**Independent associations of *TOMM40* and *APOE* variants with body mass index**

Alexander M. Kulminski1, Yury Loika1, Irina Culminskaya1, Jian Huang1, Konstantin G. Arbeev1, Olivia Bagley1, Mary F. Feitosa2, Joseph M. Zmuda3, Kaare Christensen4, Anatoliy I. Yashin1, and the Long Life Family Study research group.

1Biodemography of Aging Research Unit, Social Science Research Institute, Duke University, Durham, NC 27708-0408, USA.

2Division of Statistical Genomics, Department of Genetics, Washington University School of Medicine, 520 South Euclid Avenue, Campus Box 8506-98-601, St Louis, MO 63110-1093, USA

3 Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 De Soto St, Pittsburgh, PA 15261, USA

4The Danish Aging Research Center, University of Southern Denmark, 5000 Odense C, Denmark

**SUPPORTING INFORMATION**

Supporting information includes one Text and ten Tables.

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**1. Supporting Acknowledgment Text**

**Text S1:** Supporting Acknowledgment Text.

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The Health and Retirement Study (HRS) genetic data is sponsored by the Genetics Resource with HRS April 21, 2010, version G Page 5 of 7 National Institute on Aging (grant numbers U01AG009740, RC2AG036495, and RC4AG039029) and was conducted by the University of Michigan. This manuscript was not prepared in collaboration with HRS investigators and does not necessarily reflect the opinions or views of HRS.

**2. Supporting Tables**

**Table S1**. Basic demographic information for the genotyped participants in the selected studies.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | N | BMI\*, kg/m2  mean (SD) | Men (%) | Birth year, mean (SD) | Birth year, range | Age at baseline, mean (SD) | Number of visits |
| ARIC | 408 | 27.31 (5.02) | 214 (52.45) | 1933.64 (5.69) | 1922–1944 | 53.89 (5.60) | 4 |
| CARDIA | 1,362 | 23.60 (3.98) | 644 (47.28) | 1957.46 (3.47) | 1950–1965 | 25.62 (3.34) | 6 |
| CHS | 4,008 | 26.29 (4.43) | 1,744 (43.51) | 1914.10 (5.75) | 1890–1925 | 72.88 (5.62) | 3 |
| HRS | 9,358 | 27.63 (5.64) | 3,937 (42.07) | 1938.16 (10.48) | 1905–1975 | 69.65 (10.96) | 12 |
| FHS\_1 | 636 | 24.11 (3.45) | 211 (33.18) | 1911.79 (4.18) | 1895–1920 | 35.81 (4.34) | 22 |
| FHS\_2 | 3,059 | 25.08 (4.19) | 1,405 (45.93) | 1935.74 (9.62) | 1910–1965 | 34.77 (9.78) | 8 |
| FHS\_3 | 3,951 | 26.90 (5.56) | 1,855 (46.95) | 1960.46 (8.94) | 1930–1980 | 40.16 (8.83) | 1 |
| MESA | 703 | 27.78 (5.29) | 325 (46.23) | 1939.46 (10.44) | 1917–1957 | 61.55 (10.43) | 5 |
| LLFS | 4,378 | 27.18 (5.29) | 1,980 (45.23) | 1937.35 (15.63) | 1896–1983 | 69.98 (15.55) | 2 |
| Total | 27,863 | 26.71 (5.26) | 12,315 (44.20) | 1937.78 (17.17) | 1890–1983 | 58.80 (19.37) |  |

N denotes genotyped sample after excluding individuals with missing genotyping and phenotyping information.

ARIC = the Atherosclerosis Risk in Communities study, CARDIA = Coronary Artery Risk Development in Young Adults study, CHS = the Cardiovascular Health Study; HRS = the Health and Retirement Study; FHS\_1 = the Framingham Heart Study (FHS) original cohort; FHS\_2 = the FHS offspring cohort, FHS\_3 = the FHS 3rd generation cohort, MESA = Multi-Ethnic Study of Atherosclerosis, LLFS = Long Life Family Study.

\*Body mass index (BMI) is representatively shown at baseline or first available examination.

SD = standard deviation.

**Table S2**. Coding of the *APOE* common polymorphism.

|  |  |  |  |
| --- | --- | --- | --- |
|  | rs7412\_CC | rs7412\_Ct | rs7412\_tt |
| rs429358\_TT | ε3/ε3 | ε2/ε3 | ε2/ε2 |
| rs429358\_Tc | ε3/ε4 | ε2/ε4 | -- |
| rs429358\_cc | ε4/ε4 | -- | -- |

*APOE*=apolipoprotein E;

Upper (lower) case letters after SNP ID denote major (minor) allele.

