**Supporting Information**

**Table A**. ***AGER* SNP identifiers**

| **1000G SNPID** | **dbSNP (GRCh37.p10)** |
| --- | --- |
| rs146434120 | rs146434120 |
| chr6:32148909:D | NA |
| rs191750543 | rs191750543 |
| rs181811810 | rs181811810 |
| rs143357175 | rs143357175 |
| rs115535092 | rs2071288 |
| rs114564020 | rs114564020 |
| rs148720361 | rs3134941 |
| rs115168643 | rs2853807 |
| rs147062909 | rs55640627 |
| rs116515025 | rs9391855 |
| rs115963005 | rs3134940 |
| rs116334026 | rs204996 |
| rs115696666 | rs77170610 |
| rs186754929 | rs186754929 |
| chr6:32150272:I | NA |
| rs116217240 | rs184003 |
| rs114971929 | rs17846798 |
| rs189984228 | rs17846810 |
| rs182584636 | rs17846809 |
| rs142232164 | rs142232164 |
| rs1035798 | rs1035798 |
| rs146383902 | rs2269422 |
| rs114062306 | rs35795092 |
| rs114177847 | rs2070600 |
| rs116828224 | rs80096349 |
| rs115111668 | rs115111668 |
| rs115914022 | rs3131300 |
| rs115663512 | rs1800684 |

**Table B. Power calculations for analyses of *AGER* SNPs and clinical outcomes[[1]](#endnote-1),[[2]](#endnote-2)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Type 1 error** | **N** | **Events** | **Proportion of variance in ln(sRAGE) explained by SNP** | **OR[[3]](#endnote-3)** | **Power[[4]](#endnote-4)** |
| **Whites (rs2070600)** |  |  |  |  |  |  |
| All-cause death | 0.05 | 9017 | 2439 | 0.22 | 0.52 | 1 |
| CHD | 0.05 | 8562 | 921 | 0.22 | 0.79 | 0.83 |
| Heart Failure | 0.05 | 8502 | 1213 | 0.22 | 0.61 | 1 |
| Diabetes mellitus | 0.05 | 8130 | 2017 | 0.22 | 0.57 | 1 |
| CKD | 0.05 | 8380 | 1048 | 0.22 | 1.07 | 0.17 |
| **Blacks (rs2071288)** |  |  |  |  |  |  |
| All-cause death | 0.05 | 2871 | 995 | 0.26 | 0.52 | 1 |
| CHD | 0.05 | 2754 | 377 | 0.26 | 0.79 | 0.52 |
| Heart Failure | 0.05 | 2635 | 529 | 0.26 | 0.61 | 0.99 |
| Diabetes mellitus | 0.05 | 2293 | 867 | 0.26 | 0.57 | 1 |
| CKD | 0.05 | 2476 | 447 | 0.26 | 1.07 | 0.1 |

**Table C. Bivariate associations with sRAGE levels (N =2329)[[5]](#endnote-5)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Beta for ln(sRAGE) | 95% CI | P value |
| Age, years | -0.001 | (-0.004, 0.002) | 0.51 |
| Male | -0.15 | (-0.18, -0.11) | <0.0001 |
| White race | 0.48 | (0.37, 0.59) | <0.0001 |
| Education |  |  |  |
| ≤11 years | ref | - | - |
| High school or college | 0.08 | (-0.04, 0.05) | 0.73 |
| More than college | 0.03 | (-0.01, 0.08) | 0.17 |
| BMI | -0.01 | (-0.02, -0.01) | <0.0001 |
| Prevalent CHD | -0.05 | (-0.13, 0.03) | 0.26 |
| Prevalent diabetes |  |  |  |
| eGFR, mg/min/1.73m2 | -0.03 | (-0.004, -0.002) | <0.0001 |
| Fasting glucose, mmol/l | -0.01 | (-0.03, 0.01) | 0.18 |

