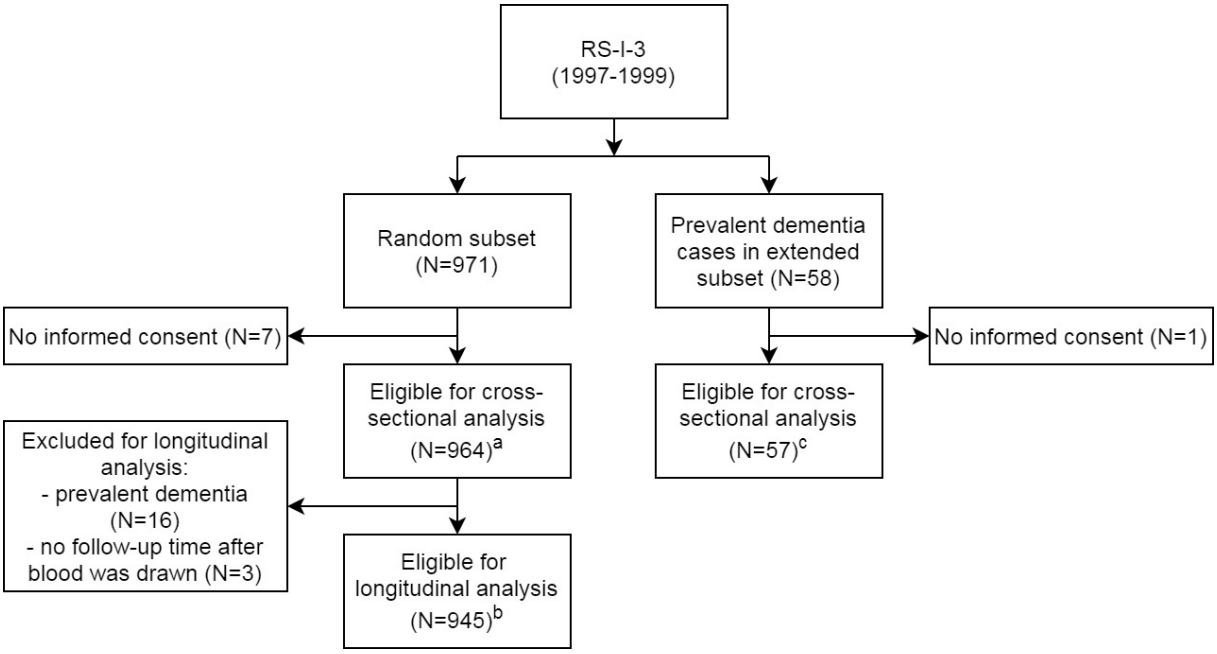
# Supplemental Online Content

Chen J, Mooldijk SS, Licher S, et al. Assessment of advanced glycation end products and receptors and the risk of dementia. *JAMA Netw Open*. 2021;4(1):e2033012. doi:10.1001/jamanetworkopen.2020.33012



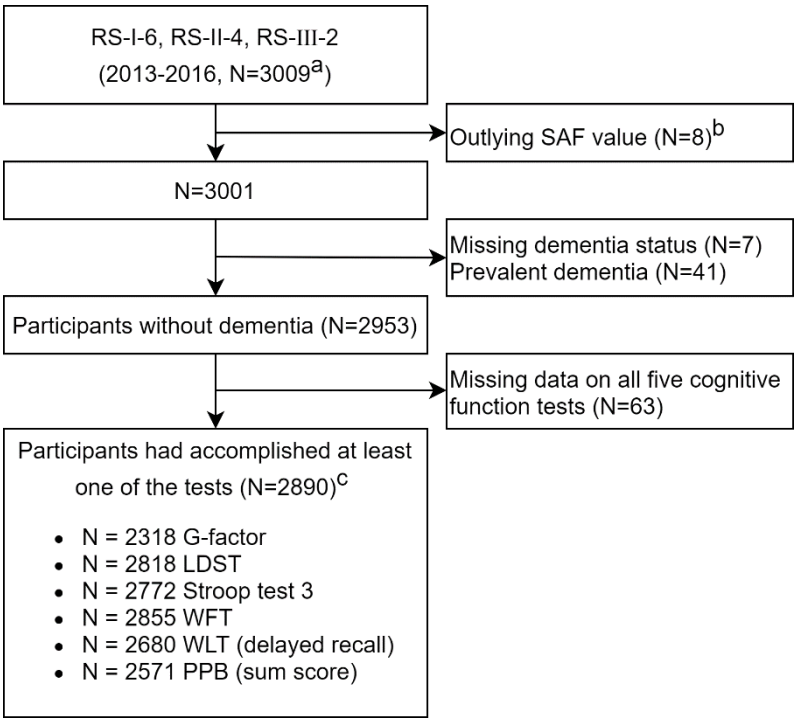
This supplemental material has been provided by the authors to give readers additional information about their work.

**eFigure 1.** Flow Diagram for Study Population for Cross-Sectional and Longitudinal Analyses With EN-RAGE and S-RAGE




Flow diagram for participants of the EN-RAGE and S-RAGE subset.
[a] 1 participant had EN-RAGE missing, 2 had outlying EN-RAGE, leaving 961 eligible for prevalence analysis with EN-RAGE. There were no missing, or outlying values for S-RAGE.
[b] 1 participant had EN-RAGE missing, 2 had outlying EN-RAGE, leaving 942 eligible for incidence analysis with EN-RAGE. There were no missing, or outlying values for S-RAGE.
[c] 1 participant had EN-RAGE missing, 1 other participant had S-RAGE missing, leaving 56 eligible for prevalence analysis.

