Lipid and Metabolic Syndrome Traits in Coronary Artery Disease: A Mendelian Randomization Study

**Data Supplement**

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A

LDL-C Effect Size from MVP vs LDL-C Effect Size from GLGC

- Line of Best Fit
- Line of Unity (y=x)

145 SNPs
$R^2 = .93$

B

HDL-C Effect Size from MVP vs HDL-C Effect Size from GLGC

- Line of Best Fit
- Line of Unity (y=x)

147 SNPs
$R^2 = .87$

C

TG Effect Size from MVP vs TG Effect Size from GLGC

- Line of Best Fit
- Line of Unity (y=x)

146 SNPs
$R^2 = .91$
Supplemental Figure S1: Comparison of lipid trait effects from Million Veteran Program and Global Lipid Genetics Consortium GWAS

Points represent genome-wide significant lipid trait SNPs selected from the Million Veteran Program (MVP) GWAS where data from the Global Lipid Genetics Consortium (GLGC) GWAS was also available. Regression line (solid) and line of unity e.g. MVP estimate = GLGC estimate (dashed) are shown. Shaded (gray) region represents 95% confidence band for line of best fit. Deviation of solid line from dashed line represents attenuation of average effect estimate magnitude in the larger Million Veteran Program dataset. 

(A-C) Plot of LDL-C (A), HDL-C (B), or TG (C) effect size in s.d. units from GLGC against LDL-C (A), HDL-C (B), or TG (C) effect size in s.d. units from MVP.
Supplemental Figure S2

(A) HDL-C SNPs filtered at $P<2e-05$ for pleiotropic traits

57 SNPs after filtering

(B) HDL-C SNPs filtered at $P<0.05$ for pleiotropic traits

13 SNPs after filtering

(C) HDL-C SNPs filtered at $P<0.1$ for pleiotropic traits

6 SNPs after filtering

(D) TG SNPs filtered at $P<2e-05$ for pleiotropic traits

36 SNPs after filtering

(E) TG SNPs filtered at $P<0.05$ for pleiotropic traits

3 SNPs after filtering

(F) TG SNPs filtered at $P<0.1$ for pleiotropic traits

2 SNPs after filtering
Supplemental Figure S2: Presence of residual pleiotropy in sets of lipid trait-restricted SNPs

Each plot represents a histogram of pleiotropic trait P-values for restricted sets of HDL-C and TG SNPs generated by filtering out SNPs with significant associations for other lipid and metabolic syndrome traits at the specified P-value threshold. P-value for pleiotropic trait represents the minimum (most significant) of other lipid and metabolic syndrome trait P-values for a given HDL-C or TG SNP. (A-B) Distributions of pleiotropic trait P-values for 57 HDL-C SNPs (A) or 36 TG SNPs (B) generated by filtering out pleiotropic SNPs at a Bonferroni-corrected P-value threshold of \( P < 2 \times 10^{-5} \). (C-D) Distributions of pleiotropic trait P-values for 13 HDL-C SNPs (C) or 3 TG SNPs (D) generated by filtering out pleiotropic SNPs at a nominal P-value threshold of \( P < 0.05 \). (E-F) Distributions of pleiotropic trait P-values for 6 HDL-C SNPs (E) or 2 TG SNPs (F) generated by filtering out pleiotropic SNPs at a liberal P-value threshold of \( P < 0.1 \).
Supplemental Table S1. Genetic overlap at 185 lipid SNPs from Do, et al.

| Exposure | Pleiotropic Trait | BMI, T2D, or SBP |
|----------|------------------|------------------|
|          | LDL-C            | HDL-C            | TG   | BMI | T2D | SBP | BMI, T2D, or SBP |
| LDL-C    | 91%             | 30%             | 34%  | 18% | 9%  | 16% | 36%             |
| HDL-C    | 21%             | 87%             | 51%  | 28% | 22% | 26% | 47%             |
| TG       | 40%             | 63%             | 90%  | 28% | 22% | 32% | 52%             |

