**SUPPLEMENTARY MATERIAL**

# Quantitative and Qualitative Role of Antagonistic Heterogeneity in Genetics of Blood Lipids

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Supplementary materials include one Text, one Figure and four Tables.

## 1. Supplementary Text

### Supplementary Acknowledgment Text.

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The Health and Retirement Study (HRS) genetic data is sponsored by the Genetics Resource with HRS April 21, 2010, version G Page 5 of 7 National Institute on Aging (grant numbers U01AG009740, RC2AG036495, and RC4AG039029) and was conducted by the University of Michigan. This manuscript was not prepared in collaboration with HRS investigators and does not necessarily reflect the opinions or views of HRS.

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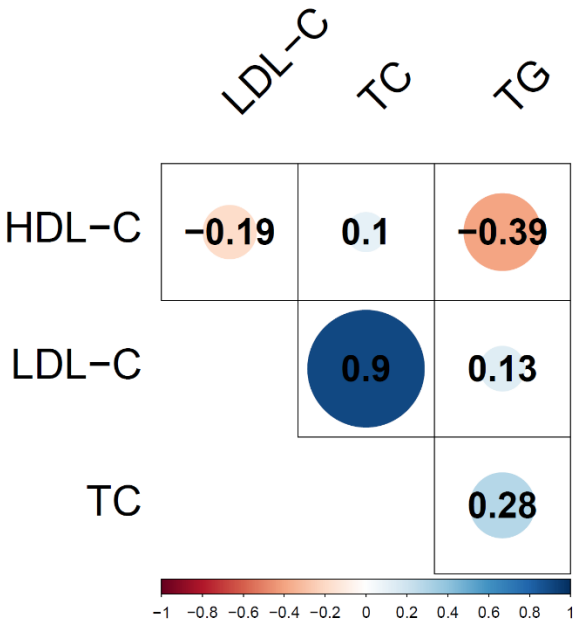
The Coronary Artery Risk Development in Young Adults Study (CARDIA) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (N01-HC95095 & N01-HC48047), University of Minnesota (N01-HC48048), Northwestern University (N01-HC48049), and Kaiser Foundation Research Institute (N01-HC48050). This manuscript was not approved by CARDIA. The opinions and conclusions contained in this publication are solely those of the authors, and are not endorsed by CARDIA or the NHLBI and should not be assumed to reflect the opinions or conclusions of either. Genotyping for the CARDIA GENEVA cohort was supported by grant U01 HG004729 from the National Human Genome Research Institute.

## 2. Supplementary Figures

**Supplementary Figure 1. Pair-wise correlation coefficients between lipid traits.**
Correlation coefficients, *r*, are representatively given as in the Atherosclerosis Risk in Communities Study. Phenotypes include: high-density lipoprotein cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C); total cholesterol (TC); and triglycerides (TG).



## 3. Supplementary Tables

**Supplementary Table 1. Basic characteristics of cohorts included in the analyses and the available sample sizes.**

| Cohort | Sample size | Age (SD), years | BC range | Gender, female (%) | HDL-C (SD), [mg/dl] | LDL-C (SD), [mg/dl] | TC (SD), [mg/dl] | TG (SD), [mg/dl] |
|---|---|---|---|---|---|---|---|---|
| **ARIC** | 9,593 | 54.33 (6.55) | 1921-1944 | 53.01 | 50.50 (17.15) | 137.63 (36.63) | 214.91 (39.37) | 137.48 (89.47) |
| **CARDIA** | 1,666 | 25.55 (6.21) | 1950-1965 | 53.42 | 52.06 (14.04) | 108.61 (31.64) | 176.42 (34.12) | 78.66 (67.64) |
| **CHS** | 3,218 | 72.39 (5.82) | 1890-1925 | 60.20 | 55.12 (15.10) | 130.54 (34.98) | 212.83 (39.01) | 140.36 (82.18) |
| **FHS_C1** | 875 | 53.66 (13.65) | 1885-1920 | 60.12 | 53.42 (15.77) | 189.79 (44.02) | 242.55 (46.01) | 125.99 (98.49) |
| **FHS_C2** | 3,298 | 35.13 (13.63) | 1910-1960 | 52.21 | 56.91 (15.62) | 117.37 (35.66) | 190.24 (39.41) | 73.94 (102.79) |
| **FHS_C3** | 3,883 | 40.01 (9.34) | 1930-1980 | 53.23 | 61.01 (16.08) | 104.78 (32.09) | 185.30 (35.42) | 97.61 (90.44) |
| **HRS** | 4,021 | 72.47 (8.77) | 1916-1975 | 59.95 | 58.99 (19.73) | 99.28 (35.34) | 186.35 (42.07) | 135.93 (63.95) |
| **MESA** | 2,364 | 64.25 (10.30) | 1917-1957 | 51.40 | 53.26 (15.44) | 113.44 (32.32) | 192.65 (36.61) | 130.34 (80.65) |
| **WHI** | 984 | 64.28 (7.99) | 1914-1943 | 100.00 | 57.00 (14.93) | 140.58 (35.46) | 228.03 (38.30) | 154.64 (82.62) |

**Cohorts**: Atherosclerosis Risk in Communities Study (ARIC); Coronary Artery Risk Development in Young Adults (CARDIA); Cardiovascular Health Study (CHS); Framingham Heart Study (FHS) original cohort (FHS_C1); FHS Offspring (FHS_C2); FHS 3$^{rd}$ generation cohort (FHS_C3), Health and Retirement Study (HRS); the Multi-Ethnic Study of Atherosclerosis (MESA), and the Genomics and Randomized Trials Network (GARNET) sub-study of the Women's Health Initiative (WHI).

**Quantitative markers (lipids)**: high-density lipoprotein cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C); total cholesterol (TC); and triglycerides (TG).

BC denotes birth cohorts; SD denotes standard deviation.

**Supplementary Table 2. Replicated genetic associations with lipid traits with at most minor effect of antagonistic genetic heterogeneity.**

| SNP info | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **ID** | **SNP** | **Chr** | **Position** | **Locus** | **Gene** | **Function** | **EA** | **EAF** |
| 1 | rs16827981 | 1 | 23,435,538 | ASAP3 | LUZP1 | UTR-5 | a | 0.18 |
| 2 | rs693668 | 1 | 55,521,109 | PCSK9 | PCSK9 | intron | g | 0.35 |
| 3 | rs10889332 | 1 | 62,950,858 | ANGPTL3 | DOCK7 | intron, UTR-3 | t | 0.33 |
| 4 | rs629301 | 1 | 109,818,306 | SORT1 | CELSR2 | UTR-3 | g | 0.22 |
| 5 | rs629301 | 1 | 109,818,306 | SORT1 | CELSR2 | UTR-3 | g | 0.22 |
| 6 | rs4846914 | 1 | 230,295,691 | GALNT2 | GALNT2 | intron | g | 0.40 |
| 7 | rs556107 | 1 | 234,853,059 | IRF2BP2 | | intergenic | c | 0.47 |
| 8 | rs7575840 | 2 | 21,273,490 | APOB | | intergenic | t | 0.33 |
| 9 | rs7575840 | 2 | 21,273,490 | APOB | | intergenic | t | 0.33 |
| 10 | rs41360247 | 2 | 44,073,656 | ABCG5/8 | ABCG8 | intron,nearGene-5 | c | 0.07 |
| 11 | rs41360247 | 2 | 44,073,656 | ABCG5/8 | ABCG8 | intron,nearGene-5 | c | 0.07 |
| 12 | rs7371606 | 2 | 136,806,774 | RAB3GAP1 | | intergenic | g | 0.34 |
| 13 | rs3846663 | 5 | 74,655,726 | HMGCR | HMGCR | intron | t | 0.38 |
| 14 | rs3846663 | 5 | 74,655,726 | HMGCR | HMGCR | intron | t | 0.38 |
| 15 | rs9391858 | 6 | 32,341,398 | HLA | C6orf10, LOC101929163 | intron,nearGene-5 | g | 0.14 |
| 16 | rs1564348 | 6 | 160,578,860 | LPA | SLC22A1 | intron | c | 0.16 |
| 17 | rs1564348 | 6 | 160,578,860 | LPA | SLC22A1 | intron | c | 0.16 |
| 18 | rs4466298 | 7 | 17,992,014 | SNX13 | | intergenic | a | 0.45 |
| 19 | rs17145738 | 7 | 72,982,874 | MLXIPL | TBL2 | nearGene-3 | t | 0.12 |
| 20 | rs13230111 | 7 | 130,437,124 | KLF14 | LOC105375508 | intron | g | 0.48 |
| 21 | rs1461729 | 8 | 9,187,242 | PPP1R3B | LOC157273 | intron | a | 0.09 |
| 22 | rs17482753 | 8 | 19,832,646 | LPL | | intron | t | 0.10 |
| 23 | rs17482753 | 8 | 19,832,646 | LPL | | intron | t | 0.10 |
| 24 | rs17321515 | 8 | 126,486,409 | TRIB1 | | intergenic | g | 0.47 |
| 25 | rs17321515 | 8 | 126,486,409 | TRIB1 | | intergenic | g | 0.47 |
| 26 | rs17321515 | 8 | 126,486,409 | TRIB1 | | intergenic | g | 0.47 |
| 27 | rs10761779 | 10 | 65,274,927 | JMJD1C | JMJD1C | intron | g | 0.49 |
| 28 | rs174547 | 11 | 61,570,783 | FADS1-2-3 | FADS1 | intron | c | 0.33 |
| 29 | rs651821 | 11 | 116,662,579 | APOA1 | APOA5 | UTR-5 | c | 0.07 |
| 30 | rs9989419 | 16 | 56,985,139 | CETP | | intergenic | a | 0.39 |
| 31 | rs10438978 | 18 | 47,158,186 | LIPG | LOC105372112 | intron | t | 0.17 |
| 32 | rs1122608 | 19 | 11,163,601 | LDLR | SMARCA4 | intron | t | 0.25 |
| 33 | rs1122608 | 19 | 11,163,601 | LDLR | SMARCA4 | intron | t | 0.25 |
| 34 | rs10401969 | 19 | 19,407,718 | CILP2 | SUGP1 | intron | c | 0.07 |
| 35 | rs10401969 | 19 | 19,407,718 | CILP2 | SUGP1 | intron | c | 0.07 |
| 36 | rs10401969 | 19 | 19,407,718 | CILP2 | SUGP1 | intron | c | 0.07 |
| 37 | rs4420638 | 19 | 45,422,946 | APOE | APOC1 | nearGene-3 | g | 0.16 |
| 38 | rs4420638 | 19 | 45,422,946 | APOE | APOC1 | nearGene-3 | g | 0.16 |
| 39 | rs753381 | 20 | 39,797,465 | TOP1 | PLCG1 | missense | t | 0.45 |
| 40 | rs7679 | 20 | 44,576,502 | PLTP | PCIF1 | UTR-3 | c | 0.19 |

