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Two-sample Mendelian randomization analysis reveals causal relationships between blood lipids and venous thromboembolism

Wei Huang,[1,2*] Yan Zou,[2*] Kun Zhang,[2*] Shi Yao,[3] Shi-Hao Tang,[2] Hao Wu,[2] Peng-Fei Wang,[1] Han-Zhong Xue,[1] Tie-Lin Yang,[2] Kun Zhang[1] and Yan Guo[1,2]

[1]Department of Trauma Surgery, Honghui Hospital, College of Medicine, Xi'an Jiaotong University; [2]Key Laboratory of Biomedical Information Engineering of Ministry of Education, Biomedical Informatics & Genomics Center, School of Life Science and Technology, Xi'an Jiaotong University and [3]National and Local Joint Engineering Research Center of Biodiagnosis and Biotherapy, The Second Affiliated Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, China

WH, YZ and KZ contributed equally as co-first authors.

Correspondence: Y. Guo
guoyan253@xjtu.edu.cn

K. Zhang
hhyyzk@126.com

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Supplementary Material

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Supplementary Methods

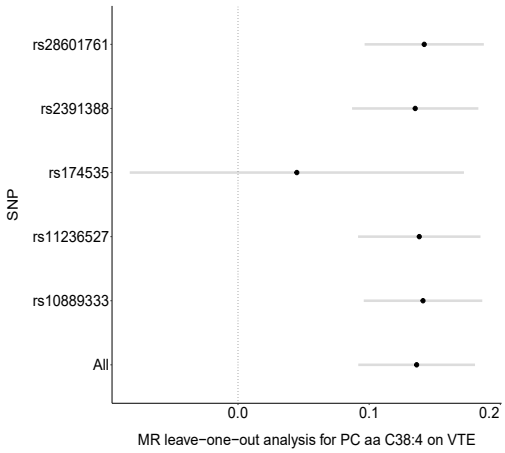
Genetic Instruments Selection and Data Harmonization

Using three-step approaches, we obtained the effective instrumental variables (IVs) of each exposure. Genetic IVs must conform to three hypotheses: (1) have a strong robust correlation with exposure; (2) were independent of confounding associated with exposures and outcomes; (3) only affect the outcome through exposures, but not through other ways[3]. According to these hypotheses, we first selected independent SNPs by clump algorithm module of plink1.9 software[4]. The 1000 Genomes European data was used as reference the panel for linkage disequilibrium (LD) estimation (r^2 threshold = 0.001, window size = 1000kb, *P* value threshold = 5×10^{-8}). Next, we performed a heterogeneity test using the RadialMR package[5] which identified outlier pleiotropic SNPs via modified Q statistics. The threshold for outlier definition is *P* value < 0.05. Finally, we used F-statistics to evaluate the IVs strength for each exposure, while an F-statistic < 10 was considered to be weak intensity[6]. After IVs selection, we harmonized the effect alleles and adjusted β values in the outcome data to make it consistent with the exposure data[1].