Percent of SNPs that are genome-wide significant ($P < 1 \times 10^{-8}$) for the exposure trait in Do, et al. with a secondary (pleiotropic trait) exposure that is significant after Bonferroni correction ($P < 2 \times 10^{-5}$). Diagonal entries for the lipid traits represent replication in the Million Veteran Program dataset.
Supplemental Table S2. SNPs identified as pleiotropic outliers by MR-PRESSO.

| SNP          | Outlier test P < 0.05 in: | Locus | LDL-C Beta | LDL-C P  | HDL-C Beta | HDL-C P  | TG Beta | TG P  |
|--------------|---------------------------|-------|------------|----------|------------|----------|---------|-------|
| rs186696265  | LT MR LTMS MR             | LPA   | 0.186      | 4.2E-40  | 0.025      | 8.1E-02  | -0.022  | 1.2E-01|
| rs10455872   | LT MR LTMS MR             | LPA   | -0.088     | 2.8E-54  | -0.021     | 2.3E-04  | 0.013   | 2.3E-02|
| rs11751347   | LT MR LPA                 |       | -0.035     | 6.0E-11  | -0.064     | 2.4E-32  | 0.037   | 4.2E-12|
| rs4977574    | LT MR 9p21                |       | 0.017      | 2.3E-10  | -0.001     | 6.3E-01  | 0.007   | 1.1E-02|
| rs653178     | LT MR SH2B3               |       | 0.026      | 3.7E-20  | 0.021      | 3.8E-14  | -0.002  | 4.6E-01|
| rs2306363    | LT MR MALATI              |       | 0.015      | 4.3E-05  | 0.023      | 4.6E-10  | -0.017  | 2.3E-06|
| rs28394864   | LT MR ZNF652              |       | 0.0001     | 9.7E-01  | -0.011     | 9.0E-05  | 0.022   | 8.0E-15|
| rs79949326   | LT MR DAGLB               |       | 0.011      | 1.2E-03  | 0.024      | 3.2E-13  | 0.002   | 6.4E-01|
| rs10811647   | LTMS MR 9p21              |       | 0.011      | 7.2E-05  | -0.005     | 1.1E-01  | 0.008   | 7.5E-03|

| SNP          | BMI Beta | BMI P       | T2D Beta | T2D P       | SBP Beta | SBP P       | CAD Beta | CAD P       |
|--------------|----------|-------------|----------|-------------|----------|-------------|----------|-------------|
| rs186696265  | -0.0016  | 8.5E-01     | 0.023    | 4.1E-01     | 0.525    | 1.1E-04     | 0.546    | 2.0E-97     |
| rs10455872   | 0.0045   | 1.8E-01     | -0.020   | 1.0E-01     | -0.073   | 2.3E-01     | -0.314   | 2E-153      |
| rs11751347   | -0.0004  | 9.0E-01     | 0.015    | 1.6E-01     | -0.096   | 6.5E-02     | -0.077   | 3.6E-14     |
| rs4977574    | 0.0018   | 2.8E-01     | -0.028   | 8.1E-06     | -0.094   | 1.7E-03     | -0.179   | 9E-223      |
| rs653178     | 0.0091   | 1.3E-08     | -0.021   | 1.5E-03     | -0.576   | 6.8E-80     | -0.055   | 1.1E-23     |
| rs2306363    | 0.0021   | 3.8E-01     | -0.040   | 3.8E-07     | -0.436   | 5.2E-31     | -0.041   | 4.9E-09     |
| rs28394864   | 0.0082   | 1.8E-05     | 0.002    | 7.1E-01     | 0.244    | 5.6E-16     | 0.040    | 1.7E-12     |
| rs79949326   | 0.0006   | 7.7E-01     | -0.024   | 1.2E-03     | -0.101   | 3.8E-03     | -0.031   | 1.7E-06     |
| rs10811647   | 0.0016   | 3.9E-01     | -0.045   | 2.0E-12     | -0.041   | 1.8E-01     | -0.147   | 1E-159      |

LT MR: Lipid trait MR

LTMS MR: Lipid and metabolic syndrome trait MR

Beta: Effect size from GWAS association
Supplemental Table S3. Multivariable MR of lipid traits in CAD, including 8 SNPs identified as pleiotropic outliers by MR-PRESSO.

