# Supplemental materials

# Causal Effects of Circulating Lipid Traits on Epithelial Ovarian

# Cancer: A Two-Sample Mendelian Randomization Study

**Contents**

**Supplemental Table S1.** Associations of genetically predicted apolipoprotein A1 (APOA1) with EOC risks in MR analyses

| Main outcome | Method | No. of SNPs | OR (95% CI) | P for association | P for heterogeneity test | P for MR-Egger intercept | P for MR-PRESSO Global test |
|---|---|---|---|---|---|---|---|
| | IVW | 263 | 1.02(0.95-1.11) | 0.562 | <1 x10-3 | 0.824 | |
| | MR Egger | 263 | 1.01(0.89-1.15) | 0.851 | <1 x10-3 | | |
| All EOC | Weighted median | 263 | 0.97(0.87-1.10) | 0.666 | | | |
| | MR-PRESSO (outlier corrected, 1 outlier) | 262 | 1.01(1.01-1.02) | 0.722 | | | <1 x10-4 |
| | IVW | 263 | 1.17(0.93-1.48) | 0.176 | 0.002 | 0.102 | |
| | MR Egger | 263 | 0.92(0.64-1.33) | 0.662 | 0.002 | | |
| Clear cell OC | Weighted median | 263 | 1.07(0.76-1.52) | 0.692 | | | |
| | MR-PRESSO (raw, 0 outliers) | 263 | 1.17(1.15-1.18) | 0.189 | | | 0.001 |
| | IVW | 263 | 0.96(0.82-1.13) | 0.635 | 0.061 | 0.722 | |
| | MR Egger | 263 | 1.00(0.78-1.28) | 0.987 | 0.057 | | |
| Endometrioid OC | Weighted median | 263 | 1.03(0.82-1.30) | 0.799 | | | |
| | MR-PRESSO (raw, 0 outliers) | 263 | 0.95(0.94-0.96) | 0.539 | | | 0.051 |
| LMPOC | IVW | 263 | 0.87(0.75-1.01) | 0.066 | 0.245 | 1.000 | |

| | Method | N | OR(CI) | | | | |
|---|---|---|---|---|---|---|---|
| | MR Egger | 263 | 0.87(0.69-1.10) | 0.251 | 0.231 | | |
| | Weighted median | 263 | 0.81(0.64-1.03) | 0.080 | | | |
| | MR-PRESSO (raw, 0 outliers) | 263 | 0.86(0.86-0.87) | 0.053 | | | 0.239 |
| HGLGSOC | IVW | 263 | 1.03(0.95-1.13) | 0.474 | 0.001 | 0.879 | |
| | MR Egger | 263 | 1.02(0.89-1.18) | 0.744 | 0.001 | | |
| | Weighted median | 263 | 1.00(0.87-1.15) | 0.990 | | | |
| | MR-PRESSO (outlier corrected, 1 outlier) | 262 | 1.02(1.02-1.02) | 0.641 | | | 0.002 |
| HGSOC | IVW | 263 | 1.04(0.95-1.15) | 0.362 | $<1 \times 10^{-3}$ | 0.888 | |
| | MR Egger | 263 | 1.04(0.89-1.20) | 0.647 | $<1 \times 10^{-3}$ | | |
| | Weighted median | 263 | 0.99(0.86-1.14) | 0.902 | | | |
| | MR-PRESSO (outlier corrected, 1 outlier) | 262 | 1.03(1.03-1.04) | 0.491 | | | $<1 \times 10^{-3}$ |
| LGSOC | IVW | 263 | 0.84(0.66-1.08) | 0.180 | 0.384 | 0.834 | |
| | MR Egger | 263 | 0.82(0.55-1.21) | 0.319 | 0.368 | | |
| | Weighted median | 263 | 0.86(0.59-1.26) | 0.446 | | | |
| | MR-PRESSO (raw, 0 outliers) | 263 | 0.84(0.82-0.85) | 0.155 | | | 0.348 |