**Table S3**. Genotyping information.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Total | ARIC | CARDIA | CHS | HRS | FHS\_1 | FHS\_2 | FHS\_3 | MESA | LLFS |
| Sample | 27,863 | 408 | 1,362 | 4,008 | 9,358 | 636 | 3,059 | 3,951 | 703 | 4,378 |
| Rs2075650 genotypes | | | | | | | | | | |
| AA | 76.22 | 70.83 | 73.57 | 76.95 | 74.58 | 81.76 | 75.74 | 76.28 | 74.96 | 80.03 |
| Ag | 22.22 | 26.96 | 24.74 | 21.78 | 23.50 | 17.30 | 22.79 | 22.10 | 23.33 | 18.94 |
| gg | 1.56 | 2.21 | 1.69 | 1.27 | 1.92 | 0.94 | 1.47 | 1.62 | 1.71 | 1.03 |
| MAF | 12.67 | 15.59 | 14.06 | 12.16 | 13.67 | 9.59 | 12.43 | 12.67 | 13.38 | 13.66 |
| *pHWE* | 0.345 | 0.852 | 0.433 | 0.176 | 0.804 | 0.360 | 0.875 | 0.943 | 0.869 | 0.402 |
| Rs157580 genotypes | | | | | | | | | | |
| AA | 36.18 | 34.80 | 36.42 | 35.43 | 37.51 | 38.05 | 35.01 | 33.71 | 40.97 | 36.09 |
| Ag | 48.60 | 50.00 | 48.53 | 48.90 | 47.74 | 47.33 | 48.71 | 50.19 | 44.95 | 49.31 |
| gg | 15.22 | 15.20 | 15.05 | 15.67 | 14.75 | 14.62 | 16.28 | 16.10 | 14.08 | 14.60 |
| MAF | 39.52 | 40.20 | 39.31 | 40.12 | 38.62 | 38.29 | 40.04 | 41.20 | 36.55 | 37.70 |
| *pHWE* | 0.511 | 0.417 | 0.570 | 0.270 | 0.481 | 0.327 | 0.154 | 0.024 | 0.564 | 0.726 |
| Rs7412 genotypes | | | | | | | | | | |
| CC | 84.39 | 86.03 | 85.61 | 83.91 | 84.36 | 86.79 | 85.32 | 85.17 | 84.07 | 82.71 |
| Ct | 14.99 | 12.25 | 13.73 | 15.39 | 15.10 | 12.89 | 14.28 | 14.20 | 14.79 | 16.58 |
| tt | 0.62 | 1.72 | 0.66 | 0.70 | 0.54 | 0.32 | 0.42 | 0.63 | 1.14 | 0.71 |
| MAF | 8.12 | 7.85 | 7.53 | 8.40 | 8.09 | 6.77 | 7.15 | 7.73 | 8.41 | 7.40 |
| *pHWE* | 0.547 | 0.002 | 0.436 | 0.917 | 0.686 | 0.129 | 0.794 | 0.738 | 0.130 | 1.000 |
| Rs429358 genotypes | | | | | | | | | | |
| TT | 76.19 | 74.27 | 77.09 | 75.97 | 74.05 | 80.50 | 76.95 | 75.70 | 73.97 | 80.47 |
| Tc | 22.23 | 23.28 | 21.73 | 22.83 | 23.94 | 18.87 | 21.41 | 22.70 | 23.90 | 18.46 |
| cc | 1.58 | 2.45 | 1.18 | 1.20 | 2.01 | 0.63 | 1.64 | 1.60 | 2.13 | 1.07 |
| MAF | 12.70 | 14.09 | 12.05 | 12.62 | 13.98 | 10.07 | 12.13 | 12.95 | 13.96 | 13.87 |
| *pHWE* | 0.194 | 0.417 | 0.441 | 0.020 | 0.580 | 0.184 | 0.872 | 0.724 | 0.873 | 0.336 |
| *APOE* genotypes | | | | | | | | | | |
| ε2/ε2 | 0.62 | 1.72 | 0.66 | 0.70 | 0.55 | 0.31 | 0.39 | 0.63 | 1.14 | 0.71 |
| ε2/ε3 | 12.86 | 10.05 | 12.26 | 13.02 | 12.93 | 11.00 | 12.36 | 11.79 | 12.52 | 14.69 |
| ε2/ε4 | 2.13 | 2.21 | 1.47 | 2.37 | 2.17 | 1.89 | 1.93 | 2.40 | 2.28 | 1.90 |
| ε3/ε3 | 62.70 | 62.50 | 64.17 | 62.25 | 60.58 | 69.18 | 64.20 | 63.28 | 60.31 | 65.07 |
| ε3/ε4 | 20.11 | 21.08 | 20.26 | 20.46 | 21.77 | 16.99 | 19.48 | 20.30 | 21.62 | 16.56 |
| ε4/ε4 | 1.58 | 2.44 | 1.18 | 1.20 | 2.00 | 0.63 | 1.64 | 1.60 | 2.13 | 1.07 |
| ε2 | 8.12 | 7.85 | 7.53 | 8.40 | 8.10 | 6.76 | 7.54 | 7.73 | 8.54 | 9.01 |
| ε3 | 79.19 | 78.07 | 80.43 | 78.99 | 77.93 | 83.18 | 80.12 | 79.33 | 77.38 | 80.70 |
| ε4 | 12.70 | 14.09 | 12.05 | 12.62 | 13.97 | 10.07 | 12.35 | 12.95 | 14.08 | 10.30 |

N=sample size after excluding individuals with missing genotyping and phenotypic information.

