

Table S1. Pearson correlation of age with the tested variables

| Variable                  | Ctrl (n = 142)              |                | AD (n = 117)                |                |
|---------------------------|-----------------------------|----------------|-----------------------------|----------------|
|                           | Correlation Coefficient (r) | <i>p</i> value | Correlation Coefficient (r) | <i>p</i> value |
| ALT (IU/L)                | -0.151                      | NS             | 0.0451                      | NS             |
| Creatinine (mg/dL)        | -0.0259                     | NS             | 0.0646                      | NS             |
| Fasting Glucose (mg/dL)   | -0.121                      | NS             | 0.00676                     | NS             |
| HbA1c (%)                 | -0.234                      | NS             | 0.0732                      | NS             |
| HDL-C (mg/dL)             | <b>-0.244</b>               | <b>0.0289</b>  | 0.0275                      | NS             |
| LDL-C (mg/dL)             | -0.181                      | NS             | -0.214                      | NS             |
| Total Cholesterol (mg/dL) | <b>-0.198</b>               | <b>0.0459</b>  | -0.0949                     | NS             |
| Total protein (g/L)       | -0.0325                     | NS             | -0.0981                     | NS             |
| Triglycerides (mg/dL)     | 0.0805                      | NS             | 0.153                       | NS             |
| A $\beta$                 | 0.13                        | NS             | 0.0786                      | NS             |
| Acrolein adducts          | -0.0886                     | NS             | 0.147                       | NS             |

The *p* values represent the probability of being wrong in the association between the variables and shown as NS with no statistical significance ( $p \geq 0.05$ ). A $\beta$ , amyloid-beta; AD, Alzheimer's disease; ALT, alanine transaminase; Ctrl, control; HbA1c, glycohemoglobin A1; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NS, no statistical significance.

Table S2. Statistical significance of demographic and clinical data (*p* value) between the groups.

| Testing group     | MetS             |                  |                  | AD-N             |                  | AD- M            |
|-------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Pairing group     | HC               | AD-N             | AD- M            | HC               | AD- M            | HC               |
| Gender            | NS               | NS               | NS               | NS               | NS               | NS               |
| Age               | NS               | <b>&lt;0.001</b> | <b>&lt;0.001</b> | <b>&lt;0.001</b> | No               | <b>&lt;0.001</b> |
| ALT               | NS               | NS               | NS               | NS               | NS               | NS               |
| Creatinine        | NS               | NS               | <b>0.016</b>     | NS               | NS               | <b>0.009</b>     |
| Fasting glucose   | <b>&lt;0.001</b> | <b>0.008</b>     | NS               | NS               | <b>&lt;0.001</b> | <b>&lt;0.001</b> |
| HbA1c             | NS               | <b>0.004</b>     | NS               | NS               | <b>0.007</b>     | NS               |
| HDL-C             | NS               | <b>0.039</b>     | <b>0.003</b>     | NS               | <b>&lt;0.001</b> | <b>&lt;0.001</b> |
| LDL-C             | NS               | NS               | <b>0.006</b>     | NS               | NS               | NS               |
| Total cholesterol | NS               | NS               | NS               | NS               | NS               | NS               |
| Total protein     | NS               | NS               | NS               | NS               | NS               | NS               |
| Triglycerides     | <b>0.001</b>     | <b>&lt;0.001</b> | NS               | NS               | <b>&lt;0.001</b> | <b>&lt;0.001</b> |

The *p* values with no statistical significance ( $p \geq 0.05$ ) were shown as NS. AD-M, Alzheimer's disease with metabolic disturbance; AD-N, Alzheimer's disease with normal metabolism; ALT, alanine transaminase; HC, healthy control; HbA1c, glycohemoglobin A1; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MetS, metabolic syndrome; NS, no statistical significance

