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Yu-Han Chiu
Harvard University

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A prospective analysis of circulating saturated and monounsaturated fatty acids and risk of non-Hodgkin lymphoma

Short running title: Saturated and monounsaturated fatty acids and NHL

Yu-Han Chiu¹⁻², Kimberly A. Bertrand³, Shumin Zhang⁴, Francine Laden^{2,5-6}, Mara M. Epstein⁷, Bernard A. Rosner^{6,8}, Stephanie Chiuve^{1,9}, Hannia Campos^{1,10}, Edward L. Giovannucci^{1-2,6}, Jorge E. Chavarro^{1-2,6}, and Brenda M. Birmann^{6*}

¹ Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA;

² Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA;

³ Slone Epidemiology Center, Boston University, Boston, MA, USA;

⁴ Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA;

⁵ Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA;

⁶ Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital Boston, MA, USA;

⁷ Department of Medicine and the Meyers Primary Care Institute, University of Massachusetts Medical School, Worcester, MA, USA;

⁸ Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA 02115 USA;

⁹ AbbVie Pharmaceuticals, North Chicago, IL, USA;

and ¹⁰ Centro de Investigación e Innovación en Nutrición Translacional y Salud, Universidad Hispanoamericana, San José, Costa Rica

***Corresponding author and person to whom reprint requests should be addressed:**

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Brenda M. Birmann, Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115.

Phone: (617) 525-2251

Fax: (617) 525-2008

Email: brenda.birmann@channing.harvard.edu

Novelty & Impact:

Erythrocyte fatty acids represent an integrated measure of diet and metabolism. However, few biomarker studies have examined NHL risk associated with these fatty acids. In a nested case control study, we found levels of erythrocyte very-long-chain saturated fatty acids (VLCsFA) were inversely associated with risks of some types of B cell non-Hodgkin lymphoma (B-NHL) and T-NHL, suggesting that endogenous fatty acids or the processes from which these VLCsFA arise may influence lymphomagenesis.

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Abbreviations used: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Health Professionals Follow-up

Study (HPFS), Non-Hodgkin lymphoma (NHL), Nurses' Health Study (NHS), erythrocyte (RBC), saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), very long chain saturated fatty acids (VLSFA).

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Abstract

Circulating saturated (SFA) and monounsaturated fatty acids (MUFA), which are predominantly derived from endogenous metabolism, may influence non-Hodgkin lymphoma (NHL) risk by modulating inflammation or lymphocyte membrane stability. However, few biomarker studies have evaluated NHL risk associated with these fats. We conducted a prospective study of 583 incident NHL cases and 583 individually matched controls with archived pre-diagnosis red blood cell (RBC) specimens in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS). RBC membrane fatty acid levels were measured using gas chromatography. Using multivariable logistic regression, we estimated odds ratios (OR) and 95% confidence intervals (CI) for risk of NHL and major NHL subtypes including T cell NHL (T-NHL), B cell NHL (B-NHL) and three individual B-NHLs: chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma. RBC SFA and MUFA levels were not associated with NHL risk overall. However, RBC very long chain SFA levels (VLCSFA; 20:0, 22:0, 23:0) were inversely associated with B-NHLs other than CLL/SLL; ORs (95% CIs) per standard deviation (SD) increase in level were 0.81 (0.70, 0.95) for 20:0, 0.82 (0.70, 0.95) for 22:0, and 0.82 (0.70, 0.96) for 23:0 VLCSFA. Also, both VLCSFA and MUFA levels were inversely associated with T-NHL [ORs (95% CIs) per SD: VLCSFA, 0.63 (0.40, 0.99); MUFA, 0.63 (0.40, 0.99)]. The findings of inverse associations for VLCSFAs with B-NHLs other than CLL/SLL and for VLCSFA and MUFA with T-NHL suggest an influence of fatty acid metabolism on lymphomagenesis.

Keywords: non-Hodgkin lymphoma, erythrocyte, fatty acids, *de novo* lipogenesis

Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies originating from the lymphatic system, with a large majority ($\geq 85\%$) arising from B cell-lymphocytes (B-NHL).¹ In 2017, 72,240 new cases of NHL (including chronic lymphocytic leukemia, CLL) and 20,140 deaths from NHL were expected in the United States.² Severe immune compromise is the strongest and most consistent risk factor for NHL.³ However, most cases arise in persons without overt immune dysfunction. Other known risk factors such as family history of hematologic cancer, human immunodeficiency virus and certain other infectious agents, autoimmune disease and exposure to immune-modulating chemicals (e.g, pesticides) explain only a small proportion of cases.³ Furthermore, there is strong evidence for etiologic heterogeneity across individual histologic subtypes of NHL.^{4,5} A role for dietary fat intake is suggested by reports of an increased risk of NHL in relation to higher saturated, *trans* and animal fat and red meat consumption,⁶ including for common histologic subtypes of B cell NHL such as diffuse large B cell lymphoma (DLBCL) and CLL.⁷ Published studies also observed a decreased NHL risk in relation to higher intake of fish and vegetables,⁸⁻¹⁰ however, few studies have examined biomarkers of fatty acids, direct measures that could better characterize endogenous exposure to fatty acids, including those synthesized endogenously and not acquired via the diet, in relation to NHL risk.

