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# Lipid trait variants and the risk of non-Hodgkin lymphoma subtypes: A Mendelian Randomization Study

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**Running title: Lipid traits and NHL risk - a Mendelian Randomization study**

**Abstract**

**Background**

Lipid traits have been inconsistently linked to risk of non-Hodgkin lymphoma (NHL). We examined the association of genetically predicted lipid traits with risk of diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), follicular (FL) and marginal zone (MZL) lymphoma using Mendelian randomization (MR) analysis.

**Methods**

GWAS data from the InterLymph Consortium were available for 2661 DLBCLs, 2179 CLLs, 2142 FLs, 824 MZLs, and 6221 controls. SNPs associated ($P<5x10^{-8}$) with high-density lipoprotein (HDL, N=164), low-density lipoprotein (LDL, N=137), total cholesterol (TC, N=161), and triglycerides (TG, N=123) were used as instrumental variables (IV), explaining 14.6%, 27.7%, 16.8% and 12.8% of phenotypic variation, respectively. Associations between each lipid trait and NHL subtype were calculated using the MR inverse variance-weighted method, estimating odds ratios (OR) per standard deviation, and 95% confidence intervals (CI).

**Results**

HDL was positively associated with DLBCL (OR=1.14, CI:1.00-1.30) and MZL (OR=1.09, CI:1.01-1.18), while TG was inversely associated with MZL risk (OR=0.90, CI:0.83-0.99) all at nominal significance ($P<0.05$). A positive trend was observed for HDL with FL risk (OR=1.08, CI:0.99-1.19; P=0.087). No associations were noteworthy after adjusting for multiple testing.

**Conclusions**

We did not find evidence of a clear or strong association of these lipid traits with the most common NHL subtypes. While these IVs have been previously linked to other cancers, our findings do not support any causal associations with these NHL subtypes.

**Impact**

Our results suggest that prior reported inverse associations of lipid traits are not likely to be causal and could represent reverse causality or confounding.

## Introduction

Lipid traits such as high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), and triglyceride (TG) have been suggested as non-Hodgkin lymphoma (NHL) risk factors; however, results are inconclusive. Of the strongest studies addressing this hypothesis(1–3), a nested case-control study from the Multi-Ethnic Cohort (275 NHL cases and 549 controls) found inverse associations of TC and HDL, but not LDL or TG, with NHL risk(1). In the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study cohort study, HDL was inversely associated with NHL risk during the first 10 years of follow-up, but not with diagnoses after 10 years of follow-up(2). Recently, a large case-control study from the Cancer Research Network examined the relationship of cholesterol with lymphomagenesis in the 10 years prior to lymphoma diagnosis and found that lymphoma cases had lower estimated TC, HDL, and LDL levels than controls, but this was mainly observed in the 3-4 years prior to diagnosis/index date(3). The authors concluded that low cholesterol could indicate an altered systemic metabolic profile associated with the natural history of lymphoma pre-diagnosis and a potential biomarker of subclinical disease. However, it is not established if the observed inverse association between TC and HDL and risk of NHL is a result of protective actions of these lipids and lipoproteins, confounding or reverse causation.

Currently, single nucleotide polymorphisms (SNPs) associated with lipid traits explain 12-28% of the total variation in these traits in populations of European ancestry(4). Here we apply a Mendelian randomization (MR) analysis to examine the possibility of a causal relationship between four genetically predicted lipid traits and the risk of four common NHL subtypes: diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and marginal zone lymphoma (MZL).

## Materials and Methods

GWAS data from the InterLymph Consortium were available for 2661 DLBCLs, 2179 CLLs, 2142 FLs, 824 MZLs, and 6221 controls of European descent(5–8). SNPs associated ($P<5x10^{-8}$) with HDL (N=164), LDL (N=137), TC (N=161), and TG (N=123) that were identified through the Global Lipids Genetics Consortium, were used as instrumental variables (IV)(4). SNPs were not in strong linkage disequilibrium ($r^2<0.05$). MR estimates for the association between each lipid trait and NHL subtype were calculated using the inverse variance-weighted (IVW), simple median, and weighted median methods, after testing for evidence of pleiotropy using MR-Egger regression to test for violation of the standard IV assumptions(9). Associations were reported as odds ratios (OR) per standard deviation increase in the MR genetic risk score along with 95% confidence intervals (CI). We defined statistical significance by a Bonferroni-corrected threshold of P<0.003 (0.05/16=0.003, 16 comparisons of 4 lipid traits across 4 NHL subtypes).

