Supplemental Materials for "Genetic association of long-chain acyl-CoA synthetase 1 variants with fasting glucose, diabetes and subclinical atherosclerosis"

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Characteristics of the MESA participants

The genetic association analyses in MESA included 2,467 Caucasians, 2,559 African Americans, 2,114 Hispanics and 707 Chinese, evenly distributed between males and females. The median age of participants in each ethnic group ranged from 60-63 years. Caucasians had lower diabetes prevalence at baseline (6.2%) than Chinese (13.9%; *P*=$1.2\text{x}10^{-10}$), African American (17.4%; *P*=$5.9\text{x}10^{-32}$) and Hispanic (18.7%; *P*=$2.2\text{x}10^{-35}$) participants (Table S1). Chinese participants had lower BMI than Caucasian (median 27, *P*=$2.8\ \text{x}10^{-73}$), African American (29, *P*=$3.4\ \text{x}10^{-142}$), and Hispanic (29, *P*=$1.5\ \text{x}10^{-129}$) participants.

Fasting glucose was lower in Caucasian participants (median 87) than Chinese (92, *P*=$1.2\text{x}10^{-14}$), African American (92, *P*=$6.4\text{x}10^{-30}$) and Hispanic (93, *P*=$6.9\text{x}10^{-46}$) participants. Fasting insulin was lower in Caucasian participants (median 7.5) than African American (8.8, *P*=$1.2\text{x}10^{-4}$) and Hispanic (9.5, *P*=$4.2\text{x}10^{-14}$) participants, and was lower in Chinese (7.7) than Hispanic (9.5, *P*=$1.1\text{x}10^{-3}$) participants (Table S1).

Traits associated with subclinical atherosclerosis also exhibited ethnic differences, with cIMT lower in Hispanic (median 0.81 mm) and Chinese (median 0.81 mm) participants than African American (median 0.86 mm) and Caucasian participants (median 0.85 mm) (grouped comparison *P*=$4.4\text{x}10^{-18}$). Similarly, iIMT was lower in Chinese (median 0.73 mm) and Hispanic (median 0.84 mm) participants compared to African American (median 0.91 mm) and Caucasian (median 0.89 mm) participants (grouped comparison *P*=$3.7\text{x}10^{-25}$). The prevalence of CAC in Caucasian participants (57.3%) was higher than in Chinese (51.2%; *P*=$3.9\text{x}10^{-3}$), Hispanics (46.4%; *P*=$1.9\text{x}10^{-13}$) and African American (43.5%; *P*=$2.8\text{x}10^{-22}$) participants. In those with prevalent CAC, the median of Agatston scores ranged from 67-78 units in Chinese, African American and Hispanic participants, while CAC was notably higher (112 units) in Caucasian participants (Table S2; grouped comparison *P*=$3.3\text{x}10^{-6}$). Compared to those without diabetes, MESA participants with diabetes showed increased prevalence of CAC (*P*=$6.4\text{x}10^{-20}$ in pooled analysis across race/ethnic groups) and consistently higher values of cIMT (*P*=$4.1\text{x}10^{-33}$) and iIMT (*P*=$2.8\text{x}10^{-23}$) compared to those without diabetes. These relationships held true comparing participants with and without diabetes for each of the four race/ethnic groups (Table S2).

Table S1: Characteristics of MESA participants across four race/ethnic groups

Participant characteristics*	**Caucasian**	**African American**	**Hispanic**	**Chinese**
No. subjects	2467	2559	2114	707
Women	1188 (48.2)	1121 (43.8)	974 (46.1)	354 (50.1)
Age, years	63 [54, 71]	60 [53, 68]	60 [53, 68]	63 [54, 71]
Diabetes at baseline (yes/no)	153 (6.2)	442 (17.4)	394 (18.7)	97 (13.9)
Diabetes at exam 4 (yes/no)	204 (10.0)	445 (20.2)	398 (22.2)	98 (17.4)
BMI	27 [24, 30]	29 [26, 34]	29 [26, 32]	24 [22, 26]
Hypertension (yes/no)	948 (38.4)	1536 (60.0)	878 (41.5)	268 (37.9)
Ever-Smoke (yes/no)	1371 (55.7)	1348 (53.0)	967 (45.8)	177 (25.1)
Current-Smoke (yes/no)	276 (11.5)	492 (19.4)	288 (13.8)	39 (5.5)
Subclinical atherosclerosis				
Common IMT, mm	0.85 [0.73, 0.97]	0.86 [0.75, 0.99]	0.81 [0.72, 0.93]	0.81 [0.71, 0.92]
Internal IMT, mm	0.89 [0.72, 1.38]	0.91 [0.70, 1.30]	0.84 [0.68, 1.19]	0.73 [0.60, 0.94]
CAC present / absent	1414 (57.3)	1103 (43.5)	974 (46.4)	362 (51.2)
Agatston score, units	112 [24, 368]	71 [18, 268]	78 [19, 287]	67 [22, 200]
Fasting glucose	87 [81, 95]	92 [84, 102]	93 [85, 105]	92 [85, 101]
Fasting insulin	7.5 [5.5,10.9]	8.8 [6.0, 12.6]	9.5 [6.5, 14.0]	7.7 [6.0, 10.8]

** Data are presented as N (%) for binary measures or median [IQR] for continuous measure. Sample sizes are reported for the subset of individuals with data available for at least one of the phenotypes of interest.*

Table S2: Summary of measures of subclinical atherosclerosis traits, stratified by diabetes status in MESA participants across four race/ethnic groups.