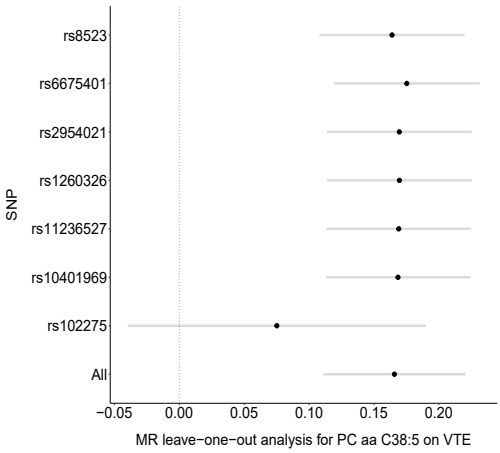
MR Analyses

The IVW method with multiplicative random effects model can be applied to the summary data estimates in the presence of observed heterogeneity[7], which was deemed as the main MR method in our study. The MR-RAPS method is robust to both systematic and idiosyncratic pleiotropy, especially for MR estimation with many weak instruments[8]. It is recommended in cases where exposure and outcomes are both complex traits. MR-Egger method allows all genetic variants to be pleiotropic but requires to be satisfied with the Instrument Strength Independent of Direct Effect (InSIDE) assumption. It assumes that the pleiotropic effect is the same in all variables. This means that pleiotropy leads to bias, but not to additional heterogeneity[7]. The enhancement of the pleiotropy robustness of the MR-Egger method leads to the violation of no measurement error (NOME) in the SNP exposure effects assumption, which can be evaluated by the regression dilution I^2 (GX)[9]. When I^2 (GX) is close to 1, the attenuation due to NOME violation will be negligible. If I^2 (GX) < 0.9, the Simulation Extrapolation (SIMEX) method should be employed to correct this regression dilution bias. Since invalid instrumental variables do not directly affect the median estimate, the weighted median method is able to accurately calculate causal association effects when less than 50% of the genetic variation violates the MR hypothesis[10]. For the weighted mode method, the NOME assumption is not necessary. It relaxed the IV assumption, showing less bias and a lower type I error rate[11].

Supplementary Figures



MR leave−one−out analysis for PC aa C38:4 on VTE



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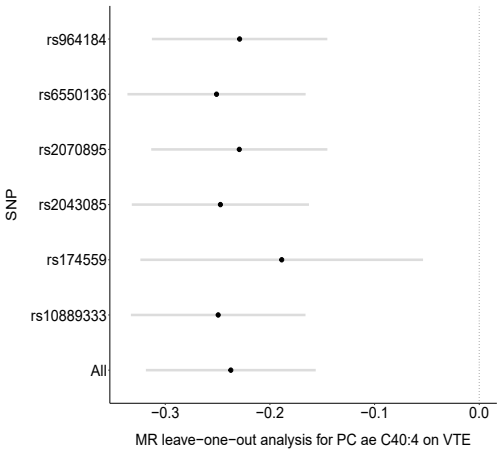

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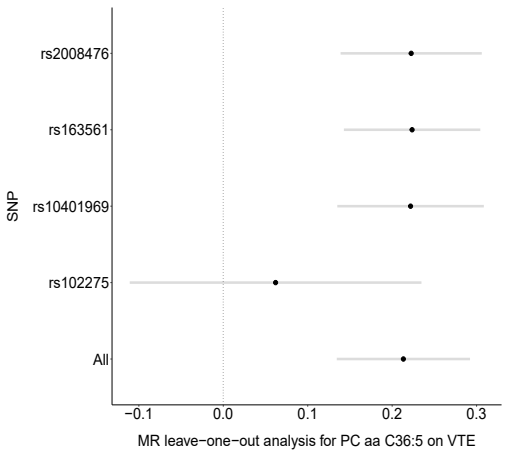
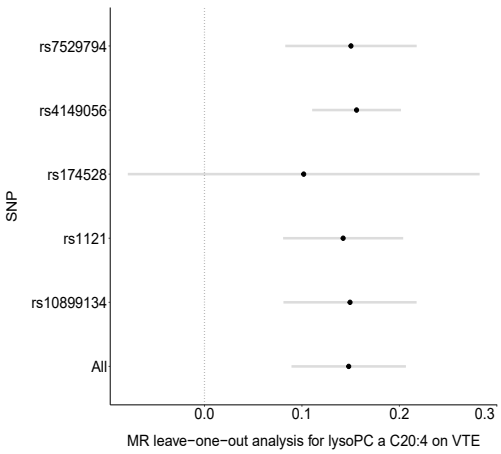
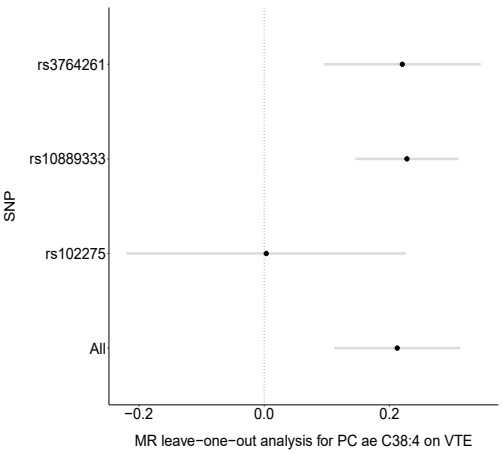