**Supplementary Table 2**. (continue)

| SNP info | Current Study | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Trait_1_unconditional | | | | | | | Trait_1_conditional | | | | | | |
| ID | Trait pair | Trait_1 | Beta | SE | P-value | Direction | $I^2$ | HetPVal | Beta | SE | P-value | dlogP | Direction | $I^2$ | HetPVal |
| 1 | HDL-TC | TC | 2.13 | 0.39 | 5.55E-08 | +++++++++ | 11 | 3.40E-01 | 2.14 | 0.39 | 3.56E-08 | 0.19 | +++++++++ | 6 | 3.90E-01 |
| 2 | HDL-LDL | LDL-C | -1.57 | 0.29 | 8.92E-08 | --------+ | 22 | 2.51E-01 | -1.60 | 0.29 | 3.59E-08 | 0.40 | --------+ | 23 | 2.39E-01 |
| 3 | HDL-TC | TC | -2.44 | 0.32 | 3.11E-14 | -------+- | 55 | 2.47E-02 | -2.38 | 0.32 | 8.84E-14 | -0.45 | -------+- | 50 | 4.17E-02 |
| 4 | LDL-TG | LDL-C | -6.03 | 0.34 | 1.85E-72 | --------- | 4 | 4.03E-01 | -6.03 | 0.33 | 3.10E-73 | 0.78 | --------- | 6 | 3.85E-01 |
| 5 | HDL-TC | TC | -5.80 | 0.36 | 2.13E-57 | --------- | 0 | 5.95E-01 | -5.88 | 0.36 | 4.22E-60 | 2.70 | --------- | 0 | 5.33E-01 |
| 6 | HDL-LDL | HDL-C | -0.70 | 0.13 | 3.69E-08 | ----?---- | 8 | 3.65E-01 | -0.70 | 0.13 | 3.81E-08 | -0.01 | ----?---- | 0 | 4.39E-01 |
| 7 | HDL-TC | TC | -1.71 | 0.30 | 1.70E-08 | --------- | 0 | 5.81E-01 | -1.65 | 0.30 | 4.18E-08 | -0.39 | --------- | 0 | 6.35E-01 |
| 8 | HDL-LDL | LDL-C | 3.26 | 0.30 | 3.91E-28 | +++++++++ | 31 | 1.70E-01 | 3.22 | 0.29 | 2.61E-28 | 0.18 | +++++++++ | 24 | 2.28E-01 |
| 9 | HDL-TC | TC | 3.19 | 0.32 | 2.59E-23 | +++++++++ | 25 | 2.20E-01 | 3.23 | 0.32 | 2.80E-24 | 0.97 | +++++++++ | 20 | 2.67E-01 |
| 10 | LDL-TG | LDL-C | -3.56 | 0.55 | 1.25E-10 | --------? | 0 | 9.53E-01 | -3.60 | 0.55 | 5.51E-11 | 0.36 | --------? | 0 | 9.47E-01 |
| 11 | TC-TG | TC | -3.63 | 0.61 | 1.93E-09 | --------? | 0 | 7.05E-01 | -3.68 | 0.58 | 2.42E-10 | 0.90 | --------? | 0 | 9.50E-01 |
| 12 | HDL-TC | TC | 1.95 | 0.34 | 7.05E-09 | +++++++?? | 52 | 5.35E-02 | 1.92 | 0.33 | 1.00E-08 | -0.15 | +++++++?? | 47 | 7.77E-02 |
| 13 | HDL-LDL | LDL-C | 2.51 | 0.32 | 1.88E-15 | ++++?+++? | 24 | 2.44E-01 | 2.63 | 0.31 | 3.16E-17 | 1.78 | ++++?+++? | 23 | 2.52E-01 |
| 14 | TC-TG | TC | 2.79 | 0.34 | 1.75E-16 | ++++?+++? | 0 | 6.33E-01 | 2.80 | 0.32 | 3.28E-18 | 1.73 | ++++?+++? | 0 | 5.24E-01 |
| 15 | HDL-TC | TC | 2.40 | 0.43 | 3.18E-08 | +++++++++ | 19 | 2.78E-01 | 2.36 | 0.43 | 3.60E-08 | -0.05 | +++++++++ | 23 | 2.39E-01 |
| 16 | LDL-TG | LDL-C | 2.32 | 0.39 | 2.42E-09 | ++++++++- | 0 | 6.50E-01 | 2.27 | 0.39 | 4.14E-09 | -0.23 | ++++++++- | 0 | 4.84E-01 |
| 17 | HDL-TC | TC | 2.40 | 0.42 | 1.41E-08 | ++++++++- | 0 | 7.58E-01 | 2.45 | 0.42 | 4.87E-09 | 0.46 | ++++++++- | 4 | 8.41E-01 |
| 18 | HDL-LDL | HDL-C | -0.70 | 0.12 | 5.59E-09 | --------- | 0 | 8.04E-01 | -0.69 | 0.12 | 8.48E-09 | -0.18 | --------- | 0 | 5.65E-01 |
| 19 | TC-TG | TG | -10.97 | 0.91 | 1.71E-33 | --------- | 0 | 4.36E-01 | -10.38 | 0.87 | 6.72E-33 | -0.59 | -+------- | 12 | 3.32E-01 |
| 20 | HDL-LDL | HDL-C | 0.67 | 0.12 | 4.33E-08 | ++++++++? | 0 | 5.20E-01 | 0.67 | 0.12 | 3.24E-08 | 0.13 | ++++++++? | 0 | 4.42E-01 |
| 21 | TC-TG | TC | -3.46 | 0.51 | 1.75E-11 | --------- | 0 | 4.97E-01 | -3.45 | 0.49 | 1.96E-12 | 0.95 | --------- | 0 | 9.47E-01 |
| 22 | HDL-LDL | HDL-C | 2.59 | 0.20 | 5.12E-38 | +++++++++ | 50 | 4.06E-02 | 2.54 | 0.20 | 1.75E-37 | -0.53 | +++++++++ | 41 | 9.62E-02 |
| 23 | TC-TG | TG | -12.82 | 0.96 | 7.69E-41 | --------- | 55 | 2.32E-02 | -12.95 | 0.91 | 9.73E-46 | 4.90 | --------- | 62 | 6.94E-03 |
| 24 | HDL-LDL | LDL-C | -1.95 | 0.28 | 4.63E-12 | --------- | 0 | 9.50E-01 | -1.79 | 0.28 | 1.15E-10 | -1.40 | --------- | 0 | 9.80E-01 |
| 25 | HDL-TC | TC | -2.44 | 0.30 | 1.09E-15 | --------- | 0 | 9.77E-01 | -2.60 | 0.30 | 7.75E-18 | 2.15 | --------- | 0 | 9.88E-01 |
| 26 | LDL-TG | TG | -6.12 | 0.67 | 3.66E-20 | --------- | 43 | 8.24E-02 | -4.61 | 0.55 | 7.79E-17 | -3.33 | --------- | 0 | 7.01E-01 |
| 27 | TC-TG | TG | -3.85 | 0.67 | 1.09E-08 | --------- | 0 | 7.60E-01 | -3.71 | 0.64 | 8.12E-09 | 0.13 | --------- | 0 | 9.33E-01 |
| 28 | HDL-LDL | HDL-C | -0.99 | 0.13 | 9.49E-15 | -+----+-- | 65 | 3.77E-03 | -1.08 | 0.13 | 1.93E-17 | 2.69 | -+----+-- | 64 | 5.00E-03 |
| 29 | TC-TG | TG | 21.70 | 1.59 | 1.22E-42 | +++++++++ | 8 | 2.38E-01 | 18.46 | 1.52 | 4.87E-34 | -8.60 | +++++++++ | 30 | 1.75E-01 |
| 30 | HDL-TG | HDL-C | -2.04 | 0.16 | 1.73E-39 | -----??-- | 0 | 5.80E-01 | -1.91 | 0.14 | 2.75E-40 | 0.80 | -----??-- | 0 | 5.59E-01 |
| 31 | HDL-TG | HDL-C | -1.41 | 0.16 | 8.12E-19 | --------? | 21 | 2.66E-01 | -1.43 | 0.15 | 2.72E-22 | 3.48 | --------? | 0 | 4.72E-01 |
| 32 | LDL-TG | LDL-C | -2.71 | 0.35 | 1.24E-14 | ----?-+-? | 46 | 8.48E-02 | -2.71 | 0.35 | 6.79E-15 | 0.26 | ----?---? | 42 | 1.13E-01 |
| 33 | TC-TG | TC | -2.51 | 0.38 | 3.14E-11 | ----?-+-? | 13 | 3.29E-01 | -2.52 | 0.36 | 2.44E-12 | 1.11 | ----?---? | 24 | 2.44E-01 |
| 34 | HDL-TC | TC | -4.53 | 0.58 | 4.52E-15 | --------- | 41 | 9.18E-02 | -4.52 | 0.57 | 2.37E-15 | 0.28 | --------- | 46 | 6.04E-02 |
| 35 | HDL-TG | TG | -8.63 | 1.13 | 1.91E-14 | --------- | 0 | 4.58E-01 | -8.08 | 1.02 | 2.01E-15 | 0.98 | --------- | 11 | 3.48E-01 |
| 36 | HDL-LDL | LDL-C | -2.95 | 0.53 | 2.78E-08 | +-------- | 42 | 9.03E-02 | -2.81 | 0.53 | 8.97E-08 | -0.51 | +-------- | 32 | 1.65E-01 |
| 37 | HDL-LDL | LDL-C | 5.02 | 0.41 | 5.32E-35 | ++++++?+? | 60 | 2.14E-02 | 4.72 | 0.40 | 8.25E-32 | -3.19 | ++++++?+? | 59 | 2.39E-02 |
| 38 | HDL-TC | TC | 5.01 | 0.44 | 2.51E-30 | ++++++?+? | 66 | 7.39E-03 | 5.24 | 0.43 | 1.55E-33 | 3.21 | ++++++?+? | 62 | 1.47E-02 |
| 39 | HDL-LDL | LDL-C | -1.51 | 0.28 | 7.27E-08 | -------+- | 37 | 1.22E-01 | -1.54 | 0.28 | 3.06E-08 | 0.38 | -------+- | 36 | 1.31E-01 |
| 40 | HDL-TC | HDL-C | -1.03 | 0.15 | 6.59E-12 | -------- | 0 | 9.41E-01 | -1.03 | 0.15 | 5.79E-12 | 0.06 | --------- | 0 | 9.33E-01 |