**eFigure 2.** Flow Diagram for Study Population for Skin Autofluorescence and Cognition Outcomes



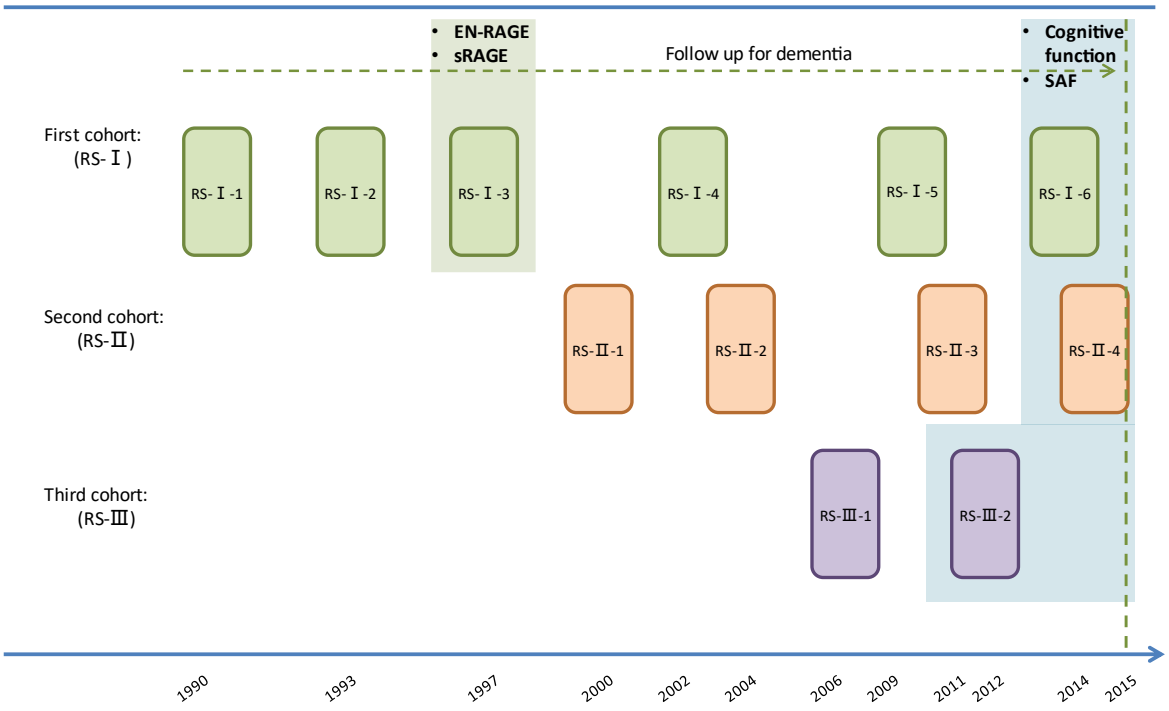

Flow diagram for participants of the SAF subset. SAF, skin auto-fluorescence; IC, informed consent; LDST, letter-digit substitution task; WFT, verbal fluency test; WLT (delayed recall), 15-word learning test (delayed recall); PPB, Purdue pegboard test.

[a] N=3029 had SAF measurement, of whom 20 with no informed consent were excluded.

[b] Values outside of the mean ± 4SD range were defined as outlying values.

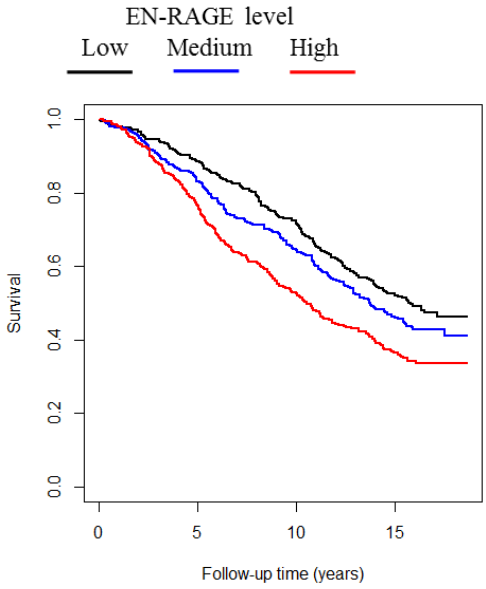
[c] Participants with outlying cognitive test values were excluded for each analysis respectively (N=3 for G-factor, N=1 for LDST, N=1 for Stroop test 3, N=1 for PPB sum score).

## eFigure 3 Timeline of data collection.




Abbreviations: EN-RAGE, Extracellular Newly identified RAGE binding protein; sRAGE, soluble form of the receptor for AGEs (RAGE); SAF, skin autofluorescence; RS, Rotterdam Study.
The number following each subcohort denotes the round of visit.

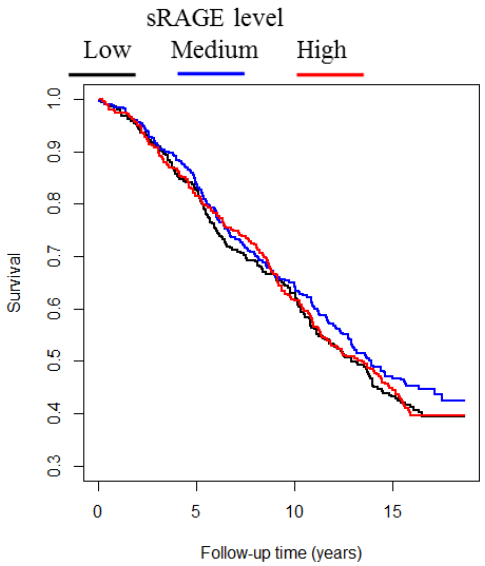
**eFigure 4.** Kaplan-Meier Survival Curves for Overall Survival by EN-RAGE Tertile




| Follow-up time (years) | 0 | 5 | 10 | 15 |
|---|---|---|---|---|
| No. At risk | | | | |
| Low | 314 | 276 | 220 | 137 |
| Medium | 320 | 261 | 202 | 130 |
| High | 308 | 235 | 161 | 103 |

Unadjusted survival curves for overall survival by EN-RAGE tertile. Number of participants at risk at start of follow-up, after 5, 10 and 15 years, per tertile, are presented underneath the graph.

