# Electronic supplementary material (ESM):

# Associations of dicarbonyl stress with complement activation: the CODAM study

**The PDF file includes:**

**ESM Table 1 Associations of plasma α-dicarbonyls, free and protein-bound AGEs with C3a and sC5b-9 — Additional adjustment for plasma lipids, renal function, C3 levels, and glucose metabolism status**

**ESM Table 2 Stratified analyses for the associations of plasma α-dicarbonyls, free and protein-bound AGEs with C3a and sC5b-9 according to the presence of diabetes**

**ESM Table 3 Sensitivity analyses for the associations of plasma α-dicarbonyls, free and protein-bound AGEs with C3a and sC5b-9**

**ESM Table 4 Associations of *GLO1* polymorphism with plasma α-dicarbonyls, free and protein-bound AGEs**

**ESM Table 1** Associations of plasma α-dicarbonyls, free and protein-bound AGEs with C3a and sC5b-9 — Additional adjustment for plasma lipids, renal function, C3 levels, and glucose metabolism status (*n=530*)

| Variable | Full model plus: | C3a (SD) β | 95% CI | *p* value | sC5b-9 (SD) β | 95% CI | *p* value |
|---|---|---|---|---|---|---|---|
| *α-dicarbonyls* | | | | | | | |
| **MGO (SD)** | Lipids | 0.02 | (−0.07, 0.10) | 0.735 | 0.02 | (−0.07, 0.11) | 0.607 |
| | GMS | 0.01 | (−0.08, 0.10) | 0.803 | 0.01 | (−0.09, 0.10) | 0.902 |
| | eGFR | 0.02 | (−0.07, 0.10) | 0.719 | 0.01 | (−0.08, 0.10) | 0.851 |
| | C3 | 0.00 | (−0.08, 0.09) | 0.940 | 0.01 | (−0.08, 0.10) | 0.826 |
| **GO (SD)** | Lipids | −0.05 | (−0.15, 0.04) | 0.232 | −0.11 | (−0.21, −0.02) | 0.019 |
| | GMS | −0.06 | (−0.15, 0.03) | 0.213 | −0.12 | (−0.21, −0.03) | 0.011 |
| | eGFR | −0.06 | (−0.14, 0.03) | 0.227 | −0.12 | (−0.21, −0.03) | 0.012 |
| | C3 | 0.00 | (−0.09, 0.09) | 0.967 | −0.08 | (−0.17, 0.01) | 0.086 |
| **3-DG (SD)** | Lipids | 0.01 | (−0.10, 0.11) | 0.885 | 0.09 | (−0.02, 0.20) | 0.100 |
| | GMS | −0.00 | (−0.12, 0.12) | 0.972 | 0.06 | (−0.06, 0.18) | 0.326 |
| | eGFR | 0.00 | (−0.10, 0.11) | 0.981 | 0.08 | (−0.03, 0.19) | 0.162 |