**Supplementary Table 2**. (continue)

| SNP info | Current Study | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Trait_2_conditional | | | | | | | Trait_2_conditional | | | | | | |
| ID | Trait pair | Trait_2 | Beta | SE | P-value | Direction | $I^2$ | HetPVal | Beta | SE | P-value | dlogP | Direction | $I^2$ | HetPVal |
| 1 | HDL-TC | HDL-C | 0.09 | 0.16 | 5.85E-01 | +---+++++ | 0 | 8.17E-01 | -0.02 | 0.16 | 9.03E-01 | -0.19 | -----++-+ | 0 | 7.92E-01 |
| 2 | HDL-LDL | HDL-C | -0.01 | 0.13 | 9.45E-01 | ++---++-+ | 0 | 9.23E-01 | -0.12 | 0.13 | 3.61E-01 | 0.42 | -+----+-+ | 0 | 9.15E-01 |
| 3 | HDL-TC | HDL-C | -0.26 | 0.13 | 3.74E-02 | ----+--+- | 13 | 3.27E-01 | -0.18 | 0.13 | 1.52E-01 | -0.61 | ----+-++- | 9 | 3.64E-01 |
| 4 | LDL-TG | TG | -0.88 | 0.78 | 2.62E-01 | ++-----+- | 24 | 2.26E-01 | 0.97 | 0.67 | 1.51E-01 | 0.24 | +----+-++ | 50 | 4.40E-02 |
| 5 | HDL-TC | HDL-C | 0.43 | 0.15 | 3.58E-03 | +-+++++-- | 36 | 1.30E-01 | 0.65 | 0.15 | 7.57E-06 | 2.67 | +-+++++-- | 42 | 8.59E-02 |
| 6 | HDL-LDL | LDL-C | -0.38 | 0.30 | 2.07E-01 | +++-?+--- | 22 | 2.59E-01 | -0.65 | 0.30 | 3.06E-02 | 0.83 | +++-?---- | 18 | 2.89E-01 |
| 7 | HDL-TC | HDL-C | -0.01 | 0.12 | 9.54E-01 | ++-+-+--- | 0 | 4.68E-01 | 0.07 | 0.12 | 5.80E-01 | 0.22 | ++-+-+-+- | 0 | 6.77E-01 |
| 8 | HDL-LDL | HDL-C | -0.12 | 0.13 | 3.30E-01 | ++----++- | 0 | 6.03E-01 | 0.08 | 0.13 | 5.43E-01 | -0.22 | ++-+-+++- | 0 | 5.23E-01 |
| 9 | HDL-TC | HDL-C | -0.12 | 0.13 | 3.30E-01 | ++----++- | 0 | 6.03E-01 | -0.25 | 0.13 | 4.97E-02 | 0.82 | -+----++- | 0 | 4.36E-01 |
| 10 | LDL-TG | TG | -0.22 | 1.34 | 8.70E-01 | --++-++-? | 0 | 5.05E-01 | 0.95 | 1.13 | 3.97E-01 | 0.34 | +-++-++-? | 0 | 5.07E-01 |
| 11 | TC-TG | TG | -0.22 | 1.34 | 8.70E-01 | --++-++-? | 0 | 5.05E-01 | 1.95 | 1.28 | 1.29E-01 | 0.83 | -+++-+++? | 23 | 2.51E-01 |
| 12 | HDL-TC | HDL-C | 0.13 | 0.13 | 3.13E-01 | +++++--?? | 27 | 2.21E-01 | 0.04 | 0.13 | 7.83E-01 | -0.40 | ++++---?? | 15 | 3.12E-01 |
| 13 | HDL-LDL | HDL-C | 0.29 | 0.13 | 2.90E-02 | ++++?+++? | 0 | 9.31E-01 | 0.50 | 0.13 | 1.31E-04 | 2.34 | ++++?+++? | 0 | 9.82E-01 |
| 14 | TC-TG | TG | -0.35 | 0.74 | 6.42E-01 | ---+?-+-? | 0 | 7.81E-01 | -2.12 | 0.71 | 2.69E-03 | 2.38 | ----?---? | 0 | 8.58E-01 |
| 15 | HDL-TC | HDL-C | 0.16 | 0.17 | 3.59E-01 | +++++-+-+ | 28 | 1.97E-01 | 0.05 | 0.17 | 7.68E-01 | -0.33 | +++---+-+ | 32 | 1.60E-01 |
| 16 | LDL-TG | TG | 1.50 | 0.92 | 1.05E-01 | +++++++-+ | 26 | 2.10E-01 | 0.60 | 0.75 | 4.21E-01 | -0.60 | +++++-+-+ | 50 | 4.13E-02 |
| 17 | HDL-TC | HDL-C | -0.29 | 0.16 | 7.03E-02 | --+++--+- | 0 | 5.64E-01 | -0.39 | 0.16 | 1.48E-02 | 0.68 | ---+----- | 0 | 7.37E-01 |
| 18 | HDL-LDL | LDL-C | -0.03 | 0.28 | 9.24E-01 | --+--++-+ | 42 | 8.72E-02 | -0.22 | 0.28 | 4.25E-01 | 0.34 | --+-+++-+ | 48 | 5.45E-02 |
| 19 | TC-TG | TC | -1.03 | 0.46 | 2.55E-02 | +-----+-- | 33 | 1.52E-01 | 0.38 | 0.44 | 3.96E-01 | -1.19 | +--++++-- | 47 | 5.69E-02 |
| 20 | HDL-LDL | LDL-C | -0.13 | 0.28 | 6.39E-01 | ++--+---? | 0 | 5.24E-01 | 0.10 | 0.28 | 7.32E-01 | -0.06 | ++-+++--? | 0 | 5.44E-01 |
| 21 | TC-TG | TG | 0.21 | 1.12 | 8.53E-01 | +---+++-- | 46 | 6.37E-02 | 2.21 | 1.07 | 3.91E-02 | 1.34 | +-+-+++-- | 26 | 2.17E-01 |
| 22 | HDL-LDL | LDL-C | 0.31 | 0.46 | 4.98E-01 | +++-+--+- | 0 | 6.27E-01 | 1.13 | 0.45 | 1.27E-02 | 1.59 | ++++++-++ | 0 | 8.20E-01 |
| 23 | TC-TG | TC | 0.55 | 0.50 | 2.69E-01 | +-+-+--++ | 14 | 3.15E-01 | 2.27 | 0.48 | 2.00E-06 | 5.13 | ++++++-++ | 0 | 5.04E-01 |
| 24 | HDL-LDL | HDL-C | 0.56 | 0.12 | 3.16E-06 | +++++++++ | 0 | 9.83E-01 | 0.38 | 0.12 | 1.68E-03 | -2.73 | +-++++++ | 0 | 9.49E-01 |
| 25 | HDL-TC | HDL-C | 0.56 | 0.12 | 3.16E-06 | +++++++++ | 0 | 9.83E-01 | 0.66 | 0.12 | 4.04E-08 | 1.89 | +++++++++ | 0 | 9.61E-01 |
| 26 | LDL-TG | LDL-C | -1.95 | 0.28 | 4.63E-12 | --------- | 0 | 9.50E-01 | -1.66 | 0.28 | 3.14E-09 | -2.83 | --------- | 0 | 9.83E-01 |
| 27 | TC-TG | TC | -0.29 | 0.30 | 3.45E-01 | ++----+-- | 30 | 1.83E-01 | 0.18 | 0.29 | 5.42E-01 | -0.20 | +-+--+++- | 22 | 2.50E-01 |
| 28 | HDL-LDL | LDL-C | -1.72 | 0.30 | 5.96E-09 | ---+----- | 45 | 6.93E-02 | -2.03 | 0.29 | 4.20E-12 | 3.15 | -+-+----- | 54 | 2.64E-02 |
| 29 | TC-TG | TC | 4.48 | 0.62 | 3.38E-13 | +++++++++ | 31 | 1.74E-01 | 1.66 | 0.59 | 5.07E-03 | -10.18 | ++++-++-+ | 33 | 1.58E-01 |
| 30 | HDL-TG | TG | 2.29 | 0.84 | 6.60E-03 | +++++??++ | 0 | 4.90E-01 | -1.99 | 0.77 | 9.37E-03 | -0.15 | -++--??-- | 29 | 2.10E-01 |
| 31 | HDL-TG | TG | -0.35 | 0.86 | 6.87E-01 | +-+++++-? | 24 | 2.38E-01 | -3.17 | 0.79 | 6.10E-05 | 4.05 | --------? | 3 | 4.06E-01 |
| 32 | LDL-TG | TG | -0.39 | 0.81 | 6.33E-01 | -+++?-+-? | 43 | 1.01E-01 | 0.90 | 0.69 | 1.91E-01 | 0.52 | -+++?+++? | 0 | 6.39E-01 |
| 33 | TC-TG | TG | -0.39 | 0.81 | 6.33E-01 | -+++?-+-? | 43 | 1.01E-01 | 1.21 | 0.77 | 1.16E-01 | 0.74 | -+++?+++? | 52 | 5.22E-02 |
| 34 | HDL-TC | HDL-C | 0.35 | 0.23 | 1.31E-01 | -+-+-++++ | 0 | 8.94E-01 | 0.50 | 0.23 | 2.89E-02 | 0.66 | -+-++++++ | 0 | 9.37E-01 |
| 35 | HDL-TG | HDL-C | 0.35 | 0.23 | 1.31E-01 | -+-+-++++ | 0 | 8.94E-01 | -0.29 | 0.21 | 1.75E-01 | -0.12 | -+----+-- | 0 | 6.06E-01 |
| 36 | HDL-LDL | HDL-C | 0.35 | 0.23 | 1.31E-01 | -+-+-++++ | 0 | 8.94E-01 | 0.10 | 0.23 | 6.66E-01 | -0.71 | -+-+-++++ | 0 | 9.57E-01 |
| 37 | HDL-LDL | HDL-C | -0.97 | 0.18 | 8.13E-08 | ----?-?-? | 0 | 4.66E-01 | -0.54 | 0.18 | 2.82E-03 | -4.54 | +++-?-?-? | 25 | 2.50E-01 |
| 38 | HDL-TC | HDL-C | -0.97 | 0.18 | 8.13E-08 | ----?-?-? | 0 | 4.66E-01 | -1.15 | 0.17 | 3.40E-11 | 3.38 | ------?-? | 0 | 8.04E-01 |
| 39 | HDL-LDL | HDL-C | -0.01 | 0.12 | 9.58E-01 | -+--++-+- | 0 | 4.30E-01 | -0.14 | 0.12 | 2.49E-01 | 0.58 | -+--+--+- | 5 | 3.97E-01 |
| 40 | HDL-TC | TC | -0.24 | 0.39 | 5.45E-01 | --+-++--- | 3 | 4.12E-01 | 0.06 | 0.39 | 8.74E-01 | -0.21 | --+-++-+- | 5 | 3.91E-01 |