| Multivariable MR-IVW | OR  | CI     | P          | I²  |
|----------------------|-----|--------|------------|-----|
| LDL-C                | 1.60| 1.47 - 1.74 | 1.8 × 10⁻²³ | 90% |
| HDL-C                | 0.86| 0.78 - 0.94 | 0.0013     | 90% |
| TG                   | 1.21| 1.09 - 1.33 | 0.00022    | 90% |

| Multivariable MR-Egger | OR  | CI     | P          | I²  | Int.    | Int. P |
|------------------------|-----|--------|------------|-----|---------|--------|
| LDL-C                  | 1.66| 1.49 - 1.84 | 2.6 × 10⁻¹⁹ | 90% | -0.0020 | 0.23   |
| HDL-C                  | 0.86| 0.77 - 0.97 | 0.014      | 90% | -0.00027 | 0.88   |
| TG                     | 1.20| 1.07 - 1.36 | 0.0024     | 90% | 8.6 × 10⁻⁵ | 0.96   |

Results of multivariable regression of CAD effect size on LDL-C, HDL-C, and TG effect size with the intercept fixed at zero (multivariable MR-IVW), or with estimation of the intercept (multivariable MR-Egger), including 8 pleiotropic SNPs identified by MR-PRESSO.

MR-IVW: Mendelian randomization, inverse-variance weighted

MR-Egger: Mendelian randomization-Egger regression

OR: odds ratio per unit change in exposure trait

CI: 95% confidence interval

Int.: MR-Egger Intercept
Supplemental Table S4. Multivariable MR of lipid and metabolic syndrome traits in CAD, including
3 SNPs identified as pleiotropic outliers by MR-PRESSO.

|            | Multivariable MR-IVW | Multivariable MR-Egger |
|------------|----------------------|------------------------|
|            | OR       | CI       | P          | I^2  | OR       | CI       | P          | I^2  | Int.    | Int. P |
| LDL-C      | 1.56     | 1.47 - 1.65 | 3.6 × 10^{-50} | 77%  | 1.66     | 1.56 - 1.76 | 2.1 × 10^{-54} | 77%  | -0.0019 | 1.6 × 10^{6} |
| HDL-C      | 0.88     | 0.83 - 0.93 | 2.3 × 10^{-5}   | 77%  | 0.88     | 0.83 - 0.94 | 0.00025 | 77%  | -0.00024 | 0.60 |
| TG         | 1.15     | 1.07 - 1.22 | 3.0 × 10^{-5}   | 77%  | 1.17     | 1.10 - 1.26 | 6.3 × 10^{-6}   | 77%  | -0.00078 | 0.084 |
| BMI        | 1.32     | 1.23 - 1.41 | 8.5 × 10^{-16}  | 77%  | 1.47     | 1.33 - 1.62 | 7.0 × 10^{-14}  | 77%  | -0.0016 | 0.0039 |
| T2D        | 1.09     | 1.06 - 1.12 | 2.7 × 10^{-9}   | 77%  | 1.07     | 1.04 - 1.11 | 7.1 × 10^{-5}   | 77%  | 0.00090 | 0.090 |
| SBP        | 1.038    | 1.034 - 1.042 | 1.8 × 10^{-73}  | 77%  | 1.036    | 1.031 - 1.042 | 1.1 × 10^{-38}  | 77%  | 0.00032 | 0.52 |

Results of multivariable regression of CAD effect size on LDL-C, HDL-C, TG, BMI, T2D, and SBP
effect size with the intercept fixed at zero (multivariable MR-IVW), or with estimation of the intercept
(multivariable MR-Egger), including 3 pleiotropic SNPs identified by MR-PRESSO.

