Serum Lipid Trajectories in the Years Before a Lymphoma Diagnosis

Joan Fortuny,[1] Estel Plana,[1] James A. Kaye[2]

[1]RTI Health Solutions, Barcelona, Spain
[2]RTI Health Solutions, Waltham, United States

DISCLOSURES

No relationships to disclose.

BACKGROUND

- Lymphoid malignancies (lymphomas) were the seventh most common type of cancer in Europe in 2018, with close to 750,000 new diagnoses made.[1]
- Risk factors for lymphoma are still poorly understood.
- Serum cholesterol levels are low in patients newly diagnosed with a lymphoma.[2]
- Only one study to date[3] has examined the trajectory of cholesterol levels in the years before a lymphoma diagnosis and has found lower levels than those observed in a group of non-cancer controls using United States (US) claims data. Alford et al.[3] adjusted their analyses only for age, sex, health plan, and calendar time.

OBJECTIVE

- To test whether the results of the Alford study[3] can be replicated by:
  1. **Describing the trajectories of serum cholesterol levels** (total, low- and high-density lipoprotein cholesterol) **in the years before a diagnosis of lymphoma**
     - In a European (United Kingdom [UK]) population
     - In a different setting (UK electronic medical records vs. US administrative claims databases)
     - Expanding the analyses to triglycerides (intended as a negative control exposure)
     - Assessing a longer lookback period (i.e., up to 20 years when data allowed)
     - Adjusting for potential confounders that were not available in the Alford et al. study
  2. **Comparing the lipid trajectories** of lymphoma patients to those of a non-cancer population

METHODS

- This non-interventional database **case-control study** included:
  - **Lymphoma cases** diagnosed between 1 January 2000 and 31 December 2017
  - Up to 5 non-cancer **controls** per case matched on practice, sex, year, and age at lymphoma diagnosis date (index date)
- Study participants were aged ≥ 40 years at the index date; had no evidence of another cancer, HIV infection, or organ transplantation before or on the index date; and had ≥ 1 cholesterol measurement before the index date and before the first prescription of a hypolipidemic drug.
- General practitioner data **(GOLD)** from the Clinical Practice Research Datalink in the UK were used. When linkage was available, hospital data **(Hospital Episode Statistics)** were also used.
- **Random-intercept multilevel** (i.e., test, patient, and case-control status) **linear regression models** were used to estimate the values of cholesterol and triglycerides at each test. The dependent variables were (1) time to index date, (2) case-control status, (3) time-varying potential confounders measured at each test, and (4) time-invariant variables measured at the index date. The matching variables (i.e., practice, sex, and calendar year and at index date) were considered adjusted for by keeping clustering. The relationship between time and total serum cholesterol (**TSc**), high-density lipoprotein cholesterol (**HLDc**), low-density lipoprotein cholesterol (**LDLc**), and triglyceride levels was modeled as a quartic polynomial with interaction with case-control status.

- Lymphomas were categorised as:
  - **Hodgkin's lymphoma** (HL)
  - **Non-Hodgkin's lymphoma** (NHL)
    - T-cell lymphoma (T-cell NHL)
      - Mycosis fungoides/Sézary disease
      - Mature T-/NK-cell lymphoma
      - Peripheral or cutaneous T-cell lymphoma
      - Anaplastic large cell lymphoma
      - Other T-cell lymphomas
    - B-cell lymphoma (B-cell NHL)
      - Plasma cell neoplasm (PCN)
      - Diffuse large B-cell lymphoma (DLBCL)
      - Chronic/small lymphocytic leukemia (CLL/SLL)
      - Follicular lymphoma (FL)
- A sensitivity analysis was conducted among never users of a lipid-lowering drug that had at least one cholesterol measurement within the year before the index date. Patients included in this analysis:
  - Were not affected by a potentially informative censoring that could occur by disregarding cholesterol measurements after the prescription of a lipid-lowering drug if the population treated with a hypolipemiant had a different risk of lymphoma than those not treated
  - Had data on cholesterol levels measured close to the index date