Erythrocyte fatty acids represent an integrated measure of diet and metabolic processes, and individual fatty acids may have different associations with risk of NHL. Specifically, even-numbered saturated fatty acids [SFAs; e.g., myristic acid (14:0), palmitic acid (16:0), stearic acid (18:0)] and monounsaturated fatty acids [MUFA; e.g., palmitoleic acid (16:1n-7), oleic

acid (18:1n-9)] are mainly produced via *de novo* lipogenesis, a process by which excess carbohydrates are converted to fat and for which multiple plausible mechanisms support an influence on lymphomagenesis. For example, *in vivo* study treatment with ST1326, an inhibitor of carnitine-palmitoyl transferase 1A, prevented lymphomagenesis in mice by reducing the availability of a fundamental substrate for *de novo* lipogenesis.¹¹ Additionally, the even-numbered SFA and MUFA were found to be correlated with composite inflammation measures¹² and may thus influence risk of NHL via pro-inflammatory mechanisms.¹² On the other hand, odd-numbered SFA [e.g., pentadecanoic acid (15:0) and heptadecanoic acid (17:0)] primarily reflect dairy fat consumption and not endogenous synthesis.¹³ A meta-analysis suggested a positive association of dairy product consumption with risk of NHL.¹⁴ Lastly, another class of SFAs called very long chain saturated fatty acids (VLCSFAs), featuring 20 or more carbons, also has biologic plausibility for influencing NHL risk.¹⁵ In contrast to *de novo* lipogenesis, which occurs in the cytosol, VLCSFA can be produced endogenously in the endoplasmic reticulum and are associated with resolution of inflammation.¹⁶ Recent experimental evidence suggests that the VLCSFA content of ceramide, a type of sphingolipid, has a profound influence on ceramide-induced apoptosis,¹⁷ which may, in turn, influence lymphocyte growth and survival. Collectively, these biochemical data suggest that pre-diagnosis biomarkers of circulating SFA, VLCSFA and MUFA may be associated with risk of NHL and/or individual NHL subtypes.

To date, only one prospective study (275 cases and 549 controls) has examined the relationship of circulating fatty acids and risk of NHL; this study reported associations of higher levels of certain erythrocyte SFAs (16:0 and 18:0) with increased risk of NHL overall and no association for MUFA.¹⁸ However, the study lacked data on VLCSFA and had limited ability to

evaluate individual subtypes. To gain further insight into the relations of these fatty acids with risk of NHL and major NHL subtypes, we conducted a case-control study of pre-diagnosis erythrocyte membrane SFA, MUFA, and VLCFA levels nested in the prospective Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS).

Materials and methods

Study population

The source populations were two ongoing prospective cohorts, the NHS (N=121,700 women, aged 30-55 at baseline in 1976) and the HPFS (N=51,529 men, aged 40-75 at baseline in 1986). Enrollment and follow-up methods are similar in both populations and are published in detail elsewhere.¹⁹ Briefly, questionnaires are mailed to participants every other year to assess lifestyle factors and health status, with a high follow-up rate (>90%) in each cycle. Deaths among cohort participants are identified by next-of-kin, the postal service or searches of the National Death Index. Blood samples were collected in 1989-90 from 32,826 NHS participants and in 1993-94 from 18,018 HPFS participants using protocols described previously.²⁰ The present study was approved by the Institutional Review Boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health. Informed consent to join the cohorts was implied by return of the baseline questionnaire; participants provided written informed consent at time of biospecimen collection.

Selection of Cases and Controls

NHL diagnoses among NHS and HPFS participants are typically first identified via self-report in the follow-up questionnaires and then confirmed by review of medical records and

pathology reports, or by linkage to tumor registries. Diagnoses that are identified first through death follow-up are also confirmed, when possible, by medical record review or linkage to tumor registries. Major histologic subtypes of NHL were determined according to the World Health Organization (WHO) classification of lymphomas^{1,21,22} based on morphology and immunophenotype as recorded in medical records and pathology reports. For diagnoses of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and follicular lymphoma (FL), immunophenotype information was not required for tissue diagnoses as morphology can reliably diagnose these histology subtypes.¹