| | C3 | −0.02 | (−0.12, 0.08) | 0.708 | 0.06 | (−0.05, 0.17) | 0.269 |
| *Free AGEs* | | | | | | | |
| **CML (SD)** | Lipids | 0.01 | (−0.08, 0.10) | 0.860 | −0.03 | (−0.12, 0.07) | 0.576 |
| | GMS | 0.01 | (−0.08, 0.10) | 0.808 | −0.02 | (−0.11, 0.07) | 0.658 |
| | eGFR | 0.02 | (−0.07, 0.11) | 0.678 | −0.04 | (−0.13, 0.06) | 0.450 |
| | C3 | 0.01 | (−0.07, 0.10) | 0.803 | −0.02 | (−0.11, 0.07) | 0.662 |
| **CEL (SD)** | Lipids | −0.05 | (−0.14, 0.04) | 0.264 | −0.07 | (−0.16, 0.02) | 0.140 |
| | GMS | −0.05 | (−0.13, 0.04) | 0.278 | −0.07 | (−0.16, 0.02) | 0.125 |
| | eGFR | −0.04 | (−0.13, 0.05) | 0.362 | −0.09 | (−0.18, 0.00) | 0.062 |
| | C3 | −0.05 | (−0.14, 0.03) | 0.229 | −0.07 | (−0.16, 0.02) | 0.121 |
| **MG−H1 (SD)** | Lipids | −0.05 | (−0.14, 0.04) | 0.272 | −0.04 | (−0.13, 0.06) | 0.431 |
| | GMS | −0.04 | (−0.13, 0.05) | 0.341 | −0.03 | (−0.12, 0.06) | 0.496 |
| | eGFR | −0.04 | (−0.13, 0.05) | 0.405 | −0.05 | (−0.14, 0.05) | 0.339 |
| | C3 | −0.04 | (−0.12, 0.05) | 0.377 | −0.03 | (−0.12, 0.06) | 0.549 |
| *Protein-bound AGEs* | | | | | | | |
| **CML (SD)** | Lipids | −0.09 | (−0.18, 0.01) | 0.070 | −0.06 | (−015, 0.04) | 0.245 |
| | GMS | −0.08 | (−0.17, 0.01) | 0.097 | −0.04 | (−0.14, 0.06) | 0.410 |
| | eGFR | −0.07 | (−0.17, 0.02) | 0.114 | −0.06 | (−0.15, 0.04) | 0.246 |
| | C3 | −0.04 | (−0.13, 0.05) | 0.364 | −0.02 | (−0.12, 0.07) | 0.662 |
| **CEL (SD)** | Lipids | −0.16 | (−0.25, −0.08) | <0.001 | −0.07 | (−0.16, 0.01) | 0.100 |
| | GMS | −0.17 | (−0.25, −0.08) | <0.001 | −0.08 | (−0.17, 0.01) | 0.069 |
| | eGFR | −0.16 | (−0.25, −0.08) | <0.001 | −0.09 | (−0.17, −0.00) | 0.048 |
| | C3 | −0.17 | (−0.25, −0.09) | <0.001 | −0.09 | (−0.17, −0.00) | 0.043 |
| **Pentosidine (SD)** | Lipids | −0.06 | (−0.15, 0.03) | 0.217 | 0.14 | (0.05, 0.23) | 0.003 |
| | GMS | −0.05 | (−0.14, 0.04) | 0.264 | 0.15 | (0.05, 0.24) | 0.002 |
| | eGFR | −0.05 | (−0.14, 0.05) | 0.314 | 0.14 | (0.05, 0.23) | 0.003 |
| | C3 | −0.03 | (−0.12, 0.06) | 0.534 | 0.16 | (0.07, 0.25) | <0.001 |