Group	**Subclinical atherosclerosis trait**	**Caucasian**	**African American**	**Hispanic**	**Chinese**
No diabetes	No. subjects	2315	2115	1720	609
	Common IMT, mm	0.84 [0.73, 0.97]	0.85 [0.75, 0.97]	0.80 [0.70, 0.92]	0.80 [0.70, 0.91]
	Internal IMT, mm	0.89 [0.71, 1.36]	0.88 [0.69, 1.25]	0.82 [0.67, 1.12]	0.73 [0.59, 0.90]
	CAC present / absent	1293 (55.9)	851 (40.8)	734 (43.0)	294 (48.4)
	Agatston score, units	109 [24, 364]	61 [15, 229]	68 [18, 232]	60 [17, 152]
Diabetes	No. subjects	153	442	394	97
	Common IMT, mm	0.95 [0.83, 1.06]	0.92 [0.80, 1.06]	0.87 [0.76, 1.02]	0.87 [0.79, 1.00]
	Internal IMT, mm	1.12 [0.78, 1.60]	1.03 [0.76, 1.62]	0.99 [0.73, 1.52]	0.80 [0.63, 1.51]
	CAC present / absent	120 (78.9)	246 (57.1)	237 (60.5)	67 (68.4)
	Agatston score, units	128 [35, 491]	112 [26, 440]	133 [29, 558]	145 [51, 476]

Data are presented N (%) for binary measures or median [IQR] for continuous measure Sample sizes are reported for the subset of individuals with data available for at least one of the selected subclinical atherosclerosis phenotypes.

Table S3: Results for association of fasting glucose with *ACSL1* SNP rs4862423 in analyses stratified by diabetes status in MESA. Results are shown for rs4862423 effect allele T (vs. other allele C).

		No diabetes				**Diabetes**				**All**			
Group	**Effect allele freq.**	**N**	**Beta**	**SE**	***P*-value**	**N**	**Beta**	**SE**	***P*-value**	**N**	**Beta**	**SE**	***P*-value**
Caucasian	0.407	2309	0.005	0.003	0.120	123	-0.012	0.032	0.718	2432	0.005	0.004	0.227
African American	0.268	2103	0.009	0.004	0.033	393	-0.003	0.026	0.922	2496	0.005	0.007	0.458
Hispanic	0.0502	1717	0.001	0.004	0.774	361	0.033	0.025	0.180	2078	0.013	0.008	0.109
Chinese	0.661	608	-0.002	0.006	0.719	87	-0.040	0.033	0.224	695	-0.007	0.009	0.462
Meta-analysis			0.004	0.002	0.037		-0.000	0.014	0.979		0.005	0.003	0.110

Results are shown for genetic association analysis with covariate adjustment for BMI in addition to the basic model (age, sex, study site and principal components of ancestry), since BMI was included in the model used by the MAGIC consortium effort in which this SNP was identified.

Table S4: Results for association of glucose with *ACSL1* SNP rs7681334 in analyses stratified by diabetes status in MESA. Results are shown for rs7681334 effect allele A (vs. other allele G).

		No diabetes				**Diabetes**				**All**			
Group	**Effect allele freq.**	**N**	**Beta**	**SE**	***P*-value**	**N**	**Beta**	**SE**	***P*-value**	**N**	**Beta**	**SE**	***P*-value**
Caucasian	0.497	2309	0.000	0.003	0.998	123	-0.025	0.027	0.343	2432	-0.001	0.004	0.774
African American	0.450	2103	0.004	0.003	0.200	393	-0.009	0.021	0.685	2496	-0.001	0.006	0.829
Hispanic	0.647	1717	0.005	0.004	0.231	361	0.044	0.025	0.084	2078	0.014	0.008	0.072
Chinese	0.944	608	0.003	0.012	0.773	87	0.000	0.075	0.996	695	0.012	0.017	0.496
Meta-analysis			0.003	0.002	0.177		-0.002	0.014	0.860		0.001	0.003	0.677

Table S5: Results for association of diabetes status at follow-up exam 4 with *ACSL1* SNP rs735949 in MESA. Results are shown for rs735959 effect allele T (vs. other allele C).