**Supplementary Table 2**. (continue)

| SNP info | Prior Studies | | |
|---|---|---|---|
| ID | Lead SNP | LD, % | Effect sign |
| 1 | rs1077514 | 0.4 | ??-? |
| 2 | rs2479409 | 4.6 | ?++? |
| 3 | rs2131925 | 100 | ?--- |
| 4 | rs629301 | 100 | ?--? |
| 5 | rs629301 | 100 | ?--? |
| 6 | rs4846914 | 100 | -??+ |
| 7 | rs514230 | 94 | ?--? |
| 8 | rs1367117 | 82.8 | ?++? |
| 9 | rs1367117 | 82.8 | ?++? |
| 10 | rs4299376 | 4.1 | ?++? |
| 11 | rs4299376 | 4.1 | ?++? |
| 12 | rs7570971 | 34.7 | ??+? |
| 13 | rs12916 | 93.9 | ?++? |
| 14 | rs12916 | 93.9 | ?++? |
| 15 | rs3177928 | 96.6 | ?++? |
| 16 | rs1564348 | 100 | ?++? |
| 17 | rs1564348 | 100 | ?++? |
| 18 | rs4142995 | 13.8 | -??? |
| 19 | rs17145738 | 100 | +??- |
| 20 | rs4731702 | 100 | +??? |
| 21 | rs9987289 | 73.4 | ---? |
| 22 | rs12678919 | 100 | +??- |
| 23 | rs12678919 | 100 | +??- |
| 24 | rs2954029 | 98 | +--- |
| 25 | rs2954029 | 98 | +--- |
| 26 | rs2954029 | 98 | +--- |
| 27 | rs10761731 | 85 | ???- |
| 28 | rs174546 | 100 | ---+ |
| 29 | rs964184 | 51.9 | +--- |
| 30 | rs3764261 | 23.2 | +-+- |
| 31 | rs7241918 | 96.4 | -?-? |
| 32 | rs6511720 | 20.2 | ?--? |
| 33 | rs6511720 | 20.2 | ?--? |
| 34 | rs10401969 | 100 | ?--- |
| 35 | rs10401969 | 100 | ?--- |
| 36 | rs10401969 | 100 | ?--- |
| 37 | rs4420638 | 100 | -++? |
| 38 | rs4420638 | 100 | -++? |
| 39 | rs6029526 | 72.3 | ?++? |
| 40 | rs6065906 | 100 | -??+ |

**SNP info**

ID is a sequential single nucleotide polymorphism (SNP) number; Chr = chromosome; Position is position in base pairs; Locus denotes locus name as used in previous studies; EA denotes minor allele used as an effect allele in an additive genetic model; EAF = EA frequency.

**Current Study**

Trait pair = a pair of lipid traits examined.

Beta denotes effect size and direction of the genetic association; SE = standard error.

Direction shows the signs of associations in each of the included cohorts ordered as CHS, FHS_C1, FHS_C2, FHS_C3, HRS, ARIC, CARDIA, MESA, and WHI, where "+" and "-" denote positive (increase) and negative (decrease) signs of statistical effects, respectively, and "?" indicates the lack of estimate.

$I^2$ is coefficient of heterogeneity in the meta-analysis; HetPVal is heterogeneity *p*-value in the meta-analysis.

dlogP is the difference of the log-base-10-transformed *p*-values in the unconditional and conditional analyses.

**Prior Studies**

Lead SNP is leading SNP identified in previous studies; LD = linkage disequilibrium between the lead SNPs and SNPs identified in the current study; Effect sign shows directions of genome-wide significant associations of the lead SNPs with HDL-C, LDL-C, TC, and TG reported in previous studies. Symbols "+" and "-" denote positive (increase) and negative (decrease) signs of statistical effects attained GW significance (i.e., $p \leq p_{GW}$), respectively, and "?" indicates associations, which did not attain GW significance level (i.e., $p > p_{GW}$).

**Supplementary Table 3. Replicated genetic associations with lipid traits substantially strengthened by dissecting antagonistic genetic heterogeneity.**

| SNP info | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **ID** | **SNP** | **Chr** | **Position** | **Locus** | **Gene** | **Function** | **EA** | **EAF** |
| 1 | rs4350231 | 1 | 62,922,660 | ANGPTL3 | DOCK7 | intron | a | 0.33 |
| 2 | rs4846914 | 1 | 230,295,691 | GALNT2 | GALNT2 | intron | g | 0.40 |
| 3 | rs780094 | 2 | 27,741,237 | GCKR | GCKR | intron | t | 0.42 |
| 4 | rs780094 | 2 | 27,741,237 | GCKR | GCKR | intron | t | 0.42 |
| 5 | rs6716987 | 2 | 136,963,494 | RAB3GAP1 | | intergenic | a | 0.34 |
| 6 | rs1461729 | 8 | 9,187,242 | PPP1R3B | LOC157273 | intron | a | 0.09 |
| 7 | rs1461729 | 8 | 9,187,242 | PPP1R3B | LOC157273 | intron | a | 0.09 |
| 8 | rs17321515 | 8 | 126,486,409 | TRIB1 | | intergenic | g | 0.47 |
| 9 | rs12686004 | 9 | 107,653,426 | ABCA1 | ABCA1 | intron | a | 0.12 |
| 10 | rs1051006 | 11 | 47,306,585 | LRP4 | MADD | missense | a | 0.17 |
| 11 | rs174547 | 11 | 61,570,783 | FADS1-2-3 | FADS1 | intron | c | 0.33 |
| 12 | rs174547 | 11 | 61,570,783 | FADS1-2-3 | FADS1 | intron | c | 0.33 |
| 13 | rs174547 | 11 | 61,570,783 | FADS1-2-3 | FADS1 | intron | c | 0.33 |
| 14 | rs651821 | 11 | 116,662,579 | APOA1 | APOA5 | UTR-5 | c | 0.07 |
| 15 | rs651821 | 11 | 116,662,579 | APOA1 | APOA5 | UTR-5 | c | 0.07 |
| 16 | rs7120963 | 11 | 116,830,261 | APOA1 | SIK3 | intron | t | 0.36 |
| 17 | rs261332 | 15 | 58,727,325 | LIPC | LIPC | intron | a | 0.20 |
| 18 | rs261332 | 15 | 58,727,325 | LIPC | LIPC | intron | a | 0.20 |
| 19 | rs289715 | 16 | 57,008,508 | CETP | CETP | intron | a | 0.12 |
| 20 | rs10468274 | 16 | 67,922,342 | LCAT | NRN1L | intron | a | 0.17 |
| 21 | rs16996185 | 19 | 19,720,788 | CILP2 | PBX4 | intron | g | 0.08 |
| 22 | rs3208856 | 19 | 45,296,806 | APOE | CBLC | missense | t | 0.03 |
| 23 | rs4420638 | 19 | 45,422,946 | APOE | APOC1 | nearGene-3 | g | 0.16 |