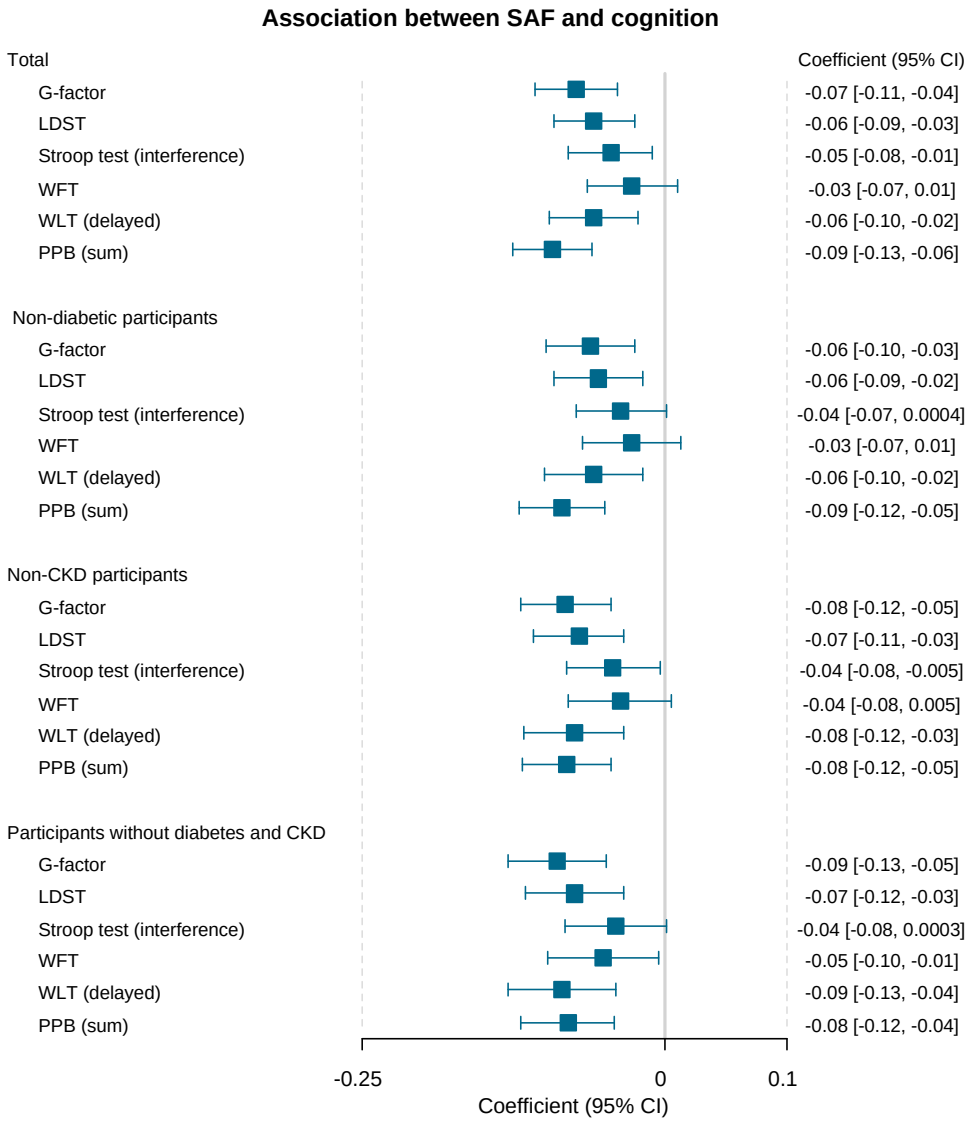
**eFigure 5.** Kaplan-Meier Survival Curve for Overall Survival by S-RAGE Tertile




| Follow-up time (years) | 0 | 5 | 10 | 15 |
|---|---|---|---|---|
| No. At risk | | | | |
| Low | 309 | 254 | 291 | 116 |
| Medium | 321 | 266 | 204 | 135 |
| High | 315 | 254 | 1689 | 120 |

Unadjusted survival curves for dementia free survival (left) and overall survival (right) by S-RAGE tertile. Number of participants at risk at start of follow-up, after 5, 10 and 15 years, per tertile, are presented underneath the graph.

## eFigure 6 Association of SAF and cognition after excluding participants with diabetes, CKD or both.




Abbreviations: CKD, chronic kidney disease; LDST, letter-digit substitution task; WFT, verbal fluency test; WLT, word learning test (delayed recall); PPB (sum), sum score Purdue pegboard tests including tests on left hand, right hand and both hands.
Forest plot of the associations between z-score of SAF and G-factor and the performance of individual cognitive function tests in the total population and after excluding participants with diabetes, CKD or both. The original score of Stroop test (interference task) was inversely transformed. After transformation, higher score corresponds to better performance. Coefficients [95% CI]s are the difference in G-factor and z-scores of test parameters in association with one SD difference in SAF, obtained from the linear regression Model 2, adjusting for age, sex, diabetes, education, *APOE* ε4 carrier status, smoking status and eGFR. For the non-diabetic subgroups, diabetes status was not used in the model for adjustment.