Concentrations of α-dicarbonyls, AGEs, C3a, and sC5b-9 were standardized. Concentrations of AGEs, C3a, and triacylglycerol were $\log^2$-transformed prior to standardization

Lipids: adjusted for age, sex, lifestyle (smoking status, alcohol consumption, physical activity, and energy intake), medication use (glucose-lowering, lipid-modifying, and/or antihypertensive), and waist circumference (full model) + plasma lipids (concentrations of triacylglycerol, total cholesterol, and HDL-cholesterol). GMS: full model + glucose metabolism status (GMS). eGFR: full model + renal function (eGFR). C3: full model + C3 concentration

**ESM Table 2** Stratified analyses for the associations of plasma α-dicarbonyls, free and protein-bound AGEs with C3a and sC5b-9 according to the presence of diabetes (*n=530*)

| Variable | | C3a (SD) | | | sC5b-9 (SD) | | |
|---|---|---|---|---|---|---|---|
| | | β | 95% CI | *p* value | β | 95% CI | *p* value |
| *α-dicarbonyls* | | | | | | | |
| **MGO (SD)** | NDM | −0.04 | (−0.15, 0.07) | 0.487 | −0.05 | (−0.15, 0.06) | 0.393 |
| | T2DM | 0.13 | (−0.01, 0.28) | 0.073 | 0.13 | (−0.05, 0.31) | 0.155 |
| | | *p for interaction* | | 0.083 | *p for interaction* | | 0.098 |
| **GO (SD)** | NDM | −0.10 | (−0.23, 0.04) | 0.154 | −0.15 | (−028, −0.02) | 0.024 |
| | T2DM | −0.04 | (−0.15, 0.08) | 0.537 | −0.10 | (−0.24, 0.04) | 0.171 |
| | | *p for interaction* | | 0.598 | *p for interaction* | | 0.602 |
| **3-DG (SD)** | NDM | −0.06 | (−0.24, 0.12) | 0.485 | −0.03 | (−0.20, 0.15) | 0.774 |
| | T2DM | 0.07 | (−0.08, 0.21) | 0.371 | 0.12 | (−0.06, 0.30) | 0.193 |
| | | *p for interaction* | | 0.168 | *p for interaction* | | 0.248 |
| *Free AGEs* | | | | | | | |
| **CML (SD)** | NDM | 0.03 | (−0.08, 0.24) | 0.637 | 0.04 | (−0.06, 0.14) | 0.413 |
| | T2DM | −0.05 | (−0.21, 0.12) | 0.567 | −0.21 | (−0.41, −0.01) | 0.040 |
| | | *p for interaction* | | 0.535 | *p for interaction* | | 0.010 |
| **CEL (SD)** | NDM | −0.04 | (−0.15, 0.07) | 0.455 | 0.01 | (−0.09, 0.11) | 0.872 |
| | T2DM | −0.10 | (−0.25, 0.05) | 0.188 | −0.29 | (−0.47, −0.10) | 0.003 |
| | | *p for interaction* | | 0.719 | *p for interaction* | | 0.004 |
| **MG-H1 (SD)** | NDM | −0.03 | (−0.14, 0.08) | 0.581 | −0.02 | (−0.13, 0.09) | 0.687 |
| | T2DM | −0.09 | (−023, 0.06) | 0.252 | −0.05 | (−0.23, 0.14) | 0.616 |
| | | *p for interaction* | | 0.588 | *p for interaction* | | 0.578 |
| *Protein-bound AGEs* | | | | | | | |
| **CML (SD)** | NDM | −0.09 | (−0.21, 0.03) | 0.143 | 0.05 | (−0.07, 0.016) | 0.410 |
| | T2DM | −0.06 | (−0.21, 0.08) | 0.393 | −0.24 | (−0.42, −0.06) | 0.010 |
| | | *p for interaction* | | 0.743 | *p for interaction* | | 0.027 |
| **CEL (SD)** | NDM | *−0.23* | *(−0.33, −0.12)* | <0.001 | −0.02 | (−0.12, 0.08) | 0.703 |
| | T2DM | −0.05 | (−0.19, 0.08) | 0.429 | −0.21 | (−0.38, −0.05) | 0.013 |
| | | *p for interaction* | | 0.039 | *p for interaction* | | 0.066 |
| **Pentosidine (SD)** | NDM | −0.02 | (−0.14, 0.09) | 0.717 | 0.17 | (0.06, 0.28) | 0.003 |
| | T2DM | −0.13 | (−0.27, 0.01) | 0.070 | 0.11 | (−0.07, 0.29) | 0.214 |
| | | *p for interaction* | | 0.146 | *p for interaction* | | 0.555 |

Concentrations of α-dicarbonyls, AGEs, C3a, and sC5b-9 were standardized. Concentrations of AGEs and C3a were $\log_2$-transformed prior to standardization

NDM, analyses were performed in individuals without diabetes (n=392). T2DM, analyses were performed in individuals with T2DM (n=138)

All adjusted for age, sex, lifestyle (smoking status, alcohol consumption, physical activity, and energy intake), medication use (glucose-lowering, lipid-modifying, and/or antihypertensive), and waist circumference