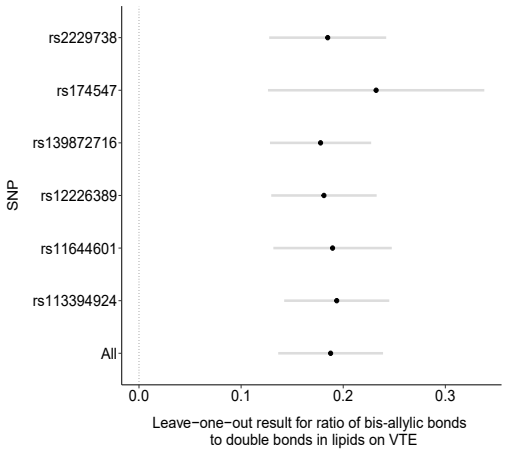
MR leave−one−out analysis for PC aa C36:5 on VTE



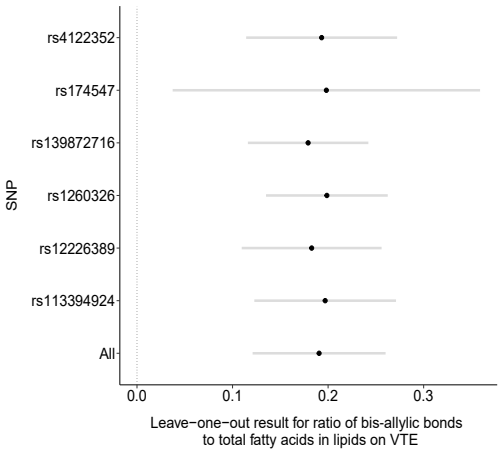
MR leave−one−out analysis for lysoPC a C20:4 on VTE



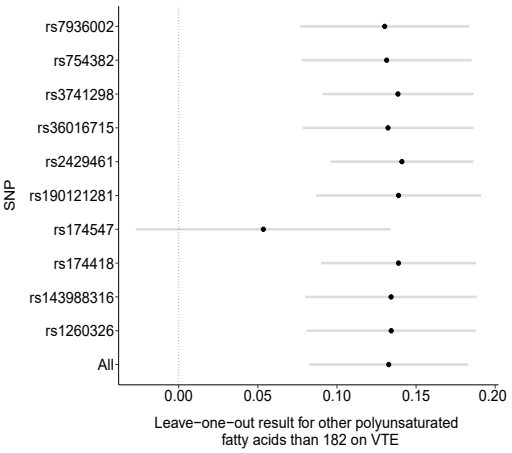
MR leave−one−out analysis for PC ae C38:4 on VTE



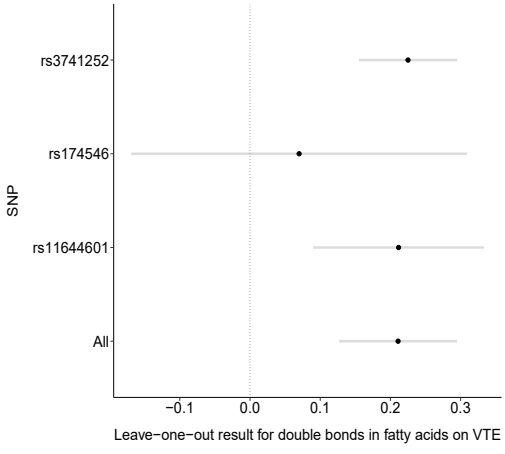
Leave−one−out result for ratio of bis−allylic bonds
to double bonds in lipids on VTE