Table S3. Correlation of all tested variables

|            | Creatinine      | Glucose                        | HbA1c                           | HDL-C                          | LDL-C                           | T-Chol.                         | TP                            | TG                               | Aβ                              | ACR                             | NA1 IgG                          | NA2 IgG                        | NA1 IgM                         | NA2 IgM                         | ACRA1 IgG                        | ACRA2 IgG                         | ACRA1 IgM                         | ACRA2 IgM                         |
|------------|-----------------|--------------------------------|---------------------------------|--------------------------------|---------------------------------|---------------------------------|-------------------------------|----------------------------------|---------------------------------|---------------------------------|----------------------------------|--------------------------------|---------------------------------|---------------------------------|----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| ALT        | -0.0725<br>0.32 | 0.00597<br>0.935               | 0.00153<br>0.989                | -0.15<br>0.0854                | 0.0767<br>0.34                  | 0.0322<br>0.669                 | <b>0.152</b><br><b>0.0325</b> | -0.0244<br>0.733                 | 0.0671<br>0.348                 | 0.0686<br>0.337                 | 0.0667<br>0.351                  | 0.0269<br>0.707                | 0.0621<br>0.385                 | -0.00101<br>0.989               | -0.0433<br>0.545                 | -0.0548<br>0.443                  | 0.00342<br>0.962                  | -0.0449<br>0.53                   |
| Creatinine |                 | <b>0.194</b><br><b>0.00558</b> | -0.0579<br>0.573                | <b>-0.219</b><br><b>0.0121</b> | <b>-0.159</b><br><b>0.0452</b>  | -0.0481<br>0.524                | -0.00312<br>0.964             | <b>0.164</b><br><b>0.0176</b>    | 0.0706<br>0.308                 | <b>0.188</b><br><b>0.00627</b>  | 0.0558<br>0.421                  | -0.0352<br>0.612               | <b>-0.146</b><br><b>0.0349</b>  | -0.102<br>0.141                 | -0.0288<br>0.678                 | -0.0735<br>0.289                  | -0.0702<br>0.311                  | 0.0137<br>0.843                   |
| Glucose    |                 |                                | <b>0.392</b><br><b>8.73E-05</b> | <b>-0.219</b><br><b>0.011</b>  | -0.112<br>0.161                 | -0.00177<br>0.981               | 0.00599<br>0.932              | <b>0.24</b><br><b>0.00049</b>    | 0.0591<br>0.396                 | <b>0.192</b><br><b>0.0054</b>   | -0.00527<br>0.94                 | -0.0103<br>0.883               | -0.0354<br>0.612                | -0.0953<br>0.171                | 0.0216<br>0.756                  | 0.0745<br>0.285                   | -0.0473<br>0.498                  | 0.0458<br>0.511                   |
| HbA1c      |                 |                                |                                 | -0.0499<br>0.696               | 0.00232<br>0.983                | -0.0264<br>0.809                | -0.0453<br>0.656              | <b>0.265</b><br><b>0.00794</b>   | -0.121<br>0.234                 | -0.0241<br>0.813                | 0.0091<br>0.929                  | -0.0601<br>0.555               | 0.0761<br>0.454                 | -0.074<br>0.467                 | -0.00836<br>0.935                | -0.0371<br>0.715                  | <b>0.301</b><br><b>0.00248</b>    | 0.136<br>0.18                     |
| HDL-C      |                 |                                |                                 |                                | <b>0.413</b><br><b>6.09E-06</b> | <b>0.375</b><br><b>1.03E-05</b> | 0.117<br>0.178                | <b>-0.341</b><br><b>5.23E-05</b> | <b>-0.234</b><br><b>0.00624</b> | <b>-0.354</b><br><b>2.6E-05</b> | -0.0923<br>0.287                 | -0.0285<br>0.743               | -0.119<br>0.17                  | -0.0341<br>0.695                | <b>-0.224</b><br><b>0.00906</b>  | -0.0369<br>0.671                  | -0.127<br>0.142                   | -0.043<br>0.62                    |
| LDL-C      |                 |                                |                                 |                                |                                 | <b>0.729</b><br><b>2.81E-26</b> | 0.0166<br>0.834               | -0.0196<br>0.805                 | <b>-0.228</b><br><b>0.00355</b> | <b>-0.209</b><br><b>0.0075</b>  | 0.00386<br>0.961                 | 0.0139<br>0.86                 | 0.0183<br>0.817                 | 0.0631<br>0.425                 | 0.0279<br>0.724                  | 0.0312<br>0.694                   | 0.0552<br>0.486                   | -0.0334<br>0.673                  |
| T-Chol.    |                 |                                |                                 |                                |                                 |                                 | 0.0305<br>0.681               | <b>0.248</b><br><b>0.0007</b>    | <b>-0.175</b><br><b>0.0173</b>  | -0.133<br>0.0718                | -0.0521<br>0.483                 | -0.0753<br>0.31                | -0.00689<br>0.926               | 0.0285<br>0.701                 | 0.0519<br>0.484                  | 0.0276<br>0.71                    | 0.0247<br>0.739                   | -0.0629<br>0.396                  |
| TP         |                 |                                |                                 |                                |                                 |                                 |                               | -0.0152<br>0.808                 | -0.0452<br>0.469                | <b>-0.25</b><br><b>4.8E-05</b>  | <b>-0.163</b><br><b>0.00856</b>  | 0.0313<br>0.617                | -0.117<br>0.0607                | 0.0759<br>0.224                 | <b>0.266</b><br><b>0.0000145</b> | 0.0357<br>0.568                   | -0.0145<br>0.817                  | 0.0822<br>0.188                   |