For the present analysis we included all incident first primary diagnoses of NHL (i.e., ICD codes, of 200, 202 and 204.1) that occurred at least 3 months after blood collection among cohort participants with archived blood specimens and no history of cancer (other than non-melanoma skin cancer) at NHL diagnosis. We confirmed 583 incident cases of NHL (251 men and 332 women) through 2010, including 158 CLL/SLL, 86 diffuse large B-cell lymphoma (DLBCL), 89 FL, and 25 T cell NHL (all subtypes combined; T-NHL). The remaining cases included 225 patients with less common B cell (B-)NHL subtypes [mantle cell lymphoma (N=15), marginal zone lymphoma (N=42), Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (N=17), unclassified B cell (N=38)], pre-B cell (N=5), pre-T cell (N=3) and unclassified NHL (N=105). Eligible controls were alive and free of cancer (except non-melanoma skin cancer) at the date of the corresponding case's NHL diagnosis. Controls were individually matched to cases by baseline age (± 1 year), cohort/gender, race, fasting status at blood draw (≥ 8 hours v. not), and date of blood draw (± 1 month).

Exposure assessment

The fatty acid distribution in erythrocytes was analyzed by gas-liquid chromatography as previously described.²³ Briefly, fatty acid methyl esters were prepared by direct transesterification and separated by gas chromatography. Individual fatty acids were identified by comparing their peak retention times with those of known pure certified standards (NuCheck Prep, Elysium, MN) using the CHEMSTATION A. 0.8.03 software (Agilent Technologies) for analyses. The level of each individual fatty acid represents the percentage of the total area of the identified fatty acids. Coefficients of variation for all fatty acids (Supplemental Table 1) were measured by analyzing quality control (QC) samples randomly distributed throughout the study samples, with values ranging from 2.6% for oleic acid (18:1n-9) to 32.5% for myristic acid (14:0) in the NHS, and from 1.4% for oleic acid (18:1n-9) to 18.4% for myristic acid (14:0) in the HPFS. The within-batch coefficients of variation ranged from 1.3% for oleic acid to 20.3% for myristic acid in the NHS, and 1.2% for oleic acid to 16.1% for myristic acid in the HPFS. Samples for matched case-control pairs were ordered randomly within sets and assayed in the same analytic run, with the technician blinded to case-control or QC status, to reduce any effect of inter-assay variability.

Statistical analysis

Given that the association between fatty acids and risk of NHL may vary by subtype,^{4,5} we performed analyses for NHL overall and also separately for the histologic subtypes with sufficient numbers, including three common mature B-NHL subtypes (CLL, DLBCL, and FL), and T-NHL in aggregate. We also examined all B-NHLs in aggregate, both with and without CLL/SLL; although classified by the WHO as a mature B-NHL,¹ CLL/SLL is more frequently asymptomatic

and indolent in clinical course than other common B-NHLs²⁴ and has the highest genetic predisposition among NHL subtypes,²⁵ supporting a hypothesis for etiologic differences for CLL from other common B-NHLs.⁴

After excluding outliers (n=10) using the Rosner extreme Studentized deviate method,²⁶ we modeled the SFA and MUFA individually and by class, as well as the ratio of oleic acid to stearic acids (as an index of stearyl-CoA desaturase, the rate limiting step for biosynthesis of MUFA²⁷) as continuous variables. We conducted unconditional logistic regression to estimate the odds ratios (ORs) and 95% confident intervals (95% CIs) of overall NHL per standard deviation (SD) increase in fatty acid level. We also conducted analyses utilizing cubic splines to explore potential non-linearity in the association of RBC fatty acid markers with NHL endpoints. *A priori*, we analyzed data separately by cohort and assessed heterogeneity by cohort in random effects meta-analysis and the Cochrane Q test.²⁸ For most associations, we did not observe significant heterogeneity by cohort (i.e., by sex) and thus we conducted our primary analyses in the pooled study populations. To examine fatty acid associations with NHL across individual histologic subtypes (CLL, DLBCL, FL, other B-NHL, T-NHL), we fit unconditional polytomous logistic regression and tested for heterogeneity in subtype-specific associations. All models included adjustment for the matching factors. We also considered models that additionally adjusted for other known or putative risk factors for NHL including smoking history (never vs. ever),²⁹ alcohol consumption (tertile),³⁰ and body mass index (<25 vs. $\geq 25\text{kg/m}^2$);³¹ however, effect estimates were essentially unchanged and these covariates were not retained in final models. Lastly, to explore whether the observed association is more relevant to earlier or later onset of NHL or more pertinent to proximal or distant exposure (i.e., exposure

predating NHL by a decade or longer), we examined effect modification by age at blood draw (<60 vs. ≥60 years) and follow-up time (<10 vs. ≥10 years) by introducing cross product terms to the main models of the fatty acid associations with risk of overall NHL and of B-NHL (in aggregate, with or without CLL/SLL). T-NHL and individual B-NHL subtypes had insufficient numbers to permit separate examination of effect modification. All statistical analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). Results were considered to be statistically significant when $P < 0.05$ (2-tailed).