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|---|---|---|---|---|---|---|---|
| LGLMSOC | IVW | 263 | 0.84(0.73-0.98) | 0.022 | 0.464 | 0.559 | |
| | MR Egger | 263 | 0.80(0.63-1.01) | 0.061 | 0.453 | | |
| | Weighted median | 263 | 0.89(0.70-1.11) | 0.296 | | | |
| | MR-PRESSO (raw, 0 outliers) | 263 | 0.83(0.82-0.84) | 0.014 | | | 0.361 |
| LMSOC | IVW | 263 | 0.84(0.71-1.01) | 0.059 | 0.648 | 0.642 | |
| | MR Egger | 263 | 0.80(0.60-1.06) | 0.124 | 0.635 | | |
| | Weighted median | 263 | 0.90(0.68-1.20) | 0.478 | | | |
| | MR-PRESSO (raw, 0 outliers) | 263 | 0.83(0.82-0.84) | 0.034 | | | 0.589 |
| MOC: invasive and low malignant potential | IVW | 263 | 1.04(0.88-1.22) | 0.640 | 0.043 | 0.117 | |
| | MR Egger | 263 | 1.22(0.94-1.59) | 0.130 | 0.050 | | |
| | Weighted median | 263 | 1.15(0.88-1.51) | 0.296 | | | |
| | MR-PRESSO (raw, 0 outliers) | 263 | 1.06(1.05-1.07) | 0.480 | | | 0.042 |
| Invasive MOC | IVW | 263 | 1.15(0.93-1.42) | 0.185 | 0.193 | 0.078 | |
| | MR Egger | 263 | 1.45(1.04-2.03) | 0.028 | 0.221 | | |
| | Weighted median | 263 | 1.23(0.86-1.74) | 0.258 | | | |

| | Method | SNP | OR(95%CI) | P | | | |
|---|---|---|---|---|---|---|---|
| | MR-PRESSO (raw, 0 outliers) | 263 | 1.18(1.17-1.20) | 0.113 | | | 0.196 |
| LMMOC | IVW | 263 | 0.91(0.72-1.14) | 0.393 | 0.337 | 0.538 | |
| | MR Egger | 263 | 0.99(0.69-1.42) | 0.957 | 0.328 | | |
| | Weighted median | 263 | 1.03(0.70-1.52) | 0.887 | | | |
| | MR-PRESSO (raw, 0 outliers) | 263 | 0.92(0.90-0.93) | 0.445 | | | 0.354 |

Abbreviations: APOA1, apolipoprotein A1; MR, mendelian randomization; IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval; SNP, single-nucleotide polymorphism; OC, ovarian cancer; EOC, epithelial ovarian cancer; SOC, serous ovarian cancer; MOC, mucinous ovarian cancer; LMPOC, low malignant potential ovarian cancer; HGLGSOC, high-grade and low-grade serous ovarian cancer; HGSOC, high-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer; LGLMSOC, serous ovarian cancer: low-grade and low malignant potential; LMSOC, serous ovarian cancer: low malignant potential; LMMOC, low malignant potential mucinous ovarian cancer.

**Supplemental Table S2.** Associations of genetically predicted apolipoprotein B (APOB) with EOC risks in MR analyses.

| Main outcome | Method | No. of SNPs | OR (95% CI) | P for association | P for heterogeneity test | P for MR-Egger intercept | P for MR-PRESSO Global test |
|---|---|---|---|---|---|---|---|
| All EOC | IVW | 176 | 1.03(0.95-1.11) | 0.461 | 0.001 | 0.001 | |
| | MR Egger | 176 | 1.00(0.90-1.11) | 0.959 | 0.001 | | |
| | Weighted median | 176 | 1.04(0.93-1.15) | 0.512 | | | |
| | MR-PRESSO (raw, 0 outliers) | 176 | 1.03(1.02-1.04) | 0.436 | | | 0.001 |
| Clear cell OC | IVW | 176 | 1.01(0.82-1.25) | 0.895 | 0.173 | 0.836 | |
| | MR Egger | 176 | 0.99(0.75-1.32) | 0.965 | 0.161 | | |
| | Weighted median | 176 | 1.15(0.84-1.57) | 0.395 | | | |
| | MR-PRESSO (raw, 0 outliers) | 176 | 1.02(1.00-1.04) | 0.856 | | | 0.170 |
| Endometrioid OC | IVW | 176 | 1.06(0.90-1.24) | 0.516 | 0.002 | 0.734 | |
| | MR Egger | 176 | 1.03(0.82-1.28) | 0.805 | 0.001 | | |
| | Weighted median | 176 | 0.95(0.74-1.21) | 0.660 | | | |
| | MR-PRESSO (raw, 0 outliers) | 176 | 1.05(1.04-1.07) | 0.528 | | | 0.002 |
| LMPOC | IVW | 176 | 0.92(0.80-1.07) | 0.271 | 0.262 | 0.502 | |