## Results

In our study sample, there was no evidence of violation of the assumptions for the associations tested using MR-Egger regression. We found at nominal significance (P<0.05) that genetically predicted HDL was positively associated with DLBCL ($OR_{IVW}$=1.14, CI:1.00-1.30, P=0.049 , **Figure 1.A**), and MZL ($OR_{IVW}$=1.09, CI:1.01-1.18, P=0.027, **Figure 1.B**); while TG was inversely associated with risk of MZL ($OR_{IVW}$=0.90, CI:0.83-0.99, P=0.025, **Figure 1.C**) (**Table 1**). In addition, we observed a suggestive positive trend for genetically predicted HDL and FL risk ($OR_{IVW}$=1.08, CI:0.99-1.19; P=0.087, **Figure 1.D**)(**Table 1**). Using the simple median and weighted median methods did not change the conclusions (**Figure 1.A-D**). No associations were noteworthy after adjusting for multiple testing.

## Discussion

Our large study of NHL found no evidence of a causal association for these lipid traits with the most common B-cell NHL subtypes. The amount of variance accounted for by these SNPs for the lipid traits is larger than for many MR studies, and the IVs have been previously associated with other cancers such as colorectal and prostate cancers. MR is an important tool for appraising causality in epidemiology and may be even more important for establishing null results(9). We found no robust association between the genetic variants associated with the lipid traits and risk of any of the NHL subtypes, suggesting that there might be very little or no effect of lipid traits on these NHL subtypes. We realize that our null findings may be due to a lack of power, although at an exposure prevalence of 50% we had >99% power to detect a RR (as small as 0.70 for DLBCL, CLL and FL (each with over 2000 cases) and MZL (with over 800 cases) with a type I error rate of 0.003. In addition, MR results can be biased if the assumptions are violated, although these biases would be unlikely to move the effect estimate to zero when there is a true (non-zero) effect; in order for this to happen, the biases would have to align perfectly(9). Our results are in agreement with most studies that have assessed history of hyperlipidemia or statin use with risk of NHL and suggest that published inverse associations could be due to reverse causality or confounding.

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## Tables

Table 1: Associations between B-cell non-Hodgkin lymphoma subtypes per standard deviation increase in the MR genetic risk score for each lipid trait

| | | MR-Egger | | | Inverse-weighted variance | | |
|---|---|---|---|---|---|---|---|
| | | OR per SD increase | 95% CI | P | OR per SD increase | 95% CI | P |
| DLBCL | HDL | 1.14 | 0.94-1.38 | 0.176 | **1.14** | **1.00-1.30** | **0.049** |
| | LDL | 0.78 | 0.53-1.15 | 0.211 | 0.96 | 0.74-1.24 | 0.738 |
| | TC | 0.91 | 0.74-1.12 | 0.381 | 1.05 | 0.91-1.22 | 0.488 |
| | TG | 1.02 | 0.81-1.30 | 0.862 | 1.08 | 0.92-1.25 | 0.337 |
| CLL | HDL | 0.97 | 0.81-1.17 | 0.761 | 1.09 | 0.96-1.23 | 0.192 |
| | LDL | 0.95 | 0.71-1.26 | 0.708 | 1.00 | 0.82-1.23 | 0.983 |
| | TC | 0.93 | 0.76-1.14 | 0.511 | 0.96 | 0.84-1.11 | 0.597 |
| | TG | 0.95 | 0.82-1.09 | 0.438 | 0.94 | 0.84-1.05 | 0.292 |
| FL | HDL | 1.04 | 0.93-1.17 | 0.506 | 1.08 | 0.99-1.19 | 0.087 |
| | LDL | 1.03 | 0.83-1.28 | 0.779 | 1.04 | 0.89-1.22 | 0.585 |
| | TC | 1.05 | 0.91-1.22 | 0.516 | 1.07 | 0.96-1.18 | 0.219 |
| | TG | 0.98 | 0.84-1.14 | 0.777 | 1.01 | 0.90-1.13 | 0.864 |
| MZL | HDL | 1.09 | 0.98-1.21 | 0.123 | **1.09** | **1.01-1.18** | **0.027** |
| | LDL | 0.94 | 0.77-1.15 | 0.556 | 0.90 | 0.78-1.03 | 0.137 |
| | TC | 0.98 | 0.88-1.10 | 0.771 | 0.98 | 0.90-1.06 | 0.560 |
| | TG | **0.84** | **0.73-0.96** | **0.008** | **0.90** | **0.83-0.99** | **0.025** |

