Supplemental Materials Text File

Supplemental Table I. *Association of instrumental variable SNPs with sRAGE levels in the Framingham Heart Study and the INTERVAL study*

Abbreviations: EAF = Effect Allele Frequency; GWAS = Genome Wide Association Study; SE = Standard Error; SNP = Single Nucleotide Polymorphism

In the Framingham Heart Study (FHS), genome-wide genotyping was conducted using the Affymetrix 500K mapping arrays, 50 K supplemental Human Gene Focused arrays (Affymetrix, Inc. Santa Clara, CA), and the Illumina Human Exome BeadChip v.1.0 (Exome Chip; Illumina, Inc., San Diego, CA). Genotypes from Affymetrix arrays were imputed using the 1000 Genomes reference panel build 37 phase 1 v3. SNPs with imputation quality ratio $r^2 < 0.5$ were excluded. For INTERVAL, the Affymetrix Axiom UK Biobank Array (Affymetrix, Inc., Santa Clara, CA) was imputed to a combined 1000 Genomes/UK10K reference panel. For additional methodological details, please refer to Yao et al.[18]

For imputed genotypes, an additive genetic model with a population mean = 0 and standard deviation (SD) = 1 for all rank-normalized protein levels was used. Beta (i.e., estimated effect size) for the pQTL GWAS in FHS and INTERVAL is the number of SD change in rank-normalized protein value per effect allele increase.

* Based on GWAS of protein level in 6,861 FHS participants as outlined in Yao et al.[18]
** Based on replication cohort GWAS of protein level in 3,301 INTERVAL participants as summarized by Yao et al.[18]

Supplemental Table II. *sRAGE levels in 6,861 Framingham Heart Study participants by rs2070600 variant genotype*

Abbreviations: SD = Standard Deviation; sRAGE = Soluble Receptor for Advanced Glycation End-Products

Plasma sRAGE levels by rs2070600 genotype in 6,861 Framingham Heart Study (FHS) participants; genotype data for this variant were obtained using the Illumina Human Exome BeadChip (Exome Chip; Illumina, Inc., San Diego, CA).

Supplemental Table III. *Association of sRAGE cis-pQTL variants with self-reported and doctor-diagnosed asthma in UK Biobank GWAS*

Abbreviations: OR = Odds Ratio; SNP = Single Nucleotide Polymorphism; 95% CI = 95% Confidence Interval

UK Biobank GWAS of self-reported asthma included 53,598 cases and 409,335 controls while doctor diagnosed asthma included 14,283 cases and 98,300 controls. OR values for the two asthma UK Biobank GWAS is in the odds ratio of asthma per risk allele.

Supplemental Table IV. *Medication usage in 375 asthmatic Framingham Heart Study participants based on self-reported data*

In the Framingham Heart Study (FHS), Offspring cohort, Exam 7, asthma medication was gauged through "yes" or "no" questions. The table above contains data for those who answered "yes" to at least one of the following questions:

- G074: Taking bronchodilators and aerosols as interim medications
- G672: Are you currently taking any medicines (inhalers, aerosols, or tablets) for asthma?
- G682: Are you currently taking any inhaled steroid medications?

The first category ("inhaled corticosteroids only") includes participants who answered affirmatively to exclusive G682 *and* those who answered affirmatively to both G682 and G672. The second category ("bronchodilator/beta-agonist only") includes participants who answered affirmatively to exclusively G074 and those who answered affirmatively to both G074 and G672. The third category ("both inhaled corticosteroid and bronchodilator/beta-agonist") includes participants who answered affirmatively to both G682 and G074 and those who answered affirmatively to all three questions. Those who answered affirmatively to exclusive G672 fell into the last ("Other medications") category.

In Third Generation cohort, Exam 1, medication use was recorded using the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) classification system in 195 participants who matched our original definition of asthma. The table includes data from participants taking selective beta-2-adrenoreceptor agonists (R03AC) and inhaled glucocorticoids (R03BA).

