**Supplementary Tables**

**Type-I error rates in simulation settings 1 and 2.** Type-I error rates were calculated as the fraction of traits with p-values below the alpha value.

|  |  |  |
| --- | --- | --- |
| **Alpha** | **Setting 1** | **Setting 2** |
| 0.1 | 0.124 | 0.117 |
| 0.05 | 0.064 | 0.064 |
| 0.01 | 0.009 | 0.013 |
| 0.005 | 0.003 | 0.006 |
| 0.001 | 0.002 | 0.000 |

**Comparison with Regression.** The list of simulation scenarios where BADGERS and regression analysis made different statistical decisions (i.e. only one method claimed statistical significance at p<0.05) in simulation setting 3.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Pvalue**  **cutoff** | **Trait\_ID** | **reg-effect** | **reg-se** | **reg-z** | **reg-p** | **badgers-effect** | **badgers-se** | **badgers-z** | **badgers-p** |
| 0.015 | C67 | 0.614 | 0.315 | 1.947 | 0.052 | 1.535 | 1.460E-04 | 2.091 | 0.037 |
| 0.015 | 22620\_1 | 0.045 | 0.024 | 1.903 | 0.057 | 0.054 | 0.029 | 2.098 | 0.036 |
| 0.015 | 20003\_1140879778 | 0.393 | 0.204 | 1.929 | 0.054 | 0.398 | 4.121E-04 | 1.973 | 0.049 |
| 0.015 | 20541 | 0.060 | 0.030 | 1.985 | 0.047 | 0.057 | 0.018 | 1.942 | 0.052 |
| 0.010 | 1150\_3 | 0.138 | 0.078 | 1.776 | 0.076 | 0.163 | 0.003 | 1.984 | 0.047 |
| 0.008 | 41248\_1001 | 0.215 | 0.113 | 1.906 | 0.057 | 0.242 | 0.001 | 2.021 | 0.043 |
| 0.008 | 20126\_3 | 0.080 | 0.043 | 1.867 | 0.062 | 0.107 | 0.008 | 2.158 | 0.031 |
| 0.008 | 3799 | 0.034 | 0.019 | 1.842 | 0.066 | 0.044 | 0.043 | 2.093 | 0.036 |
| 0.008 | 20426 | 0.029 | 0.014 | 2.098 | 0.036 | 0.023 | 0.089 | 1.784 | 0.074 |
| 0.005 | 5133\_raw | 0.009 | 0.005 | 1.901 | 0.057 | 0.010 | 0.690 | 2.067 | 0.039 |
| 0.005 | 22617\_2132 | 0.122 | 0.058 | 2.109 | 0.035 | 0.005 | 0.051 | 0.106 | 0.051 |
| 0.005 | 20003\_1140911698 | 2.934 | 1.415 | 2.073 | 0.038 | 2.569 | 8.596E-06 | 1.921 | 0.055 |