| TG         |                 |                                |                                 |                                |                                 |                                 |                               |                                  | 0.02<br>0.748                   | <b>0.156</b><br><b>0.0119</b>   | 0.0391<br>0.531                  | 0.0888<br>0.154                | 0.0409<br>0.512                 | 0.0599<br>0.337                 | 0.0993<br>0.111                  | 0.0121<br>0.847                   | -0.0565<br>0.365                  | 0.0506<br>0.417                   |
| Aβ         |                 |                                |                                 |                                |                                 |                                 |                               |                                  |                                 | <b>0.29</b><br><b>2E-06</b>     | <b>0.251</b><br><b>0.0000435</b> | <b>0.162</b><br><b>0.00913</b> | 0.0788<br>0.206                 | 0.0297<br>0.634                 | <b>0.182</b><br><b>0.00336</b>   | 0.0267<br>0.669                   | 0.0604<br>0.333                   | 0.0176<br>0.779                   |
| ACR        |                 |                                |                                 |                                |                                 |                                 |                               |                                  |                                 |                                 | <b>0.21</b><br><b>0.000672</b>   | -0.00214<br>0.973              | 0.0215<br>0.73                  | -0.102<br>0.1                   | 0.0184<br>0.768                  | -0.101<br>0.105                   | -0.00265<br>0.966                 | <b>-0.141</b><br><b>0.0232</b>    |
| NA1 IgG    |                 |                                |                                 |                                |                                 |                                 |                               |                                  |                                 |                                 |                                  | <b>0.198</b><br><b>0.00139</b> | <b>0.326</b><br><b>7.91E-08</b> | 0.11<br>0.0777                  | <b>0.173</b><br><b>0.00525</b>   | 0.0866<br>0.165                   | -0.0623<br>0.318                  | <b>-0.124</b><br><b>0.0464</b>    |
| NA2 IgG    |                 |                                |                                 |                                |                                 |                                 |                               |                                  |                                 |                                 |                                  |                                | <b>0.188</b><br><b>0.00239</b>  | <b>0.34</b><br><b>1.95E-08</b>  | <b>0.324</b><br><b>9.87E-08</b>  | <b>0.135</b><br><b>0.0297</b>     | 0.0206<br>0.742                   | 0.0712<br>0.254                   |
| NA1 IgM    |                 |                                |                                 |                                |                                 |                                 |                               |                                  |                                 |                                 |                                  |                                |                                 | <b>0.387</b><br><b>1.14E-10</b> | 0.0531<br>0.395                  | 0.0222<br>0.722                   | <b>0.285</b><br><b>0.00000304</b> | 0.116<br>0.0616                   |
| NA2 IgM    |                 |                                |                                 |                                |                                 |                                 |                               |                                  |                                 |                                 |                                  |                                |                                 |                                 | <b>0.152</b><br><b>0.0145</b>    | 0.0196<br>0.753                   | <b>0.271</b><br><b>0.00000987</b> | 0.0941<br>0.131                   |
| ACRA1 IgG  |                 |                                |                                 |                                |                                 |                                 |                               |                                  |                                 |                                 |                                  |                                |                                 |                                 |                                  | <b>0.289</b><br><b>0.00000216</b> | 0.0959<br>0.124                   | -0.0366<br>0.558                  |
| ACRA2 IgG  |                 |                                |                                 |                                |                                 |                                 |                               |                                  |                                 |                                 |                                  |                                |                                 |                                 |                                  |                                   | 0.0151<br>0.808                   | <b>0.203</b><br><b>0.00101</b>    |
| ACRA1 IgM  |                 |                                |                                 |                                |                                 |                                 |                               |                                  |                                 |                                 |                                  |                                |                                 |                                 |                                  |                                   |                                   | <b>0.273</b><br><b>0.00000857</b> |