*APOE*=apolipoprotein E; MAF=minor allele frequency; *pHWE*=*p*-value for Hardy-Weinberg Equilibrium.

Upper (lower) case letters denote major (minor) allele.

ARIC = the Atherosclerosis Risk in Communities study, CARDIA = Coronary Artery Risk Development in Young Adults study, CHS = the Cardiovascular Health Study; HRS = the Health and Retirement Study; FHS\_1 = the Framingham Heart Study (FHS) original cohort; FHS\_2 = the FHS offspring cohort, FHS\_3 = the FHS 3rd generation cohort, MESA = Multi-Ethnic Study of Atherosclerosis, LLFS = Long Life Family Study.

Values for genotypes are shown as percentage (%) of participants

**Table S4**. Contingency tables for the selected polymorphisms.

A)

|  |  |  |  |
| --- | --- | --- | --- |
|  | rs429358\_TT | rs429358\_Tc | rs429358\_cc |
| rs2075650\_AA | 19,653 (70.53) | 1,545 (5.55) | 38 (0.14) |
| rs2075650\_Ag | 1,540 (5.53) | 4,498 (16.14) | 154 (0.55) |
| rs2075650\_gg | 35 (0.13) | 151 (0.54) | 249 (0.89) |

B)

|  |  |  |  |
| --- | --- | --- | --- |
|  | rs429358\_TT | rs429358\_Tc | rs429358\_cc |
| rs157580\_AA | 6,393 (22.94) | 3,266 (11.72) | 418 (1.50) |
| rs157580\_Ag | 10,635 (38.17) | 2,883 (10.35) | 23 (0.08) |
| rs157580\_gg | 4,200 (15.07) | 40 (0.14) | 0 (0.00) |

C)

|  |  |  |  |
| --- | --- | --- | --- |
|  | rs7412\_CC | rs7412\_Ct | rs7412\_tt |
| rs2075650\_AA | 17,466 (62.69) | 3,598 (12.91) | 172 (0.62) |
| rs2075650\_Ag | 5,616 (20.16) | 575 (2.06) | 1 (0.00) |
| rs2075650\_gg | 431 (1.55) | 4 (0.01) | 0 (0.00) |

D)

|  |  |  |  |
| --- | --- | --- | --- |
|  | rs7412\_CC | rs7412\_Ct | rs7412\_tt |
| rs157580\_AA | 8,912 (31.99) | 1,139 (4.09) | 32 (0.11) |
| rs157580\_Ag | 11,264 (40.43) | 2,186 (7.85) | 91 (0.33) |
| rs157580\_gg | 3,337 (11.98) | 852 (3.06) | 51 (0.18) |

E)

|  |  |  |  |
| --- | --- | --- | --- |
|  | rs157580\_AA | rs157580\_Ag | rs157580\_gg |
| rs2075650\_AA | 6,301 (22.61) | 10,698 (38.40) | 4,237 (15.21) |
| rs2075650\_Ag | 3,346 (12.01) | 2,843 (10.20) | 3 (0.01) |
| rs2075650\_gg | 435 (1.56) | 0 (0.00) | 0 (0.00) |

F)

|  |  |  |  |
| --- | --- | --- | --- |
|  | rs7412\_CC | rs7412\_Ct | rs7412\_tt |
| rs429358\_TT | 17,470 (62.70) | 3,585 (12.87) | 173 (0.62) |
| rs429358\_Tc | 5,602 (20.11) | 592 (2.12) | 0 (0.00) |
| rs429358\_cc | 441 (1.58) | 0 (0.00) | 0 (0.00) |

G)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *APOE* genotypes: | ε2ε2 | ε2ε3 | ε2ε4 | ε3ε3 | ε3ε4 | ε4ε4 |
| rs2075650\_AA | 172 (0.62) | 3,437 (12.34) | 161 (0.58) | 16,044 (57.58) | 1,384 (4.97) | 38 (0.14) |
| rs2075650\_Ag | 1 (0.00) | 146 (0.52) | 429 (1.54) | 1,393 (5.00) | 4,069 (14.60) | 154 (0.55) |
| rs2075650\_gg | 0 (0.00) | 2 (0.01) | 2 (0.01) | 33 (0.12) | 149 (0.53) | 249 (0.89) |

H)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *APOE* genotypes: | ε2ε2 | ε2ε3 | ε2ε4 | ε3ε3 | ε3ε4 | ε4ε4 |
| rs157580\_AA | 31 (0.11) | 905 (3.25) | 234 (0.84) | 5,457 (19.59) | 3,037 (10.90) | 418 (1.50) |
| rs157580\_Ag | 91 (0.33) | 1,837 (6.59) | 349 (1.25) | 8,707 (31.25) | 2,534 (9.09) | 23 (0.08) |
| rs157580\_gg | 51 (0.18) | 843 (3.03) | 9 (0.03) | 3,306 (11.87) | 31 (0.11) | 0 (0.00) |

Tables show the number and percentage in parentheses of subjects with a given genotype.

