Lipid Trait Variants and the Risk of Non-Hodgkin Lymphoma Subtypes: A Mendelian Randomization Study

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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 lymphoma (FL), and marginal zone lymphoma (MZL) using Mendelian randomization (MR) analysis.

Methods: Genome-wide association study data from the InterLymph Consortium were available for 2,661 DLBCLs, 2,179 CLLs, 2,142 FLs, 824 MZLs, and 6,221 controls. SNPs associated (P < 5 x 10^-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; 95% CI, 1.00–1.30) and MZL (OR = 1.09; 95% CI, 1.01–1.18), while TG was inversely associated with MZL risk (OR = 0.90; 95% 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; 95% 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, ever, 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 to 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 prediagnosis and a potential biomarker of subclinical disease. However, it is not established whether 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 (SNP) associated with lipid traits explain 12% to 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

Genome-wide association study data from the InterLymph Consortium were available for 2,661 DLBCLs, 2,179 CLLs, 2,142 FLs, 824 MZLs, and 6,221 controls of European descent (5–8). SNPs associated ($P < 5 \times 10^{-8}$) 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; ref. 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 four lipid traits across four 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.
Table 1. Associations between B-cell NHL subtypes per SD increase in the MR genetic risk score for each lipid trait.

| Trait | OR per SD Increase (95% CI) | MR-Egger | IVW |
|-------|-------------------------------|----------|-----|
| LDL   | 1.14 (0.94–1.38)              | 0.176    | 1.14 (1.00–1.30) | 0.049 |
| HDL   | 0.97 (0.81–1.17)              | 0.716    | 0.98 (0.94–1.02) | 0.273 |
| TC    | 0.91 (0.74–1.12)              | 0.381    | 1.07 (0.91–1.26) | 0.216 |
| TG    | 1.02 (0.81–1.30)              | 0.862    | 1.08 (0.92–1.25) | 0.437 |
| MZL   | 1.04 (0.83–1.28)              | 0.779    | 1.04 (0.89–1.22) | 0.585 |
| FL    | 0.95 (0.82–1.09)              | 0.458    | 0.94 (0.84–1.05) | 0.292 |
| HDL   | 1.06 (0.94–1.18)              | 0.516    | 1.07 (0.96–1.18) | 0.219 |
| LDL   | 0.98 (0.84–1.14)              | 0.777    | 1.01 (0.90–1.13) | 0.864 |
| TC    | 1.03 (0.91–1.22)              | 0.483    | 0.98 (0.87–1.03) | 0.157 |
| TG    | 0.98 (0.84–1.14)              | 1.02     | 1.08 (1.00–1.10) | 0.027 |
| OR per SD Increase (95% CI) | 0.008    | 0.90 (0.83–0.99) | 0.025 |

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

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 risk of NHL (OR = 0.90; 95% CI, 0.83–0.99; P = 0.025; Fig. 1C; Table 1). In addition, we observed a suggestive positive trend for genetically predicted HDL and FL risk (OR = 1.08; 95% CI, 0.99–1.19; P = 0.087; Fig. 1D; Table 1).

Using the simple median and weighted median methods did not change the conclusions (Fig. 1A–D). No associations were noteworthy after adjusting for multiple testing.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
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