Results

Cases and controls had similar distributions of selected characteristics at blood draw, in part due to effective matching (Table 1). Overall, participants had a mean age of 61 years at blood draw, 43% were male, and 96% were white. We observed modest positive pairwise correlations among individual VLCSFAs (20:0, 22:0, 23:0, and 24:0) and for (even-numbered) SFA that were closely related within the *de novo* lipogenesis pathway (for example, $r=0.69$ for 14:0 and 16:0; Table 2); an exception was stearic acid (18:0), which had inverse correlations with other even-numbered long chain SFAs. Most odd-numbered fatty acids were also correlated with each other, and we noted inverse correlations of palmitic acid (16:0) and palmitoleic acids (16:1n-7C) with VLCSCFA.

Among women and men combined, there was no evidence of linear or non-linear relationship between individual fatty acids (SFAs, MUFA, VLCSCFA) and NHL risk overall. Nonetheless, when we examined fatty acid associations with major NHL subtypes, RBC VLCSCFA were inversely associated with the aggregated endpoint comprising all B-NHL types except

CLL/SLL (Table 3). Specifically, the multivariable-adjusted ORs (95% CIs) per SD increase in VLCSCFA level were 0.81 (0.70, 0.95) for 20:0, 0.82 (0.70, 0.95) for 22:0, 0.82 (0.70, 0.96) for 23:0, and 0.93 (0.80, 1.09) for 24:0 VLCSFAs. We also noted similar suggestive inverse associations for those fatty acids with follicular lymphoma and DLBCL (but not with CLL/SLL) and suggestive inverse associations of similar magnitude for T-NHLs (Table 3).

We also examined the relationship of individual long chain SFA as well as the sums of even-numbered SFA and of odd-numbered SFA with risk of NHL (Table 4). There was a suggestive positive association between 16:0 and B-NHL except CLL/SLL [OR=1.16 (95%CI: 0.99, 1.35)]. None of the other individual SFA or summed SFA had an association with any NHL endpoints (Table 4).

Summed and individual MUFA were also not associated with major histologic NHL subtypes; an exception was T-NHL (Table 5). Specifically, the adjusted OR (95%CI) for risk of T-NHL per SD increase in sum of MUFA was 0.63 (95%CI: 0.40, 0.99), and this association was mainly driven by 18:1n-9C, which is oleic acid (Table 5). When VLCSCFA and MUFA were mutually adjusted in the same model, the results were consistent [OR per SD: 0.60 (0.38, 0.95) and 0.60 (0.38, 0.95) for VLCSCFA and MUFA, respectively]. The ratio of oleic acid to stearic acid (18:1n-9c/18:0), examined as an index of stearyl-CoA desaturase activity,²⁷ was not associated with risk of any NHL endpoint.

Lastly, we stratified the analysis by age at blood draw and by time since blood draw. We noted a positive association between even-numbered SFA levels and risk of B-NHL for participants age <60 years at blood draw but not for participants ≥60 years at blood draw (P-

interaction=0.07). The positive associations were slightly stronger for B-NHLs other than CLL/SLL than for all B-NHLs combined (Supplemental Table 2). Previously noted associations of VLCsFA and MUFA with NHL endpoints did not vary notably by age at blood draw. We found no appreciable differences in the association between any individual or summed fatty acids and NHL when stratified by time since blood draw.

Discussion

In this prospective nested case-control study, we found an inverse association between pre-diagnosis RBC VLCsFA and incidence of B-NHL other than CLL. In addition, higher levels of RBC VLCsFA and MUFA were associated with a lower risk of T-NHL, and, especially among those <60 years at blood draw, higher levels of even-numbered SFAs were suggestively associated with an increased future risk of B-NHL. In contrast, total SFA and other long chain SFA were not associated with risk of any NHL endpoint.

To our knowledge, this is the first study exploring the association between circulating VLCsFA and risk of hematological malignancies. Emerging evidence suggests a beneficial association of VLCsFAs (but not shorter chain SFAs) with several health outcomes including atrial fibrillation, diabetes mellitus, and sudden cardiac arrest.³²⁻³⁵ The present findings appear to extend this evidence to B-NHLs other than CLL/SLL, suggesting an inverse association via mechanisms that are as yet unknown. One plausible mechanism by which VLCsFA could protect against B cell lymphomagenesis is the activation of proliferator-activated receptor gamma (PPAR- γ). PPAR- γ is an important transcription factor in B cells and has anti-proliferative and pro-differentiation properties.³⁶ Recently, an animal study showed that VLCFAs acted as

agonists of PPAR γ ,³⁷ possibly explaining the inverse association of VLCFAs with incident B-NHL.