**Supplementary Table 3**. (continue)

| SNP info | Current Study | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Trait_1_unconditional | | | | | | | Trait_1_conditional | | | | | | |
| ID | Trait pair | Trait_1 | Beta | SE | P-value | Direction | $I^2$ | HetPVal | Beta | SE | P-value | dlogP | Direction | $I^2$ | HetPVal |
| 1 | HDL-TG | TG | -3.82 | 0.68 | 1.94E-08 | --------- | 33 | 1.51E-01 | -4.35 | 0.62 | 2.07E-12 | 3.97 | --------- | 11 | 3.45E-01 |
| 2 | TC-TG | TG | 3.57 | 0.75 | 1.75E-06 | ++++?++++ | 31 | 1.79E-01 | 3.89 | 0.71 | 4.95E-08 | 1.55 | ++++?++++ | 36 | 1.45E-01 |
| 3 | HDL-TG | TG | 7.72 | 0.68 | 3.96E-30 | +++++++++ | 44 | 7.55E-02 | 7.73 | 0.61 | 2.18E-36 | 6.26 | +++++++++ | 47 | 5.97E-02 |
| 4 | LDL-TC | TC | 2.32 | 0.31 | 3.29E-14 | +++++++++ | 0 | 9.46E-01 | 1.45 | 0.13 | 9.93E-30 | 15.52 | +++++++++ | 4 | 4.02E-01 |
| 5 | TC-TG | TC | 1.73 | 0.34 | 3.63E-07 | +++++++?? | 6 | 3.81E-01 | 1.87 | 0.32 | 7.86E-09 | 1.66 | +++++++?? | 19 | 2.87E-01 |
| 6 | HDL-LDL | HDL-C | -1.19 | 0.20 | 4.02E-09 | ------+-- | 20 | 2.64E-01 | -1.34 | 0.20 | 2.42E-11 | 2.22 | --------- | 27 | 2.07E-01 |
| 7 | HDL-LDL | LDL-C | -2.20 | 0.47 | 3.43E-06 | --------- | 0 | 9.85E-01 | -2.61 | 0.47 | 2.71E-08 | 2.10 | --------- | 0 | 9.37E-01 |
| 8 | HDL-TC | HDL-C | 0.56 | 0.12 | 3.16E-06 | +++++++++ | 0 | 9.83E-01 | 0.66 | 0.12 | 4.04E-08 | 1.89 | +++++++++ | 0 | 9.61E-01 |
| 9 | HDL-LDL | HDL-C | -0.88 | 0.18 | 1.04E-06 | -+------- | 9 | 3.58E-01 | -1.01 | 0.18 | 1.71E-08 | 1.78 | -+------- | 9 | 3.58E-01 |
| 10 | HDL-TG | HDL-C | 0.80 | 0.16 | 7.86E-07 | +-++++++++ | 17 | 2.91E-01 | 0.82 | 0.15 | 4.23E-08 | 1.27 | +-++++++++ | 31 | 1.74E-01 |
| 11 | TC-TG | TC | -2.18 | 0.32 | 1.61E-11 | --------- | 3 | 4.07E-01 | -2.55 | 0.31 | 1.14E-16 | 5.15 | -+------- | 49 | 4.66E-02 |
| 12 | TC-TG | TG | 3.42 | 0.71 | 1.53E-06 | +-+-+++++ | 43 | 8.08E-02 | 4.66 | 0.68 | 7.59E-12 | 5.30 | +-++++++++ | 60 | 1.13E-02 |
| 13 | HDL-LDL | LDL-C | -1.72 | 0.30 | 5.96E-09 | ---+----- | 45 | 6.93E-02 | -2.03 | 0.29 | 4.20E-12 | 3.15 | -+-+----- | 54 | 2.64E-02 |
| 14 | HDL-TC | HDL-C | -1.64 | 0.24 | 4.13E-12 | --------- | 31 | 1.71E-01 | -1.80 | 0.24 | 1.92E-14 | 2.33 | --------- | 24 | 2.32E-01 |
| 15 | HDL-TC | TC | 4.48 | 0.62 | 3.38E-13 | +++++++++ | 31 | 1.74E-01 | 4.91 | 0.61 | 9.22E-16 | 2.56 | +++++++++ | 8 | 4.38E-01 |
| 16 | HDL-TG | TG | 5.46 | 0.72 | 2.65E-14 | +++++++++ | 42 | 8.85E-02 | 6.20 | 0.65 | 1.82E-21 | 7.16 | +++++++++ | 0 | 5.04E-01 |
| 17 | LDL-TC | TC | 2.39 | 0.38 | 2.31E-10 | +++++++++ | 0 | 7.95E-01 | 2.27 | 0.16 | 8.12E-46 | 35.45 | +++++++++ | 0 | 7.39E-01 |
| 18 | HDL-TG | HDL-C | 1.58 | 0.15 | 2.73E-25 | +++++++++ | 34 | 1.49E-01 | 1.81 | 0.14 | 3.71E-38 | 12.87 | +-++++++++ | 35 | 1.35E-01 |
| 19 | HDL-TG | HDL-C | 1.92 | 0.20 | 7.47E-23 | +++++++++ | 0 | 7.28E-01 | 1.94 | 0.18 | 3.60E-27 | 4.32 | +++++++++ | 0 | 6.92E-01 |
| 20 | HDL-TG | HDL-C | 0.94 | 0.16 | 5.51E-09 | ++++++-++ | 45 | 7.14E-02 | 0.98 | 0.15 | 4.27E-11 | 2.11 | ++++++-++ | 45 | 7.13E-02 |
| 21 | HDL-TG | TG | -7.76 | 1.19 | 6.58E-11 | ------?-- | 16 | 3.03E-01 | -7.71 | 1.07 | 4.56E-13 | 2.16 | ------?-- | 32 | 1.75E-01 |
| 22 | TC-TG | TC | -4.71 | 0.92 | 2.74E-07 | ------?-? | 70 | 3.20E-03 | -5.48 | 0.87 | 3.01E-10 | 2.96 | ------?-? | 68 | 4.46E-03 |
| 23 | HDL-TC | HDL-C | -0.97 | 0.18 | 8.13E-08 | ----?-?-? | 0 | 4.66E-01 | -1.15 | 0.17 | 3.40E-11 | 3.38 | ------?-? | 0 | 8.04E-01 |

**Supplementary Table 3**. (continue)

| SNP info | Current Study | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Trait_2_conditional | | | | | | | Trait_2_conditional | | | | | | |
| ID | Trait pair | Trait_2 | Beta | SE | P-value | Direction | $I^2$ | HetPVal | Beta | SE | P-value | dlogP | Direction | $I^2$ | HetPVal |
| 1 | HDL-TC | HDL-C | -0.31 | 0.13 | 1.35E-02 | ----+--+- | 7 | 3.78E-01 | -0.57 | 0.12 | 8.07E-07 | 6.09 | --------- | 0 | 7.21E-01 |
| 2 | HDL-LDL | TC | -0.40 | 0.33 | 2.17E-01 | +++-?--+- | 20 | 2.73E-01 | -0.90 | 0.31 | 3.75E-03 | 1.76 | -++-?---- | 35 | 1.46E-01 |
| 3 | HDL-TC | HDL-C | 0.00 | 0.12 | 9.83E-01 | ++++----- | 13 | 3.26E-01 | 0.58 | 0.11 | 2.05E-07 | 6.68 | +++++++-+- | 0 | 5.69E-01 |
| 4 | LDL-TG | LDL-C | 0.92 | 0.28 | 1.12E-03 | +++++++++ | 0 | 9.72E-01 | -1.05 | 0.12 | 2.84E-19 | 15.60 | --------- | 22 | 2.45E-01 |
| 5 | HDL-TC | TG | -1.02 | 0.72 | 1.59E-01 | -+----+?? | 0 | 7.74E-01 | -2.13 | 0.69 | 2.09E-03 | 1.88 | -+-----?? | 0 | 7.01E-01 |
| 6 | HDL-LDL | LDL-C | -2.20 | 0.47 | 3.43E-06 | --------- | 0 | 9.85E-01 | -2.61 | 0.47 | 2.71E-08 | 2.10 | --------- | 0 | 9.37E-01 |
| 7 | HDL-TC | HDL-C | -1.19 | 0.20 | 4.02E-09 | ------+-- | 20 | 2.64E-01 | -1.34 | 0.20 | 2.42E-11 | 2.22 | --------- | 27 | 2.07E-01 |
| 8 | HDL-LDL | TC | -2.44 | 0.30 | 1.09E-15 | --------- | 0 | 9.77E-01 | -2.60 | 0.30 | 7.75E-18 | 2.15 | --------- | 0 | 9.88E-01 |
| 9 | HDL-TC | LDL-C | -1.32 | 0.43 | 1.91E-03 | -+--+---+ | 0 | 4.45E-01 | -1.60 | 0.42 | 1.38E-04 | 1.14 | -+--+---+ | 21 | 2.52E-01 |
| 10 | LDL-TG | TG | 0.01 | 0.92 | 9.90E-01 | -+--+++-- | 0 | 9.40E-01 | 1.98 | 0.84 | 1.84E-02 | 1.73 | ++++++++- | 0 | 9.43E-01 |
| 11 | TC-TG | TG | 3.42 | 0.71 | 1.53E-06 | +-+-+++++ | 43 | 8.08E-02 | 4.66 | 0.68 | 7.59E-12 | 5.30 | +-++++++ | 60 | 1.13E-02 |
| 12 | HDL-TC | TC | -2.18 | 0.32 | 1.61E-11 | --------- | 3 | 4.07E-01 | -2.55 | 0.31 | 1.14E-16 | 5.15 | -+------- | 49 | 4.66E-02 |
| 13 | HDL-LDL | HDL-C | -0.99 | 0.13 | 9.49E-15 | -+----+-- | 65 | 3.77E-03 | -1.08 | 0.13 | 1.93E-17 | 2.69 | -+----+-- | 64 | 5.00E-03 |
| 14 | TC-TG | TC | 4.48 | 0.62 | 3.38E-13 | +++++++++ | 31 | 1.74E-01 | 4.91 | 0.61 | 9.22E-16 | 2.56 | +++++++++ | 0 | 4.38E-01 |
| 15 | HDL-TC | HDL-C | -1.64 | 0.24 | 4.13E-12 | --------- | 31 | 1.71E-01 | -1.80 | 0.24 | 1.92E-14 | 2.33 | --------- | 24 | 2.32E-01 |
| 16 | LDL-TG | HDL-C | 0.24 | 0.13 | 5.95E-02 | +-++++--+ | 55 | 2.43E-02 | 0.68 | 0.12 | 4.91E-09 | 7.08 | +-++++++ | 44 | 7.45E-02 |
| 17 | HDL-TC | LDL-C | 0.05 | 0.35 | 8.75E-01 | -+++---++ | 0 | 9.16E-01 | -1.90 | 0.15 | 3.49E-38 | 37.40 | --------- | 0 | 8.43E-01 |
| 18 | HDL-LDL | TG | 3.27 | 0.82 | 6.17E-05 | ++++-++++ | 12 | 3.35E-01 | 6.82 | 0.74 | 3.57E-20 | 15.24 | +++++++++ | 0 | 8.15E-01 |
| 19 | TC-TG | TG | -0.27 | 1.03 | 7.90E-01 | ---++--+- | 26 | 2.11E-01 | 3.98 | 0.94 | 2.25E-05 | 4.54 | +-++++++- | 22 | 2.48E-01 |
| 20 | HDL-LDL | TG | 0.29 | 0.88 | 7.43E-01 | -+-++++-+ | 0 | 9.84E-01 | 2.54 | 0.80 | 1.49E-03 | 2.70 | +++++++++ | 0 | 9.77E-01 |
| 21 | TC-TG | HDL-C | 0.12 | 0.23 | 6.05E-01 | -+-+-+?+- | 5 | 3.89E-01 | -0.42 | 0.21 | 4.26E-02 | 1.15 | -+---+?-- | 48 | 6.26E-02 |
| 22 | HDL-LDL | TG | 5.75 | 2.01 | 4.19E-03 | +-++++?+? | 10 | 3.57E-01 | 8.49 | 1.91 | 8.67E-06 | 2.68 | +-++++?+? | 0 | 4.46E-01 |
| 23 | TC-TG | TC | 5.01 | 0.44 | 2.51E-30 | ++++++?+? | 66 | 7.39E-03 | 5.24 | 0.43 | 1.55E-33 | 3.21 | ++++++?+? | 62 | 1.47E-02 |

**Supplementary Table 3**. (continue)

| SNP info | Current Study Efficiency | | | Prior Studies | | |
|---|---|---|---|---|---|---|
| ID | Str | N | A | Lead SNP | LD, % | Effect sign |
| 1 | 51 | 9 | AP | rs1077514 | 0.4 | ??-? |
| 2 | 27 | 6 | AP | rs2479409 | 4.6 | ?++? |
| 3 | 21 | 7 | P | rs2131925 | 100 | ?--- |
| 4 | 115 | 9 | P | rs629301 | 100 | ?--? |
| 5 | 26 | 6 | AP | rs629301 | 100 | ?--? |
| 6 | 26 | 9 | AP | rs4846914 | 100 | -??+ |
| 7 | 38 | 9 | AP | rs514230 | 94 | ?--? |
| 8 | 34 | 9 | AP | rs1367117 | 82.8 | ?++? |
| 9 | 30 | 6 | AP | rs1367117 | 82.8 | ?++? |
| 10 | 21 | 7 | AP | rs4299376 | 4.1 | ?++? |
| 11 | 48 | 8 | AP | rs4299376 | 4.1 | ?++? |
| 12 | 91 | 8 | AP | rs7570971 | 34.7 | ??+? |
| 13 | 38 | 6 | AP | rs12916 | 93.9 | ?++? |
| 14 | 20 | 9 | AP | rs12916 | 93.9 | ?++? |
| 15 | 21 | 9 | AP | rs3177928 | 96.6 | ?++? |
| 16 | 53 | 8 | AP | rs1564348 | 100 | ?++? |
| 17 | 368 | 9 | P | rs1564348 | 100 | ?++? |
| 18 | 52 | 8 | AP | rs4142995 | 13.8 | -??? |
| 19 | 20 | 8 | P | rs17145738 | 100 | +??- |
| 20 | 26 | 8 | AP | rs4731702 | 100 | +??? |
| 21 | 21 | 6 | P | rs9987289 | 73.4 | ---? |
| 22 | 45 | 6 | AP | rs12678919 | 100 | +??- |
| 23 | 48 | 7 | AP | rs12678919 | 100 | +??- |

**SNP info**

ID is a sequential single nucleotide polymorphism (SNP) number; Chr = chromosome; Position is position in base pairs; Locus denotes locus name as used in previous studies.