T2DM, type 2 diabetes mellitus

**ESM Table 3** Sensitivity analyses for the associations of plasma α-dicarbonyls, free and protein-bound AGEs with C3a and sC5b-9

| Variable | Outcome | | | | | |
|---|---|---|---|---|---|---|
| | C3a (SD) | | | sC5b-9 (SD) | | |
| | β | 95 % CI | *p* value | β | 95 % CI | *p* value |
| *No chronic or acute infections; n=494 [a]* | | | | | | |
| **α-dicarbonyls** | | | | | | |
| **MGO (SD)** | 0.01 | (−0.08, 0.10) | 0.883 | −0.02 | (−0.11, 0.08) | 0.740 |
| **GO (SD)** | −0.05 | (−0.14, 0.05) | 0.327 | −0.08 | (−0.18, 0.01) | 0.087 |
| **3-DG (SD)** | −0.01 | (−0.13, 0.10) | 0.831 | 0.03 | (−0.09, 0.14) | 0.670 |
| *Free AGEs* | | | | | | |
| **CML (SD)** | 0.03 | (−0.06, 0.12) | 0.518 | −0.02 | (−0.11, 0.08) | 0.727 |
| **CEL (SD)** | −0.04 | (−0.13, 0.05) | 0.383 | −0.06 | (−0.15, 0.04) | 0.245 |
| **MG-H1 (SD)** | −0.04 | (−0.13, 0.05) | 0.399 | −0.02 | (−0.11, 0.08) | 0.737 |
| **Protein-bound AGEs** | | | | | | |
| **CML (SD)** | −0.08 | (−0.18, 0.01) | 0.088 | −0.05 | (−0.15, 0.05) | 0.316 |
| **CEL (SD)** | −0.18 | (−0.26, −0.09) | <0.001 | −0.09 | (−0.18, 0.00) | 0.042 |
| **Pentosidine (SD)** | −0.05 | (−0.14, 0.04) | 0.300 | 0.14 | (0.04, 0.23) | 0.006 |
| *No autoimmune disease; n=459 [b]* | | | | | | |
| **α-dicarbonyls** | | | | | | |
| **MGO (SD)** | −0.01 | (−0.1, 0.08) | 0.805 | 0.01 | (−0.09, 0.11) | 0.832 |
| **GO (SD)** | −0.06 | (−0.15, 0.04) | 0.253 | −0.11 | (−0.20, −0.01) | 0.038 |
| **3-DG (SD)** | −0.01 | (−0.12, 0.10) | 0.836 | 0.06 | (−0.05, 0.18) | 0.280 |
| *Free AGEs* | | | | | | |
| **CML (SD)** | 0.00 | (−0.09, 0.10) | 0.933 | −0.03 | (−0.12, 0.07) | 0.572 |
| **CEL (SD)** | −0.07 | (−0.16, 0.03) | 0.158 | −0.08 | (−0.18, 0.01) | 0.096 |
| **MG-H1 (SD)** | −0.05 | (−0.14, 0.05) | 0.329 | −0.05 | (−0.15, 0.04) | 0.285 |
| **Protein-bound AGEs** | | | | | | |
| **CML (SD)** | −0.11 | (−0.21, −0.01) | 0.029 | −0.06 | (−0.16, 0.04) | 0.263 |