**eTable 1.** Summary of Missing Value in Covariates

| Variable | Percentage missing, % | |
|---|---|---|
| | **EN-RAGE and S-RAGE analyses** | **SAF analyses** |
| Diabetes status | 9.6 | 0.8 |
| Education | 0.9 | 1.5 |
| *APOE* ε4 carrier status | 4.1 | 6.2 |
| Smoking | 2.1 | 1.2 |
| eGFR | 2.5 | 3.7 |
| Systolic blood pressure | 1.2 | 2.5 |
| Diastolic blood pressure | 1.2 | 2.5 |
| HDL cholesterol | 1.7 | 3.7 |
| Total cholesterol | 2.0 | 3.7 |
| Triglycerides | 2.5 | 3.7 |
| Lipid lowering medication | 10.0 | 0.8 |
| Depressive symptoms | 8.8 | 1.0 |

N = 1021 for EN-RAGE and S-RAGE analysis; N=2890 for SAF analysis. In total, 578 (14.8%) participants had missing value in at least one of the covariates, including 322 out of 2890 participants (11.1%) for the SAF analysis, and 256 out of 1021 (25%) participants for the EN-RAGE and S-RAGE analysis.

**eTable 2.** EN-RAGE and S-RAGE in Association With Dementia Prevalence and Incidence, Stratified by Sex and *APOE* ε4 Carrier Status

| **A** | **Dementia prevalence** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Women** | | **Men** | | ***APOE* ε4 carriers** | | ***APOE* ε4 non-carriers** | |
| **EN-RAGE tertiles** | **n/N** | **OR[a] (95% CI)** | **n/N** | **OR[a] (95% CI)** | **n/N** | **OR[b] (95% CI)** | **n/N** | **OR[b] (95% CI)** |
| Low | 6/197 | 1.00 Reference | 3/127 | 1.00 Reference | 4/67 | 1.00 Reference | 5/250 | 1.00 Reference |
| Medium | 11/180 | 1.72 (0.54-5.49) | 5/157 | 0.75 (0.12-4.69) | 11/114 | 1.45 (0.39-5.35) | 4/211 | 0.88 (0.21-3.62) |
| High | 27/185 | 2.82 (0.98-8.12) | 20/171 | 4.38 (0.92-20.93) | 25/117 | 2.68 (0.77-9.28) | 18/216 | 3.40 (1.13-10.25) |
| Per SD Ln | 44/562 | 1.41 (0.95-2.10) | 28/455 | 2.30 (1.36-3.88) | 40/298 | 1.50 (1.00-2.26) | 27/677 | 1.79 (1.15-2.78) |
| | P = 0.20 | | | | P = 0.48 | | | |
| | **Dementia incidence** | | | | | | | |
| | **Women** | | **Men** | | ***APOE* ε4 carriers** | | ***APOE* ε4 non-carriers** | |
| **EN-RAGE tertiles** | **n/N** | **HR[a] (95% CI)** | **n/N** | **HR[a] (95% CI)** | **n/N** | **HR[b] (95% CI)** | **n/N** | **HR[b] (95% CI)** |
| Low | 42/190 | 1.00 Reference | 19/124 | 1.00 Reference | 16/62 | 1.00 Reference | 44/245 | 1.00 Reference |
| Medium | 40/169 | 1.18 (0.74-1.86) | 24/151 | 1.18 (0.62-2.25) | 31/102 | 1.43 (0.77-2.66) | 31/207 | 0.86 (0.53-1.37) |
| High | 19/158 | 0.65 (0.37-1.15) | 16/150 | 0.72 (0.35-1.48) | 10/92 | 0.55 (0.24-1.26) | 22/197 | 0.73 (0.43-1.24) |
| Per SD Ln | 101/517 | 0.90 (0.73-1.11) | 59/425 | 0.85 (0.62-1.15) | 57/256 | 0.82 (0.61-1.11) | 97/649 | 0.89 (0.71-1.10) |
| | P = 0.72 | | | | P = 0.39 | | | |

| **B** | **Dementia prevalence** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Women** | | **Men** | | ***APOE* ε4 carriers** | | ***APOE* ε4 non-carriers** | |
| **S-RAGE tertiles** | **n/N** | **OR[a] (95% CI)** | **n/N** | **OR[a] (95% CI)** | **n/N** | **OR[b] (95% CI)** | **n/N** | **OR[b] (95% CI)** |
| Low | 20/164 | 1.00 Reference | 15/182 | 1.00 Reference | 18/122 | 1.00 Reference | 15/211 | 1.00 Reference |
| Medium | 15/197 | 0.58 (0.24-1.42) | 5/144 | 0.48 (0.13-1.76) | 10/86 | 0.75 (0.27-2.06) | 7/136 | 0.36 (0.13-1.01) |
| High | 10/203 | 0.35 (0.13-0.97) | 7/130 | 0.34 (0.09-1.25) | 12/91 | 0.70 (0.27-1.86) | 5/232 | 0.23 (0.07-0.78) |
| Per SD Ln | 45/564 | 0.62 (0.41-0.93) | 27/456 | 0.51 (0.30-0.86) | 40/299 | 0.83 (0.53-1.30) | 27/679 | 0.50 (0.33-0.76) |
| | P = 0.99 | | | | P = 0.06 | | | |