We are not aware of mechanistic explanations for the apparent lack of association of the VLCFAs with CLL/SLL. We also found an inverse association between VLCFA and T-NHL. An *in vitro* study reported that certain acyl fatty acids, such as 22:0 and 24:0, but not shorter chain acyl fatty acids, are cytotoxic to T cell acute lymphoblastic leukemia cell lines.¹⁷ However, it remains unknown whether a similar effect exists *in vivo* or would confer protection against developing T-NHL.

We also noted that RBC MUFA levels were inversely associated with incident T cell lymphoma, and that this association was mainly driven by oleic acid. Although the influence of MUFA on T cell lymphomagenesis is largely unexplored, the conversion of stearic to oleic acid, which is catalyzed by stearoyl-CoA desaturase,²⁷ was found to play a key role in T cell proliferation in humans,³⁸ suggesting that stearoyl-CoA desaturase activity may be up-regulated in T cell lymphomagenesis. However, we did not find an association between the pre-diagnosis ratio of oleic to stearic acids and risk of T cell lymphoma, suggesting that the observed inverse associations of RBC oleic acid with T-NHL may not be mediated by stearoyl-CoA desaturase activity. Notably, our study only included 25 T-NHL cases, and thus the associations for many T-NHL-specific findings, including the ratio of oleic to stearic acid, were imprecise. A larger prospective examination of oleic acid and NHL risk deserves further consideration.

Previous studies investigating circulating palmitic (16:0) and stearic acid (18:0) and risk of NHL are scarce but generally consistent with our findings of modest positive associations for B-NHL. A positive association of these fatty acids with NHL risk is plausible due to their role in

the induction of inflammation,^{39,40} a condition characterized in part by up-regulation of B cell activating cytokines. In a small case-control study (47 cases and 27 controls) that compared serum fatty acid profiles between NHL patients and healthy controls in Serbia, significantly higher levels of SFA (16:0 and 18:0) were found in NHL patients.⁴¹ In a prospective nested study in the Multiethnic Cohort (MEC) with 275 cases and 549 controls,¹⁸ Morimoto et al. found a positive association of erythrocyte SFA (16:0 and 18:0) with total NHL risk (OR of highest tertile versus lowest tertile: 1.57, 95%CI: 1.03-2.39). The latter study included too few cases for conclusive subtype-specific analysis and did not report indication of heterogeneity by NHL cell type or histologic subtype for SFAs. In the present analysis, the association between SFA and B-NHL was limited to participants <60 years of age at blood draw. This age-specific association was not explained by the latency period (i.e., we did not observe differences in these associations by follow-up interval) and thus may suggest a source of etiologic heterogeneity for B-NHL in younger and older patients. Alternatively, this could be a chance finding.

When interpreting these findings, it is important to note that erythrocyte membrane SFA and MUFA are poor biomarkers of their intake.^{42,43} Even-numbered SFA and MUFA in RBC are likely to represent a mixture of endogenously synthesized SFA and MUFA from Acyl CoA via the *de novo* lipogenesis pathway,⁴⁴ intake of dietary precursors of Acyl CoA, such as carbohydrates,⁴³ as well as intake of SFAs or MUFAs.⁴² VLCSFAs in RBCs are also likely to represent a mixture of the elongation products of palmitic acid and intake of nuts that contain small amounts of VLCSFAs.⁴⁵ Therefore, the observed relations between VLCSCFA and B-NHL other than CLL/SLL as well as MUFA and T-NHL are most likely due primarily to differences in fatty acid metabolism between cases and controls rather than to differences in their diet.

An important limitation of our study is that RBC fatty acids, which reflect exposure over the past few months,⁴⁶ were assessed only at a single time point and may not reflect longer-term exposure or exposure at times most relevant to susceptibility or pathogenesis. Second, measurement error in the fatty acid levels is possible, especially for those with high observed CVs (14:0 and 15:0) in the embedded QC samples. However, the effect is most likely non-differential, which may have attenuated true associations. Third, the majority of our study population is white, and results may not be generalizable to other racial/ethnic groups, although we are not aware of biologic hypotheses that the associations would differ by race/ethnicity. Furthermore, we examined a large number of biomarker associations with various NHL-related endpoints and did not observe levels of statistical significance that would have withstood adjustment for multiple comparisons. We recognize that chance could explain our nominally significant findings, although their biologic plausibility provides some reassurance of their credibility. Finally, because of small numbers of cases for some individual NHL subtypes, statistical power was limited, and caution is warranted in the interpretation of subtype-specific results. Nonetheless, with a combined total of 583 incident NHL cases and 583 individually matched controls, this analysis is the largest to date to examine biomarkers of fatty acid-related risk of NHL and major NHL subtypes and, to our knowledge, the first to examine VLCSFAs in relation to NHL risk. Additional strengths of this study include its prospective design, long follow-up since blood draw, and consideration of potential confounding by suspected NHL risk factors.