Gene is a plausible biological candidate gene in the locus or the nearest annotated gene to the lead SNP was assigned; EA denotes minor allele used as an effect allele in an additive genetic model; EAF = EA frequency.

**Current Study**

Trait pair = a pair of lipid traits examined

Beta denotes effect size and direction of the genetic association; SE = standard error.

Direction shows the signs of associations in each of the included cohorts ordered as CHS, FHS_C1, FHS_C2, FHS_C3, HRS, ARIC, CARDIA, MESA, and WHI, where "+" and "-" denote positive (increase) and negative (decrease) signs of statistical effects, respectively, and "?" indicates the lack of estimate.

$I^2$ is coefficient of heterogeneity in the meta-analysis; HetPVal is heterogeneity *p*-value in the meta-analysis.
dlogP is the difference of the log-base-10-transformed *p*-values in the unconditional and conditional analyses.
Str denotes the strength of antagonistic heterogeneity defined as the relative change of log-transformed *p*-values (%), i.e., $100\times(\log_{10}(p_{cond})-\log_{10}(p_{uncond}))/\log_{10}(p_{uncond})$.
Column N shows the number of cohorts in which antagonistic heterogeneity was replicated; Column A reports anterior (A) and posterior (P) antagonistic heterogeneity observed in our unconditional and conditional analyses, respectively.

**Prior Studies**

Lead SNP is leading SNP identified in previous studies; LD = linkage disequilibrium between the lead SNPs and SNPs identified in the current study; Effect sign shows directions of genome-wide significant associations of the lead SNPs with HDL-C, LDL-C, TC, and TG reported in previous studies. Symbols "+" and "-" denote positive (increase) and negative (decrease) signs of statistical effects attained GW significance (i.e., $p\leq p_{GW}$), respectively, and "?" indicates associations, which did not attain GW significance level (i.e., $p>p_{GW}$).

**Supplementary Table 4. Extended table showing new genetic associations with lipid traits and the associations strongly affected by antagonistic genetic heterogeneity.**

| SNP info | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **ID** | **SNP** | **Chr** | **Position** | **Locus** | **Gene** | **Function** | **EA** | **EAF** |
| 1 | rs4350231 | 1 | 62,922,660 | ANGPTL3 | DOCK7 | intron | a | 0.33 |
| 2 | rs6544366 | 2 | 21,204,025 | APOB | | intergenic | t | 0.23 |
| 3 | rs780094 | 2 | 27,741,237 | GCKR | GCKR | intron | t | 0.42 |
| 4 | rs780094 | 2 | 27,741,237 | GCKR | GCKR | intron | t | 0.42 |
| 5 | rs10928512 | 2 | 135,451,302 | RAB3GAP1 | TMEM163 | intron | g | 0.47 |
| 6 | rs7607980 | 2 | 165,551,201 | COBLL1 | COBLL1 | missense | c | 0.12 |
| 7 | rs2394895 | 6 | 31,206,979 | HLA | | intergenic | c | 0.26 |
| 8 | rs2394895 | 6 | 31,206,979 | HLA | | intergenic | c | 0.26 |
| 9 | rs2394895 | 6 | 31,206,979 | HLA | | intergenic | c | 0.26 |
| 10 | rs9267531 | 6 | 31,636,742 | HLA | CSNK2B,LY6G5B | intron, nearGene-5 | g | 0.10 |
| 11 | rs9267531 | 6 | 31,636,742 | HLA | CSNK2B,LY6G5B | intron, nearGene-5 | g | 0.10 |
| 12 | rs17145738 | 7 | 72,982,874 | MLXIPL | TBL2 | nearGene-3 | t | 0.12 |
| 13 | rs17145738 | 7 | 72,982,874 | MLXIPL | TBL2 | nearGene-3 | t | 0.12 |
| 14 | rs13230111 | 7 | 130,437,124 | KLF14 | LOC105375508 | intron | g | 0.48 |
| 15 | rs263 | 8 | 19,812,812 | LPL | LPL | intron | t | 0.18 |
| 16 | rs3890182 | 9 | 107,647,655 | ABCA1 | ABCA1 | intron | a | 0.12 |
| 17 | rs3890182 | 9 | 107,647,655 | ABCA1 | ABCA1 | intron | a | 0.12 |
| 18 | rs651821 | 11 | 116,662,579 | APOA1 | APOA5 | UTR-5 | c | 0.07 |
| 19 | rs11216162 | 11 | 116,728,277 | APOA1 | SIK3 | intron | a | 0.18 |
| 20 | rs11216162 | 11 | 116,728,277 | APOA1 | SIK3 | intron | a | 0.18 |
| 21 | rs11216162 | 11 | 116,728,277 | APOA1 | SIK3 | intron | a | 0.18 |
| 22 | rs7120963 | 11 | 116,830,261 | APOA1 | SIK3 | intron | t | 0.36 |
| 23 | rs7120963 | 11 | 116,830,261 | APOA1 | SIK3 | intron | t | 0.36 |
| 24 | rs7298565 | 12 | 109,937,534 | MVK | UBE3B | missense | g | 0.46 |
| 25 | rs1109559 | 12 | 123,757,861 | SBNO1 | CDK2AP1 | nearGene-5 | g | 0.31 |
| 26 | rs1109559 | 12 | 123,757,861 | SBNO1 | CDK2AP1 | nearGene-5 | g | 0.31 |
| 27 | rs2038280 | 14 | 39,983,128 | FBXO33 | LOC105370460 | intron | g | 0.20 |
| 28 | rs261332 | 15 | 58,727,325 | LIPC | LIPC | intron | a | 0.20 |
| 29 | rs261332 | 15 | 58,727,325 | LIPC | LIPC | intron | a | 0.20 |
| 30 | rs289715 | 16 | 57,008,508 | CETP | CETP | intron | a | 0.12 |
| 31 | rs289715 | 16 | 57,008,508 | CETP | CETP | intron | a | 0.12 |
| 32 | rs10468274 | 16 | 67,922,342 | LCAT | NRN1L | intron | a | 0.17 |
| 33 | rs10468274 | 16 | 67,922,342 | LCAT | NRN1L | intron | a | 0.17 |
| 34 | rs10438978 | 18 | 47,158,186 | LIPG | LOC105372112 | intron | t | 0.17 |
| 35 | rs10438978 | 18 | 47,158,186 | LIPG | LOC105372112 | intron | t | 0.17 |

