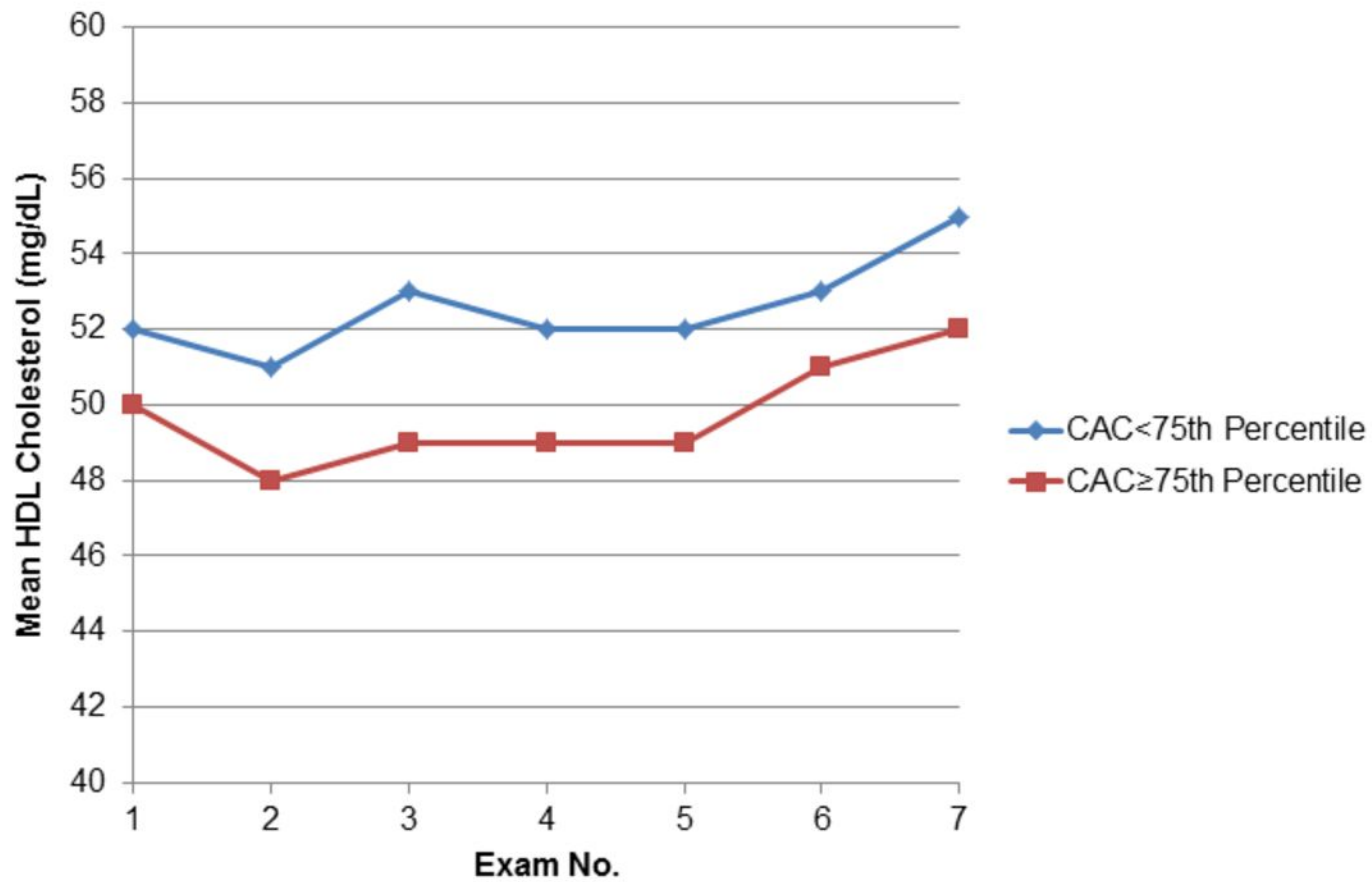