In conclusion, we report the first evidence that RBC membrane VLCSFA levels are associated with a lower risk of B-NHL other than CLL/SLL, and with T-NHL. We also observed an

inverse association for MUFA levels, especially oleic acid, with T-NHL and a suggestive positive association of even-numbered SFA levels with B-NHL, especially at younger ages. Collectively these results support the hypothesis that endogenous fatty acids and/or the metabolic processes from which they arise may influence risk of NHL. Further epidemiologic and molecular biologic studies to clarify these associations and investigate the underlying mechanisms could yield novel insights into lymphomagenesis and opportunities for NHL prevention.

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Authorship Contributions:

BMB designed the study and acquired the data, Y-HC analyzed data, Y-HC, BMB, and JEC interpreted the data and wrote the manuscript; all the authors critically reviewed the manuscript for important intellectual content and gave final approval; BMB and Y-HC had primary responsibility for the final contents.

Disclosure of Conflicts of Interest:

Dr. Stephanie Chiuve is the employee at AbbVie. None of the authors reported a conflict of interest related to the study.

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Accepted Article

Table 1. Characteristics of study population at blood draw among 1166 participants in the NHS and HPFS

	Cases of NHL (N=583), by major histologic subtype					Controls
	Follicular	DLBCL	CLL/SLL	T cell	Other ⁷	
N	89	86	158	25	225	583
	Median (25 th , 75 th) or N (%)					
Male, n (%)	28 (31)	21 (24)	78 (49)	10 (40)	114 (51)	251 (43)
Age at blood drawn, years	60 (53, 64)	61 (56, 66)	61 (54, 67)	58 (53, 68)	62 (56, 68)	61 (54, 67)
Fasting at blood draw, N (%)	64 (72)	55 (64)	96 (61)	17 (68)	118 (53)	359 (62)
Age at diagnosis, years	69 (63, 75)	71 (65, 76)	70 (65, 77)	67 (62, 74)	72 (65, 77)	-
Years between blood draw and diagnosis	11.0 (5.0, 14.7)	10.5 (5.8, 15.4)	9.6 (5.2, 14.8)	5.3 (3.3, 10.3)	8.9 (4.8, 13.9)	-
Smoking status						
Current smokers, N (%)	8 (9)	7 (8)	13 (8)	2 (8)	22 (10)	45 (8)
Past smokers, N (%)	33 (37)	35 (41)	66 (42)	11 (44)	100 (44)	280 (48)
Never smokers, N (%)	48 (54)	42 (49)	78 (49)	12 (48)	98 (44)	248 (43)
White / Caucasian, n (%)	85 (96)	81 (94)	154 (97)	25 (100)	213 (95)	561 (96)
Height, cm	168 (163, 173)	165 (163, 173)	170 (163, 178)	170 (165, 178)	170 (163, 178)	170 (163, 178)
Baseline BMI ¹ , kg/m ²	24 (23, 28)	25 (23, 30)	25 (23, 27)	24 (22, 25)	25 (23, 27)	25 (23, 28)
Young adult BMI ² , kg/m ²	21 (20, 24)	21 (20, 23)	22 (20, 24)	21 (20, 23)	22 (20, 24)	22 (20, 24)
Alcohol intake ³ , g/day	1.9 (0, 7.3)	2.7 (0, 8.9)	4.5 (0.5, 12.1)	5.2 (0.9, 14.1)	3.7 (0.8, 12.9)	3.4 (0, 12.5)
RBC SFA ⁴ , %	39.7 (38.6, 40.6)	39.7 (38.5, 40.8)	39.7 (38.6, 40.6)	39.4 (38.9, 40.6)	39.6 (38.9, 40.7)	39.7 (38.7, 40.7)
RBC VLCSFA ⁵ , %	7.0 (6.4, 7.8)	7.0 (6.5, 7.6)	7.2 (6.5, 7.9)	6.7 (6.1, 7.3)	7.1 (6.4, 7.7)	7.1 (6.5, 7.8)

RBC MUFA ⁶ , %	17.8 (16.7, 18.7)	17.5 (16.9, 18.7)	17.7 (16.9, 18.7)	17.0 (16.6, 17.8)	18.0 (17.0, 18.7)	17.7 (16.9, 18.8)
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Abbreviations: CLL/SLL, lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B- cell lymphoma; FL, follicular lymphoma; HPFS, Health Professionals' Follow-up Study; MUFA, monounsaturated fatty acids; NHL, Non-Hodgkin lymphoma; NHS, Nurses' Health Study; RBC, red blood cell; SFA, saturated fatty acids; and VLCSFA, very long-chain saturated fatty acids.