**Supplementary Table 4**. (continue)

| SNP info | Current Study | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Trait_1_unconditional | | | | | | | Trait_1_conditional | | | | | | |
| ID | Trait pair | Trait_1 | Beta | SE | P-value | Direction | $I^2$ | HetPVal | Beta | SE | P-value | dlogP | Direction | $I^2$ | HetPVal |
| 1 | HDL-TG | HDL-C | -0.31 | 0.13 | 1.35E-02 | ----+--+- | 7 | 3.78E-01 | -0.57 | 0.12 | 8.07E-07 | 6.09 | --------- | 0 | 7.21E-01 |
| 2 | HDL-TC | HDL-C | 0.78 | 0.15 | 1.20E-07 | +-++++++? | 0 | 7.87E-01 | 0.85 | 0.15 | 5.86E-09 | 1.31 | +-++++++? | 0 | 7.66E-01 |
| 3 | HDL-TG | HDL-C | 0.00 | 0.12 | 9.83E-01 | ++++----- | 13 | 3.26E-01 | 0.58 | 0.11 | 2.05E-07 | 6.68 | +++++++-+- | 0 | 5.69E-01 |
| 4 | LDL-TC | LDL-C | 0.92 | 0.28 | 1.12E-03 | +++++++++ | 0 | 9.72E-01 | -1.05 | 0.12 | 2.84E-19 | 15.60 | --------- | 22 | 2.45E-01 |
| 5 | HDL-LDL | LDL-C | 1.55 | 0.28 | 3.59E-08 | ++++++++? | 0 | 5.69E-01 | 1.65 | 0.28 | 3.12E-09 | 1.06 | ++++++++? | 0 | 5.67E-01 |
| 6 | TC-TG | TG | -5.09 | 0.91 | 2.27E-08 | ---+----- | 41 | 9.48E-02 | -4.96 | 0.87 | 1.19E-08 | 0.28 | ---+----- | 45 | 6.94E-02 |
| 7 | HDL-TG | HDL-C | -0.51 | 0.14 | 1.71E-04 | -+------- | 7 | 3.79E-01 | -0.62 | 0.12 | 8.14E-07 | 2.32 | --------- | 26 | 2.11E-01 |
| 8 | LDL-TC | LDL-C | 0.32 | 0.32 | 3.21E-01 | ++++---++ | 14 | 3.79E-01 | 0.72 | 0.13 | 5.09E-08 | 6.80 | +++++++++ | 45 | 6.89E-02 |
| 9 | LDL-TC | TC | -0.41 | 0.35 | 2.38E-01 | +--+---+- | 0 | 6.14E-01 | -0.78 | 0.14 | 3.56E-08 | 6.82 | --------- | 23 | 2.36E-01 |
| 10 | HDL-TG | TG | -4.34 | 1.04 | 3.16E-05 | ----+-+-- | 9 | 3.60E-01 | -5.28 | 0.95 | 2.81E-08 | 3.05 | ------+-- | 20 | 2.63E-01 |
| 11 | LDL-TC | LDL-C | -0.49 | 0.46 | 2.88E-01 | -+-++--+- | 22 | 2.45E-01 | 0.86 | 0.19 | 3.53E-06 | 4.91 | +++++++++ | 35 | 1.40E-01 |
| 12 | LDL-TC | LDL-C | 0.22 | 0.43 | 6.04E-01 | +--++++-- | 39 | 1.06E-01 | 1.04 | 0.18 | 2.61E-09 | 8.36 | +-++++++++ | 0 | 9.42E-01 |
| 13 | LDL-TC | TC | -1.03 | 0.46 | 2.55E-02 | +-----+-- | 33 | 1.52E-01 | -1.20 | 0.19 | 2.55E-10 | 8.00 | --------- | 0 | 9.57E-01 |
| 14 | LDL-TG | TG | -2.83 | 0.67 | 2.29E-05 | --------? | 19 | 2.77E-01 | -3.14 | 0.56 | 2.66E-08 | 2.94 | --------? | 2 | 4.13E-01 |
| 15 | TC-TG | TC | 0.77 | 0.39 | 4.86E-02 | +-+-+--+? | 60 | 3.73E-02 | 1.88 | 0.38 | 5.22E-07 | 4.97 | +-++++++? | 39 | 1.19E-01 |
| 16 | LDL-TC | LDL-C | -0.83 | 0.42 | 4.97E-02 | ++-----+- | 36 | 1.30E-01 | 0.94 | 0.18 | 1.76E-07 | 5.45 | ++++++-+- | 0 | 7.21E-01 |
| 17 | LDL-TC | TC | -1.99 | 0.46 | 1.52E-05 | -+-----+- | 35 | 1.38E-01 | -1.28 | 0.19 | 3.27E-11 | 5.67 | -+------- | 0 | 7.60E-01 |
| 18 | LDL-TC | LDL-C | 2.26 | 0.56 | 6.05E-05 | ++++-++-+ | 48 | 5.11E-02 | -1.17 | 0.23 | 5.43E-07 | 2.05 | --------- | 0 | 6.38E-01 |
| 19 | HDL-TG | TG | 2.29 | 0.87 | 8.84E-03 | -+-++++++ | 0 | 8.20E-01 | 3.96 | 0.80 | 6.53E-07 | 4.13 | +++++++++ | 0 | 7.72E-01 |
| 20 | LDL-TC | LDL-C | -0.18 | 0.36 | 6.25E-01 | +--+--++- | 0 | 4.36E-01 | -1.11 | 0.15 | 4.53E-13 | 12.14 | --------- | 0 | 7.13E-01 |
| 21 | LDL-TC | TC | 1.19 | 0.40 | 2.60E-03 | ++++++++- | 0 | 6.20E-01 | 1.30 | 0.17 | 8.27E-15 | 11.50 | +++++++++ | 0 | 8.70E-01 |
| 22 | HDL-TG | HDL-C | 0.24 | 0.13 | 5.95E-02 | +-++++--+ | 55 | 2.43E-02 | 0.68 | 0.12 | 4.91E-09 | 7.08 | +-++++++++ | 44 | 7.45E-02 |
| 23 | LDL-TC | LDL-C | 0.68 | 0.29 | 1.92E-02 | -+++-++++ | 45 | 6.92E-02 | -0.84 | 0.12 | 8.73E-12 | 9.34 | --------- | 24 | 2.31E-01 |
| 24 | TC-TG | TC | -1.61 | 0.30 | 1.10E-07 | -------- | 0 | 8.29E-01 | -1.62 | 0.29 | 2.55E-08 | 0.64 | --------- | 0 | 8.19E-01 |
| 25 | TC-TG | TC | 1.71 | 0.33 | 1.82E-07 | ++++++++- | 0 | 7.04E-01 | 1.80 | 0.31 | 9.04E-09 | 1.30 | +++++++++- | 34 | 1.44E-01 |
| 26 | HDL-LDL | HDL-C | 0.54 | 0.13 | 3.78E-05 | ++++++-++ | 0 | 7.11E-01 | 0.64 | 0.13 | 8.69E-07 | 1.64 | +++++++++ | 0 | 6.84E-01 |
| 27 | TC-TG | TC | 2.15 | 0.41 | 1.22E-07 | ++++?+-+? | 48 | 7.26E-02 | 2.20 | 0.39 | 1.32E-08 | 0.97 | ++++?+++? | 39 | 1.34E-01 |
| 28 | HDL-TG | TG | 3.27 | 0.82 | 6.17E-05 | ++++-++++ | 12 | 3.35E-01 | 6.82 | 0.74 | 3.57E-20 | 15.24 | +++++++++ | 0 | 8.15E-01 |
| 29 | LDL-TC | LDL-C | 0.05 | 0.35 | 8.75E-01 | -+++---++ | 0 | 9.16E-01 | -1.90 | 0.15 | 3.49E-38 | 37.40 | --------- | 0 | 8.43E-01 |
| 30 | LDL-TC | LDL-C | -0.93 | 0.44 | 3.54E-02 | ---+----- | 21 | 2.61E-01 | -1.83 | 0.18 | 1.38E-23 | 21.41 | --------- | 0 | 4.93E-01 |
| 31 | LDL-TC | TC | 1.22 | 0.48 | 1.17E-02 | --++++++- | 30 | 1.82E-01 | 1.99 | 0.20 | 3.25E-23 | 20.56 | +-++++++++ | 17 | 2.95E-01 |
| 32 | LDL-TC | LDL-C | -0.05 | 0.37 | 8.90E-01 | ++-++---+ | 0 | 5.17E-01 | -0.89 | 0.16 | 1.02E-08 | 7.94 | -+------- | 0 | 5.90E-01 |
| 33 | LDL-TC | TC | 0.92 | 0.40 | 2.31E-02 | ++++++-++ | 0 | 4.59E-01 | 1.04 | 0.17 | 8.71E-10 | 7.42 | +++++++++ | 0 | 5.28E-01 |
| 34 | LDL-TC | LDL-C | -0.06 | 0.38 | 8.65E-01 | -+-+--+-? | 0 | 5.65E-01 | 1.14 | 0.16 | 2.59E-13 | 12.52 | +++++++++? | 0 | 6.35E-01 |
| 35 | LDL-TC | TC | -1.69 | 0.41 | 3.76E-05 | ------+-? | 0 | 7.41E-01 | -1.36 | 0.17 | 8.28E-16 | 10.66 | --------? | 0 | 7.20E-01 |