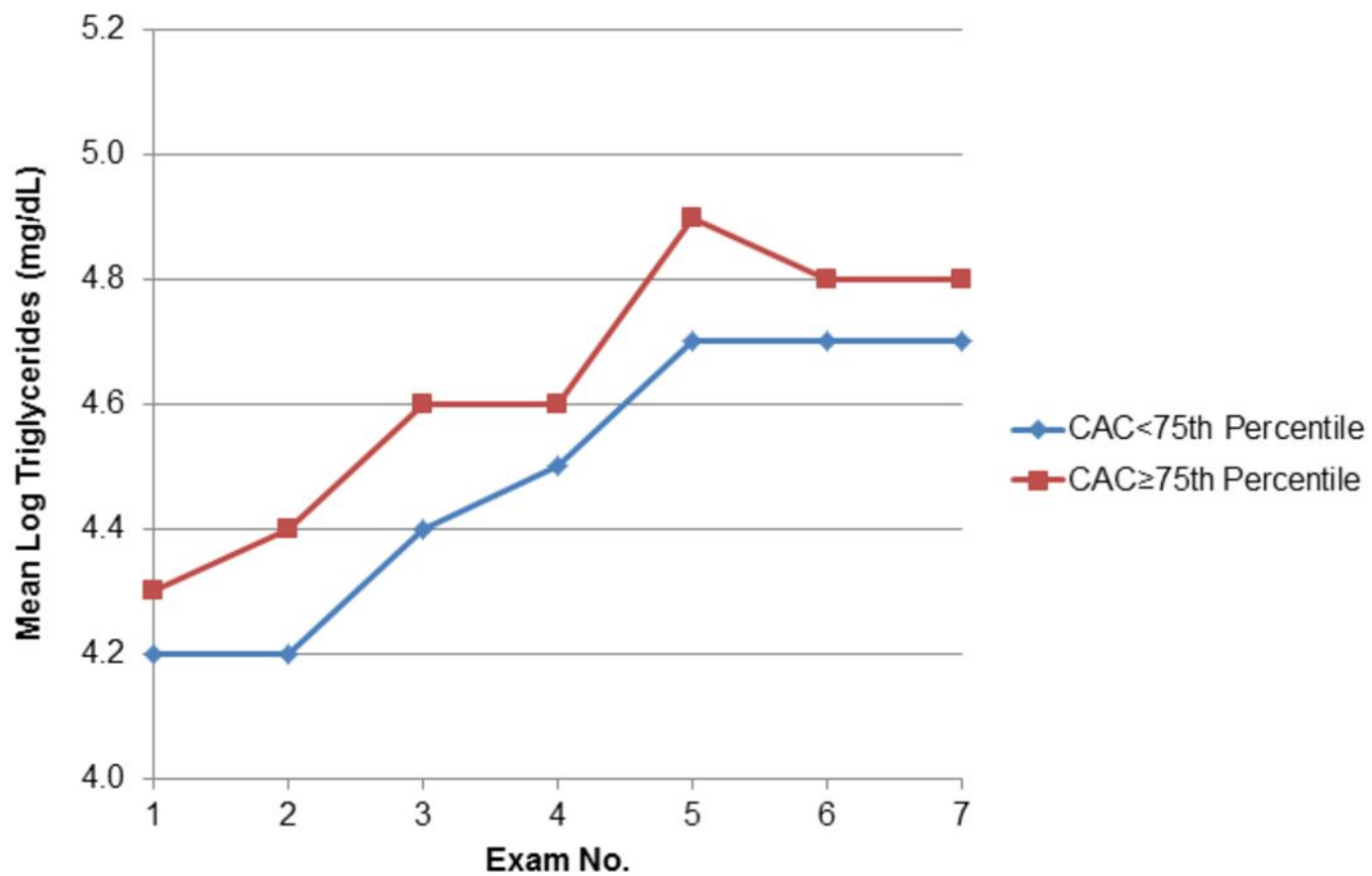