In each cell, the correlation coefficient (r) was shown at the top and the *p* value at the bottom. The values with statistical significance (p < 0.05) were shown in **bold red**. Aβ, amyloid-beta; ACR, acrolein adducts; ACRA1, acrolein-modified amyloid-beta residues 1-16; ACRA2, acrolein-modified amyloid-beta residues 17-28; ALT, alanine transaminase; HbA1c, glycohemoglobin A1; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; NA1, native amyloid-beta residues 1-16; NA2, native amyloid-beta residues 17-28; T-Chol, total cholesterol; TG, triglycerides; TP, total protein.

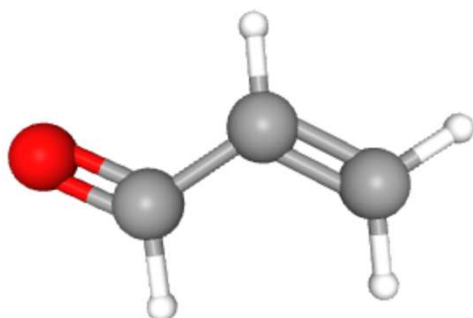
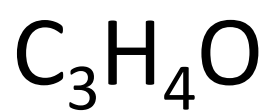
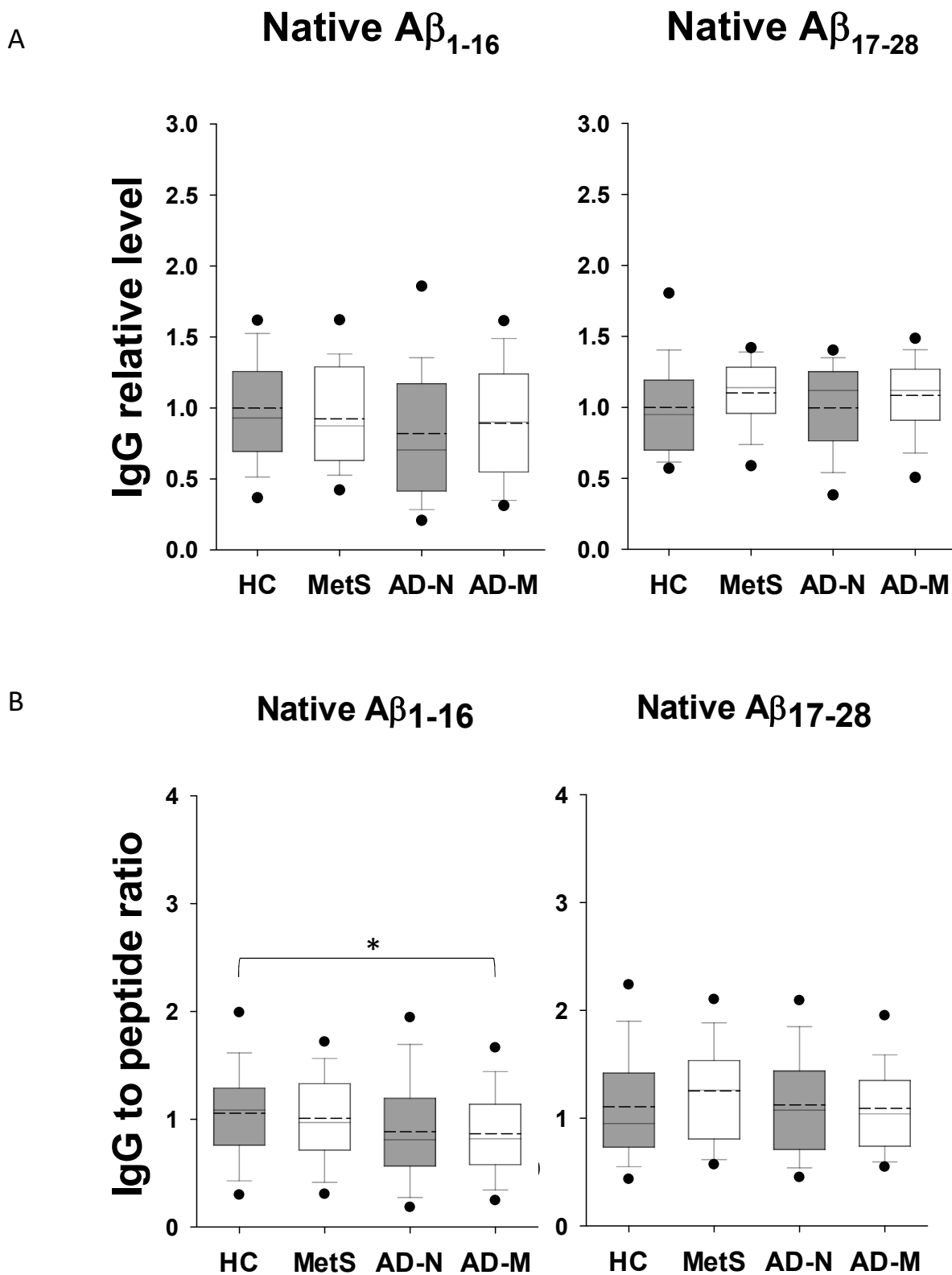
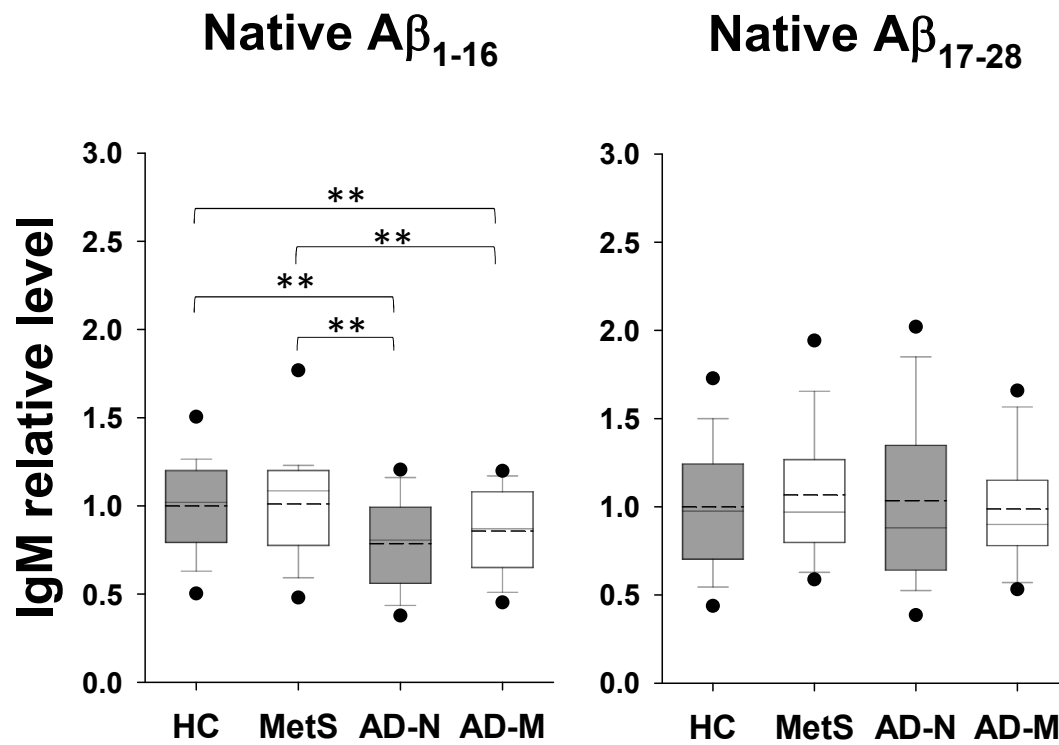


Fig. S1. Acrolein structure. PubChem, *Acrolein*. National Center for Biotechnology Information, 2022. Retrieved from <https://pubchem.ncbi.nlm.nih.gov/compound/Acrolein>.