**Marginal and conditional associations of 15 representative traits with AD.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Marginal Analysis** | | | **Conditional Analysis** | | |
| **Trait** | **Effect** | **SE** | **P** | **Effect** | **SE** | **P** |
| Illnesses of mother: Alzheimer's disease/dementia | 1.885 | 0.101 | 3.7e-77 | 1.808 | 0.102 | 8.1e-71 |
| Illnesses of father: Alzheimer's disease/dementia | 1.495 | 0.136 | 5.2e-28 | 1.394 | 0.138 | 3.8e-24 |
| Non-cancer illness code, self-reported: high cholesterol | 0.536 | 0.068 | 2.5e-15 | 0.535 | 0.069 | 5.3e-15 |
| Qualifications: College or University degree | -0.154 | 0.022 | 4.4e-12 | -0.137 | 0.024 | 9.9e-09 |
| 3mm strong meridian angle (left) | -0.042 | 0.010 | 2.8e-05 | -0.064 | 0.011 | 1.1e-08 |
| Any dementia | 9.084 | 1.399 | 8.5e-11 | 8.073 | 1.423 | 1.4e-08 |
| Final attempt correct: yes | -0.561 | 0.087 | 9.1e-11 | -0.494 | 0.090 | 3.8e-08 |
| Able to pay rent/mortgage as an adult | -0.086 | 0.020 | 2.3e-05 | -0.103 | 0.023 | 5.8e-06 |
| Time to complete round | 0.001 | 0.0002 | 2.8e-09 | 0.001 | 0.0002 | 7.5e-06 |
| Fluid intelligence score | -0.073 | 0.010 | 2.4e-14 | -0.043 | 0.010 | 1.3e-05 |
| Treatment/medication code: garlic product | 1.221 | 0.256 | 1.9e-06 | 1.088 | 0.253 | 1.7e-05 |
| Mother still alive | -0.408 | 0.074 | 4.3e-08 | -0.319 | 0.076 | 2.7e-05 |
| Unable to work because of sickness or disability | 0.701 | 0.124 | 1.7e-08 | 0.455 | 0.125 | 2.6e-04 |
| Duration of moderate activity | 0.146 | 0.025 | 7.4e-09 | 0.092 | 0.026 | 3.6e-04 |
| Non-butter spread type details: Flora Pro-Active or Benecol | 0.310 | 0.065 | 2.0e-06 | 0.179 | 0.073 | 0.014 |

**Results for Mendelian randomization based on the MR-IVW approach.** Among 1,738 heritable UK-biobank traits, 9 traits reached Bonferroni-corrected statistical significance in the meta-analysis.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trait** | **ID** | **Effect** | **SE** | **P** |
| Illnesses of mother: Alzheimer's disease/dementia | 20110\_10 | 27.974 | 0.857 | 1.09E-233 |
| Illnesses of father: Alzheimer's disease/dementia | 20107\_10 | 45.725 | 2.595 | 1.68E-69 |
| Any dementia | KRA\_PSY\_DEMENTIA | 845.495 | 161.889 | 1.76E-07 |
| Treatment/medication code: insulin product | 20003\_1140883066 | -11.032 | 2.213 | 6.16E-07 |
| Non-cancer illness code, self-reported: polymyalgia rheumatica | 20002\_1377 | -29.634 | 6.165 | 1.54E-06 |
| Non-cancer illness code, self-reported: high cholesterol | 20002\_1473 | 10.220 | 2.220 | 4.14E-06 |
| Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Cholesterol lowering medication | 6153\_1 | 10.258 | 2.230 | 4.23E-06 |
| Medication for cholesterol, blood pressure or diabetes: Cholesterol lowering medication | 6177\_1 | 6.971 | 1.646 | 2.28E-05 |
| Non-butter spread type details: Flora Pro-Active or Benecol | 2654\_2 | 16.374 | 3.902 | 2.72E-05 |