Group	**Effect allele freq.**	**N**	**Beta**	**SE**	***P*-value**
Caucasian	0.853	2033	0.269	0.161	0.094
African American	0.948	2203	-0.343	0.163	0.035
Hispanic	0.909	1795	-0.034	0.142	0.812
Chinese	0.9993	-	-	-	-
Meta-analysis			-0.033	0.089	0.716

Table S6: Results for association of Agatston Calcium Score with *ACSL1* SNP rs7681334 in analyses stratified by diabetes status in MESA. Results are shown for rs7681334 effect allele A (vs. other allele G).

		No diabetes				**Diabetes**				**All**			
Group	**Effect allele freq.**	**N**	**Beta**	**SE**	***P*-value**	**N**	**Beta**	**SE**	***P*-value**	**N**	**Beta**	**SE**	***P*-value**
Caucasian	0.497	1293	-0.130	0.068	0.055	120	-0.075	0.227	0.742	1414	-0.126	0.065	0.052
African American	0.450	851	-0.263	0.088	0.003	246	0.121	0.173	0.484	1103	-0.167	0.079	0.036
Hispanic	0.647	734	-0.117	0.095	0.220	237	-0.041	0.223	0.853	974	-0.107	0.089	0.229
Chinese	0.944	294	0.041	0.249	0.869	67	0.378	0.581	0.518	362	0.087	0.234	0.710
Meta-analysis			-0.157	0.046	0.001		0.038	0.115	0.741		-0.126	0.043	0.003

Table S7: Results for association of Agatston Calcium Score with *ACSL1* SNP rs4862423 in analyses stratified by diabetes status in MESA. Results are shown for rs4862423 effect allele T (vs. other allele C).

		No diabetes				**Diabetes**				**All**			
Group	**Effect allele freq.**	**N**	**Beta**	**SE**	***P*-value**	**N**	**Beta**	**SE**	***P*-value**	**N**	**Beta**	**SE**	***P*-value**
Caucasian	0.408	1293	-0.150	0.073	0.041	120	0.238	0.276	0.391	1414	-0.124	0.070	0.077
African American	0.268	851	-0.281	0.103	0.006	246	-0.023	0.203	0.909	1103	-0.220	0.093	0.018
Hispanic	0.502	734	-0.168	0.098	0.087	237	0.013	0.210	0.952	974	-0.120	0.090	0.182
Chinese	0.659	294	0.115	0.137	0.401	67	0.409	0.295	0.171	362	0.182	0.127	0.151
Meta-analysis			-0.150	0.048	0.002		0.105	0.118	0.372		-0.108	0.045	0.016

Table S8: Results for association of coronary heart disease with *ACSL1* SNPs in the CARDIoGRAMplusC4D Consortium.

			CHD				
			CARDIoGRAMplusC4D consortium				
SNP ID	**Effect Allele**	**Non-effect Allele**	**Beta**	**se**	***P*-value**	**N case**	**N ctrl**
rs7681334	G	A	-0.003	0.009	7.50E-01	63,746	130,681
rs735949	T	C	0.003	0.013	8.31E-01		
rs4862423	T	C	0.033	0.021	1.11E-01	8,670	47,159

Table S9: Expression quantitative trait locus (eQTL) analysis using MuTHER

				In Fat			In LCL			In Skin		
PROBE	**Gene**	**SNP**	**EA**	**Beta**	**se**	***P*-value**	**Beta**	**se**	***P*-value**	**Beta**	**se**	***P*-value**
ILMN_1684585	*ACSL1*	rs7681334	G	0.027	0.036	0.447	-0.010	0.019	0.594	0.008	0.028	0.761
ILMN_1684585	*ACSL1*	rs735949	T	0.082	0.054	0.131	0.017	0.028	0.561	0.083	0.043	0.054
ILMN_1684585	*ACSL1*	rs4862423	T	-0.035	0.037	0.351	0.007	0.020	0.734	0.012	0.029	0.684

Primary SNP	**Most significant SNP per probe**					
	In Fat					
	SNP	**EA**	**Beta**	**se**	***P*-value**	**r-sq**
rs7681334	rs11734447	T	0.172	0.059	0.004	0.06
rs735949	rs11734447	T	0.172	0.059	0.004	0.063
rs4862423	rs11734447	T	0.172	0.059	0.004	0.027
Primary SNP	**Most significant SNP per probe**					
	In LCL					
	SNP	**EA**	**Beta**	**se**	***P*-value**	**r-sq**
rs7681334	rs11734447	T	0.060	0.031	0.055	0.06
rs735949	rs11734447	T	0.060	0.031	0.055	0.063
rs4862423	rs11734447	T	0.060	0.031	0.055	0.027
Primary SNP	**Most significant SNP per probe**					
	In Skin					
	SNP	**EA**	**Beta**	**se**	***P*-value**	**r-sq**
rs7681334	rs745805	T	-0.122	0.038	0.001	0.089
rs735949	rs745805	T	-0.122	0.038	0.001	0.832
rs4862423	rs745805	T	-0.122	0.038	0.001	0.123

The r-sq measures the LD between the primary SNP and the most significant SNP. R-sq's were retrieved from 1000G pilot 1 CEU using SNAP.