Upper (lower) case letters after SNP ID denote major (minor) allele.

*APOE*=apolipoprotein E

**Table S5**. Associations of rs2075650 polymorphism with BMI of carriers of APOE alleles in a mega sample of 27,863 individuals from seven longitudinal studies.

|  |  |  |  |
| --- | --- | --- | --- |
| APOE allele carriers | β | SE | *p*-value |
| ε2ε2 | -1.72 | 16.4 | 9.17E-01 |
| ε2ε3 | 0.99 | 1.42 | 4.88E-01 |
| ε2ε4 | -0.36 | 1.60 | 8.20E-01 |
| ε3ε3 | -1.01 | 0.46 | 2.65E-02 |
| ε3ε4 | -0.52 | 0.48 | 2.85E-01 |
| ε4ε4 | 0.68 | 1.35 | 6.16E-01 |

Additive genetic model with minor allele of rs2075650 polymorphism as an effect allele.

**Table S6**. Univariate and multivariate associations of selected polymorphisms with BMI in a mega sample of 27,863 individuals from seven longitudinal studies conditional on the rs157580 polymorphism.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Polymorphism | Model 1 | | | | Model 2 | | | Model 3 | | | Model 4 | | | Model 5 | | | Model 6 | | |
|  | β | SE | *p*-value | β | | SE | *p*-value | β | SE | *p*-value | β | SE | *p*-value | β | SE | *p*-value | β | SE | *p*-value |
| rs2075650\* | -1.29 | 0.22 | 3.97E-09 | -1.34 | | 0.23 | 4.91E-09 |  |  |  |  |  |  |  |  |  |  |  |  |
| rs157580\* | 0.15 | 0.15 | 3.03E-01 | -0.13 | | 0.16 | 4.22E-01 | -0.13 | 0.16 | 4.04E-01 | 0.12 | 0.15 | 4.12E-01 | -0.15 | 0.16 | 3.48E-01 | -0.12 | 0.16 | 4.44E-01 |
| rs429358\* | -1.38 | 0.22 | 2.78E-10 |  | |  |  | -1.43 | 0.23 | 3.34E-10 |  |  |  |  |  |  |  |  |  |
| rs7412\* | 0.58 | 0.27 | 3.04E-02 |  | |  |  |  |  |  | 0.56 | 0.27 | 3.82E-02 |  |  |  |  |  |  |
| ε2ε2† | -1.23 | 1.30 | 3.45E-01 |  | |  |  |  |  |  |  |  |  | -1.19 | 1.30 | 3.60E-01 |  |  |  |
| ε2ε3† | 0.55 | 0.31 | 8.26E-02 |  | |  |  |  |  |  |  |  |  | 0.56 | 0.31 | 7.43E-02 |  |  |  |
| ε2ε4† | -0.66 | 0.71 | 3.54E-01 |  | |  |  |  |  |  |  |  |  | -0.70 | 0.71 | 3.28E-01 |  |  |  |
| ε3ε4† | -1.41 | 0.26 | 7.68E-08 |  | |  |  |  |  |  |  |  |  | -1.47 | 0.27 | 5.26E-08 |  |  |  |
| ε4ε4† | -2.41 | 0.82 | 3.32E-03 |  | |  |  |  |  |  |  |  |  | -2.53 | 0.83 | 2.31E-03 |  |  |  |
| ε2‡ | 0.46 | 0.31 | 1.36E-01 |  | |  |  |  |  |  |  |  |  |  |  |  | 0.47 | 0.31 | 1.25E-01 |
| ε4‡ | -1.48 | 0.26 | 6.50E-09 |  | |  |  |  |  |  |  |  |  |  |  |  | -1.54 | 0.26 | 6.67E-09 |

Model 1: Associations of rs2075650, rs157580, rs429358, rs7412, *APOE* genotypes, and *APOE* alleles separately. The *APOE* ε2 allele was defined as the ε2ε2 or ε2ε3 genotypes. The *APOE* ε4 allele was defined as the ε3ε4 or ε4ε4 genotypes. The ε2/ε4 genotype was excluded from definition of the ε2 or ε4 carrier status.

Model 2: Bivariate model of additive effects of rs157580 and rs2075650 SNPs.

Model 3: Bivariate model of additive effects of rs157580 and rs429358 SNPs.

Model 4: Bivariate model of additive effects of rs157580 and rs7412 SNPs.

Model 5: Multivariate model of additive effects of rs157580 and *APOE* genotypes.

Model 6: Multivariate model of additive effects of rs157580 and *APOE* alleles.

\* Additive genetic model with minor allele as an effect allele.

† Genotypic model for *APOE* with the ε3ε3 genotype as a reference.

‡ Allelic model for *APOE* with the ε3ε3 genotype as a reference.