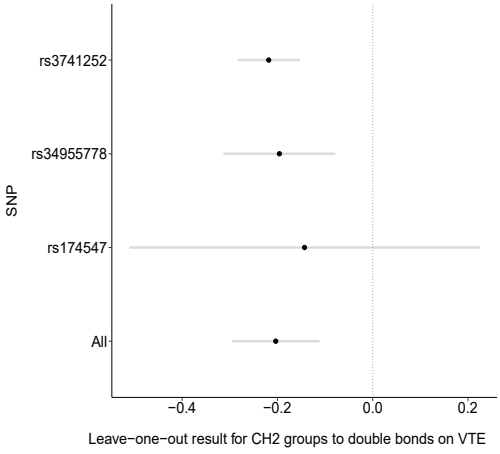
Leave−one−out result for ratio of bis−allylic bonds
to total fatty acids in lipids on VTE



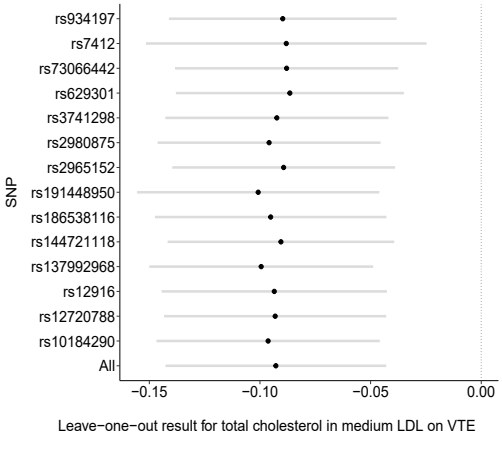
Leave−one−out result for other polyunsaturated
fatty acids than 182 on VTE



Leave−one−out result for double bonds in fatty acids on VTE



Leave−one−out result for CH2 groups to double bonds on VTE



Leave−one−out result for total cholesterol in medium LDL on VTE

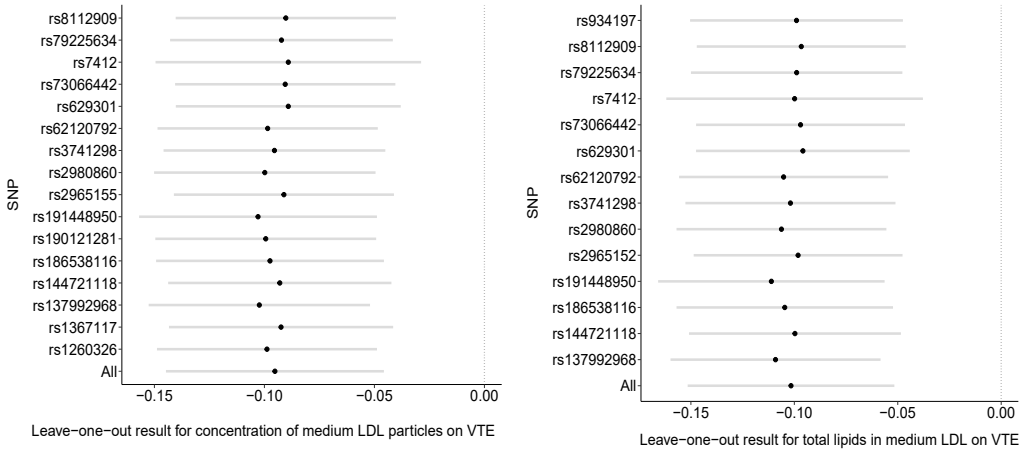


Figure S1. The plot of leave-one-out analysis for 14 significant lipids and lipid-related traits on VTE.