Supplemental Figure 1a



Supplemental Figure 1b



Supplemental Figure 1c

SUPPLEMENTAL FIGURE LEGEND

Supplemental Figure 1a-c. Longitudinal measures of lipid levels in participants free of lipid-lowering therapy.

Longitudinal measures of LDL-C (1a), HDL-C (1b), and TG (1c) from Exam 1-7 in the FHS Offspring Cohort, excluding participants on lipid-lowering therapy at each Exam and stratified by extent of CAC.

SUPPLEMENTAL TABLES

Supplemental Table 1. Single nucleotide polymorphisms (SNPs) represented in the each of the lipid genetic risk scores.

SNP Name	Chromosome	Position	MAF	Call Rate	R ²	Genotyping Platform	Lipid Type		
rs10195252	2	165,221,337	39	100	0.99	Imputed		TG	
rs1030431	8	59,474,251	34	100	0.97	Imputed	LDL-C		TC
rs10401969	19	19,268,718	7	100		Illumina	LDL-C	TG	TC
rs1042034	2	21,078,786	20	100		Affymetrix		HDL-C	TG
rs10761731	10	64,697,616	42	100	1	Imputed		TG	
rs10808546	8	126,565,000	42	100	0.93	Imputed		HDL-C	
rs10832963	11	18,620,817	26	100	0.91	Imputed			TC
rs1084651	6	161,009,807	16	100	0.85	Imputed		HDL-C	
rs11065987	12	110,556,807	45	100		Illumina	LDL-C		TC
rs11136341	8	145,115,531	41	100	0.8	Imputed	LDL-C		TC
rs11153594	6	116,461,284	44	99		Affymetrix	LDL-C		
rs11220462	11	125,749,162	14	100		Affymetrix	LDL-C		
rs11220463	11	125,753,421	10	100	0.83	Imputed			TC
rs1129555	10	113,900,711	31	100		Affymetrix	LDL-C		
rs11613352	12	56,078,847	20	100	1	Imputed		TG	
rs11649653	16	30,825,988	41	100		Affymetrix		TG	
rs1169288	12	119,901,033	34	100	0.98	Imputed	LDL-C		TC
rs11776767	8	10,721,339	38	100	1	Imputed		TG	
rs12027135	1	25,648,320	48	100	0.99	Imputed	LDL-C		TC
rs12310367	12	123,052,631	35	100	1	Imputed		TG	
rs12328675	2	165,249,046	13	100	0.99	Imputed		HDL-C	
rs1260326	2	27,584,444	45	100		Illumina		TG	TC
rs12670798	7	21,573,877	23	100	0.98	Imputed	LDL-C		
rs12678919	8	19,888,502	9	100		Illumina		HDL-C	TG
rs12916	5	74,692,295	38	100	0.97	Imputed	LDL-C		TC
rs12967135	18	56,000,003	22	100	1	Imputed		HDL-C	
rs13107325	4	103,407,732	8	100		Affymetrix		HDL-C	

rs1321257	1	228,371,935	39	100	0.96	Imputed		TG	
rs13238203	7	71,767,603	3	100	0.38	Imputed		TG	
rs1367117	2	21,117,405	31	100	0.98	Imputed	LDL-C		TC
rs1495743	8	18,317,580	21	100		Affymetrix		TG	
rs1515100	2	226,837,161	37	100	1	Imputed		HDL-C	
rs1532085	15	56,470,658	38	100	0.97	Imputed		HDL-C	TC
rs1553318	5	156,411,901	37	100	0.96	Imputed		TG	
rs1564348	6	160,498,850	16	100		Affymetrix	LDL-C		TC
rs1689800	1	180,435,508	35	100	0.97	Imputed		HDL-C	
rs16942887	16	66,485,543	11	100	1	Imputed		HDL-C	
rs17145738	7	72,620,810	11	100		Illumina		HDL-C	
rs174546	11	61,326,406	33	100	0.99	Imputed		TG	
rs174550	11	61,328,054	33	100	0.99	Imputed			TC
rs174583	11	61,366,326	33	100	0.94	Imputed	LDL-C		
rs174601	11	61,379,716	35	100	0.83	Imputed		HDL-C	
rs1800562	6	26,201,120	6	100		Affymetrix	LDL-C		TC
rs1800961	20	42,475,778	3	100		Illumina		HDL-C	TC
rs181362	22	20,262,068	19	100	1	Imputed		HDL-C	
rs1883025	9	106,704,122	27	100		Illumina		HDL-C	TC
rs1961456	8	18,299,989	31	100	0.94	Imputed			TC
rs2000999	16	70,665,594	21	100	0.91	Imputed	LDL-C		TC
rs2068888	10	94,829,632	47	100	0.74	Imputed		TG	
rs2072183	7	44,545,705	26	100	0.49	Imputed			TC
rs2126259	8	9,222,556	9	100	1	Imputed	LDL-C		TC
rs2131925	1	62,798,530	33	100	1	Imputed		TG	
rs217386	7	44,567,220	46	100	0.92	Imputed	LDL-C		
rs2247056	6	31,373,469	24	100	1	Imputed		TG	
rs2255141	10	113,923,876	31	100	1	Imputed			TC
rs2277862	20	33,616,196	16	100	0.97	Imputed			TC
rs2285942	7	21,549,442	15	100	0.91	Imputed			TC
rs2290159	3	12,603,920	22	100	1	Imputed			TC
rs2293889	8	116,668,374	42	100	0.98	Imputed		HDL-C	