**Table S7**. Multivariate associations of selected polymorphisms with BMI in a mega sample of 27,863 individuals from seven longitudinal studies.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Polymorphism | Model 1 | | | Model 2 | | |
|  | β | SE | *p*-value | β | SE | *p*-value |
| rs2075650\_1 | -0.83 | 0.34 | 1.34E-02 | -0.84 | 0.35 | 1.46E-02 |
| rs2075650\_2 | -0.32 | 1.03 | 7.55E-01 | -1.11 | 0.89 | 2.08E-01 |
| rs157580\_1 | -0.56 | 0.23 | 1.50E-02 | -0.52 | 0.23 | 2.54E-02 |
| rs157580\_2 | 0.19 | 0.33 | 5.64E-01 | -0.18 | 0.33 | 5.88E-01 |
| ε2ε2 | -1.25 | 1.30 | 3.36E-01 |  |  |  |
| ε2ε3 | 0.53 | 0.32 | 9.25E-02 |  |  |  |
| ε2ε4 | -0.11 | 0.75 | 8.86E-01 |  |  |  |
| ε3ε4 | -0.93 | 0.35 | 7.42E-03 |  |  |  |
| ε4ε4 | -2.29 | 1.02 | 2.51E-02 |  |  |  |
| ε2 |  |  |  | 0.44 | 0.31 | 1.53E-01 |
| ε4 |  |  |  | -0.96 | 0.35 | 5.55E-03 |

Genotypic models with major allele homozygous genotype as a reference for SNPs and the ε3ε3 genotype as a reference for the APOE polymorphism.

The *APOE* ε2 allele was defined as the ε2ε2 or ε2ε3 genotypes.

The *APOE* ε4 allele was defined as the ε3ε4 or ε4ε4 genotypes.

The ε2/ε4 genotype was excluded from definition of the ε2 or ε4 carrier status.

Model 1: Multivariate model of additive effects of rs2075650, rs157580 SNPs and APOE genotypes.

Model 2: Multivariate model of additive effects of rs2075650, rs157580 SNPs and APOE alleles.

**Table S8**. Associations of compound genotypes composed of rs2075650 and rs429358 SNPs with BMI in a mega sample of 27,863 individuals from seven longitudinal studies.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| SNP genotype | | Sample | Model | | |
| rs2075650 | rs429358 | N | β | SE | *p*-value |
| 0 | 0 | 19,653 | Reference |  |  |
| 0 | 1 | 1,545 | -0.94 | 0.45 | 3.63E-02 |
| 0 | 2 | 38 | -1.64 | 2.77 | 5.53E-01 |
| 1 | 0 | 1,540 | -0.78 | 0.45 | 8.67E-02 |
| 1 | 1 | 4,498 | -1.68 | 0.28 | 3.00E-09 |
| 1 | 2 | 154 | -4.11 | 1.37 | 2.78E-03 |
| 2 | 0 | 35 | -3.20 | 2.94 | 2.33E-01 |
| 2 | 1 | 151 | -1.30 | 1.39 | 3.50E-01 |
| 2 | 2 | 249 | -1.72 | 1.07 | 1.10E-01 |

Genotypic models with major allele homozygous genotype as a reference.

0/1/2 codes major-homozygous/heterozygous/minor-homozygous genotypes.

**Table S9**. Associations of polygenic scores accounting for sum of minor alleles of rs2075650, rs429358 and rs157580 SNPs with BMI in a mega sample of 27,863 individuals from seven longitudinal studies.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Number of minor alleles | Model 1 | | | Model 2 | | |
|  | β | SE | *p*-value | β | SE | *p*-value |
| 0 | Reference |  |  | Reference |  |  |
| 1 | -0.86 | 0.33 | 9.39E-03 | -0.54 | 0.28 | 5.37E-02 |
| 2 | -1.69 | 0.28 | 1.80E-09 | -0.88 | 0.30 | 3.45E-03 |
| 3 | -2.72 | 0.98 | 5.59E-03 | -2.29 | 0.41 | 3.19E-08 |
| 4 | -1.73 | 1.08 | 1.10E-01 | -2.33 | 1.08 | 3.08E-02 |

Genotypic models with major allele homozygous genotype as a reference.

Model 1: Associations of polygenic score constructed by summation of numbers of minor alleles of two SNPs, rs2075650 and rs429358.

Model 2: Associations of polygenic score constructed by summation of numbers of minor alleles of three SNPs, rs2075650, rs429358 and rs157580.