| | Dementia incidence | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Women | | Men | | *APOE* ε4 carriers | | *APOE* ε4 non-carriers | |
| **S-RAGE tertiles** | **n/N** | **HR[a] (95% CI)** | **n/N** | **HR[a] (95% CI)** | **n/N** | **HR[b] (95% CI)** | **n/N** | **HR[b] (95% CI)** |
| Low | 28/144 | 1.00 Reference | 23/165 | 1.00 Reference | 22/103 | 1.00 Reference | 28/195 | 1.00 Reference |
| Medium | 37/182 | 0.98 (0.59-1.63) | 17/139 | 0.88 (0.45-1.72) | 14/76 | 0.92 (0.45-1.87) | 38/229 | 1.01 (0.61-1.65) |
| High | 36/192 | 0.95 (0.57-1.58) | 20/123 | 1.33 (0.70-2.53) | 21/78 | 1.24 (0.65-2.37) | 32/227 | 1.00 (0.59-1.68) |
| Per SD Ln | 101/518 | 0.89 (0.72-1.11) | 60/427 | 1.02 (0.77-1.33) | 57/257 | 0.94 (0.69-1.28) | 98/651 | 0.91 (0.74-1.13) |
| | P = 0.31 | | | | P = 0.61 | | | |

Associations of plasma EN-RAGE (A) and S-RAGE (B) levels with dementia prevalence and incidence. Odds ratio's (OR) and hazard ratio's (HR) are presented across tertile groups with the low-level group as reference; and by one standard deviation higher of natural logarithm of EN-RAGE and S-RAGE. All ORs were obtained from logistic regression and HRs from Cox regression, adjusting for age, sex, diabetes, education, *APOE* ε4 carrier status, smoking and eGFR (model 2). P-values for the corresponding interaction terms were calculated using the biomarkers continuously (per standard deviation of natural logarithm). The sample sizes for stratified analyses by *APOE* ε4 carrier status were smaller than those for sex stratified analyses because of missing value in *APOE* genotype. The slightly different sample sizes for EN-RAGE and S-RAGE were due to exclusion of outlying values.

[a]Sex was not used in the model for adjustment.

[b]*APOE* ε4 was not used in the model for adjustment.

**eTable 3.** EN-RAGE and S-RAGE and Dementia Incidence With Increasing Duration of Follow-Up

(A)

| Follow-up duration | Events (low/medium/high) | HR (95% CI) | |
|---|---|---|---|
| | | Medium EN-RAGE | High EN-RAGE |
| 4 | 6/12/10 | 2.00 (0.73-5.48) | 1.50 (0.52-4.29) |
| 8 | 19/24/21 | 1.27 (0.68-2.39) | 1.13 (0.59-2.15) |
| 12 | 37/39/27 | 1.09 (0.68-1.73) | 0.83 (0.50-1.40) |
| 18.7 | 61/64/35 | 1.08 (0.76-1.55) | 0.65 (0.42-1.00) |

(B)

| Follow-up duration | Events (low/medium/high) | HR (95% CI) | |
|---|---|---|---|
| | | Medium S-RAGE | High S-RAGE |
| 4 | 10/7/11 | 0.77 (0.28-2.09) | 1.11 (0.45-2.75) |
| 8 | 21/22/21 | 1.16 (0.62-2.17) | 1.12 (0.60-2.12) |
| 12 | 29/32/42 | 1.22 (0.72-2.07) | 1.67 (1.02-2.75) |
| 18.7 | 51/54/56 | 1.04 (0.70-1.55) | 1.22 (0.82-1.81) |

Associations of plasma EN-RAGE (A) and S-RAGE (B) levels with dementia incidence. HRs per cumulatively increasing duration of follow-up were obtained from Cox regression models by censoring all participants still at risk at 4, 8 and 12 years after baseline, and after total follow-up of 18.7 years. The group with the lowest plasma levels was used as a reference. All estimates were adjusted for covariates using Model 2, including age, sex, diabetes, education, *APOE* ε4 carrier status, smoking and eGFR.