rs2332328	14	23,952,898	50	100	0.5	Imputed	LDL-C			
rs2412710	15	40,471,079	2	100	0.86	Imputed			TG	
rs247616	16	55,547,091	32	100	0.94	Imputed	LDL-C			
rs2479409	1	55,277,238	37	100		Affymetrix	LDL-C			TC
rs261342	15	56,518,445	21	100	0.94	Imputed			TG	
rs2652834	15	61,183,920	21	100	0.89	Imputed		HDL-C		
rs2737229	8	116,717,740	28	100	0.97	Imputed				TC
rs2807834	1	219,037,216	31	99		Affymetrix	LDL-C			TC
rs2814944	6	34,660,775	15	97		Affymetrix		HDL-C		
rs2814982	6	34,654,538	10	100	0.68	Imputed				TC
rs2902940	20	38,524,901	29	100	0.97	Imputed				TC
rs2902941	20	38,524,928	34	100	0.96	Imputed	LDL-C			
rs2923084	11	10,345,358	16	100	0.9	Imputed		HDL-C		
rs2925979	16	80,092,291	29	100	0.83	Imputed		HDL-C		
rs2929282	15	42,033,223	4	100	0.92	Imputed			TG	
rs2943645	2	226,807,424	37	100	0.99	Imputed			TG	
rs2954022	8	126,551,803	44	100	0.98	Imputed	LDL-C			TC
rs2954029	8	126,560,154	44	100		Illumina			TG	
rs3136441	11	46,699,823	13	100	0.96	Imputed		HDL-C		
rs3177928	6	32,520,413	14	99		Affymetrix	LDL-C			TC
rs3741414	12	56,130,316	22	100	0.84	Imputed		HDL-C		
rs3757354	6	16,235,386	20	100	0.98	Imputed	LDL-C			TC
rs3764261	16	55,550,825	31	98		Affymetrix		HDL-C		TC
rs3850634	1	62,823,186	33	100	1	Imputed	LDL-C			TC
rs386000	19	59,484,573	20	100	0.36	Imputed		HDL-C		
rs4082919	17	73,889,077	49	100	0.88	Imputed		HDL-C		
rs4148008	17	64,386,889	34	100	1	Imputed		HDL-C		
rs4297946	20	39,244,689	44	100		Affymetrix				TC
rs4299376	2	43,926,080	32	100	0.89	Imputed	LDL-C			TC
rs439401	19	50,106,291	39	100	0.2	Imputed			TG	
rs4420638	19	50,114,786	16	100		Illumina	LDL-C	HDL-C		TC
rs442177	4	88,249,285	39	100	1	Imputed			TG	