**Table S10**. Multivariate associations of rs2075650, rs157580, rs429358, and rs7412 with BMI in younger and older individuals in the mega sample of 27,863 individuals from seven longitudinal studies.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Age30 | | | Age35 | | | Age40 | | | Age45 | | | Age50 | | |
|  |  | Nind | | Nobs | Nind | | Nobs | Nind | | Nobs | Nind | | Nobs | Nind | | Nobs |
| Sample size | young | 3,068 | | 5,503 | 4,590 | | 10,018 | 6,208 | | 15,064 | 7,885 | | 20,382 | 10,018 | | 26,866 |
| old | 27,266 | | 139,484 | 26,512 | | 134,969 | 25,155 | | 129,923 | 23,537 | | 124,605 | 22,558 | | 118,121 |
| TOTAL | 30,334 | | 144,987 | 31,102 | | 144,987 | 31,363 | | 144,987 | 31,422 | | 144,987 | 32,576 | | 144,987 |
| Polymorphism | Sample | β | SE | *p*-value | β | SE | *p*-value | β | SE | *p*-value | β | SE | *p*-value | β | SE | *p*-value |
| rs2075650\_Ag | young | -1.56 | 0.89 | 7.79E-02 | -1.28 | 0.75 | 8.67E-02 | -1.51 | 0.66 | 2.21E-02 | -1.51 | 0.61 | 1.27E-02 | -1.50 | 0.55 | 6.61E-03 |
| rs2075650\_Ag | old | -0.84 | 0.34 | 1.39E-02 | -0.83 | 0.35 | 1.61E-02 | -0.74 | 0.35 | 3.69E-02 | -0.70 | 0.36 | 5.55E-02 | -0.62 | 0.37 | 9.52E-02 |
| rs2075650\_gg | young | 0.21 | 2.74 | 9.38E-01 | 1.75 | 2.36 | 4.58E-01 | 0.59 | 2.09 | 7.78E-01 | -0.82 | 1.90 | 6.66E-01 | -1.12 | 1.73 | 5.16E-01 |
| rs2075650\_gg | old | -0.41 | 1.05 | 6.94E-01 | -0.69 | 1.06 | 5.16E-01 | -0.83 | 1.09 | 4.44E-01 | -0.39 | 1.12 | 7.26E-01 | -0.08 | 1.15 | 9.44E-01 |
| rs157580\_Ag | young | -0.69 | 0.65 | 2.89E-01 | -0.30 | 0.53 | 5.72E-01 | -0.62 | 0.47 | 1.84E-01 | -0.71 | 0.43 | 9.81E-02 | -0.67 | 0.39 | 8.55E-02 |
| rs157580\_Ag | old | -0.59 | 0.23 | 1.19E-02 | -0.64 | 0.24 | 6.84E-03 | -0.61 | 0.24 | 1.25E-02 | -0.63 | 0.25 | 1.21E-02 | -0.61 | 0.25 | 1.61E-02 |
| rs157580\_gg | young | 0.15 | 0.92 | 8.67E-01 | -0.67 | 0.76 | 3.79E-01 | -0.31 | 0.67 | 6.37E-01 | 0.04 | 0.61 | 9.54E-01 | 0.69 | 0.55 | 2.11E-01 |
| rs157580\_gg | old | -0.31 | 0.34 | 3.63E-01 | -0.40 | 0.34 | 2.37E-01 | -0.42 | 0.35 | 2.23E-01 | -0.36 | 0.36 | 3.14E-01 | -0.36 | 0.36 | 3.20E-01 |
| rs429358\_Tc | young | 0.58 | 0.90 | 5.18E-01 | -0.11 | 0.75 | 8.87E-01 | -0.53 | 0.66 | 4.24E-01 | 0.07 | 0.61 | 9.08E-01 | -0.08 | 0.55 | 8.81E-01 |
| rs429358\_Tc | old | -0.93 | 0.34 | 6.11E-03 | -0.99 | 0.34 | 4.00E-03 | -0.96 | 0.35 | 6.66E-03 | -1.21 | 0.36 | 8.71E-04 | -1.34 | 0.37 | 2.77E-04 |
| rs429358\_cc | young | 1.10 | 2.89 | 7.05E-01 | -0.08 | 2.30 | 9.72E-01 | 0.64 | 2.11 | 7.61E-01 | 1.08 | 1.89 | 5.69E-01 | 1.45 | 1.69 | 3.91E-01 |
| rs429358\_cc | old | -2.30 | 1.04 | 2.68E-02 | -2.26 | 1.05 | 3.15E-02 | -2.73 | 1.07 | 1.07E-02 | -3.24 | 1.09 | 3.04E-03 | -3.84 | 1.11 | 5.75E-04 |
| rs7412\_Ct | young | 1.02 | 0.83 | 2.18E-01 | 0.61 | 0.68 | 3.72E-01 | 0.53 | 0.59 | 3.71E-01 | 0.27 | 0.54 | 6.22E-01 | 0.74 | 0.49 | 1.36E-01 |
| rs7412\_Ct | old | 0.59 | 0.29 | 4.37E-02 | 0.56 | 0.30 | 6.25E-02 | 0.55 | 0.31 | 7.10E-02 | 0.62 | 0.31 | 4.60E-02 | 0.55 | 0.32 | 8.62E-02 |
| rs7412\_tt | young | -0.61 | 4.25 | 8.86E-01 | -2.48 | 3.74 | 5.07E-01 | -2.40 | 3.64 | 5.10E-01 | -3.83 | 2.77 | 1.66E-01 | -3.24 | 2.17 | 1.37E-01 |
| rs7412\_tt | old | -1.20 | 1.31 | 3.59E-01 | -1.22 | 1.33 | 3.60E-01 | -1.32 | 1.34 | 3.27E-01 | -0.44 | 1.41 | 7.55E-01 | -0.71 | 1.43 | 6.18E-01 |