**eTable 4.** Characteristics of the Skin Autofluorescence Cognition Study Population by Skin Autofluorescence Tertiles

| | **Total** | **Low SAF (1.10-2.13)** | **Medium SAF (2.17-2.50)** | **High SAF (2.53-4.40)** |
|---|---|---|---|---|
| **N** | 2890 | 959 | 897 | 1034 |
| **Age**, year | 72.51 ± 9.36 | 69.52 ± 9.46 | 72.37 ± 9.22 | 75.40 ± 8.46 |
| **Sex** (Women) | 1,640 (57) | 650 (68) | 498 (56) | 492 (48) |
| **Caucasian descent** (n=2793) | 2,675 (96) | 873 (93) | 840 (97) | 962 (97) |
| **Education levels** (n=2846) | | | | |
| Primary (n, %) | 193 (7) | 56 (6) | 51 (6) | 86 (8) |
| Lower (n, %) | 1,120 (39) | 370 (39) | 342 (39) | 408 (40) |
| Intermediate (n, %) | 871 (31) | 280 (30) | 277 (31) | 314 (31) |
| Higher (n, %) | 662 (23) | 241 (25) | 215 (24) | 206 (20) |
| **Income**, euro's/year (n=2596) | | | | |
| <25000 | 187 (7) | 49 (6) | 58 (7) | 80 (9) |
| 25000-45000 | 767 (30) | 197 (23) | 244 (30) | 326 (35) |
| 45000-65000 | 756 (29) | 233 (27) | 243 (30) | 280 (30) |
| >65000 | 886 (34) | 374 (44) | 262 (32) | 250 (27) |
| ***APOE* ε4** (n=2712) | | | | |
| no alle (n, %) | 1,977 (73) | 638 (71) | 621 (73) | 718 (74) |
| 1 alle (n, %) | 672 (25) | 237 (26) | 210 (25) | 225 (23) |
| 2 alles (n, %) | 63 (2) | 20 (2) | 22 (3) | 21 (2) |
| **Alcohol use** (n=2858) | 2,471 (86) | 836 (88) | 773 (87) | 862 (84) |
| **Smoking status** (n=2854) | | | | |
| Never (n, %) | 916 (32) | 371 (39) | 280 (32) | 265 (26) |
| Former (n, %) | 1,565 (55) | 501 (53) | 482 (55) | 582 (57) |
| Current (n, %) | 373 (13) | 79 (8) | 122 (14) | 172 (17) |
| **Body mass index**, kg/m$^2$ (n=2833) | 27.54 (4.29) | 27.18 (4.03) | 27.53 (4.35) | 27.89 (4.44) |
| **Systolic blood pressure,** mmHg (n=2817) | 144.55 (21.52) | 141.80 (20.76) | 145.20 (21.97) | 146.60 (21.58) |
| **Diastolic blood pressure**, mmHg (n=2817) | 83.71 (10.79) | 83.90 (10.76) | 84.20 (10.85) | 83.08 (10.74) |
| **Hypertension** (n=2853) | 2,128 (75) | 650 (68) | 656 (74) | 822 (81) |
| **Total cholesterol**, mg/dL (n=2782) | 211 (42) | 219 (44) | 211 (41) | 203 (42) |
| **High-density lipoprotein cholesterol**, mg/dL (n=2782) | 58 (17) | 61 (17) | 58 (17) | 56 (16) |
| *__Triglycerides__, mg/dL (n=2782) | 113.37 (85.91, 153.23) | 112.48 (86.80, 149.68) | 110.71 (85.91, 149.90) | 116.03 (86.80, 156.77) |
| **Lipid lowering medication** (n=2866) | 877 (31) | 246 (26) | 261 (29) | 370 (36) |
| *__eGFR__, mL/min/1.73 m$^2$ (n=2782) | 74.92 (65.54, 84.41) | 76.24 (67.56, 85.44) | 75.33 (66.17, 84.61) | 73.44 (62.86, 82.92) |
| **Chronic kidney disease** (n=2782) | 413 (15) | 99 (11) | 118 (14) | 196 (20) |
| **Diabetes** (n=2868) | 393 (14) | 82 (9) | 114 (13) | 197 (19) |
| **History of coronary heart diseases** (n=2878) | 192 (7) | 33 (3) | 51 (6) | 108 (11) |
| **Depressive symptom** (n=2862) | 640 (22) | 214 (22) | 196 (22) | 230 (22) |
| **SAF**, A.U. | 2.40 ± 0.49 | 1.90 ± 0.19 | 2.32 ± 0.11 | 2.92 ± 0.35 |

Abbreviations: *APOE* = apolipoprotein E; eGFR = estimated glomerular filtration rate; SAF = skin autofluorescence.

SI conversion factor: To convert total and HDL cholesterol levels to mmol/L, multiply by 0.0259; To convert triglycerides levels to mmol/L, multiply by 0.0113.
Values are shown for non-imputed data. Values are counts (valid percentages), means (standard deviations) or *median (interquartile range) in case of a skewed distribution.

**eTable 5.** Scores of Cognitive Function Tests by Skin Autofluorescence Tertiles

| | Number of included participants | Total (N=2890) | Low SAF (N=959) | Medium SAF (N=971) | High SAF (N=960) |
|---|---|---|---|---|---|
| **Stroop tests** | | | | | |
| *Stroop test 1 | 2789 | 17.44 (15.63, 19.81) | 16.84 (15.06, 18.91) | 17.59 (15.66, 19.71) | 18.17 (16.22, 20.73) |
| *Stroop test 2 | 2788 | 23.59 (20.97, 26.81) | 22.59 (20.32, 25.59) | 23.66 (21.03, 26.57) | 24.44 (21.94, 28.03) |
| *Stroop test 3 | 2773 | 48.82 (40.75, 61.24) | 44.97 (38.56, 57.19) | 48.42 (40.58, 59.29) | 53.07 (44.00, 67.25) |
| **Word fluency test** | 2855 | 22.24 ± 5.80 | 23.07 ± 5.84 | 22.35 ± 5.70 | 21.30 ± 5.72 |
| **Word learning test** | | | | | |
| Word learning test (immediate) | 2692 | 7.72 ± 2.14 | 8.21 ± 2.15 | 7.72 ± 2.06 | 7.22 ± 2.09 |
| Word learning test (delayed) | 2680 | 7.10 ± 3.13 | 7.86 ± 3.14 | 7.14 ± 3.03 | 6.29 ± 3.02 |
| *Word learning test (recognition) | 2668 | 14.00 (13.00, 15.00) | 14.00 (13.00, 15.00) | 14.00 (13.00, 15.00) | 14.00 (12.00, 15.00) |
| **Purdue pegboard tests** | | | | | |
| Purdue pegboard (both hands) | 2605 | 9.46 ± 2.02 | 10.09 ± 1.93 | 9.45 ± 1.92 | 8.80 ± 2.01 |
| Purdue pegboard (right hand) | 2664 | 12.29 ± 2.28 | 12.99 ± 2.14 | 12.36 ± 2.22 | 11.50 ± 2.24 |
| Purdue pegboard (left hand) | 2676 | 11.87 ± 2.22 | 12.48 ± 2.10 | 11.96 ± 2.16 | 11.15 ± 2.20 |
| Purdue pegboard (sum) | 2572 | 33.69 ± 5.77 | 35.61 ± 5.41 | 33.82 ± 5.55 | 31.57 ± 5.65 |
| **Letter-digit substitution test** | 2819 | 28.14 ± 7.01 | 29.78 ± 7.07 | 28.33 ± 6.77 | 26.29 ± 6.74 |
| **G-factor** | 2321 | -0.19 ± 1.01 | 0.10 ± 0.95 | -0.17 ± 0.97 | -0.52 ± 1.01 |
| **SAF, A.U.** | 2890 | 2.40 ± 0.49 | 1.90 ± 0.19 | 2.34 ± 0.12 | 2.94 ± 0.35 |