rs4660293	1	39,800,767	22	100		Affymetrix		HDL-C		
rs4731702	7	130,083,924	48	100	1	Imputed		HDL-C		
rs4759375	12	122,362,191	6	100	0.96	Imputed		HDL-C		
rs4765127	12	123,026,120	35	100		Affymetrix		HDL-C		
rs4810479	20	43,978,455	24	100	0.94	Imputed			TG	
rs4846914	1	228,362,314	40	100		Illumina		HDL-C		
rs492602	19	53,898,229	49	100		Illumina				TC
rs514230	1	232,925,220	50	100	0.98	Imputed	LDL-C			TC
rs5756931	22	36,875,979	41	100	0.93	Imputed			TG	
rs581080	9	15,295,378	19	100	0.94	Imputed				TC
rs605066	6	139,871,359	40	100	1	Imputed		HDL-C		
rs6065906	20	43,987,422	18	100	0.95	Imputed		HDL-C		
rs629301	1	109,619,829	21	100	0.95	Imputed	LDL-C			TC
rs643531	9	15,286,034	14	100		Affymetrix		HDL-C		
rs6450176	5	53,333,782	26	100	0.93	Imputed		HDL-C		
rs645040	3	137,409,312	24	100	1	Imputed			TG	
rs649129	9	135,144,125	22	100	0.93	Imputed	LDL-C			
rs651007	9	135,143,696	18	94		Affymetrix				TC
rs6511720	19	11,063,306	13	100		Illumina	LDL-C			TC
rs6759321	2	136,039,146	36	100	1	Imputed				TC
rs6882076	5	156,322,875	37	100	1	Imputed	LDL-C			TC
rs7115089	11	122,035,801	38	100	0.97	Imputed		HDL-C		
rs7134375	12	20,365,025	41	100	0.76	Imputed		HDL-C		
rs7134594	12	108,484,576	55	100	1	Imputed		HDL-C		
rs7205804	16	55,562,390	47	100	0.72	Imputed			TG	
rs7206971	17	42,780,114	50	99		Affymetrix				TC
rs7225700	17	42,746,803	35	100	1	Imputed	LDL-C			
rs7239867	18	45,418,715	16	100	1	Imputed				TC
rs7241918	18	45,414,951	16	100	1	Imputed		HDL-C		
rs7255436	19	8,339,196	46	100	0.65	Imputed		HDL-C		
rs737337	19	11,208,493	7	100	0.89	Imputed		HDL-C		
rs7515577	1	92,782,026	18	100	1	Imputed				TC

rs7811265	7	72,572,446	19	100	0.98	Imputed			TG	
rs7941030	11	122,027,585	39	100	0.97	Imputed				TC
rs838880	12	123,827,546	32	100	0.86	Imputed		HDL-C		
rs881844	17	35,063,744	33	100	1	Imputed		HDL-C		
rs909802	20	39,370,229	45	100	1	Imputed	LDL-C			
rs9488822	6	116,419,586	38	99		Affymetrix				TC
rs964184	11	116,154,127	14	100		Illumina	LDL-C	HDL-C	TG	TC
rs9686661	5	55,897,543	22	100	0.96	Imputed			TG	
rs9987289	8	9,220,768	8	100	1	Imputed		HDL-C		

MAF = Minor allele frequency. LDL-C = Low-density lipoprotein cholesterol. HDL-C = high-density lipoprotein cholesterol. TG = Triglycerides. TC = Total cholesterol.

Preference for inclusion was given to Illumina genotypes, followed by 550K genotypes, and finally imputed genotypes.

[ENREF 22](#) Of the 132 SNPs in the 95 loci, 13 were genotyped on the Illumina panel, 21 were genotyped on the Affymetrix 550K chips, and 98 were available from imputation. Call rate was > 94% for all genotyped SNPs, and only one SNP had imputation $R^2 < 0.3$.