| | Method | N | OR(95%CI) | P | | | |
|---|---|---|---|---|---|---|---|
| | MR Egger | 176 | 0.88(0.72-1.07) | 0.208 | 0.252 | | |
| | Weighted median | 176 | 0.94(0.76-1.16) | 0.549 | | | |
| | MR-PRESSO (raw, 0 outliers) | 176 | 0.92(0.91-0.94) | 0.286 | | | 0.277 |
| HGLGSOC | IVW | 176 | 1.01(0.93-1.10) | 0.773 | 0.006 | 0.279 | |
| | MR Egger | 176 | 0.97(0.86-1.09) | 0.601 | 0.006 | | |
| | Weighted median | 176 | 1.00(0.89-1.13) | 0.980 | | | |
| | MR-PRESSO (raw, 0 outliers) | 176 | 1.01(1.01-1.02) | 0.757 | | | 0.007 |
| HGSOC | IVW | 176 | 1.01(0.93-1.11) | 0.785 | 0.004 | 0.330 | |
| | MR Egger | 176 | 0.97(0.86-1.10) | 0.644 | 0.004 | | |
| | Weighted median | 176 | 1.04(0.92-1.17) | 0.558 | | | |
| | MR-PRESSO (raw, 0 outliers) | 176 | 1.01(1.01-1.02) | 0.771 | | | 0.006 |
| LGSOC | IVW | 176 | 1.08(0.84-1.38) | 0.558 | 0.096 | 0.738 | |
| | MR Egger | 176 | 1.04(0.74-1.45) | 0.836 | 0.088 | | |
| | Weighted median | 176 | 0.98(0.67-1.43) | 0.929 | | | |
| | MR-PRESSO (raw, 0 outliers) | 176 | 1.08(1.06-1.10) | 0.545 | | | 0.109 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| LGLMSOC | IVW | 176 | 1.03(0.89-1.19) | 0.683 | 0.286 | 0.199 | |
| | MR Egger | 176 | 0.94(0.78-1.15) | 0.570 | 0.299 | | |
| | Weighted median | 176 | 0.95(0.75-1.19) | 0.640 | | | |
| | MR-PRESSO (raw, 0 outliers) | 176 | 1.03(1.02-1.04) | 0.687 | | | 0.319 |
| LMSOC | IVW | 176 | 1.01(0.85-1.20) | 0.881 | 0.838 | 0.284 | |
| | MR Egger | 176 | 0.93(0.73-1.17) | 0.537 | 0.841 | | |
| | Weighted median | 176 | 0.98(0.75-1.28) | 0.888 | | | |
| | MR-PRESSO (raw, 0 outliers) | 176 | 1.01(1.00-1.02) | 0.892 | | | 0.857 |
| MOC: invasive and low malignant potential | IVW | 176 | 0.95(0.80-1.12) | 0.530 | 0.021 | 0.307 | |
| | MR Egger | 176 | 1.03(0.82-1.29) | 0.814 | 0.021 | | |
| | Weighted median | 176 | 1.08(0.85-1.36) | 0.545 | | | |
| | MR-PRESSO (raw, 0 outliers) | 176 | 0.95(0.94-0.97) | 0.587 | | | 0.015 |
| Invasive MOC | IVW | 176 | 1.09(0.87-1.36) | 0.447 | 0.008 | 0.230 | |
| | MR Egger | 176 | 1.24(0.91-1.68) | 0.170 | 0.009 | | |
| | Weighted median | 176 | 1.25(0.89-1.75) | 0.191 | | | |