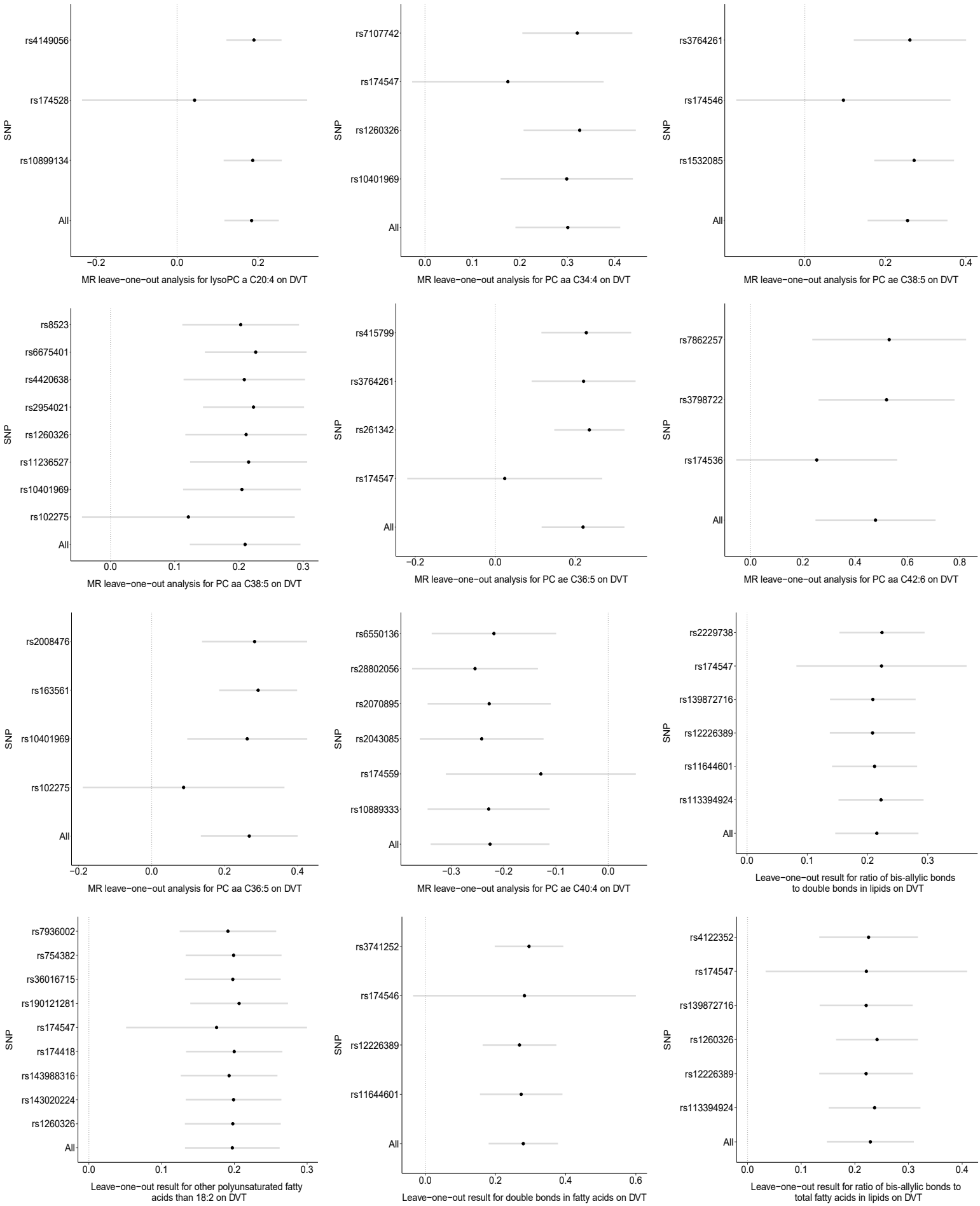


Figure S2. The plot of leave-one-out analysis for 12 significant lipids and lipid-related traits on DVT.