Supplemental Table 2. Pearson correlation coefficients between lipid genetic risk scores and lipid levels in the Framingham Heart Study Offspring Cohort

		Pearson Correlation Coefficient (ρ)	
		Total study sample ¹ (n=1156)*	No lipid treatment at any Exam ² (n=965)*
LDL-C genetic risk score	LDL-C cholesterol		
	Exam 1	0.25	0.22
	Exam 7	0.19	0.25
	Average, Exams 1-7	0.29	0.27
HDL-C genetic risk score	HDL cholesterol		
	Exam 1	-0.22	-0.23
	Exam 7	-0.24	-0.24
	Average, Exams 1-7	-0.24	-0.24
TG genetic risk score	Log triglycerides		
	Exam 1	0.17	0.14
	Exam 7	0.24	0.22
	Average, Exams 1-7	0.25	0.22

*p<0.001 for all analyses

¹ The Pearson correlation coefficient was 0.14 (p<0.0001) between the LDL-C and HDL-C genetic risk scores, 0.24 (p<0.0001) between the LDL-C and TG genetic risk scores, and 0.39 (p<0.0001) between the HDL-C and TG genetic risk scores.

² The Pearson correlation coefficient was 0.14 (p<0.0001) between the LDL-C and HDL-C genetic risk scores, 0.22 (p<0.0001) between the LDL-C and TG genetic risk scores, and 0.39 (p<0.0001) between the HDL-C and TG genetic risk scores.

Supplemental Table 3. Odds ratio of CAC \geq 75th percentile per SD increment of untreated LDL-C measure or LDL-C genetic risk score in the Framingham Heart Study Offspring Cohort

Model	OR (95% CI)	P-value
LDL cholesterol (Exam 1)	1.36 (1.19-1.56)	<0.0001
Age + sex	1.35 (1.17-1.54)	<0.0001
Age + sex + LDL-C genetic risk score		
LDL cholesterol (Exam 7)		
Age + sex	1.08 (0.95-1.22)	0.22
Age + sex + LDL-C genetic risk score	1.06 (0.93-1.20)	0.38
LDL cholesterol (average, Exams 1-7)		
Age + sex	1.35 (1.18-1.54)	<0.0001
Age + sex + LDL-C genetic risk score	1.33 (1.15-1.52)	<0.0001
LDL-C genetic risk score		
Age + sex	1.14 (1.00-1.29)	0.04
Age + sex + LDL-C (Exam 1)	1.05 (0.93-1.20)	0.44
Age + sex + LDL-C (Exam 7)	1.09 (0.96-1.24)	0.19
Age + sex + LDL-C (average, Exams 1-7)	1.05 (0.92-1.19)	0.48

Supplemental Table 4. Comparison of C-statistics for models predicting $CAC \geq 75^{\text{th}}$ percentile with and without the lipid genetic risk scores in the Framingham Heart Study Offspring Cohort

Model Covariates	C-Statistic		P-value comparing C-statistics
	Covariates only	Covariates + lipid genetic risk score	
LDL-C cholesterol			
Age + sex	0.557	0.564	0.47
Age + sex + LDL-C (Exam 1)	0.610	0.611	0.83
Age + sex + lipid treatment (Exam 7)	0.600	0.602	0.73
Age + sex + lipid treatment (Exam 7) + LDL-C (Exam 7)	0.605	0.605	0.96
Age + sex + lipid treatment (any)	0.601	0.603	0.69
Age + sex + lipid treatment (any) + LDL-C (avg., Exams 1-7)	0.620	0.620	0.94
HDL cholesterol			
Age + sex	0.557	0.562	0.37
Age + sex + HDL-C (Exam 1)	0.582	0.584	0.43
Age + sex + lipid treatment (Exam 7)	0.600	0.605	0.27
Age + sex + lipid treatment (Exam 7) + HDL-C (Exam 7)	0.607	0.609	0.52
Age + sex + lipid treatment (any)	0.601	0.605	0.28
Age + sex + lipid treatment (any) + HDL-C (avg., Exams 1-7)	0.618	0.618	0.84
Log triglycerides			
Age + sex	0.557	0.558	0.94
Age + sex + TG (Exam 1)	0.599	0.599	0.92
Age + sex + lipid treatment (Exam 7)	0.600	0.600	0.99
Age + sex + lipid treatment (Exam 7) + TG (Exam 7)	0.613	0.613	0.97
Age + sex + lipid treatment (any)	0.600	0.601	0.95
Age + sex + lipid treatment (any) + TG (avg, Exams 1-7)	0.626	0.626	0.92