| | Method | No. of SNPs | OR (95% CI) | P | | | |
|---|---|---|---|---|---|---|---|
| | MR-PRESSO (raw, 0 outliers) | 176 | 1.09(1.07-1.11) | 0.431 | | | 0.009 |
| LMMOC | IVW | 176 | 0.78(0.61-0.99) | 0.038 | 0.041 | 0.823 | |
| | MR Egger | 176 | 0.80(0.58-1.10) | 0.172 | 0.037 | | |
| | Weighted median | 176 | 0.90(0.63-1.29) | 0.570 | | | |
| | MR-PRESSO (outlier corrected, 1 outlier) | 175 | 0.77(0.76-0.79) | 0.030 | | | 0.026 |

Abbreviations: APOB, apolipoprotein B; MR, mendelian randomization; IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval; SNP, single-nucleotide polymorphism; OC, ovarian cancer; EOC, epithelial ovarian cancer; SOC, serous ovarian cancer; MOC, mucinous ovarian cancer; LMPOC, low malignant potential ovarian cancer; HGLGSOC, high-grade and low-grade serous ovarian cancer; HGSOC, high-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer; LGLMSOC, serous ovarian cancer: low-grade and low malignant potential; LMSOC, serous ovarian cancer: low malignant potential; LMMOC, low malignant potential mucinous ovarian cancer.

**Supplemental Table S3.** Associations of genetically predicted low-density lipoprotein cholesterol (LDL) with EOC risks in MR analyses.

| Main outcome | Method | No. of SNPs | OR (95% CI) | P for association | P for heterogeneity test | P for MR-Egger intercept | P for MR-PRESSO Global test |
|---|---|---|---|---|---|---|---|
| | IVW | 158 | 1.04(0.95-1.14) | 0.433 | <1 x10-3 | 0.553 | |
| | MR Egger | 158 | 1.01(0.88-1.15) | 0.927 | <1 x10-3 | | |
| All EOC | Weighted median | 158 | 1.03(0.91-1.16) | 0.617 | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 1.04(1.03-1.05) | 0.434 | | | <1 x10-3 |
| | IVW | 158 | 0.99(0.79-1.26) | 0.963 | 0.760 | 0.673 | |
| | MR Egger | 158 | 0.94(0.67-1.33) | 0.732 | 0.746 | | |
| Clear cell OC | Weighted median | 158 | 1.07(0.74-1.57) | 0.707 | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 0.99(0.98-1.01) | 0.961 | | | 0.772 |
| | IVW | 158 | 1.12(0.92-1.36) | 0.247 | 0.001 | 0.323 | |
| Endometrioid OC | MR Egger | 158 | 1.01(0.76-1.35) | 0.956 | 0.001 | | |
| | Weighted median | 158 | 1.03(0.79-1.35) | 0.803 | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 1.12(1.10-1.14) | 0.249 | | | 0.001 |