RESULTS

- During the study period, 3,302,723 patients had a valid cholesterol measurement. Among these, **11,969 cases of NHL and 473 of HL** met the study's inclusion and exclusion criteria. Controls were matched for NHL and HL cases (59,537 and 2,357, respectively).
- The most common subtypes of lymphoma were PCN, CLL, and DLBCL.
- Table 1 shows the association of covariates with a lymphoma diagnosis, mutually adjusted and matched for age, sex, and calendar year of index date.
  - Covariates such as autoimmune diseases, hepatitis C virus, and blood transfusion are known risk factors for lymphoma and, in our study, were more prevalent among lymphoma cases than among controls.
- Figure 1 through Figure 6 show the main study results.
  - For all lymphoma types, the adjusted mean cholesterol level in the years before the index date was lower in cases than in controls.
  - For most lymphoma types and subtypes, adjusted cholesterol levels showed a pronounced decrease in the 4 years before diagnosis.
  - On the other hand, triglycerides levels were not clearly related to case status.
- Figure 7 and Figure 8 show the results of the sensitivity analysis restricted to those who had never used a lipid-lowering drug and had at least one cholesterol measurement within the year before the index date.
  - Results remained similar when restricted to these patients.

Table 1. Association of Covariates With a Lymphoma Diagnosis, Mutually Adjusted and Matched for Age, Sex, and Calendar Year of Index Date

	B-Cell NHL N Cases = 9,570 N Controls = 47,621 OR (95% CI)	T-Cell NHL N Cases = 452 N Controls = 2,249 OR (95% CI)	HL N Cases = 473 N Controls = 2,357 OR (95% CI)
Hypertension	0.99(0.94-1.04)	0.78(0.61-1.00)	0.82(0.64-1.05)
Coronary heart disease	1.02(0.96-1.10)	1.42(1.02-1.96)	0.97(0.68-1.40)
Cerebrovascular disease	1.02(0.94-1.10)	0.86(0.57-1.30)	1.32(0.88-1.98)
Hyperlipidaemia	0.97(0.92-1.03)	0.90(0.67-1.21)	1.00(0.74-1.33)
T2DM	1.07(1.01-1.14)	1.29(0.94-1.77)	0.94(0.69-1.28)
Peripheral vascular disease	1.05(0.93-1.18)	1.59(0.91-2.76)	1.13(0.59-2.19)
Allergies	1.09(1.04-1.14)	2.14(1.70-2.68)	1.34(1.08-1.66)
B-cell activating disease[a]	1.42(1.28-1.58)	1.65(0.98-2.76)	1.52(0.95-2.43)
T-cell activating disease[b]	1.02(0.94-1.11)	2.53(1.87-3.42)	1.42(0.99-2.04)
Blood transfusion	2.18(1.69-2.80)	0.86(0.23-3.20)	2.88(0.97-8.54)
HCV infection	2.65(1.26-5.57)	NE	NE
Family history of cancer	1.17(1.06-1.29)	1.23(0.81-1.87)	1.69(1.13-2.52)
COPD	1.05(0.96-1.15)	0.68(0.42-1.09)	0.82(0.53-1.29)
Dementia	0.60(0.49-0.73)	1.03(0.41-2.59)	NE
Mild liver disease	0.85(0.61-1.19)	0.85(0.17-4.34)	1.12(0.24-5.23)
Moderate/severe liver disease	1.78(0.93-3.43)	1.00(0.10-10.56)	NE
Peptic ulcer	1.11(1.00-1.23)	0.89(0.52-1.51)	0.83(0.49-1.41)
Renal disease	1.86(1.56-2.20)	1.22(0.43-3.47)	0.36(0.08-1.64)
Ever prescribed NSAIDs	1.17(1.11-1.24)	0.90(0.69-1.16)	1.33(1.04-1.69)
Ever prescribed statin	0.85(0.80-0.90)	0.93(0.70-1.24)	0.87(0.65-1.17)
BMI			
Underweight	1.02(0.91-1.15)	1.12(0.65-1.92)	1.48(0.90-2.43)
Normal	1 Ref.	1 Ref.	1 Ref.
Overweight	0.88(0.83-0.93)	0.81(0.63-1.06)	0.87(0.66-1.13)
Obese	0.86(0.81-0.92)	0.77(0.57-1.05)	0.99(0.75-1.32)
Missing	0.99(0.88-1.11)	1.01(0.58-1.74)	0.96(0.55-1.68)
Smoking			
Never	1 Ref.	1 Ref.	1 Ref.
Ex-smoker	1.02(0.97-1.07)	1.04(0.82-1.33)	1.45(1.14-1.86)
Current	0.95(0.88-1.02)	1.53(1.10-2.11)	2.09(1.56-2.81)
Missing	1.12(0.85-1.48)	0.61(0.13-2.91)	2.38(0.68-8.24)
Alcohol use			
Never	1 Ref.	1 Ref.	1 Ref.
Ex-drinker	1.16(1.05-1.28)	1.32(0.79-2.21)	0.96(0.60-1.56)
Low/moderate	1.05(0.97-1.15)	1.12(0.74-1.70)	0.79(0.55-1.14)
High/very high	1.13(0.95-1.36)	0.64(0.27-1.53)	0.68(0.33-1.41)
Unknown quantity	1.12(1.02-1.22)	1.38(0.89-2.14)	0.92(0.61-1.37)
Missing	0.97(0.86-1.10)	0.96(0.54-1.72)	0.59(0.33-1.07)

BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HCV = hepatitis C virus; NE = not estimable; NSAIDs = non-steroidal anti-inflammatory drugs; OR = odds ratio; ref = reference category; T2DM = type 2 diabetes mellitus.