MR-IVW: Mendelian randomization, inverse-variance weighted
MR-Egger: Mendelian randomization-Egger regression
OR: odds ratio per unit change in exposure trait
CI: 95% confidence interval
Int.: MR-Egger Intercept
Supplemental Table S5. Lipid trait SNPs with large effect sizes.

| SNP             | Trait with Large Effect: | Locus  | LDL-C Beta | LDL-C P   | CAD Beta | CAD P  |
|-----------------|--------------------------|--------|------------|-----------|----------|--------|
| rs118147862     | LDL-C                    | APOE-C1| 0.398      | <1E-300   | 0.127    | 1.9E-16|
| rs11591147      | LDL-C                    | PCSK9  | 0.395      | 3E-257    | 0.241    | 1.9E-22|
| rs7254892       | LDL-C                    | APOE-C1| 0.337      | <1E-300   | 0.103    | 1.7E-10|
| rs143020224     | LDL-C                    | LDLR   | 0.162      | <1E-300   | 0.111    | 5.7E-34|
| rs77542162      | LDL-C                    | ABCA6  | 0.162      | 4.0E-52   | 0.023    | 0.288  |
| rs429358        | LDL-C                    | APOE-C1| 0.162      | <1E-300   | 0.089    | 3.3E-27|
| rs116843064     | HDL-C                    | ANGPTL4| 0.258      | 3E-137    | -0.140   | 3.6E-10|
| rs268           | HDL-C                    | LPL    | 0.241      | 2E-107    | -0.127   | 4.4E-8 |
| rs77960347      | HDL-C                    | LIPG   | 0.233      | 2.9E-73   | -0.104   | 8.8E-5 |
| rs72836561      | HDL-C                    | CD300LG| 0.199      | 1E-123    | -0.057   | 0.0022 |
| rs143868709     | HDL-C                    | CETP   | 0.182      | 2.0E-14   | -0.041   | 0.37   |
| rs117738782     | HDL-C                    | CETP   | 0.173      | 7.2E-24   | -0.012   | 0.72   |
| rs1801177       | HDL-C                    | LPL    | 0.162      | 3.1E-75   | -0.130   | 4.9E-9 |
| rs116843064     | TG                       | ANGPTL4| 0.252      | 6E-134    | 0.140    | 3.6E-10|
| rs61905116      | TG                       | APOA1-C3| 0.250     | <1E-300   | 0.059    | 7.2E-7 |
| rs7350481       | TG                       | APOA1-C3| 0.227     | <1E-300   | 0.056    | 1.0E-6 |
| rs268           | TG                       | LPL    | 0.217      | 4.8E-85   | 0.127    | 4.4E-8 |
| rs72836561      | TG                       | CD300LG| 0.164      | 7.5E-84   | 0.057    | 0.0022 |

Beta: Effect size from GWAS association
Large effect: Beta > 0.15 for lipid trait (in units of s.d.)
Supplemental Table S6. Lipid and metabolic trait effect sizes for selected HDL-C-modifying loci.

| SNP         | Locus | LDL Beta | LDL P   | HDL Beta | HDL P   | TG Beta | TG P   | BMI Beta | BMI P |
|-------------|-------|----------|---------|----------|---------|---------|---------|----------|-------|
| rs77960347  | LIPG  | 0.075    | 4E-09   | 0.233    | 3E-73   | 0.046   | 4E-04   | -7E-04   | 0.93  |
| rs17712538  | LIPG  | 0.008    | 0.004   | 0.018    | 9E-11   | 0.001   | 0.75    | -4E-04   | 0.80  |
| rs2156552   | LIPG  | 0.018    | 2E-06   | 0.065    | 4E-64   | 0.011   | 0.003   | 0.005    | 0.01  |
| rs9958734   | LIPG  | 0.024    | 2E-05   | 0.067    | 2E-32   | 0.009   | 0.10    | -0.003   | 0.42  |
| rs56070533  | LCAT  | 0.002    | 0.55    | 0.078    | 9E-95   | -0.009  | 0.02    | -0.002   | 0.41  |
| rs28578193  | LCAT  | -0.011   | 0.06    | 0.065    | 4E-28   | -0.007  | 0.22    | 0.004    | 0.56  |
| rs2218260   | LIPC  | 0.019    | 4E-09   | 0.001    | 0.86    | 0.008   | 0.01    | 0.001    | 0.50  |
| rs140525318 | LIPC  | -0.004   | 0.77    | 0.078    | 7E-11   | -0.019  | 0.12    | -0.004   | 0.45  |
| rs261291    | LIPC  | 0.006    | 0.03    | 0.092    | 4E-238  | 0.015   | 5E-08   | 0.001    | 0.60  |
| rs1077834   | LIPC  | 0.007    | 0.02    | 0.084    | 1E-172  | 0.021   | 5E-12   | -0.002   | 0.27  |
| rs11071371  | LIPC  | 0.005    | 0.26    | 0.053    | 3E-36   | 0.013   | 0.003   | -0.005   | 0.04  |
| rs261337    | LIPC  | -0.004   | 0.39    | 0.030    | 8E-10   | 0.003   | 0.57    | -0.003   | 0.34  |