¹Baseline BMI is the BMI reported at or in the most recent questionnaire before the year of blood draw.

²Young adult BMI is BMI at age 18 for NHS, and age 21 for HPFS.

³Cumulative average was calculated up to the most recent report before the year of blood draw.

⁴Sum of 14:0, 15:0, 16:0, 17:0, 18:0, 19:0, 20:0, 22:0, 23:0, and 24:0.

⁵Sum of 20:0, 22:0, 23:0, and 24:0.

⁶Sum of 16:1n-7C, 18:1n-9C, 18:1n-7C, 20:1n-9C, 24: 1n-9C

⁷Other NHL types include mantle cell lymphoma (N=15), marginal zone (N=42), Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (N=17), B cell-other (N=18), B cell-unclassified (N=20), pre-B cell (N=5), pre-T cell (N=3), NHL, unclassified (N=84) and missing subtype (N=21).

Table 2. Spearman correlations¹ between individual RBC saturated and monounsaturated fatty acids among the controls (n=583)

	14:0	15:0	16:0	16:1n-7	17:0	18:0	18:1n-9	19:0	20:0	22:0	23:0	24:0
14:0	1.00	0.15	0.69	0.56	-0.03	-0.40	0.24	0.11	-0.37	-0.30	-0.11	-0.18
15:0		1.0	0.14	-0.007	0.38	0.16	0.10	-0.37	0.22	-0.05	-0.05	-0.30
16:0			1.0	0.51	0.03	-0.31	0.21	0.08	-0.41	-0.52	-0.39	-0.42
16:1n-7				1.0	-0.34	-0.43	0.53	-0.15	-0.41	-0.46	-0.35	-0.31
17:0					1.0	0.36	-0.08	0.20	0.28	0.08	0.14	-0.15
18:0						1.0	-0.26	-0.09	0.48	0.24	0.03	0.04
18:1n-9							1.0	-0.18	-0.18	-0.30	-0.32	-0.37
19:0								1.0	-0.12	-0.02	0.17	0.08
20:0									1.0	0.61	0.42	0.23
22:0										1.0	0.64	0.59
23:0											1.0	0.64
24:0												1.00

¹Adjusted for age and cohort.

Table 3. Adjusted¹ odds ratios of incident NHL and their major histologic subtypes for every 1 standard deviation increase in very long chain saturated fatty acid levels.

	cases	Adjusted OR (95%CI) per SD ²				Sum of VLCSFA ³
		Very long chain saturated fatty acids (VLCSFA)				
		20:0	22:0	23:0	24:0	
All NHL	583	0.94 (0.83, 1.06)	0.91 (0.81, 1.02)	0.92 (0.82, 1.04)	0.98 (0.86, 1.11)	0.94 (0.83, 1.06)
All B cell NHL	445	0.95 (0.83, 1.08)	0.90 (0.79, 1.02)	0.92 (0.80, 1.05)	0.98 (0.85, 1.12)	0.94 (0.83, 1.08)
All B cell except CLL/SLL	287	0.81 (0.70, 0.95)	0.82 (0.70, 0.95)	0.82 (0.70, 0.96)	0.93 (0.80, 1.09)	0.87 (0.75, 1.02)
Follicular	89	0.88 (0.69, 1.12)	0.94 (0.75, 1.19)	0.90 (0.71, 1.14)	0.96 (0.75, 1.24)	0.94 (0.74, 1.19)
DLBCL	86	0.89 (0.70, 1.14)	0.80 (0.63, 1.02)	0.92 (0.73, 1.16)	0.97 (0.76, 1.24)	0.90 (0.71, 1.15)
CLL/SLL	158	1.19 (0.99, 1.42)	1.05 (0.88, 1.26)	1.10 (0.92, 1.31)	1.07 (0.88, 1.30)	1.07 (0.89, 1.29)
T cell	25	0.88 (0.57, 1.35)	0.66 (0.42, 1.04)	0.75 (0.48, 1.16)	0.64 (0.40, 1.02)	0.63 (0.40, 0.99)

Abbreviation: CLL/SLL, lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B- cell lymphoma; FL, follicular lymphoma; NHL, Non-Hodgkin lymphoma; RBC, red blood cell; SD, standard deviation; VLCSFA, very long-chain saturated fatty acids.

¹ Unconditional logistic regression adjusting for age at blood draw, cohort, race, fasting status at blood draw, date of blood draw was used for assessing the associations with all B cell, all B cell except CLL, and all NHL. For the analysis of major subtype, race was not included due to model instability.

² OR (95%CI) per SD: the odds ratio per 1 standard deviation increased in biomarker levels excluding outliers by the Rosner extreme Studentized deviated method.