**Table S10**. (continued)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Age55 | | | Age60 | | | Age65 | | | Age70 | | | Age75 | | |
|  |  | Nind | | Nobs | Nind | | Nobs | Nind | | Nobs | Nind | | Nobs | Nind | | Nobs |
| Sample size | young | 14,338 | | 39,922 | 17,444 | | 59,643 | 19,209 | | 79,143 | 22,068 | | 98,180 | 24,764 | | 116,622 |
| old | 21,430 | | 105,065 | 19,493 | | 85,344 | 16,781 | | 65,844 | 13,928 | | 46,807 | 9,843 | | 28,365 |
| TOTAL | 35,768 | | 144,987 | 36,937 | | 144,987 | 35,990 | | 144,987 | 35,996 | | 144,987 | 34,607 | | 144,987 |
| Polymorphism | Sample | β | SE | *p*-value | β | SE | *p*-value | β | SE | *p*-value | β | SE | *p*-value | β | SE | *p*-value |
| rs2075650\_Ag | young | -0.84 | 0.48 | 7.84E-02 | -0.91 | 0.43 | 3.42E-02 | -0.99 | 0.41 | 1.53E-02 | -0.99 | 0.38 | 9.26E-03 | -0.78 | 0.36 | 2.92E-02 |
| rs2075650\_Ag | old | -0.55 | 0.38 | 1.48E-01 | -0.47 | 0.40 | 2.34E-01 | -0.34 | 0.43 | 4.22E-01 | -0.20 | 0.47 | 6.73E-01 | -0.20 | 0.55 | 7.15E-01 |
| rs2075650\_gg | young | -1.61 | 1.47 | 2.76E-01 | -0.12 | 1.29 | 9.23E-01 | -0.23 | 1.23 | 8.49E-01 | 0.09 | 1.14 | 9.39E-01 | -0.19 | 1.08 | 8.61E-01 |
| rs2075650\_gg | old | -0.35 | 1.17 | 7.66E-01 | -0.43 | 1.23 | 7.29E-01 | -0.14 | 1.32 | 9.16E-01 | -0.04 | 1.47 | 9.76E-01 | 0.25 | 1.77 | 8.87E-01 |
| rs157580\_Ag | young | -0.63 | 0.33 | 5.83E-02 | -0.64 | 0.30 | 3.20E-02 | -0.53 | 0.28 | 6.31E-02 | -0.63 | 0.26 | 1.65E-02 | -0.63 | 0.25 | 1.16E-02 |
| rs157580\_Ag | old | -0.58 | 0.26 | 2.57E-02 | -0.47 | 0.27 | 8.01E-02 | -0.48 | 0.29 | 9.79E-02 | -0.42 | 0.32 | 1.87E-01 | -0.47 | 0.37 | 2.04E-01 |
| rs157580\_gg | young | 0.01 | 0.47 | 9.87E-01 | -0.17 | 0.43 | 6.87E-01 | 0.00 | 0.41 | 9.98E-01 | -0.24 | 0.38 | 5.30E-01 | -0.24 | 0.35 | 5.03E-01 |
| rs157580\_gg | old | -0.32 | 0.37 | 3.92E-01 | -0.20 | 0.39 | 6.16E-01 | -0.20 | 0.41 | 6.34E-01 | 0.06 | 0.45 | 8.94E-01 | -0.19 | 0.52 | 7.23E-01 |
| rs429358\_Tc | young | -0.08 | 0.48 | 8.73E-01 | -0.15 | 0.43 | 7.32E-01 | -0.22 | 0.41 | 5.81E-01 | -0.36 | 0.38 | 3.46E-01 | -0.71 | 0.36 | 4.76E-02 |
| rs429358\_Tc | old | -1.48 | 0.38 | 9.45E-05 | -1.69 | 0.39 | 1.94E-05 | -2.23 | 0.42 | 1.36E-07 | -2.86 | 0.47 | 7.30E-10 | -3.43 | 0.55 | 3.74E-10 |
| rs429358\_cc | young | 1.38 | 1.44 | 3.38E-01 | -1.11 | 1.27 | 3.80E-01 | -1.77 | 1.21 | 1.44E-01 | -2.20 | 1.12 | 4.92E-02 | -2.03 | 1.07 | 5.74E-02 |
| rs429358\_cc | old | -4.07 | 1.14 | 3.59E-04 | -3.89 | 1.21 | 1.31E-03 | -5.11 | 1.31 | 9.92E-05 | -5.20 | 1.53 | 6.97E-04 | -4.80 | 1.85 | 9.61E-03 |
| rs7412\_Ct | young | 0.72 | 0.42 | 8.58E-02 | 0.72 | 0.38 | 5.45E-02 | 0.62 | 0.36 | 8.48E-02 | 0.57 | 0.33 | 8.84E-02 | 0.51 | 0.31 | 1.03E-01 |
| rs7412\_Ct | old | 0.42 | 0.33 | 1.98E-01 | 0.28 | 0.34 | 4.12E-01 | 0.56 | 0.36 | 1.21E-01 | 0.70 | 0.39 | 7.47E-02 | 0.83 | 0.46 | 7.08E-02 |
| rs7412\_tt | young | -1.88 | 1.92 | 3.27E-01 | -1.54 | 1.76 | 3.81E-01 | -1.72 | 1.69 | 3.11E-01 | -0.80 | 1.55 | 6.05E-01 | -1.37 | 1.44 | 3.41E-01 |
| rs7412\_tt | old | -0.75 | 1.47 | 6.12E-01 | -0.60 | 1.56 | 7.00E-01 | -0.72 | 1.62 | 6.57E-01 | -0.96 | 1.73 | 5.77E-01 | -0.90 | 1.95 | 6.44E-01 |