| SNP         | Locus | T2D Beta | T2D P   | SBP Beta | SBP P   | CAD Beta | CAD P   |
|-------------|-------|----------|---------|----------|---------|----------|---------|
| rs77960347  | LIPG  | 0.015    | 0.59    | 0.081    | 0.55    | -0.104   | 9E-05   |
| rs17712538  | LIPG  | 0.017    | 0.009   | -8E-04   | 0.98    | -0.005   | 0.44    |
| rs2156552   | LIPG  | 0.010    | 0.24    | -0.080   | 0.04    | -0.010   | 0.16    |
| rs9958734   | LIPG  | 0.028    | 0.06    | -0.052   | 0.48    | -0.006   | 0.56    |
| rs56070533  | LCAT  | 0.001    | 0.89    | 0.034    | 0.47    | 0.019    | 0.03    |
| rs28578193  | LCAT  | -0.049   | 0.20    | -        | -       | 0.017    | 0.46    |
| rs2218260   | LIPC  | -0.014   | 0.04    | 0.033    | 0.28    | -0.009   | 0.12    |
| rs140525318 | LIPC  | -0.023   | 0.27    | -        | -       | -0.004   | 0.85    |
| rs261291    | LIPC  | -0.024   | 3E-04   | 0.045    | 0.16    | 0.019    | 0.001   |
| rs1077834   | LIPC  | -0.005   | 0.56    | 0.011    | 0.76    | 0.025    | 5E-05   |
| rs11071371  | LIPC  | -0.022   | 0.02    | 0.025    | 0.58    | 0.019    | 0.03    |
| rs261337    | LIPC  | -6E-04   | 0.96    | 0.002    | 0.98    | 0.014    | 0.18    |

Beta: Effect size from GWAS association

- : SBP data not available (missing data)
Supplemental Table S7. Lipid and metabolic trait effect sizes for selected TG-modifying loci.