Note: NHLs for which B- or T-cell subtype was not available have not been included in this table (n = 1,947 cases and 9,667 matched controls).

[a] B-cell–activating disease includes Hashimoto's thyroiditis, hemolytic anemia, myasthenia gravis, pernicious anemia, rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus.

[b] T-cell–activating disease includes celiac disease, immune thrombocytopenic purpura, inflammatory bowel disorder (Crohn's disease, ulcerative colitis), multiple sclerosis, polymyositis or dermatomyositis, psoriasis, sarcoidosis, systemic sclerosis or scleroderma, and type 1 diabetes.

Figure 1. TSc Trajectories and 95% CI Bands in the Years Before NHL or HL Diagnosis

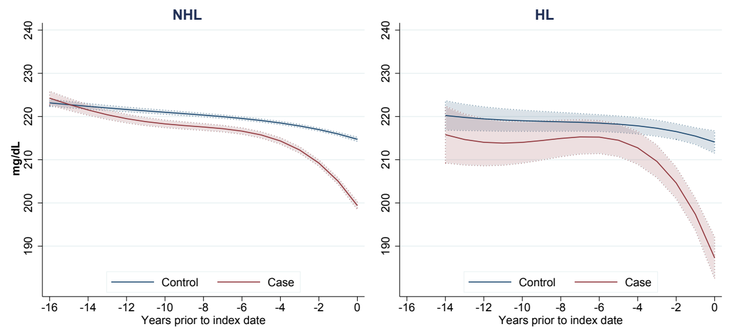


Figure 2. LDLc Trajectories and 95% CI Bands in the Years Before NHL or HL Diagnosis

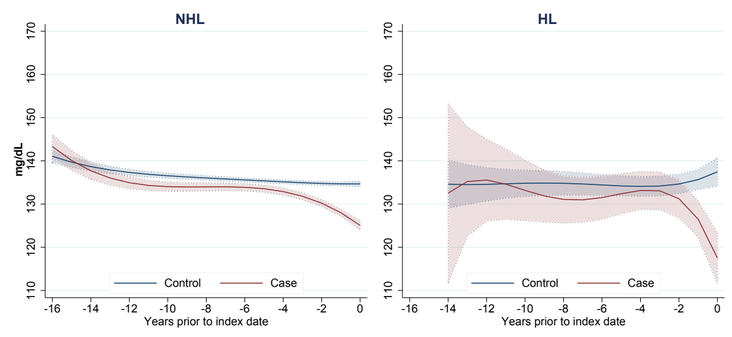


Figure 3. HDLc Trajectories and 95% CI Bands in the Years Before NHL or HL Diagnosis

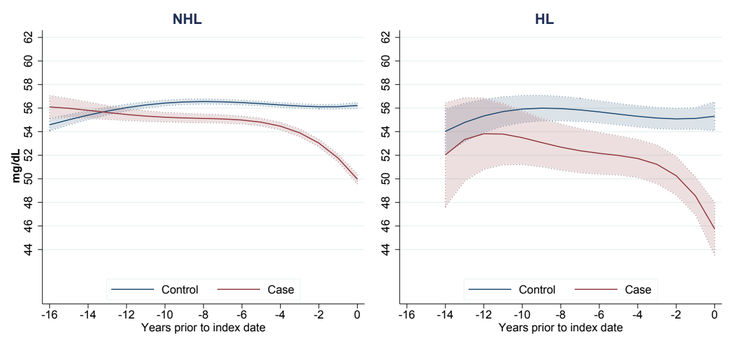


Figure 4. Triglyceride Trajectories and 95% CI Bands in the Years Before NHL or HL Diagnosis