**Results for Mendelian randomization.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trait** | **ID** | **Effect** | **SE** | **P** |
| Illnesses of mother: Alzheimer's disease/dementia | 20110\_10 | 27.974 | 0.857 | 1.09E-233 |
| Illnesses of father: Alzheimer's disease/dementia | 20107\_10 | 45.725 | 2.595 | 1.68E-69 |
| Any dementia | KRA\_PSY\_DEMENTIA | 336.398 | 68.524 | 9.14E-07 |
| Non-cancer illness code, self-reported: high cholesterol | 20002\_1473 | 10.220 | 2.220 | 4.14E-06 |
| Cholesterol lowering medication | 6153\_1 | 10.258 | 2.230 | 4.23E-06 |
| Cholesterol lowering medication | 6177\_1 | 6.971 | 1.646 | 2.28E-05 |
| Non-butter spread type details: Flora Pro-Active or Benecol | 2654\_2 | 16.374 | 3.902 | 2.72E-05 |
| Treatment/medication code: simvastatin | 20003\_1140861958 | 14.765 | 3.676 | 5.91E-05 |
| Treatment/medication code: atorvastatin | 20003\_1141146234 | 28.482 | 7.293 | 9.41E-05 |
| Qualifications: A levels/AS levels or equivalent | 6138\_2 | -1.473 | 0.392 | 1.71E-04 |
| Time spent watching television (TV) | 1070 | 0.828 | 0.225 | 2.38E-04 |
| Qualifications: None of the above | 6138\_100 | 1.558 | 0.424 | 2.40E-04 |
| Mother still alive | 1835 | -14.999 | 4.395 | 6.44E-04 |
| Job involves mainly walking or standing | 806 | 0.609 | 0.186 | 1.07E-03 |
| Duration screen displayed | 4290\_irnt | 0.438 | 0.144 | 2.35E-03 |
| FI3 : word interpolation | 4957 | -1.143 | 0.389 | 3.29E-03 |
| Qualifications: College or University degree | 6138\_1 | -0.892 | 0.323 | 5.81E-03 |
| Job involves heavy manual or physical work | 816 | 0.458 | 0.178 | 0.010 |
| Forced expiratory volume in 1-second (FEV1), predicted | 20153\_raw | -0.577 | 0.228 | 0.011 |
| Age completed full time education | 845 | -0.483 | 0.197 | 0.014 |
| Time spent using computer | 1080 | -0.652 | 0.267 | 0.015 |
| Time to complete round | 400\_raw | 0.027 | 0.014 | 0.048 |
| Duration of walks | 874\_raw | 0.006 | 0.003 | 0.050 |
| Standing height | 50\_raw | -0.017 | 0.009 | 0.052 |
| Comparative height size at age 10 | 1697 | -0.220 | 0.113 | 0.052 |
| Standing height | 50\_irnt | -0.148 | 0.077 | 0.055 |
| FI6 : conditional arithmetic | 4990 | -0.565 | 0.300 | 0.060 |
| Fluid intelligence score | 20016\_raw | -0.129 | 0.069 | 0.062 |
| Year ended full time education | 22501\_raw | -0.074 | 0.043 | 0.082 |
| Fluid intelligence score | 20016\_irnt | -0.252 | 0.148 | 0.089 |
| Treatment/medication code: garlic product | 20003\_1140911732 | 4.091 | 2.860 | 0.153 |
| Age first had sexual intercourse | 2139\_irnt | -0.233 | 0.166 | 0.162 |
| Unable to work because of sickness or disability | 6142\_4 | 1.843 | 1.361 | 0.176 |
| Time to complete round | 400\_irnt | 1.896 | 1.434 | 0.186 |
| Peak expiratory flow (PEF) | 3064\_raw | 0.002 | 0.001 | 0.190 |
| Time spend outdoors in summer | 1050 | 0.304 | 0.251 | 0.225 |
| Year ended full time education | 22501\_irnt | -0.398 | 0.334 | 0.233 |
| Qualifications: Other professional qualifications eg: nursing, teaching | 6138\_6 | -0.638 | 0.541 | 0.239 |
| Duration screen displayed | 4290\_raw | 0.001 | 0.001 | 0.255 |
| Time spent outdoors in winter | 1060 | 0.467 | 0.416 | 0.262 |
| Final attempt correct: no | 4294\_0 | 0.856 | 0.804 | 0.287 |
| Able to pay rent/mortgage as an adult | 20525 | -0.197 | 0.186 | 0.290 |
| 3mm strong meridian angle (left) | 5104\_irnt | 0.033 | 0.121 | 0.788 |
| Never eat eggs, dairy, wheat, sugar: I eat all of the above | 6144\_5 | -0.157 | 0.629 | 0.803 |
| Cheese intake | 1408 | 0.046 | 0.191 | 0.808 |
| Forced expiratory volume in 1-second (FEV1) | 3063\_raw | 0.042 | 0.185 | 0.821 |
| Duration of moderate activity | 894 | 0.042 | 0.259 | 0.870 |
| Final attempt correct: yes | 4294\_1 | 0.022 | 0.827 | 0.979 |