**Supplementary Table 4**. (continue)

| SNP info | Current Study | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Trait_2_conditional | | | | | | | Trait_2_conditional | | | | | | |
| ID | Trait pair | Trait_2 | Beta | SE | P-value | Direction | $I^2$ | HetPVal | Beta | SE | P-value | dlogP | Direction | $I^2$ | HetPVal |
| 1 | HDL-TG | TG | -3.82 | 0.68 | 1.94E-08 | --------- | 33 | 1.51E-01 | -4.35 | 0.62 | 2.07E-12 | 3.97 | --------- | 11 | 3.45E-01 |
| 2 | HDL-TC | TC | -2.14 | 0.36 | 3.69E-09 | ------+-? | 17 | 2.99E-01 | -2.34 | 0.36 | 6.71E-11 | 1.74 | ------+-? | 12 | 3.40E-01 |
| 3 | HDL-TG | TG | 7.72 | 0.68 | 3.96E-30 | +++++++++ | 44 | 7.55E-02 | 7.73 | 0.61 | 2.18E-36 | 6.26 | +++++++++ | 47 | 5.97E-02 |
| 4 | LDL-TC | TC | 2.32 | 0.31 | 3.29E-14 | +++++++++ | 0 | 9.46E-01 | 1.45 | 0.13 | 9.93E-30 | 15.52 | +++++++++ | 4 | 4.02E-01 |
| 5 | HDL-LDL | HDL-C | 0.34 | 0.12 | 4.71E-03 | +++-++++? | 0 | 5.53E-01 | 0.42 | 0.12 | 5.36E-04 | 0.94 | +++-++++? | 0 | 6.39E-01 |
| 6 | TC-TG | TC | -0.03 | 0.45 | 9.56E-01 | +--+-+--+ | 0 | 7.90E-01 | 0.50 | 0.43 | 2.50E-01 | 0.58 | ++-+++-++ | 0 | 8.45E-01 |
| 7 | HDL-TG | TG | -1.09 | 0.74 | 1.40E-01 | +---+-+-- | 0 | 4.44E-01 | -2.26 | 0.67 | 7.66E-04 | 2.26 | --------- | 27 | 2.08E-01 |
| 8 | LDL-TC | TC | -0.41 | 0.35 | 2.38E-01 | +--+---+- | 0 | 6.14E-01 | -0.78 | 0.14 | 3.56E-08 | 6.82 | --------- | 23 | 2.36E-01 |
| 9 | LDL-TC | LDL-C | 0.32 | 0.32 | 3.21E-01 | ++++---++ | 14 | 3.15E-01 | 0.72 | 0.13 | 5.09E-08 | 6.80 | +++++++++ | 45 | 6.89E-02 |
| 10 | HDL-TG | HDL-C | -0.42 | 0.20 | 3.30E-02 | --+--+-+- | 0 | 5.53E-01 | -0.72 | 0.18 | 6.32E-05 | 2.72 | -+------- | 1 | 4.27E-01 |
| 11 | LDL-TC | TC | -1.83 | 0.50 | 2.34E-04 | ----+--+- | 0 | 5.67E-01 | -1.12 | 0.20 | 3.07E-08 | 3.88 | --------- | 24 | 2.30E-01 |
| 12 | LDL-TC | TC | -1.03 | 0.46 | 2.55E-02 | +-----+-- | 33 | 1.52E-01 | -1.20 | 0.19 | 2.55E-10 | 8.00 | --------- | 0 | 9.57E-01 |
| 13 | LDL-TC | LDL-C | 0.22 | 0.43 | 6.04E-01 | +--++++-- | 39 | 1.06E-01 | 1.04 | 0.18 | 2.61E-09 | 8.36 | +-++++++ | 0 | 9.42E-01 |
| 14 | LDL-TG | LDL-C | -0.13 | 0.28 | 6.39E-01 | ++--+---? | 0 | 5.24E-01 | 0.00 | 0.28 | 9.90E-01 | -0.19 | ++-+++--? | 0 | 5.42E-01 |
| 15 | TC-TG | TG | -7.48 | 0.83 | 1.43E-19 | --------? | 22 | 2.56E-01 | -7.91 | 0.79 | 9.10E-24 | 4.20 | --------? | 34 | 1.61E-01 |
| 16 | LDL-TC | TC | -1.99 | 0.46 | 1.52E-05 | -+-----+- | 35 | 1.38E-01 | -1.28 | 0.19 | 3.27E-11 | 5.67 | -+------- | 0 | 7.60E-01 |
| 17 | LDL-TC | LDL-C | -0.83 | 0.42 | 4.97E-02 | ++-----+- | 36 | 1.30E-01 | 0.94 | 0.18 | 1.76E-07 | 5.45 | ++++++-+- | 0 | 7.21E-01 |
| 18 | LDL-TC | TC | 4.48 | 0.62 | 3.38E-13 | +++++++++ | 31 | 1.74E-01 | 1.89 | 0.25 | 8.23E-14 | 0.61 | +++++++++ | 13 | 3.28E-01 |
| 19 | HDL-TG | HDL-C | 0.83 | 0.16 | 1.73E-07 | +++++++++ | 0 | 6.73E-01 | 1.01 | 0.15 | 5.05E-12 | 4.54 | +++++++++ | 0 | 6.89E-01 |
| 20 | LDL-TC | TC | 1.19 | 0.40 | 2.60E-03 | ++++++++- | 0 | 6.20E-01 | 1.30 | 0.17 | 8.27E-15 | 11.50 | +++++++++ | 0 | 8.70E-01 |
| 21 | LDL-TC | LDL-C | -0.18 | 0.36 | 6.25E-01 | +--+--++- | 0 | 4.36E-01 | -1.11 | 0.15 | 4.53E-13 | 12.14 | --------- | 0 | 7.13E-01 |
| 22 | HDL-TG | TG | 5.46 | 0.72 | 2.65E-14 | +++++++++ | 42 | 8.85E-02 | 6.20 | 0.65 | 1.82E-21 | 7.16 | +++++++++ | 0 | 5.04E-01 |
| 23 | LDL-TC | TC | 1.94 | 0.32 | 8.27E-10 | ++++-++++ | 13 | 3.28E-01 | 1.15 | 0.13 | 4.55E-18 | 8.26 | +++++++++ | 0 | 5.21E-01 |
| 24 | TC-TG | TG | -0.22 | 0.65 | 7.35E-01 | ------+++ | 0 | 9.84E-01 | 0.77 | 0.62 | 2.16E-01 | 0.53 | +-++++++ | 0 | 1.00E+00 |
| 25 | TC-TG | TG | -0.37 | 0.70 | 6.04E-01 | --+-+-+-+ | 0 | 6.33E-01 | -1.50 | 0.68 | 2.63E-02 | 1.36 | --+-----+ | 20 | 2.61E-01 |
| 26 | HDL-LDL | LDL-C | 1.20 | 0.30 | 6.50E-05 | +++++++-- | 43 | 8.12E-02 | 1.37 | 0.30 | 3.55E-06 | 1.26 | ++++++++- | 48 | 5.24E-02 |
| 27 | TC-TG | TG | -0.65 | 0.89 | 4.62E-01 | --++?---? | 0 | 7.01E-01 | -1.94 | 0.85 | 2.23E-02 | 1.32 | ----?---? | 0 | 9.82E-01 |
| 28 | HDL-TG | HDL-C | 1.58 | 0.15 | 2.73E-25 | +++++++++ | 34 | 1.49E-01 | 1.81 | 0.14 | 3.71E-38 | 12.87 | +-++++++ | 35 | 1.35E-01 |
| 29 | LDL-TC | TC | 2.39 | 0.38 | 2.31E-10 | +++++++++ | 0 | 7.95E-01 | 2.27 | 0.16 | 8.12E-46 | 35.45 | +++++++++ | 0 | 7.39E-01 |
| 30 | LDL-TC | TC | 1.22 | 0.48 | 1.17E-02 | --++++++- | 30 | 1.82E-01 | 1.99 | 0.20 | 3.25E-23 | 20.56 | +-++++++ | 17 | 2.95E-01 |
| 31 | LDL-TC | LDL-C | -0.93 | 0.44 | 3.54E-02 | ---+----- | 21 | 2.61E-01 | -1.83 | 0.18 | 1.38E-23 | 21.41 | --------- | 0 | 4.93E-01 |
| 32 | LDL-TC | TC | 0.92 | 0.40 | 2.31E-02 | ++++++-++ | 0 | 4.59E-01 | 1.04 | 0.17 | 8.71E-10 | 7.42 | +++++++++ | 0 | 5.28E-01 |
| 33 | LDL-TC | LDL-C | -0.05 | 0.37 | 8.90E-01 | ++-++---+ | 0 | 5.17E-01 | -0.89 | 0.16 | 1.02E-08 | 7.94 | -+------- | 0 | 5.90E-01 |
| 34 | LDL-TC | TC | -1.69 | 0.41 | 3.76E-05 | ------+-? | 0 | 7.41E-01 | -1.36 | 0.17 | 8.28E-16 | 10.66 | --------? | 0 | 7.20E-01 |
| 35 | LDL-TC | LDL-C | -0.06 | 0.38 | 8.65E-01 | -+-+--+-? | 0 | 5.65E-01 | 1.14 | 0.16 | 2.59E-13 | 12.52 | +++++++++? | 0 | 6.35E-01 |

**Supplementary Table 4**. (continue)

| SNP info | Current Study Efficiency | | | Prior Studies | | |
|---|---|---|---|---|---|---|
| ID | Str | N | A | Lead SNP | LD, % | Effect sign |
| 1 | 326 | 9 | AP | rs2131925 | 97.8 | ?--- |
| 2 | 19 | 6 | AP | rs1367117 | 10.7 | ?++? |
| 3 | 88144 | 7 | P | rs1260326 | 92 | ??++ |
| 4 | 529 | 9 | P | rs1260326 | 92 | ??++ |
| 5 | 14 | 7 | AP | rs7570971 | 16 | ??+? |
| 6 | 4 | 6 | P | rs12328675 | 96.2 | +??? |
| 7 | 62 | 9 | AP | rs3177928 | 5.7 | ?++? |
| 8 | 1378 | 9 | AP | rs3177928 | 5.7 | ?++? |
| 9 | 1093 | 9 | AP | rs3177928 | 5.7 | ?++? |
| 10 | 68 | 7 | AP | rs3177928 | 2.1 | ?++? |
| 11 | 908 | 9 | P | rs3177928 | 2.1 | ?++? |
| 12 | 3813 | 8 | AP | rs17145738 | 100 | +??- |
| 13 | 502 | 8 | AP | rs17145738 | 100 | +??- |
| 14 | 63 | 5 | P | rs4731702 | 100 | +??? |
| 15 | 378 | 7 | AP | rs12678919 | 33.8 | +??- |
| 16 | 418 | 6 | P | rs1883025 | 13.8 | -?-? |
| 17 | 118 | 6 | P | rs1883025 | 13.8 | -?-? |
| 18 | 49 | 9 | P | rs964184 | 51.9 | +--- |
| 19 | 201 | 9 | AP | rs964184 | 9.9 | +--- |
| 20 | 5943 | 9 | AP | rs964184 | 9.9 | +--- |
| 21 | 445 | 9 | AP | rs964184 | 9.9 | +--- |
| 22 | 578 | 8 | AP | rs964184 | 25.2 | +--- |
| 23 | 544 | 9 | P | rs964184 | 25.2 | +--- |
| 24 | 9 | 8 | P | rs7134594 | 96 | -??? |
| 25 | 19 | 7 | AP | rs4759375 | 14.1 | +??? |
| 26 | 37 | 8 | AP | rs4759375 | 14.1 | +??? |
| 27 | 14 | 7 | AP | | | ???? |
| 28 | 362 | 8 | AP | rs1532085 | 0.3 | +?++ |
| 29 | 64325 | 9 | P | rs1532085 | 0.3 | +?++ |
| 30 | 1475 | 8 | AP | rs3764261 | 17.5 | +-+- |
| 31 | 1065 | 8 | AP | rs3764261 | 17.5 | +-+- |
| 32 | 15756 | 8 | AP | rs16942887 | 69.1 | +??? |
| 33 | 454 | 8 | AP | rs16942887 | 69.1 | +??? |
| 34 | 19932 | 8 | P | rs7241918 | 96.4 | -?-? |
| 35 | 241 | 8 | P | rs7241918 | 96.4 | -?-? |

**SNP info**

ID is a sequential single nucleotide polymorphism (SNP) number; Chr = chromosome; Position is position in base pairs; Locus denotes locus name as used in previous studies.

Gene is a plausible biological candidate gene in the locus or the nearest annotated gene to the lead SNP was assigned; EA denotes minor allele used as an effect allele in an additive genetic model; EAF = EA frequency.

**Current Study**

Trait pair = a pair of lipid traits examined

Beta denotes effect size and direction of the genetic association; SE = standard error.

Direction shows the signs of associations in each of the included cohorts ordered as CHS, FHS_C1, FHS_C2, FHS_C3, HRS, ARIC, CARDIA, MESA, and WHI, where "+" and "-" denote positive (increase) and negative (decrease) signs of statistical effects, respectively, and "?" indicates the lack of estimate.

$I^2$ is coefficient of heterogeneity in the meta-analysis; HetPVal is heterogeneity *p*-value in the meta-analysis.

dlogP is the difference of the log-base-10-transformed *p*-values in the unconditional and conditional analyses.

Str denotes the strength of antagonistic heterogeneity defined as the relative change of log-transformed *p*-values (%), i.e., $100\times(\log_{10}(p_{cond})-\log_{10}(p_{uncond}))/\log_{10}(p_{uncond})$.

Column N shows the number of cohorts in which antagonistic heterogeneity was replicated; Column A reports anterior (A) and posterior (P) antagonistic heterogeneity observed in our unconditional and conditional analyses, respectively.

**Prior Studies**

Lead SNP is leading SNP identified in previous studies; LD = linkage disequilibrium between the lead SNPs and SNPs identified in the current study; Effect sign shows directions of genome-wide significant associations of the lead SNPs with HDL-C, LDL-C, TC, and TG reported in previous studies. Symbols "+" and "-" denote positive (increase) and negative (decrease) signs of statistical effects attained GW significance (i.e., $p\leq p_{GW}$), respectively, and "?" indicates associations, which did not attain GW significance level (i.e., $p>p_{GW}$).