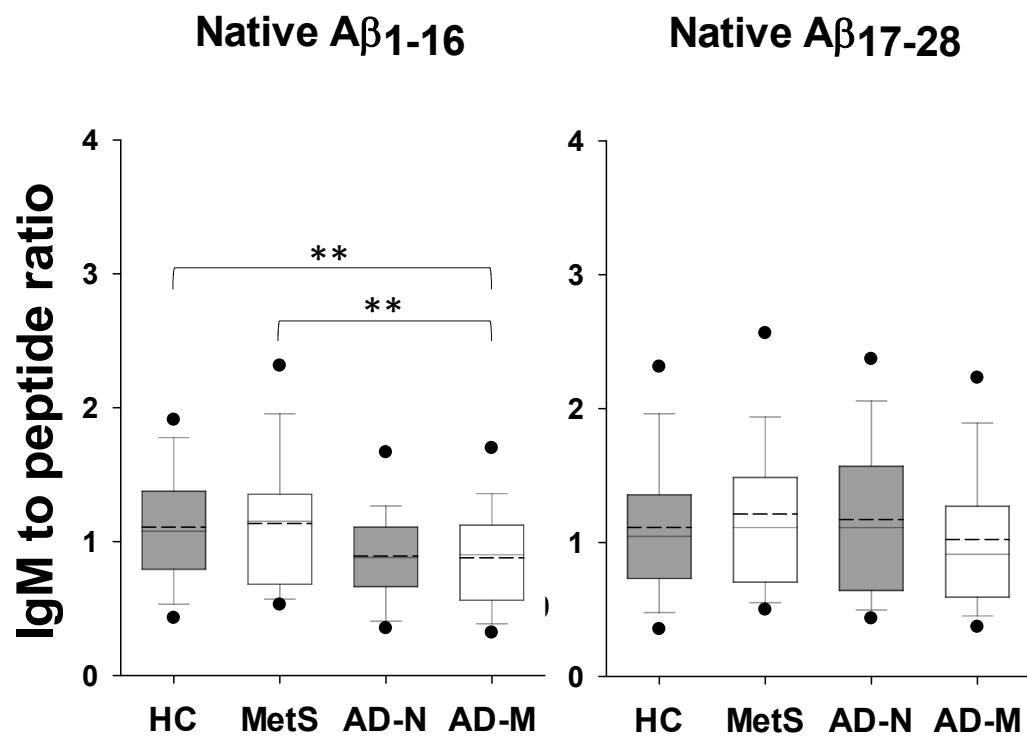


**Fig. S2. Levels of IgG autoantibodies against native A $\beta$  peptides in human serum. A.** The relative levels of IgG autoantibody recognizing native A $\beta_{1-16}$  and A $\beta_{17-28}$  peptides in each group. All the values were normalized with the mean of healthy control (HC). **B.** The ratio of the responding IgG to acrolein adducts of each subject in each group. In the box plots, the dots represent 5th and 95th percentiles. The error bars cover the 10th to 90th percentiles and the box covers 25th to 75th percentiles. The solid and dash lines within the box represent the median and mean values, respectively. A $\beta$ , amyloid beta; AD-M, Alzheimer's disease with metabolic disturbance; AD-N, Alzheimer's disease with normal metabolism; HC, healthy control; MetS, metabolic syndrome. \*  $p < 0.05$ ,

A



B



**Fig. S3. Levels of IgM autoantibodies against native A $\beta$  peptides in human serum.** The relative levels of IgM autoantibody recognizing native A $\beta_{1-16}$  and A $\beta_{17-28}$  peptides in each group. All the values were normalized with the mean of healthy control (HC). **B.** The ratio of the responding IgM to acrolein adducts of each subject in each group. In the box plots, the dots represent 5th and 95th percentiles. The error bars cover the 10th to 90th percentiles and the box covers 25th to 75th percentiles. The solid and dash lines within the box represent the median and mean values, respectively. A $\beta$ , amyloid beta; AD-M, Alzheimer's disease with metabolic disturbance; AD-N, Alzheimer's disease with normal metabolism; HC, healthy control; MetS, metabolic syndrome. \*\*  $p < 0.01$