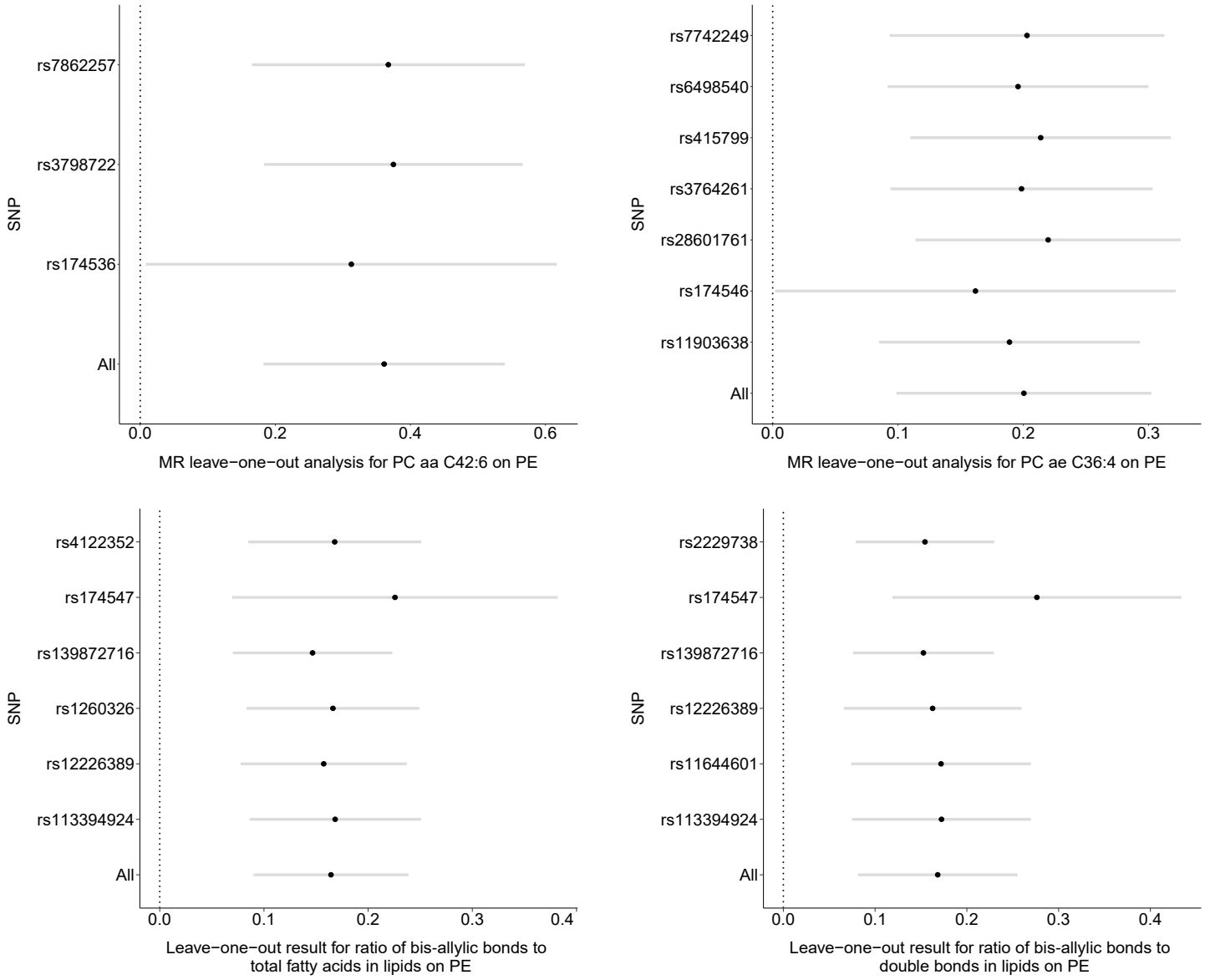


Figure S3. The plot of leave-one-out analysis for 4 significant lipids and lipid-related traits on PE.

Supplementary References

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