3.016 | 7 |
| rs9308731 | 0.62 | BCL2L11 | intronic | 1.623 | 5 |
| rs139665965 | 0.639 | BCL2L11 | intronic | 2.497 | NA |
| rs3838220 | 0.623 | BCL2L11 | intronic | 1.713 | NA |
| rs59403143 | 0.623 | BCL2L11 | intronic | **11.27** | NA |
| rs686952 | 0.663 | BCL2L11 | intronic | 3.212 | 3a |
| rs3827536 | 0.622 | BCL2L11 | intronic | 2.614 | NA |
| rs6753785 | 0.633 | BCL2L11 | UTR3 | 3.678 | 5 |
| rs35354739 | 0.640 | BCL2L11 | downstream | 2.845 | NA |
| rs36018702 | 0.647 | BCL2L11 | intergenic | 3.788 | 6 |
| rs56173510 | 0.632 | BCL2L11 | intergenic | 0.994 | 6 |
| rs590097 | 0.877 | BCL2L11 | intergenic | 6.518 | **2a** |
| rs72174338 | 0.660 | BCL2L11 | intergenic | 7.547 | NA |
| rs4849442 | 0.659 | BCL2L11 | intergenic | 3.048 | **1f** |
| rs650588 | 0.661 | AC108463.1 | intergenic | 3.308 | 3a |
| rs17558117 | 0.740 | AC108463.1 | intergenic | 3.797 | 5 |
| rs616582 | 0.740 | AC108463.1 | intergenic | 1.175 | 5 |
| rs604126 | 1 | AC108463.1 | intergenic | 2.503 | 4 |
| rs532558450 | 0.621 | AC108463.1 | intergenic | 0.125 | NA |
| rs6738028 | 0.744 | AC108463.1 | intergenic | 1.019 | 7 |
| rs71621224 | 3q29 / rs1105977 | 0.696 | ZDHHC19 | intronic | 1.019 | NA |
| rs62410541 | 0.905 | ZDHHC19 | intronic | 0.581 | 7 |
| rs62410542 | 0.924 | ZDHHC19 | intronic | 2.018 | 7 |
| rs62410543 | 0.924 | ZDHHC19 | intronic | 2.904 | 7 |
| rs71323706 | 0.944 | ZDHHC19 | intronic | 4.828 | 6 |
| rs11915002 | 0.964 | ZDHHC19 | intronic | 0.137 | 5 |
| rs11924930 | 0.643 | ZDHHC19 | intronic | 1.177 | 6 |
| rs1105977 | 1 | ZDHHC19:Y\_RNA | ncRNA\_exonic | 6.903 | 7 |
| rs1105978 | 0.615 | ZDHHC19 | intrinic | 2.716 | 5 |
| rs754637649 | 7q22.1 / rs148982377 | 0.836 | PTCD1:ATP5J2-PTCD1 | intronic | 0.629 | NA |
| rs148982377 | 1 | ZNF789 | intronic | 4.498 | 6 |
| rs117978821 | 0.737 | ZKSCAN5 | intronic | 5.396 | 6 |
| rs34670419 | 0.979 | ZKSCAN5 | UTR3 | 4.144 | 5 |
| rs10278040 | 0.607 | FAM200A | intergenic | 2.537 | 5 |
| rs118168183 | 0.660 | CYP3A7 | intergenic | 8.881 | 4 |
| rs45446698 | 0.817 | CYP3A7 | upstream | 1.483 | NA |
| rs45467892 | 0.638 | CYP3A7 | upstream | 0.09 | 7 |
| rs45575938 | 0.638 | CYP3A7 | upstream | 0.373 | NA |
| rs45494802 | 0.638 | CYP3A7 | upstream | 0.522 | 7 |
| rs7201762 | 16q23.2 / rs2911280 | 0.613 | CMIP | intronic | 2.879 | 7 |
| rs7200347 | 16q23.2 / rs2911280 | 0.613 | CMIP | intronic | 0.248 | 7 |
| rs7201098 | 0.613 | CMIP | intronic | 4.792 | 5 |
| rs7201103 | 0.613 | CMIP | intronic | 1.883 | 5 |
| rs7203208 | 0.613 | CMIP | intronic | 3.618 | 5 |
| rs13331687 | 0.613 | CMIP | intronic | 4.507 | 7 |
| rs374535301 | 0.613 | CMIP | intronic | 4.451 | 7 |
| rs77576640 | 0.613 | CMIP | intronic | 2.071 | 4 |
| rs28410432 | 0.613 | CMIP | intronic | 0.927 | 4 |
| rs28651456 | 0.613 | CMIP | intronic | 5.379 | 3a |
| rs28404001 | 0.613 | CMIP | intronic | 3.102 | 3a |
| rs13333262 | 0.624 | CMIP | intronic | 4.255 | **2b** |
| rs7196069 | 0.624 | CMIP | intronic | 1.788 | 5 |
| rs7196272 | 0.624 | CMIP | intronic | 6.323 | 4 |
| rs7198024 | 0.624 | CMIP | intronic | **11.08** | 6 |
| rs9931108 | 0.624 | CMIP | intronic | 0.016 | 3a |
| rs75584947 | 0.636 | CMIP | intronic | 6.243 | 5 |
| rs17777603 | 0.624 | CMIP | intronic | 2.006 | 3a |
| rs140409812 | 0.624 | CMIP | intronic | 5.011 | NA |
| rs9926999 | 0.624 | CMIP | intronic | 2.822 | 5 |
| rs77531223 | 0.636 | CMIP | intronic | 3.594 | 4 |
| rs9922045 | 16q23.2 / rs2911280 | 0.636 | CMIP | intronic | 0.033 | **2b** |
| rs146269222 | 0.624 | CMIP | intronic | 0.588 | NA |
| rs79388303 | 0.636 | CMIP | intronic | 0.925 | 5 |
| rs2061679 | 0.648 | CMIP | intronic | 0.241 | 7 |
| rs75217481 | 0.725 | CMIP | intronic | 4.831 | 4 |
| rs13333615 | 0.713 | CMIP | intronic | 0.901 | **2b** |
| rs9319570 | 0.713 | CMIP | intronic | 3.043 | 5 |
| rs79208952 | 0.657 | CMIP | intronic | 0.059 | 7 |
| rs76294479 | 0.713 | CMIP | intronic | 0.128 | 5 |
| rs76006132 | 0.736 | CMIP | intronic | 0.807 | 5 |
| rs58072681 | 0.736 | CMIP | intronic | 3.062 | **2a** |
| rs57159061 | 0.976 | CMIP | intronic | **10.33** | 7 |
| rs2911282 | 1 | CMIP | intronic | 1.052 | NA |
| rs2911280 | 1 | CMIP | intronic | 4.241 | NA |

Abbreviations: SNP, single-nucleotide polymorphism; DHEAS, dehydroepiandrosterone sulfate; GWAS, genome-wide association study; Chr, chromosome; EAF, effect allele frequency; EA, effect allele; OA, other allele; SE, standard error; P, p value; CADD, combined annotation-dependent depletion; FUMA, functional mapping and annotation.