**GSMR results on the IGAP GWAS dataset.** Among 1,738 heritable UK-biobank traits, 18 traits reached Bonferroni-corrected statistical significance.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trait** | **ID** | **Effect** | **SE** | **P** |
| Immature reticulocyte fraction | 30280\_irnt | 0.285 | 0.002 | 0 |
| Illnesses of mother: Alzheimer's disease/dementia | 20110\_10 | 29.210 | 0.797 | 2.38E-294 |
| Heel quantitative ultrasound index (QUI), direct entry | 3147\_irnt | 0.371 | 0.019 | 4.64E-82 |
| Arm fat mass (right) | 23120\_raw | 1.291 | 0.103 | 2.68E-36 |
| Arm fat percentage (left) | 23123\_irnt | 1.408 | 0.140 | 1.04E-23 |
| Ankle spacing width | 3143\_irnt | -0.471 | 0.060 | 4.57E-15 |
| Leg fat mass (left) | 23116\_irnt | -0.416 | 0.066 | 2.80E-10 |
| Standing height | 50\_irnt | -0.165 | 0.029 | 1.36E-08 |
| Standing height | 50\_raw | -0.017 | 0.003 | 5.71E-08 |
| Mean reticulocyte volume | 30260\_irnt | -0.166 | 0.032 | 1.66E-07 |
| Leg fat percentage (right) | 23111\_raw | -0.056 | 0.011 | 2.12E-07 |
| Lymphocyte percentage | 30180\_raw | 0.021 | 0.004 | 1.76E-06 |
| Qualifications: A levels/AS levels or equivalent | 6138\_2 | -1.515 | 0.328 | 3.77E-06 |
| Comparative height size at age 10 | 1697 | -0.229 | 0.050 | 3.77E-06 |
| Qualifications: College or University degree | 6138\_1 | -0.652 | 0.143 | 4.84E-06 |
| Trunk fat-free mass | 23129\_irnt | -0.231 | 0.051 | 6.20E-06 |
| Whole body fat-free mass | 23101\_raw | -0.022 | 0.005 | 2.17E-05 |
| Trunk predicted mass | 23130\_irnt | -0.214 | 0.051 | 2.23E-05 |