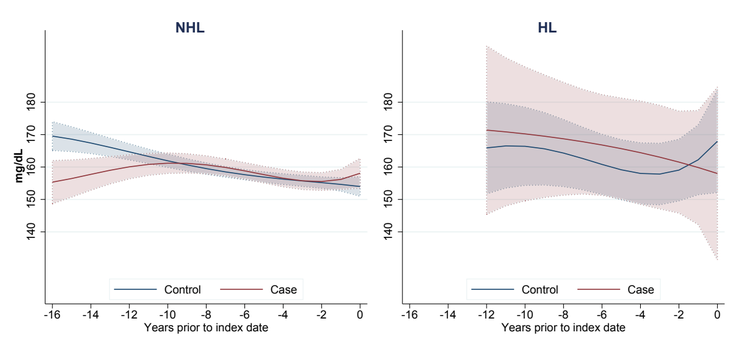


Figure 5. Cholesterol Trajectories and 95% CI Bands in the Years Before Diagnosis of B- or T-Cell Lymphoma

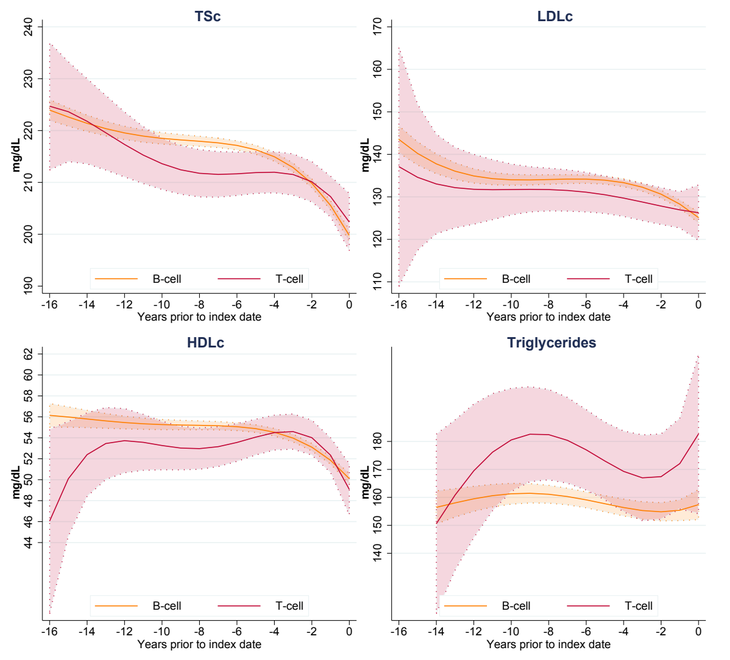


Figure 6. Cholesterol Trajectories and 95% CI Bands in the Years Before Diagnosis of PCN, DLBCL, CLL/SLL, or FL

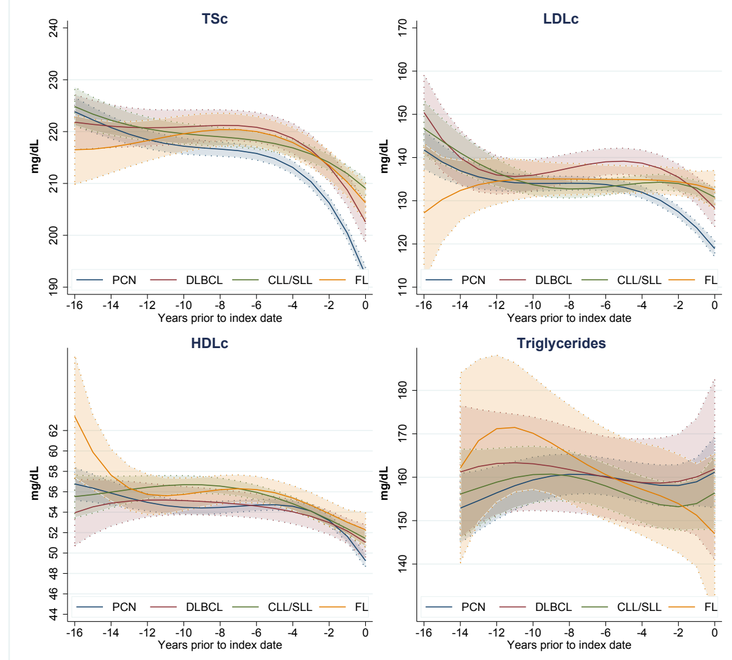


Figure 7. Sensitivity Analysis: TSc Trajectories and 95% CI Bands in the Years Before NHL or HL Diagnosis Restricted to Patients Who Had Never Used a Hypolipidemic Drug and Had ≥ 1 Measure of Cholesterol Within 1 Year Before Index Date