Supplemental Table V. *Spirometry test features according to asthma status*

Abbreviations: FEV1 = Forced Expiratory Volume in 1 Second; FVC = Forced Vital Capacity

Spirometry data were available in 315 out of 375 (84%) asthma cases and 5,381 out 6,171 (87%) non-asthmatic controls in the Framingham Heart Study (FHS). Values for FEV1, FVC, and FEV1/FVC ratio were collected in participants attending FHS Offspring cohort (Exam 7, 1998-2001) and Third Generation cohort (Exam 1, 2002-2005). Percent predicted values for FEV1 and FVC are based on prediction equations from Hankinson et al.[14]

Supplemental Table VI. *IgE levels according to asthma status*

Abbreviations: IgE = Immunoglobulin E; SD = Standard Deviation

Serum total IgE levels were measured in the Framingham Heart Study (FHS) Offspring (Exam 7, 1998-2001) and Third Generation (Exam 1, 2002-2005) cohort participants using plasma EDTA samples. Total IgE measurements were performed using the Phadia ImmunoCAP 100 system (Phadia, Uppsala, Sweden) in which an anti-IgE antibody is bound to a solid-phase carrier followed by fluoroenzyme-based quantitative measurement of total IgE. The lower limit of detection for IgE is 4.00 kU/L while upper limits were set to 10,000 kU/L.

Supplemental Table VII. *Association of inhaled corticosteroid use with plasma sRAGE level in Framingham Heart Study participants*

Abbreviations: SE = Standard Error; sRAGE = Soluble Receptor for Advanced Glycation End-Products

A total of 200 Framingham Heart Study (FHS) participants with asthma reported uses of inhaled corticosteroid medication, and the remaining 175 participants with asthma did not used inhaled corticosteroids (***Supplemental Table IV***). After adjusting for age and sex, there was no significant statistical association (p=0.368) of inhaled corticosteroid use with sRAGE levels.

Supplemental Table VIII. *Heterogeneity sensitivity results for multi-SNP Mendelian randomization in UK Biobank GWAS*

Heterogeneity tests are used in Mendelian randomization (MR) to statistically assess the compatibility of instrumental variable estimates based on individual genetic variants (i.e., if these genetic variants furnish similar estimates of causal effect if they are valid instrumental variables). There is significant heterogeneity ($p<0.05$) amongst the instrumental variables used in MR.

Supplemental Table IX. *Single SNP Mendelian randomization results based on GWAS of self-reported and doctor-diagnosed asthma in the UK Biobank*

Abbreviations: OR = Odds Ratio; SNP = Single Nucleotide Polymorphism; sRAGE = Soluble Receptor for Advanced Glycation End-Products; 95% CI = 95% Confidence Interval

Results are based on two-sample Mendelian randomization (MR) analysis of sRAGE in relation to asthma using UK Biobank GWAS of self-reported (53,598 cases, 409,335 controls) and doctor diagnosed asthma (14,283 cases, 98,300 controls). See Methods for details. Results are reported in odds ratios (OR) of asthma per 1 standard error (SE) increment in inverse-rank normalized sRAGE levels.

Supplemental Table X. *Horizontal pleiotropy sensitivity results for multi-SNP Mendelian randomization with UK Biobank GWAS*

Abbreviations: SE = Standard Error; sRAGE = Soluble Receptor for Advanced Glycation End-Products

A fundamental assumption of Mendelian randomization (MR) is that there is no horizontal pleiotropy which requires that instrumental variables used for analyses acts on the target outcome, exclusively, through the exposure of interest; this pleiotropy occurs when the variant affects other traits outside of the exposure of interest and has an impact on the target outcome. Horizontal pleiotropy also can occur when the instrumental variable directly affects the outcome. If present, horizontal pleiotropy can led to inaccurate causal estimates, loss of statistical power, and false positive causal associations. No horizontal pleiotropy occurs in the case of self-reported nor doctor-diagnosed asthma in our MR study ($p>0.05$).

Supplemental Table XI. *Replication Mendelian randomization analyses with INTERVAL sRAGE pQTL (rs2070600)*

Abbreviations: OR = Odds Ratio; SNP = Single Nucleotide Polymorphism; sRAGE = Soluble Receptor for Advanced Glycation End-Products; 95% CI = 95% Confidence Interval

INTERVAL sRAGE protein quantitative trait loci (pQTL) was derived from a separate GWAS of 3,301 INTERVAL participants as outlined in Yao et al.[18] Results are based on two-sample Mendelian randomization (MR) analysis of sRAGE in relation to asthma using UK Biobank GWAS of self-reported (53,598 cases, 409,335 controls) and doctor diagnosed asthma (14,283 cases, 98,300 controls). See Methods for details. Results are reported in odds ratios (OR) of asthma per 1 standard error (SE) increment in inverse-rank normalized sRAGE levels.

Supplemental Table XII. *Colocalization results in relation to UK Biobank GWAS*

Abbreviations: PPH4 = Posterior Probability of Hypothesis 4; SNP = Single Nucleotide Polymorphism

PPH4 equal or greater than 0.8 was considered the threshold for significant colocalization.