**Table D**. **Additional genome-wide significant loci and corresponding trans-ethnic results for sRAGE levels in whites and blacks**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP[[6]](#endnote-6)** | **Gene** | **Chr:base pair position** | **Whites** |  |  |  |  |  | **Blacks** |  |  |  |  |
|  |  |  | A1[[7]](#endnote-7)/A2 | A1 frequency | β[[8]](#endnote-8) | *P* | D’[[9]](#endnote-9) | r2d | A1 frequency | β | *P* | D’[[10]](#endnote-10) | r2e |
| **rs2070600** | *AGER* | 6:32151443 | T/C | 0.04 | -0.67 | 7.26E-16 | 0.92 | 0.84 | 0.01 | -0.63 | 1.79E-02 | 1.0 | 0.001 |
| [**rs41268928**](http://browser.1000genomes.org/Homo_sapiens/Variation/Summary?source=dbSNP;v=rs41268928) | *RNF5* | 6:32147157 | C/G | 0.04 | -0.69 | 3.46E-16 | 1 | 0.92 | 0.02 | -0.37 | 1.25E-01 | 1 | 0.001 |
| [**rs9391855**](http://browser.1000genomes.org/Homo_sapiens/Variation/Summary?source=dbSNP;v=rs9391855) | *AGER* | 6:32149801 | T/C | 0.04 | -0.67 | 5.06E-16 | 0.92 | 0.84 | 0.02 | -0.40 | 8.18E-02 | 1 | 0.001 |
| **rs2071288** | *AGER* | 6:32149260 | T/C | 0.005 | -0.43 | 1.00E-01 | 1.0 | 0.0 | 0.10 | -0.56 | 2.22E-08 | NA | NA |
| [**rs17846798**](http://browser.1000genomes.org/Homo_sapiens/Variation/Summary?source=dbSNP;v=rs17846798) | *AGER* | 6:32150498 | A/G | 0.005 | -0.43 | 1.01E-04 | 1 | 0 | 0.10 | -0.56 | 2.46E-08 | 1 | 1 |
| [**rs57409105**](http://browser.1000genomes.org/Homo_sapiens/Variation/Summary?source=dbSNP;v=rs57409105) | *RNF5* | 6:32147478 | T/G | 0.005 | -0.43 | 1.04E-01 | 1 | 0 | 0.10 | -0.56 | 2.60E-08 | 1 | 0.001 |

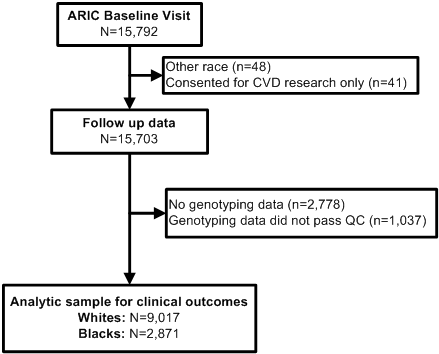
**Table E**. **Characteristics of participants with sRAGE levels and participants included in analyses of clinical outcomes[[11]](#endnote-11),[[12]](#endnote-12)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | sRAGE sample | Genetic association sample[[13]](#endnote-13) | P value |
| N | 2321 | 9590 |  |
| sRAGE, pg/ml | 983 (736.05,1279.81) | NA |  |
| Age, years | 57.06 (5.75) | 56.97 (5.70) | 0.48 |
| Male | 968 (42) | 4332 (45) | 0.002 |
| Education |  |  | 0.23 |
| ≤11 years | 475 (20) | 2056 (22) |  |
| High school graduate | 945 (41) | 3956 (41) |  |
| Attended college | 899 (39) | 3524 (37) |  |
| BMI | 28.5 (5.7) | 27.8 (5.3) | <0.001 |
| Prevalent CHD | 99 (4.3) | 545 (6.2) | 0.001 |
| eGFR | 79.3 (16.8) | 81.0 (17.8) | <0.001 |
| Fasting glucose | 5.89 (0.99) | 6.31 (2.28) | <0.001 |

**Figure A. Selection of sample for sRAGE analyses**



**Figure B. Selection of sample for genetic association analyses**



1. Type I error rate=0.05 for all calculations [↑](#endnote-ref-1)
2. Abbreviations: sRAGE, soluble receptor for advanced glycation end products; SNP, single nucleotide polymorphism; HR, hazard ratio [↑](#endnote-ref-2)
3. Odds ratio for ln(sRAGE) and outcome estimated using multivariate logistic regression with adjustment for age, sex, site (software: R). [↑](#endnote-ref-3)
4. Power calculated using Web tool (<http://glimmer.rstudio.com/kn3in/mRnd/>; Accessed 01/17/15) cited in Brion MJ, Shakhbazov K, Visscher PM: Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol* 2013;42:1497-1501. [↑](#endnote-ref-4)
5. Abbreviations: sRAGE, soluble receptor for advanced glycation end-products; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate [↑](#endnote-ref-5)
6. From dbSNP build 37 [↑](#endnote-ref-6)
7. A1 is the minor allele in whites [↑](#endnote-ref-7)
8. Mean change in ln(sRAGE) for Allele 1 vs. Allele 2 [↑](#endnote-ref-8)
9. With rs2854050 (index SNP from GWAS in whites) [↑](#endnote-ref-9)
10. With rs2071288 (index SNP from GWAS in blacks) [↑](#endnote-ref-10)
11. Continuous variables reported as means (SD) and categorical variables as n (%). Median (p25, p75) provided for sRAGE. [↑](#endnote-ref-11)
12. Abbreviations: sRAGE, soluble receptor for advanced glycation end-products; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate [↑](#endnote-ref-12)
13. Subjects with sRAGE levels excluded [↑](#endnote-ref-13)