Association between blood cholesterol and lung cancer risk: A Mendelian randomization study

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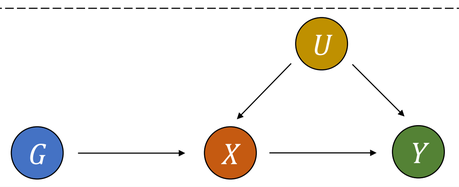
Mendelian randomization study reveals a significant inverse causal association between low-density lipoprotein cholesterol (LDL-C) level and lung cancer

BACKGROUND

- Lung cancer ranks first in terms of cancer incidence and cancer-associated deaths worldwide, underlining the important of identifying modifiable risk factors
- Due to inconsistent findings from observational epidemiologic studies, the causal association between blood cholesterol profile and lung cancer remains inconclusive
- Mendelian randomization (MR) is an analytical method, which minimizes bias from confounding and reverse causation by using genetic variants as instruments to assess causality



G: genetic instruments (SNPs)
X: exposure of interest
Y: outcome of interest
U: unobserved confounders

Fig. 1. The basic concept of MR

- The present study aims to evaluate potentially unbiased associations of genetically predicted circulating lipoprotein cholesterol levels, including high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) with the risk of lung cancer using a MR approach

METHODS

Exposure GWAS: Willer CJ	Outcome GWAS: Transdisciplinary Research Into Cancer of the Lung (TRICL)
SNPs associated with circulating lipids	SNPs associated with lung cancer and its subtypes

Statistical analyses

1. Selecting the instrumental variables (SNPs) robustly and independently associated with HDL-C/ LDL-C from exposure-GWAS summary data
   - Selecting a high *p* value cut-off ($p < 5 \times 10{-}8$)
   - Clumping SNPs in LD ($r^2 < 0.001$)
   - Removing SNPs with a minor allele frequency < 5%
2. Extracting the instrumental variables from the outcome-GWAS
3. In case of any missing requested SNPs in the outcome GWAS, the data of a SNP proxy that had LD estimate $r^2 > 0.8$ with the requested SNP retrieved
4. Harmonising the exposure and outcome datasets using same reference alleles
5. Performing MR analyses
   - Primary MR analysis: inverse variance weighted (IVW) method
   - Supplementary MR analyses: MR-Egger, weighted median, weighted mode methods
6. Performing sensitivity analyses
   - Cochran Q test
   - MR-Egger intercept test
   - Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO)

RESULTS

Table 1. Number of SNPs selected as instrumental variables (after MR-PRESSO correction)

Trait	HDL-C	LDL-C
Lung cancer	73	60
Lung adenocarcinoma	73	60
Squamous cell lung cancer	73	60
Small cell lung carcinoma	73	60

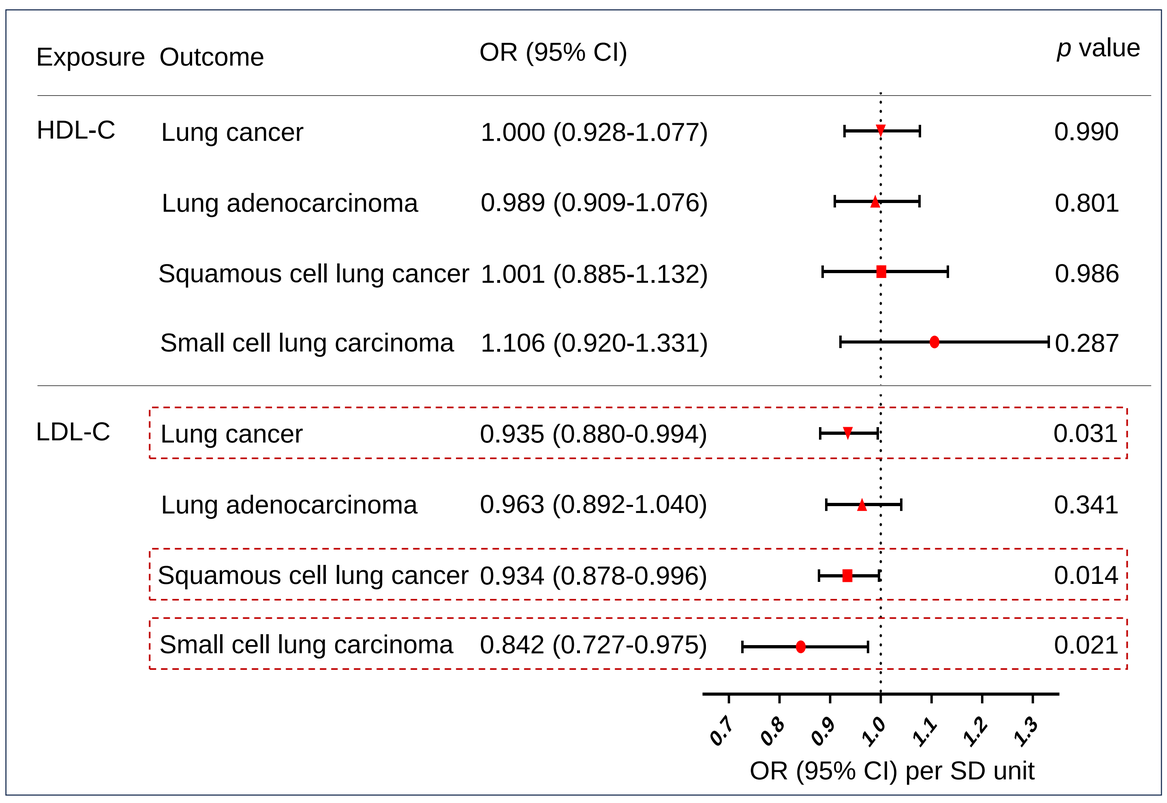


Fig. 2. Results of MR analyses of the effects of circulating lipoprotein cholesterol on risk of lung cancer and its subtypes by IVW method. The forest plot displays the odds ratio (OR) of the effect of a 1-standard–deviation (SD) increase in genetically determined HDL-C and LDL-C on risk of lung cancer and its subtypes, with error bars representing the 95% CI. The vertical dotted line delineates an OR of 1, i.e., no effect of the exposure on risk of outcome.

CONCLUSIONS

- LDL-C level appears to be significantly associated with a lower risk of lung cancer
- More interestingly, the inverse causal association of LDL-C existed only in cases of squamous cell lung cancer and small cell lung carcinoma but not lung adenocarcinoma
- No causal association observed between the genetically predicted HDL-C level and the risk of lung cancer or any of its subtypes
- Further research is warranted to investigate the possibility of whether manipulation of HDL-C/LDL-C levels can influence lung cancer risk

REFERENCE

Willer CJ et al. Discovery and refinement of loci associated with lipid levels. Nature Genetics. 2013;45(11):1274–83.

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CONFLICT OF INTEREST STATEMENT

I have no conflicts of interest to disclose

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