Values are shown for non-imputed data. Values are counts (valid percentages), means ± standard deviations or *median (interquartile range) in case of a skewed distribution.

**eTable 6.** Skin Autofluorescence and Prevalent All-Cause Dementia in the Total Population

| | **Without dementia (N=2953)** | **History of dementia (N=41)** | | **OR (95% CI)** |
|---|---|---|---|---|
| Age, years | 72.6 (9.3) | 80.9 (6.2) | Model 1[a] | 1.30 [0.96, 1.73] |
| Women, N (%) | 1671 (57) | 21 (51) | Model 2[b] | 1.31 [0.96, 1.78] |
| SAF, A.U. | 2.40 (0.49) | 2.66 (0.49) | Model 3[c] | 1.32 [0.97, 1.79] |

Descriptive values are counts (valid percentages) or means (standard deviations). ORs (95% CIs) were obtained from N=2994 participants with known information on all-cause dementia (yes/ no) and represents the OR for dementia associated with one SD higher SAF.

[a] Model 1: the association was adjusted for age, sex, and diabetes.

[b] Model 2: the association was adjusted for age, sex, diabetes, education, *APOE* ε4 carrier status, smoking status and eGFR.

[c] Model 3: In addition to model 2, the association was further adjusted for potential mediators (systolic and diastolic blood pressure, cholesterol, HDL, triglycerides, lipid lowering medication, and depressive symptoms).

**eTable 7.** Linear Regression Results for Association of Skin Autofluorescence With Cognition Adjusting for Different Sets of Covariates in the Total Study Population

| Outcome | N | Coefficient [95% CI] | | | | |
|---|---|---|---|---|---|---|
| | | Crude | Age + sex[a] | Model 1[b] | Model 2[c] | Model 3[d] |
| G-factor | 2318 | -0.29 [-0.33, -0.25] | -0.11 [-0.14, -0.07] | -0.10 [-0.13, -0.06] | -0.07 [-0.11, -0.04] | -0.07 [-0.10, -0.04] |
| LDST | 2818 | -0.24 [-0.27, -0.2] | -0.10 [-0.13, -0.06] | -0.08 [-0.12, -0.05] | -0.06 [-0.09, -0.03] | -0.06 [-0.09, -0.02] |
| Stroop test (interference) | 2772 | -0.22 [-0.25, -0.18] | -0.08 [-0.11, -0.04] | -0.07 [-0.10, -0.03] | -0.05 [-0.08, -0.01] | -0.04 [-0.08, -0.01] |
| WFT | 2855 | -0.14 [-0.17, -0.1] | -0.05 [-0.09, -0.02] | -0.05 [-0.08, -0.01] | -0.03 [-0.07, 0.01] | -0.03 [-0.07, 0.01] |
| WLT (delayed) | 2680 | -0.22 [-0.26, -0.18] | -0.08 [-0.12, -0.05] | -0.07 [-0.11, -0.04] | -0.06 [-0.10, -0.02] | -0.06 [-0.09, -0.02] |
| PPB (sum) | 2571 | -0.32 [-0.35, -0.28] | -0.12 [-0.15, -0.09] | -0.11 [-0.14, -0.08] | -0.09 [-0.13, -0.06] | -0.09 [-0.12, -0.05] |

Abbreviations: LDST, letter-digit substitution task; WFT, verbal fluency test; WLT, word learning test; PPB (sum), sum score Purdue pegboard tests including tests on left hand, right hand and both hands.

Coefficients and respective 95% CIs were obtained from linear regression models with the z-score of SAF as independent variable, representing adjusted difference in G-factor and z-scores of test parameters associated with one SD difference in SAF.

[a] Age + sex: the association was adjusted for age and sex.
[b] Model 1: the association was adjusted for age, sex and diabetes.
[c] Model 2: the association was adjusted for age, sex, diabetes, education, *APOE* ε4 carrier status, smoking status and eGFR.
[d] Model 3: In addition to model 2, the association was further adjusted for systolic and diastolic blood pressure, cholesterol, HDL, triglycerides, lipid lowering medication, and depressive symptoms.

**eTable 8.** Association of Skin Autofluorescence and Cognition by Rotterdam Study Subcohorts (Model 2)

| **Cognitive function test** | **Coefficient [95% CI]** | | |
|---|---|---|---|
| | **RS I** (N=703) | **RS II** (N=1036) | **RS III** (N=1151) |
| G-factor | -0.12 [-0.19, -0.05] | -0.06 [-0.12, -0.01] | -0.12 [-0.17, -0.07] |
| LDST | -0.08 [-0.14, -0.01] | -0.06 [-0.12, -0.01] | -0.12 [-0.18, -0.06] |
| Stroop test (interference) | -0.08 [-0.14, -0.02] | -0.04 [-0.1, 0.02] | -0.1 [-0.15, -0.04] |
| WFT | -0.08 [-0.15, -0.01] | -0.01 [-0.07, 0.05] | -0.05 [-0.12, 0.01] |
| WLT (delayed) | -0.09 [-0.16, -0.03] | -0.05 [-0.11, 0.01] | -0.09 [-0.15, -0.03] |
| PPB (sum) | -0.08 [-0.14, -0.02] | -0.12 [-0.18, -0.07] | -0.13 [-0.19, -0.08] |

Abbreviations: CI, confidence interval; RS, Rotterdam Study; LDST, letter-digit substitution task; WFT, verbal fluency test; WLT (delayed), word learning test (delayed recall); PPB (sum), sum score Purdue pegboard tests including tests on left hand, right hand and both hands.