| SNP          | Locus | LDL Beta | LDL P | HDL Beta | HDL P | TG Beta | TG P | BMI Beta | BMI P |
|--------------|-------|----------|-------|----------|-------|---------|------|----------|-------|
| rs191430997  | LPL   | -0.026   | 0.07  | -0.080   | 5E-08 | 0.096   | 5E-11| 0.013    | 0.21  |
| rs79821925   | LPL   | 0.007    | 0.71  | -0.107   | 1E-08 | 0.139   | 1E-13| -0.007   | 0.48  |
| rs7003470    | LPL   | 0.006    | 0.09  | -0.015   | 3E-05 | 0.021   | 9E-09| 0.003    | 0.18  |
| rs1027265    | LPL   | 0.004    | 0.30  | -0.038   | 3E-18 | 0.048   | 1E-28| 0.002    | 0.38  |
| rs287        | LPL   | -0.006   | 0.05  | -0.104   | 5E-260| 0.118   <1E-300| 0.006  | 0.005  |
| rs268        | LPL   | -0.047   | 1E-05 | -0.241   | 2E-107| 0.217   | 5E-85| -0.004   | 0.53  |
| rs16842      | LPL   | -0.011   | 3E-04 | -0.024   | 8E-17 | 0.022   | 1E-14| -3E-04   | 0.88  |
| rs1801177    | LPL   | -0.010   | 0.27  | -0.162   | 3E-75 | 0.144   | 1E-58| 0.002    | 0.80  |
| rs34288216   | LPL   | -0.001   | 0.70  | -0.029   | 5E-19 | 0.026   | 5E-15| -0.005   | 0.03  |
| rs8107967    | ANGPTL4| -0.002  | 0.45  | -0.017   | 2E-10 | 0.018   | 1E-10| 0.005    | 0.003 |
| rs116843064  | ANGPTL4| -0.054   | 1E-07 | -0.258   | 3E-137| 0.252   | 6E-134| -0.005   | 0.52  |
| rs11500536   | ANGPTL4| -0.007   | 0.13  | -0.030   | 8E-11 | 0.038   | 2E-16| 0.002    | 0.63  |
| rs139340094  | MLXIPL| -0.003   | 0.74  | -0.025   | 0.02  | 0.061   | 3E-09| -0.002   | 0.68  |
| rs13234131   | MLXIPL| -0.017   | 7E-05 | -0.036   | 2E-16 | 0.128   | 4E-191| -0.014   | 2E-06 |
| rs62466267   | MLXIPL| -0.008   | 0.16  | -0.016   | 0.004 | 0.047   | 1E-17| -0.002   | 0.67  |
| rs799157     | MLXIPL| 0.007    | 0.46  | -0.038   | 2E-05 | 0.087   | 3E-22| -0.012   | 0.004 |
| rs174537     | FADS1  | -0.028   | 3E-19 | -0.031   | 2E-22 | 0.062   | 2E-86| 0.003    | 0.09  |

| SNP          | Locus | T2D Beta | T2D P | SBP Beta | SBP P | CAD Beta | CAD P |
|--------------|-------|----------|-------|----------|-------|----------|-------|
| rs191430997  | LPL   | -0.002   | 0.96  | -        | -     | -9E-04   | 0.98  |
| rs79821925   | LPL   | 0.050    | 0.14  | -        | -     | 0.015    | 0.66  |
| rs7003470    | LPL   | 0.016    | 0.09  | 0.020    | 0.66  | 0.003    | 0.74  |
| rs1027265    | LPL   | 0.017    | 0.06  | -0.005   | 0.92  | 0.016    | 0.05  |
| rs287        | LPL   | 0.037    | 6E-07 | 0.073    | 0.04  | 0.045    | 9E-12 |
| rs268        | LPL   | 0.031    | 0.20  | 0.047    | 0.68  | 0.127    | 4E-08 |
| rs16842      | LPL   | -1E-04   | 0.99  | 0.013    | 0.70  | 0.017    | 0.002 |
| rs1801177    | LPL   | 0.065    | 0.01  | 0.067    | 0.58  | 0.130    | 5E-09 |
| rs34288216   | LPL   | 0.012    | 0.17  | -3E-04   | 0.99  | 0.037    | 1E-06 |
| rs8107967    | ANGPTL4| 0.044    | 1E-11 | 0.032    | 0.30  | 0.006    | 0.32  |
| rs116843064  | ANGPTL4| 0.099    | 2E-05 | 0.374    | 0.001 | 0.140    | 4E-10 |
| rs11500536   | ANGPTL4| 0.013    | 0.36  | -0.100   | 0.14  | 0.043    | 2E-04 |
| rs139340094  | MLXIPL| -0.024   | 0.33  | 0.038    | 0.74  | 0.001    | 0.94  |
| rs13234131   | MLXIPL| -0.039   | 1E-04 | 0.094    | 0.04  | 0.008    | 0.36  |
| rs62466267   | MLXIPL| 0.035    | 0.05  | 0.199    | 0.001 | 0.008    | 0.51  |
| rs799157     | MLXIPL| 0.035    | 0.04  | -        | -     | 0.030    | 0.05  |
| rs174537     | FADS1  | -0.028   | 3E-05 | -0.050   | 0.12  | -0.016   | 0.004 |
Beta: Effect size from GWAS association

- : SBP data not available (missing data)