**Mendelian randomization result after removing the *APOE* region**.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Trait** | **ID** | **Effect** | **SE** | **P** |
| Illnesses of mother: Alzheimer's disease/dementia | 20110\_10 | 10.004 | 2.086 | 1.63E-06 |
| Qualifications: A levels/AS levels or equivalent | 6138\_2 | -1.473 | 0.392 | 1.71E-04 |
| Time spent watching television (TV) | 1070 | 0.828 | 0.225 | 2.38E-04 |
| Qualifications: None of the above | 6138\_100 | 1.558 | 0.424 | 2.40E-04 |
| Job involves mainly walking or standing | 806 | 0.609 | 0.186 | 0.001 |
| Duration screen displayed | 4290\_irnt | 0.438 | 0.144 | 0.002 |
| FI3 : word interpolation | 4957 | -1.143 | 0.389 | 0.003 |
| Qualifications: College or University degree | 6138\_1 | -0.892 | 0.323 | 0.006 |
| Job involves heavy manual or physical work | 816 | 0.458 | 0.178 | 0.010 |
| Forced expiratory volume in 1-second (FEV1), predicted | 20153\_raw | -0.577 | 0.228 | 0.011 |
| Age completed full time education | 845 | -0.483 | 0.197 | 0.014 |
| Time spent using computer | 1080 | -0.652 | 0.267 | 0.015 |
| Duration of walks | 874\_raw | 0.006 | 0.003 | 0.050 |
| Time to complete round | 400\_raw | 0.004 | 0.002 | 0.051 |
| Standing height | 50\_raw | -0.017 | 0.009 | 0.052 |
| Illnesses of father: Alzheimer's disease/dementia | 20107\_10 | 5.246 | 2.701 | 0.052 |
| Comparative height size at age 10 | 1697 | -0.220 | 0.113 | 0.052 |
| Standing height | 50\_irnt | -0.148 | 0.077 | 0.055 |
| FI6 : conditional arithmetic | 4990 | -0.565 | 0.300 | 0.060 |
| Fluid intelligence score | 20016\_raw | -0.129 | 0.069 | 0.062 |
| Year ended full time education | 22501\_raw | -0.074 | 0.043 | 0.082 |
| Fluid intelligence score | 20016\_irnt | -0.252 | 0.148 | 0.089 |
| Mother still alive | 1835 | 1.223 | 0.850 | 0.150 |
| Qualifications: Other professional qualifications eg: nursing, teaching | 6138\_6 | -0.768 | 0.536 | 0.151 |
| Treatment/medication code: garlic product | 20003\_1140911732 | 4.091 | 2.860 | 0.153 |
| Age first had sexual intercourse | 2139\_irnt | -0.233 | 0.166 | 0.162 |
| Unable to work because of sickness or disability | 6142\_4 | 1.843 | 1.361 | 0.176 |
| Peak expiratory flow (PEF) | 3064\_raw | 0.002 | 0.001 | 0.190 |
| Any dementia | KRA\_PSY\_DEMENTIA | 13.507 | 11.109 | 0.224 |
| Time spend outdoors in summer | 1050 | 0.304 | 0.251 | 0.225 |
| Year ended full time education | 22501\_irnt | -0.398 | 0.334 | 0.233 |
| Duration screen displayed | 4290\_raw | 0.001 | 0.001 | 0.255 |
| Time spent outdoors in winter | 1060 | 0.467 | 0.416 | 0.262 |
| Final attempt correct: no | 4294\_0 | 0.856 | 0.804 | 0.287 |
| Able to pay rent/mortgage as an adult | 20525 | -0.197 | 0.186 | 0.290 |
| Cholesterol lowering medication | 6177\_1 | 0.188 | 0.259 | 0.469 |
| Non-butter spread type details: Flora Pro-Active or Benecol | 2654\_2 | -0.361 | 0.587 | 0.538 |
| Treatment/medication code: simvastatin | 20003\_1140861958 | -0.335 | 0.600 | 0.577 |
| Time to complete round | 400\_irnt | 0.098 | 0.221 | 0.659 |
| Cholesterol lowering medication | 6153\_1 | -0.132 | 0.323 | 0.682 |
| Non-cancer illness code, self-reported: high cholesterol | 20002\_1473 | 0.106 | 0.298 | 0.722 |
| 3mm strong meridian angle (left) | 5104\_irnt | 0.033 | 0.121 | 0.788 |
| Never eat eggs, dairy, wheat, sugar: I eat all of the above | 6144\_5 | -0.157 | 0.629 | 0.803 |
| Cheese intake | 1408 | 0.046 | 0.191 | 0.808 |
| Forced expiratory volume in 1-second (FEV1) | 3063\_raw | 0.042 | 0.185 | 0.821 |
| Duration of moderate activity | 894 | 0.042 | 0.259 | 0.870 |
| Final attempt correct: yes | 4294\_1 | 0.022 | 0.827 | 0.979 |
| Treatment/medication code: atorvastatin | 20003\_1141146234 | -0.022 | 1.023 | 0.983 |

**Details on GWAS datasets for AD endophenotypes.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Category** | **Trait** | **N** | **Ref.** |
| AD Subgroup | EPAD\_language | 3,768 | [1, 2] |
| EPAD\_memory | 4,097 |
| EPAD\_visuospatial | 3,738 |
| EPAD\_mix | 3,585 |
| EPAD\_none | 4,418 |
| CSF Biomarkers | Ab42 | 3,115 | [3, 4] |
| Ab42\_male | 1,515 |
| Ab42\_female | 1,501 |
| Ptau | 2,833 |
| Ptau\_male | 1,452 |
| Ptau\_female | 1,381 |
| Tau | 3,108 |
| Tau\_male | 1,508 |
| Tau\_female | 1,498 |
| Neuropathologic Features | CAA | 2,807 | [5] |
| NFT\_Braak\_4 | 4,735 |
| NFT\_Braak\_ordinal | 4,707 |
| LBD\_3 | 3,526 |
| LBD\_any | 3,526 |
| LBD\_ordinal | 3,525 |
| HS | 2,886 |
| NP\_any | 4,046 |
| NP\_ordinal | 4,232 |
| NP\_complete | 3,702 |
| NP\_primary | 4,914 |
| VBI\_any | 2,764 |
| VBI\_ordinal | 2,940 |