SNP				Association of SNP with protein level in FHS GWAS*				Association of SNP with protein level in INTERVAL GWAS**			
Chr:Position	**rsID**	**Effect allele**	**Other allele**	**Beta**	**SE**	**EAF**	**p**	**Beta**	**SE**	**EAF**	**p**
6:32151443	rs2070600	T	C	-0.712	0.046	0.043	5.31E-55	-0.570	0.050	0.067	3.90E-33
6:32428186	rs6923504	G	C	0.112	0.020	0.335	1.71E-08	N/A			
6:31341693	rs9266529	A	G	0.126	0.022	0.506	1.82E-08				

		Plasma sRAGE levels (pg/ml)						
rs2070600	**N**	**Mean**	**SD**	**Minimum**	**25th**	**Median**	**75th**	**Maximum**
C/C	6,260	3633.920	1164	269	2810	3500	4310	12600
C/T	558	2894.400	948	615	2230	2810	3390	6380
T/T	13	1661.540	432	850	1450	1610	2000	2470

SNP				Association of SNP with self-reported asthma (UK Biobank)			Association of SNP with doctor-diagnosed asthma (UK Biobank)		
Chr:Position	**rsID**	**Effect allele**	**Other allele**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
6:32151443	rs2070600	T	C	1.015	(1.012, 1.018)	1.20E-28	1.016	(1.010, 1.022)	6.70E-08
6:32428186	rs6923504	G	C	0.995	(0.994, 0.997)	5.50E-11	0.995	(0.992, 0.998)	0.0032
6:31341693	rs9266529	A	G	0.992	(0.991, 0.993)	1.50E-31	0.991	(0.988, 0.993)	1.60E-10

Medication use	**Participants with asthma** (n=375)
Inhaled corticosteroid only	35
Bronchodilator/beta-agonist only	146
Both inhaled corticosteroid and bronchodilator/beta-agonist	165
Other asthma medications but not inhaled corticosteroid or bronchodilator/beta-agonist	29

	Asthma Cases (n=315)	**Non-Cases** (n=5,381)
	n (%)	n (%)
Percent Predicted FEV1	--	--
≥ 100%	63 (20%)	2336 (43%)
80-99%	141 (45%)	2508 (47%)
< 80%	111 (35%)	537 (10%)
Percent Predicted FVC	--	--
≥ 100%	126 (40%)	2890 (54%)
80-99%	140 (44%)	2220 (41%)
< 80%	49 (15%)	271 (5%)
Ratio of FEV1/FVC	--	--
≥ 1.0	0 (0%)	0 (0%)
0.8-0.99	55 (17%)	1626 (30%)
0.70-0.79	124 (39%)	2872 (53%)
<0.7	136 (43%)	883 (16%)

	Asthma Cases (n=366)	**Non-Cases** (n=6,022)
IgE level, kU/L (Mean ± SD)	213 ± 378	86 ± 260

Variable	**Participants with asthma** (n=375)	**Mean sRAGE** (pg/ml)	**SE**	**p**
Inhaled corticosteroid use	200	3323.05	79.59	0.37
No inhaled corticosteroid use	175	3424.93	83.49	

	Method	Q	Degrees of freedom	p
Self-reported asthma	Inverse variance weighted	60.73	2	6.51E-14
Doctor-diagnosed asthma		18.72	2	8.61E-05

Exposure	Outcome	SNP	OR (95% CI)	p
sRAGE	Self-reported asthma	rs2070600	0.979 (0.975, 0.983)	1.24E-28
		rs6923504	0.958 (0.945, 0.970)	5.50E-11
		rs9266529	0.939 (0.929, 0.949)	1.54E-31
	Doctor-diagnosed asthma	rs2070600	0.978 (0.970, 0.986)	6.65E-08
		rs6923504	0.960 (0.934, 0.986)	0.003
		rs9266529	0.929 (0.908, 0.950)	1.56E-10

Exposure	Outcome	Egger intercept ± SE	p
sRAGE	Self-reported asthma	-0.005 ± 0.002	0.24
	Doctor-diagnosed asthma	-0.005 ± 0.003	0.32

Exposure	Outcome	# of SNP	OR (95% CI)	p
sRAGE	Self-reported asthma	1	0.974 (0.969, 0.978)	1.24E-28
	Doctor-diagnosed asthma		0.973 (0.963, 0.983)	6.65E-08

	Trait	# of SNPs	PPH4
Cis-SNPs Chromosome 6	Self-reported asthma	9,239	1.89E-17
	Doctor-diagnosed asthma	9,227	5.69E-20