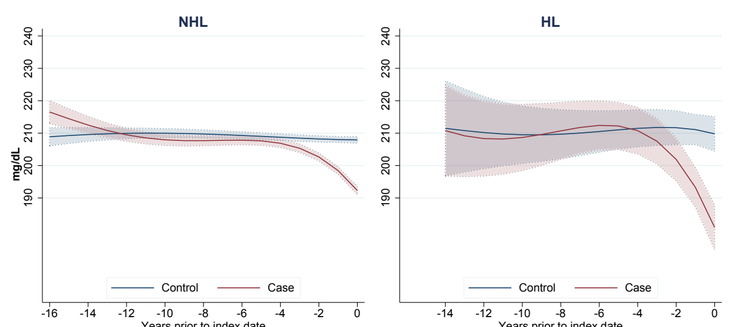


Figure 8. Sensitivity Analysis: LDL Trajectories and 95% CI Bands in the Years Before NHL or HL Diagnosis Restricted to Patients Who Had Never Used a Hypolipidemic Drug and Had ≥ 1 Measure of Cholesterol Within 1 Year Before Index Date

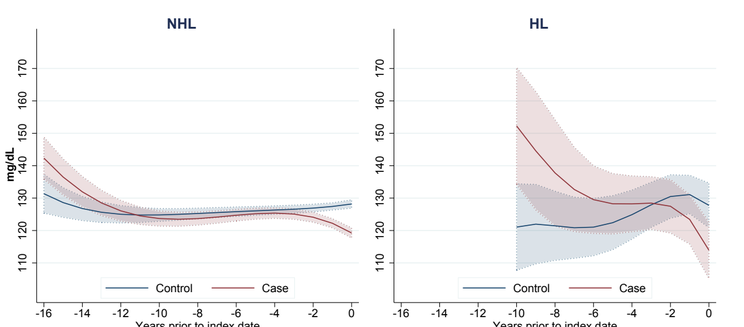
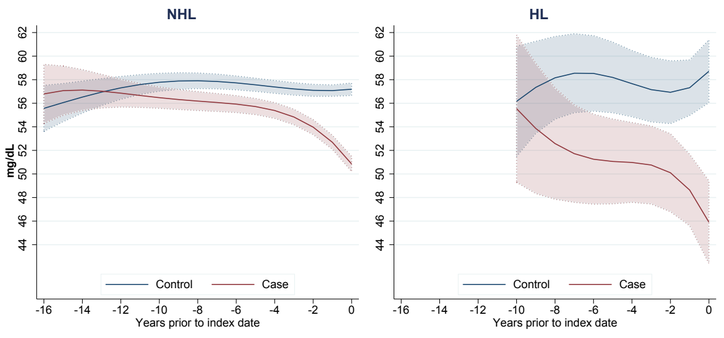


Figure 9. Sensitivity Analysis: HDL Trajectories and 95% CI Bands in the Years Before NHL or HL Diagnosis Restricted to Patients Who Had Never Used a Hypolipidemic Drug and Had ≥ 1 Measure of Cholesterol Within 1 Year Before Index Date



CONCLUSIONS

- This research is the first to replicate results of a similar study conducted in the US while adjusting for more potential confounders.
- The different behaviour of cholesterol and triglycerides, described here for the first time, suggests that the association between cholesterol levels and lymphoma has a biological basis and indicates that cholesterol may play a role in lymphomagenesis.
- The known risk factors for lymphoma show the expected behaviour with regards to risk of lymphoma in a case-control analysis setting.[4]
- The study suggests the potential role of cholesterol as a biomarker for lymphoma in the years before its diagnosis.

References

1. Ferlay JE, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. 2018. Available at: https://gco.iarc.fr/today.
2. Garg A, Hosfield EM, Brickner L. Disseminated intravascular large B cell lymphoma with slowly decreasing high-density lipoprotein cholesterol. South Med J. 2011;104(1):53-6.
3. Alford SH, Divine G, Chao C, Habel LA, Janakiraman N, Wang Y, et al. Serum cholesterol trajectories in the 10 years prior to lymphoma diagnosis. Cancer Causes Control. 2018;29(1):143-56.
4. Morton LM, Slager SL, Cerhan JR, Wang SS, Vajdic CM, et al. Etiologic heterogeneity among non-Hodgkin Lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014 Aug;2014(48):130-44.

Contact Information

Joan Fortuny, MD, PhD
E-mail: jfortuny@rti.org

RTI Health Solutions
Av. Diagonal, 605, 9-1
08028 Barcelona (Spain)

The power of **knowledge**.
The value of **understanding**.

Presented at: ICPE 2020 All Access; 16-17 September 2020