| | Method | nSNP | OR(95%CI) | P | | | |
|---|---|---|---|---|---|---|---|
| LMPOC | IVW | 158 | 0.90(0.77-1.07) | 0.230 | 0.599 | 0.918 | |
| | MR Egger | 158 | 0.90(0.71-1.14) | 0.375 | 0.577 | | |
| | Weighted median | 158 | 0.91(0.71-1.17) | 0.471 | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 0.90(0.89-0.92) | 0.224 | | | 0.607 |
| HGLGSOC | IVW | 158 | 1.03(0.93-1.13) | 0.632 | 0.006 | 0.357 | |
| | MR Egger | 158 | 0.97(0.84-1.13) | 0.723 | 0.006 | | |
| | Weighted median | 158 | 1.00(0.87-1.14) | 0.945 | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 1.03(1.02-1.03) | 0.633 | | | 0.009 |
| HGSOC | IVW | 158 | 1.03(0.93-1.15) | 0.539 | 0.002 | 0.336 | |
| | MR Egger | 158 | 0.98(0.83-1.14) | 0.769 | 0.002 | | |
| | Weighted median | 158 | 1.03(0.90-1.19) | 0.637 | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 1.03(1.03-1.04) | 0.540 | | | 0.002 |
| LGSOC | IVW | 158 | 0.96(0.72-1.28) | 0.778 | 0.261 | 0.864 | |
| | MR Egger | 158 | 0.99(0.65-1.50) | 0.948 | 0.243 | | |
| | Weighted median | 158 | 0.85(0.55-1.31) | 0.453 | | | |

| Outcome | Method | nSNP | OR (95% CI) | P | Col5 | Col6 | Col7 |
|---|---|---|---|---|---|---|---|
| | MR-PRESSO (raw, 0 outliers) | 158 | 0.96(0.94-0.98) | 0.778 | | | 0.273 |
| LGLMSOC | IVW | 158 | 1.00(0.84-1.18) | 0.961 | 0.216 | 0.714 | |
| | MR Egger | 158 | 0.96(0.74-1.24) | 0.762 | 0.202 | | |
| | Weighted median | 158 | 0.93(0.72-1.21) | 0.604 | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 1.00(0.98-1.01) | 0.961 | | | 0.232 |
| LMSOC | IVW | 158 | 1.02(0.83-1.24) | 0.875 | 0.810 | 0.531 | |
| | MR Egger | 158 | 0.95(0.70-1.27) | 0.723 | 0.800 | | |
| | Weighted median | 158 | 0.90(0.65-1.24) | 0.512 | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 1.02(1.00-1.03) | 0.869 | | | 0.815 |
| MOC: invasive and low malignant potential | IVW | 158 | 0.91(0.75-1.11) | 0.341 | 0.015 | 0.192 | |
| | MR Egger | 158 | 1.05(0.79-1.40) | 0.751 | 0.017 | | |
| | Weighted median | 158 | 1.09(0.82-1.44) | 0.565 | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 0.91(0.90-0.92) | 0.342 | | | 0.016 |
| Invasive MOC | IVW | 158 | 1.05(0.81-1.36) | 0.696 | 0.028 | 0.174 | |
| | MR Egger | 158 | 1.28(0.88-1.87) | 0.205 | 0.032 | | |

| | Method | No. of SNP | OR (95% CI) | P value | | | | P value |
|---|---|---|---|---|---|---|---|---|
| | Weighted median | 158 | 1.20(0.81-1.77) | 0.368 | | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 1.05(1.03-1.07) | 0.697 | | | | 0.028 |
| LMMOC | IVW | 158 | 0.74(0.56-0.97) | 0.030 | 0.054 | 0.590 | | |
| | MR Egger | 158 | 0.80(0.53-1.20) | 0.282 | 0.050 | | | |
| | Weighted median | 158 | 0.66(0.43-1.01) | 0.053 | | | | |
| | MR-PRESSO (raw, 0 outliers) | 158 | 0.74(0.72-0.75) | 0.031 | | | | 0.050 |

Abbreviations: LDL, low-density lipoprotein cholesterol; MR, mendelian randomization; IVW, inverse-variance weighted; OR, odds ratio; CI, confidence interval; SNP, single-nucleotide polymorphism; OC, ovarian cancer; EOC, epithelial ovarian cancer; SOC, serous ovarian cancer; MOC, mucinous ovarian cancer; LMPOC, low malignant potential ovarian cancer; HGLGSOC, high-grade and low-grade serous ovarian cancer; HGSOC, high-grade serous ovarian cancer; LGSOC, low-grade serous ovarian cancer; LGLMSOC, serous ovarian cancer: low-grade and low malignant potential; LMSOC, serous ovarian cancer: low malignant potential; LMMOC, low malignant potential mucinous ovarian cancer.