| **CEL (SD)** | −0.20 | (−0.28, −0.11) | 0.000 | −0.09 | (−0.18, 0.00) | 0.054 |
| **Pentosidine (SD)** | −0.05 | (−0.15, 0.04) | 0.284 | 0.14 | (0.04, 0.24) | 0.006 |
| *No malignant disease and/or cancer; n=508 [c]* | | | | | | |
| **α-dicarbonyls** | | | | | | |
| **MGO (SD)** | 0.01 | (−0.07, 0.10) | 0.741 | 0.03 | (−0.06, 0.12) | 0.568 |
| **GO (SD)** | −0.06 | (−0.15, 0.03) | 0.168 | −0.11 | (−0.20, −0.02) | 0.018 |
| **3-DG (SD)** | 0.01 | (−0.10, 0.12) | 0.846 | 0.09 | (−0.02, 0.20) | 0.111 |
| *Free AGEs* | | | | | | |
| **CML (SD)** | 0.00 | (−0.09, 0.09) | 0.969 | −0.02 | (−0.11, 0.07) | 0.701 |
| **CEL (SD)** | −0.06 | (−0.15, 0.03) | 0.200 | −0.07 | (−0.16, 0.02) | 0.114 |
| **MG-H1 (SD)** | −0.05 | (−0.14, 0.04) | 0.273 | −0.03 | (−0.12, 0.06) | 0.524 |
| **Protein-bound AGEs** | | | | | | |
| **CML (SD)** | −0.08 | (−0.17, 0.01) | 0.096 | −0.06 | (−0.16, 0.03) | 0.213 |
| **CEL (SD)** | −0.17 | (−0.25, −0.08) | <0.001 | −0.09 | (−0.17, 0.00) | 0.051 |
| **Pentosidine (SD)** | −0.06 | (−0.15, 0.03) | 0.201 | 0.14 | (0.05, 0.24) | 0.002 |
| *No liver disease; n=524 [d]* | | | | | | |
| **α-dicarbonyls** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **MGO (SD)** | 0.01 | (−0.07, 0.10) | 0.749 | 0.02 | (−0.07, 0.11) | 0.602 |
| **GO (SD)** | −0.05 | (−0.14, 0.04) | 0.273 | −0.11 | (−0.20, −0.02) | 0.018 |
| **3-DG (SD)** | 0.01 | (−0.10, 0.11) | 0.925 | 0.07 | (−0.04, 0.18) | 0.194 |
| *Free AGEs* | | | | | | |
| **CML (SD)** | 0.01 | (−0.08, 0.10) | 0.834 | −0.02 | (−0.11, 0.07) | 0.712 |
| **CEL (SD)** | −0.05 | (−0.13, 0.04) | 0.286 | −0.06 | (−0.15, 0.03) | 0.163 |
| **MG-H1 (SD)** | −0.05 | (−0.14, 0.04) | 0.298 | −0.03 | (−0.12, 0.06) | 0.573 |
| **Protein-bound AGEs** | | | | | | |
| **CML (SD)** | −0.08 | (−0.17, 0.01) | 0.074 | −0.05 | (−0.14, 0.05) | 0.327 |
| **CEL (SD)** | −0.17 | (−0.25, −0.08) | 0.000 | −0.08 | (−0.16, 0.01) | 0.073 |
| **Pentosidine (SD)** | −0.05 | (−0.14, 0.04) | 0.278 | 0.15 | (0.05, 0.24) | 0.002 |