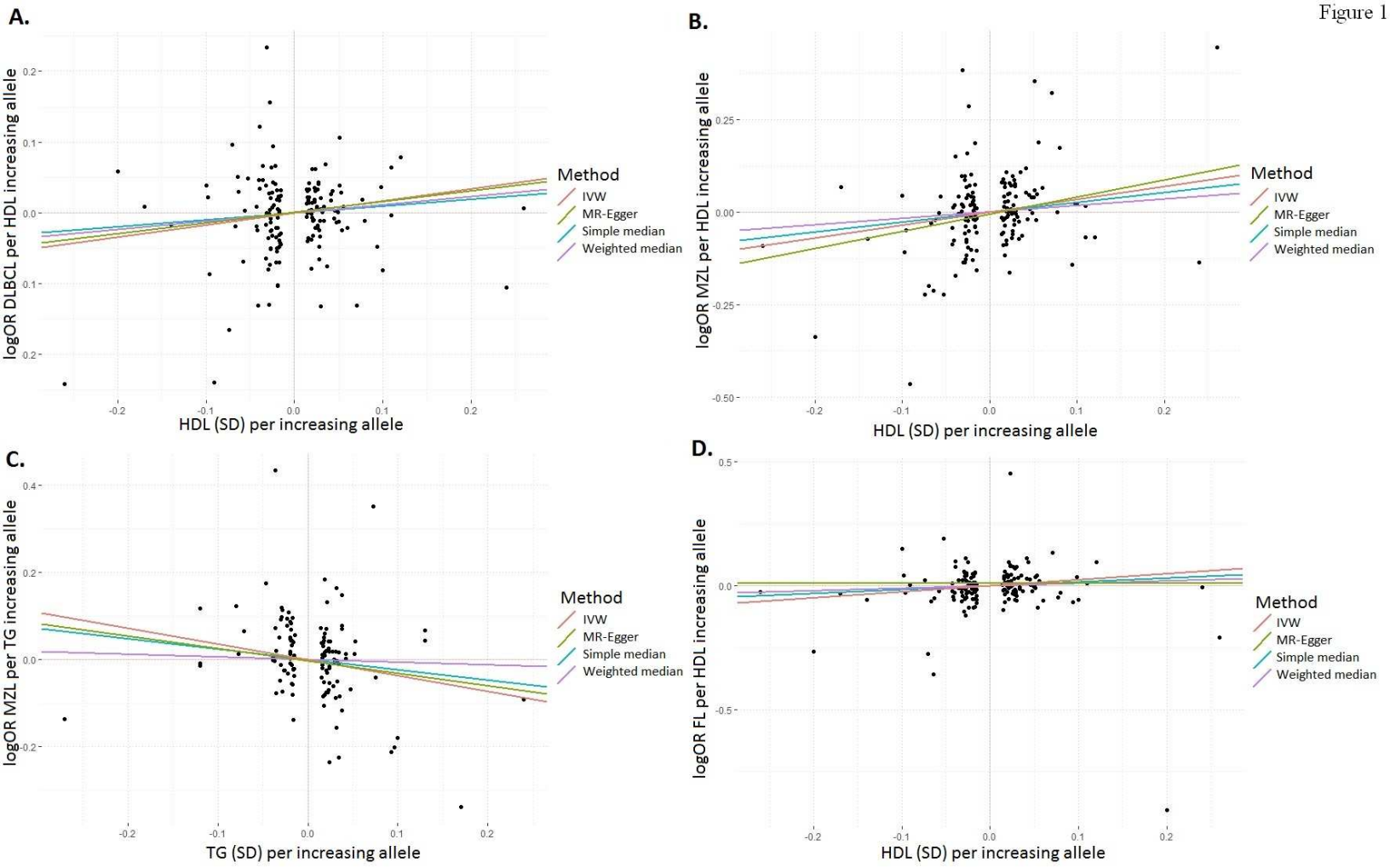
OR, odds ratio; SD, standard deviation; CI, confidence interval; MR, Mendelian randomization; DLBCL, diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MZL, marginal zone lymphoma; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride;

## Figure Legends

Figure 1: HDL and TC SNP-specific effects for risk of lymphoma subtypes

Scatter plots for lipid traits and lymphoma associations for SNPs and four MR estimates (IVW, MR-Egger, simple median, and weighted median): **(A)** HDL and DLBCL association; **(B)** HDL and MZL association; **(C)** TG and MZL association; **(D)** HDL and FL association; DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma; FL, follicular lymphoma; HDL, high-density lipoprotein; TG, triglyceride; SD, standard error; SNP, single nucleotide polymorphism; MR, mendelian randomization; IVW, inverse-variance weighted

Figure 1


A.
logOR DLBCL per HDL increasing allele
HDL (SD) per increasing allele
B.
logOR MZL per HDL increasing allele
HDL (SD) per increasing allele
C.
logOR MZL per TG increasing allele
TG (SD) per increasing allele
D.
logOR FL per HDL increasing allele
HDL (SD) per increasing allele
Method
IVW
MR-Egger
Simple median
Weighted median