**Heritability of 48 identified traits in the marginal association analysis.** All identified traits held heritability over 0.0025

|  |  |  |
| --- | --- | --- |
| **Trait** | **ID** | **H2** |
| Standing height | 50\_raw | 0.427 |
| Standing height | 50\_irnt | 0.423 |
| Forced expiratory volume in 1-second (FEV1), predicted | 20153\_raw | 0.422 |
| Fluid intelligence score | 20016\_raw | 0.228 |
| Comparative height size at age 10 | 1697 | 0.222 |
| Fluid intelligence score | 20016\_irnt | 0.221 |
| Forced expiratory volume in 1-second (FEV1) | 3063\_raw | 0.178 |
| Qualifications: College or University degree | 6138\_1 | 0.162 |
| Age first had sexual intercourse | 2139\_irnt | 0.154 |
| Year ended full time education | 22501\_raw | 0.148 |
| Year ended full time education | 22501\_irnt | 0.136 |
| Duration screen displayed | 4290\_irnt | 0.113 |
| Age completed full time education | 845 | 0.104 |
| Time spent watching television (TV) | 1070 | 0.104 |
| Peak expiratory flow (PEF) | 3064\_raw | 0.103 |
| Qualifications: None of the above | 6138\_100 | 0.103 |
| Time spent using computer | 1080 | 0.096 |
| Qualifications: A levels/AS levels or equivalent | 6138\_2 | 0.091 |
| FI6: conditional arithmetic | 4990 | 0.091 |
| Time to complete round | 400\_irnt | 0.087 |
| FI3: word interpolation | 4957 | 0.084 |
| Job involves heavy manual or physical work | 816 | 0.081 |
| Medication for cholesterol, blood pressure or diabetes: Cholesterol lowering medication | 6177\_1 | 0.080 |
| 3mm strong meridian angle (left) | 5104\_irnt | 0.077 |
| Job involves mainly walking or standing | 806 | 0.076 |
| Time spend outdoors in summer | 1050 | 0.072 |
| Cheese intake | 1408 | 0.068 |
| Time to complete round | 400\_raw | 0.062 |
| Duration screen displayed | 4290\_raw | 0.060 |
| Medication for cholesterol, blood pressure, diabetes, or take exogenous hormones: Cholesterol lowering medication | 6153\_1 | 0.057 |
| Non-cancer illness code, self-reported: high cholesterol | 20002\_1473 | 0.047 |
| Never eat eggs, dairy, wheat, sugar: I eat all of the above | 6144\_5 | 0.047 |
| Time spent outdoors in winter | 1060 | 0.044 |
| Qualifications: Other professional qualifications eg: nursing, teaching | 6138\_6 | 0.044 |
| Duration of walks | 874\_raw | 0.040 |
| Duration of moderate activity | 894 | 0.032 |
| Treatment/medication code: simvastatin | 20003\_1140861958 | 0.031 |
| Current employment status: Unable to work because of sickness or disability | 6142\_4 | 0.024 |
| Able to pay rent/mortgage as an adult | 20525 | 0.023 |
| Final attempt correct: yes | 4294\_1 | 0.021 |
| Final attempt correct: no | 4294\_0 | 0.021 |
| Illnesses of mother: Alzheimer's disease/dementia | 20110\_10 | 0.018 |
| Treatment/medication code: atorvastatin | 20003\_1141146234 | 0.014 |
| Illnesses of father: Alzheimer's disease/dementia | 20107\_10 | 0.014 |
| Non-butter spread type details: Flora Pro-Active or Benecol | 2654\_2 | 0.014 |
| Mother still alive | 1835 | 0.005 |
| Any dementia | KRA\_PSY\_DEMENTIA | 0.003 |
| Treatment/medication code: garlic product | 20003\_1140911732 | 0.003 |

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