Concentrations of α-dicarbonyls, AGEs, C3a, and sC5b-9 were standardized. Concentrations of AGEs and C3a were $\log_2$-transformed prior to standardization

All adjusted for age, sex, lifestyle (smoking status, alcohol consumption, physical activity, and energy intake), medication use (glucose-lowering, lipid-modifying, and/or antihypertensive), and waist circumference

[a] 36 participants with acute or chronic infections were excluded. [b] 71 participants were excluded, of which 61 with a (suspected) history of autoimmune disease and 10 missing information on autoimmune disease. [c] 22 participants were excluded, of which 18 with a self-reported current malignant condition/cancer and 4 missing information on malignant disease and/or cancer. [d] 6 participants with a self-reported current liver disease were excluded

**ESM Table 4** Associations of *GLO1* polymorphism with plasma α-dicarbonyls, free and protein-bound AGEs (*n=504*)

| | | rs2736654 | | | | | | rs1049346 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TT (reference) | GT | | GG | | | GG (reference) | AG | | AA | |
| | Model | | β | *p* value | β | *p* value | | | β | *p* value | β | *p* value |
| **Outcomes** | | | | | | | | | | | | |
|   MGO (SD) | 1 | – | −0.18 | 0.074 | −0.19 | 0.156 | | – | 0.09 | 0.446 | 0.02 | 0.861 |
| | 2 | – | −0.20 | 0.042 | −0.16 | 0.234 | | – | 0.09 | 0.411 | 0.08 | 0.526 |
| | 3 | – | −0.21 | 0.036 | −0.15 | 0.258 | | – | 0.09 | 0.410 | 0.08 | 0.508 |
| *Free AGEs* | | | | | | | | | | | | |
|   CML (SD) | 1 | – | −0.04 | 0.717 | −0.21 | 0.099 | | – | −0.10 | 0.340 | −0.15 | 0.232 |
| | 2 | – | −0.04 | 0.724 | −0.18 | 0.153 | | – | −0.14 | 0.197 | −0.20 | 0.117 |
| | 3 | – | −0.04 | 0.708 | −0.18 | 0.160 | | – | −0.14 | 0.197 | −0.19 | 0.120 |
|   CEL (SD) | 1 | – | −0.10 | 0.326 | −0.12 | 0.375 | | – | −0.11 | 0.317 | 0.09 | 0.478 |
| | 2 | – | −0.10 | 0.298 | −0.09 | 0.490 | | – | −0.14 | 0.211 | 0.09 | 0.497 |
| | 3 | – | −0.11 | 0.271 | −0.08 | 0.529 | | – | −0.14 | 0.212 | 0.09 | 0.478 |
|   MG-H1 (SD) | 1 | – | −0.03 | 0.776 | −0.01 | 0.961 | | – | −0.08 | 0.443 | 0.02 | 0.845 |
| | 2 | – | −0.02 | 0.846 | 0.05 | 0.702 | | – | −0.14 | 0.199 | −0.04 | 0.770 |
| | 3 | – | −0.01 | 0.885 | 0.04 | 0.739 | | – | −0.14 | 0.198 | −0.04 | 0.751 |
| *Protein-bound AGEs* | | | | | | | | | | | | |
|   CML (SD) | 1 | – | −0.06 | 0.576 | −0.03 | 0.796 | | – | −0.05 | 0.625 | 0.08 | 0.513 |
| | 2 | – | −0.03 | 0.799 | −0.07 | 0.615 | | – | −0.07 | 0.548 | 0.05 | 0.704 |
| | 3 | – | 0.01 | 0.908 | −0.11 | 0.355 | | – | −0.07 | 0.511 | 0.03 | 0.824 |
|   CEL (SD) | 1 | – | −0.16 | 0.121 | −0.00 | 0.990 | | – | 0.02 | 0.831 | 0.05 | 0.697 |
| | 2 | – | −0.15 | 0.142 | −0.01 | 0.957 | | – | −0.01 | 0.962 | 0.01 | 0.931 |
| | 3 | – | −0.15 | 0.140 | −0.01 | 0.964 | | – | −0.01 | 0.962 | 0.01 | 0.930 |
|   Pentosidine (SD) | 1 | – | −0.03 | 0.757 | −0.11 | 0.401 | | – | −0.08 | 0.491 | −0.12 | 0.360 |
| | 2 | – | −0.04 | 0.678 | −0.14 | 0.283 | | – | −0.06 | 0.559 | −0.08 | 0.537 |
| | 3 | – | −0.01 | 0.924 | −0.18 | 0.141 | | – | −0.07 | 0.528 | −0.10 | 0.417 |

The reference categories are the genotypes that were reported to be associated with the highest GLO1 activity (see reference 22–24 in the main text)

Concentrations of MGO and AGEs were standardized. Concentrations of AGEs were $\log_2$-transformed prior to standardization

Model 1: adjusted for age and sex. Model 2: model 1 + lifestyle (smoking status, alcohol consumption, physical activity, and energy intake) and medication use (glucose-lowering, lipid-modifying, and/or antihypertensive). Model 3: model 2 + waist circumference