**Table S10**. (continued)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Age80 | | | Age85 | | | Age90 | | |
|  |  | Nind | | Nobs | Nind | | Nobs | Nind | | Nobs |
| Sample size | young | 26,044 | | 130,502 | 26,670 | | 138,771 | 27,126 | | 142,797 |
| old | 6,052 | | 14,485 | 3,263 | | 6,216 | 1,499 | | 2,190 |
| TOTAL | 32,096 | | 144,987 | 29,933 | | 144,987 | 28,625 | | 144,987 |
| Polymorphism | Sample | β | SE | *p*-value | β | SE | *p*-value | β | SE | *p*-value |
| rs2075650\_Ag | young | -0.82 | 0.35 | 1.86E-02 | -0.85 | 0.34 | 1.32E-02 | -0.83 | 0.34 | 1.46E-02 |
| rs2075650\_Ag | old | 0.06 | 0.69 | 9.35E-01 | 0.12 | 0.96 | 8.97E-01 | -0.28 | 1.51 | 8.55E-01 |
| rs2075650\_gg | young | -0.27 | 1.06 | 7.98E-01 | -0.30 | 1.05 | 7.74E-01 | -0.35 | 1.04 | 7.37E-01 |
| rs2075650\_gg | old | -2.01 | 2.35 | 3.92E-01 | -3.85 | 3.48 | 2.69E-01 | -6.09 | 5.67 | 2.83E-01 |
| rs157580\_Ag | young | -0.53 | 0.24 | 2.73E-02 | -0.52 | 0.24 | 2.84E-02 | -0.55 | 0.23 | 1.83E-02 |
| rs157580\_Ag | old | -0.75 | 0.46 | 1.01E-01 | -0.16 | 0.61 | 7.97E-01 | 0.51 | 0.92 | 5.79E-01 |
| rs157580\_gg | young | -0.21 | 0.34 | 5.44E-01 | -0.17 | 0.34 | 6.10E-01 | -0.21 | 0.34 | 5.39E-01 |
| rs157580\_gg | old | -0.17 | 0.65 | 7.92E-01 | -0.36 | 0.84 | 6.68E-01 | 0.47 | 1.26 | 7.10E-01 |
| rs429358\_Tc | young | -0.85 | 0.35 | 1.47E-02 | -0.88 | 0.34 | 1.04E-02 | -0.93 | 0.34 | 5.98E-03 |
| rs429358\_Tc | old | -4.28 | 0.70 | 7.71E-10 | -3.34 | 0.98 | 6.28E-04 | -2.64 | 1.61 | 1.01E-01 |
| rs429358\_cc | young | -2.19 | 1.04 | 3.54E-02 | -2.25 | 1.04 | 3.00E-02 | -2.33 | 1.03 | 2.36E-02 |
| rs429358\_cc | old | -5.52 | 2.44 | 2.35E-02 | -3.47 | 3.54 | 3.27E-01 | -1.39 | 6.23 | 8.23E-01 |
| rs7412\_Ct | young | 0.44 | 0.30 | 1.43E-01 | 0.54 | 0.30 | 7.27E-02 | 0.61 | 0.30 | 3.99E-02 |
| rs7412\_Ct | old | 1.03 | 0.57 | 7.06E-02 | 1.40 | 0.75 | 5.96E-02 | 1.37 | 1.08 | 2.04E-01 |
| rs7412\_tt | young | -1.26 | 1.38 | 3.60E-01 | -1.11 | 1.36 | 4.13E-01 | -1.19 | 1.33 | 3.71E-01 |
| rs7412\_tt | old | 0.27 | 2.24 | 9.02E-01 | 0.62 | 2.82 | 8.26E-01 | -2.78 | 3.85 | 4.71E-01 |

Genotypic models with major allele homozygous genotype as a reference for all polymorphisms.

AgeNN denotes age cut off separating subsamples of old (age > AgeNN) and young (age <= AgeNN) individuals.

Sample size of the youngest group aged 30 years and younger was 3,068.

Sample size of the oldest group older than 90 years was 1,499.

Nind/Nobs means number of individuals/observations.

Total number of individuals is not equal to that of the sample size because an individual appear in both group if there are measurements at respective ages.