N, the number of participants who had accomplished at least one of the tests. The actual sample size of analysis for each cognitive function test may be less than the total population of the subcohort as not every participant underwent the full test battery.

Coefficients [95% CI]s are the difference in G-factor and z-scores of test parameters in association with one SD difference in SAF, obtained from the linear regression model 2, adjusting for age, sex, diabetes, education, APOE ε4 carrier status, smoking status, and eGFR.

**eTable 9.** EN-RAGE and S-RAGE in Association With Dementia Incidence After Excluding Participants With Diabetes, Chronic Kidney Disease, or Both

(A)

| | Diabetics excluded | | | CKD excluded | | | Diabetics and CKD excluded | |
|---|---|---|---|---|---|---|---|---|
| **EN-RAGE tertiles** | **n/N** | **HR* (95% CI)** | | **n/N** | **HR (95% CI)** | | **n/N** | **HR* (95% CI)** |
| Low | 50/265 | 1.00 Reference | | 48/262 | 1.00 Reference | | 38/223 | 1.00 Reference |
| Medium | 47/260 | 1.00 (0.66-1.50) | | 57/271 | 1.21 (0.81-1.79) | | 43/219 | 1.22 (0.78-1.90) |
| High | 24/221 | 0.69 (0.42-1.14) | | 26/229 | 0.64 (0.39-1.06) | | 18/165 | 0.75 (0.42-1.34) |
| Per SD Ln | 121/746 | 0.89 (0.74-1.09) | | 131/762 | 0.88 (0.73-1.07) | | 99/607 | 0.95 (0.77-1.17) |

(B)

| | Diabetics excluded | | | CKD excluded | | | Diabetics and CKD excluded | |
|---|---|---|---|---|---|---|---|---|
| **S-RAGE tertiles** | **n/N** | **HR* (95% CI)** | | **n/N** | **HR (95% CI)** | | **n/N** | **HR* (95% CI)** |
| Low | 39/234 | 1.00 Reference | | 43/264 | 1.00 Reference | | 38/223 | 1.00 Reference |
| Medium | 40/253 | 0.99 (0.62-1.57) | | 46/264 | 1.09 (0.71-1.69) | | 43/219 | 0.97 (0.59-1.60) |
| High | 43/262 | 1.09 (0.69-1.72) | | 43/237 | 1.32 (0.85-2.06) | | 18/165 | 1.08 (0.65-1.79) |
| Per SD Ln | 122/749 | 0.93 (0.76-1.14) | | 132/765 | 0.98 (0.81-1.18) | | 99/607 | 0.91 (0.73-1.15) |

Associations of plasma EN-RAGE (A) and S-RAGE (B) levels with dementia incidence. HRs are presented across tertile groups with the low-level group as reference; and by one standard deviation higher of natural logarithm of EN-RAGE and S-RAGE. All HRs were obtained from Cox regression for dementia incidence, adjusting for age, sex, diabetes, education, *APOE* ε4 carrier status, smoking and eGFR (model 2).

*Diabetes status was not used in the model for adjustment.

**eTable 10.** EN-RAGE and S-RAGE in Association With Prevalent and Incident Alzheimer Disease

(A)

| EN-RAGE tertiles | Cross-sectional | | | Longitudinal | |
|---|---|---|---|---|---|
| | n/N | OR (95% CI) | | n/N | HR (95% CI) |
| Low | 6/324 | 1.00 Reference | | 48/314 | 1.00 Reference |
| Medium | 14/337 | 2.02 (0.68-6.00) | | 54/320 | 1.18 (0.79-1.76) |
| High | 36/356 | 3.61 (1.33-9.78) | | 27/308 | 0.67 (0.41-1.09) |
| | | | | | |
| Per SD Ln | 56/1017 | 1.54 (1.10-2.16) | | 129/942 | 0.90 (0.75-1.08) |

(B)

| S-RAGE tertiles | Cross-sectional | | | Longitudinal | |
|---|---|---|---|---|---|
| | n/N | OR (95% CI) | | n/N | HR (95% CI) |
| Low | 25/346 | 1.00 Reference | | 41/309 | 1.00 Reference |
| Medium | 18/341 | 0.80 (0.37-1.75) | | 43/321 | 1.01 (0.65-1.59) |
| High | 14/333 | 0.50 (0.21-1.15) | | 46/315 | 1.22 (0.78-1.89) |
| | | | | | |
| Per SD Ln | 57/1020 | 0.72 (0.52-1.00) | | 130/945 | 0.99 (0.82-1.20) |

Associations of plasma EN-RAGE (A) and S-RAGE (B) levels with Alzheimer's disease (AD). Results were obtained from logistic models for prevalent AD and from Cox regression for incident AD. The group with the lowest plasma levels was used as a reference. All ORs and HRs were adjusted using model 2, including age, sex, diabetes, education, *APOE* ε4 carrier status, smoking and eGFR.