³ Sum of 20:0, 22:0, 23:0, and 24:0

Table 4. Adjusted¹ odds ratios of incident NHL and their major histologic subtypes for every 1 standard deviation increase in saturated long chain fatty acid levels.

	case	Adjusted OR (95%CI) per SD ²							
		Even-numbered SFA				Odd-numbered SFA			
		14:0	16:0	18:0	Sum of even-numbered SFA ³	15:0	17:0	19:0	Sum of odd-numbered SFA ⁴
All NHL	583	1.10 (0.95, 1.29)	1.07 (0.94, 1.21)	1.02 (0.89, 1.16)	1.06 (0.93, 1.20)	1.03 (0.91, 1.16)	1.06 (0.94, 1.19)	1.03 (0.89, 1.19)	1.06 (0.94, 1.20)
All B cell NHL	445	1.11 (0.94, 1.23)	1.07 (0.94, 1.23)	1.02 (0.88, 1.18)	1.08 (0.95, 1.24)	1.05 (0.92, 1.19)	1.06 (0.93, 1.21)	1.01 (0.86, 1.18)	1.07 (0.94, 1.22)
All B cell except CLL/SLL	287	1.16 (0.96, 1.41)	1.16 (0.99, 1.35)	0.98 (0.83, 1.15)	1.14 (0.98, 1.33)	1.08 (0.94, 1.25)	1.00 (0.86, 1.16)	1.00 (0.84, 1.21)	1.07 (0.92, 1.24)
Follicular	89	1.21 (0.91, 1.62)	1.03 (0.82, 1.30)	1.05 (0.81, 1.35)	1.07 (0.84, 1.35)	1.14 (0.92, 1.41)	1.20 (0.94, 1.52)	1.04 (0.78, 1.39)	1.22 (0.98, 1.54)
DLBCL	86	1.01 (0.75, 1.38)	1.13 (0.90, 1.42)	1.06 (0.82, 1.37)	1.17 (0.93, 1.48)	1.11 (0.89, 1.37)	1.02 (0.81, 1.29)	1.04 (0.77, 1.39)	1.10 (0.88, 1.39)
CLL/SLL	158	1.03 (0.81, 1.30)	0.93 (0.76, 1.12)	1.08 (0.88, 1.33)	0.96 (0.79, 1.18)	0.96 (0.79, 1.16)	1.14 (0.94, 1.38)	1.03 (0.83, 1.28)	1.04 (0.86, 1.26)
T cell	25	1.00 (0.58, 1.73)	1.12 (0.73, 1.71)	1.38 (0.87, 2.19)	1.21 (0.78, 1.88)	1.06 (0.71, 1.58)	1.40 (0.91, 2.17)	1.16 (0.71, 1.90)	1.26 (0.84, 1.89)

Abbreviation: CLL/SLL, lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B- cell lymphoma; FL, follicular lymphoma; NHL, Non-Hodgkin lymphoma; RBC, red blood cell; SD, standard deviation; SFA, saturated fatty acids.

¹ Unconditional logistic regression adjusting for age at blood draw, cohort, race, fasting status at blood draw, date of blood draw was used for assessing the associations with all B cell, all B cell except CLL, and all NHL. For the analysis of major subtype, race was not included due to model instability.

² OR (95%CI) per SD: the odds ratio per 1 standard deviation increased in biomarker levels excluding outliers by the Rosner extreme Studentized deviated method.

³ Sum of 14:0, 16:0 and 18:0

⁴ Sum of 15:0, 17:0 and 19:0

Table 5. Adjusted¹ odds ratios of incident NHL and their major histologic subtypes for every 1 standard deviation increase in monounsaturated fatty acid levels.

	Case	Adjusted OR (95%CI) per SD ²		
		MUFA		
		16:1n-7c	18:1n-9c	Sum of MUFA ³
All NHL	583	1.04 (0.89, 1.20)	1.04 (0.91, 1.18)	1.04 (0.91, 1.18)
All B cell NHL	445	1.05 (0.90, 1.24)	1.09 (0.95, 1.26)	1.09 (0.95, 1.26)
All B cell except CLL/SLL	287	1.09 (0.91, 1.30)	1.11 (0.94, 1.30)	1.10 (0.93, 1.29)
Follicular	89	0.96 (0.72, 1.29)	1.05 (0.81, 1.35)	1.05 (0.82, 1.36)
DLBCL	86	1.05 (0.79, 1.38)	1.02 (0.79, 1.31)	1.02 (0.79, 1.32)
CLL/SLL	158	0.99 (0.79, 1.25)	1.06 (0.87, 1.29)	1.08 (0.88, 1.31)
T cell	25	0.94 (0.55, 1.60)	0.64 (0.40, 1.01)	0.63 (0.40, 0.99)

Abbreviation: CLL/SLL, lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B- cell lymphoma; FL, follicular lymphoma; MUFA, monounsaturated fatty acids; NHL, Non-Hodgkin lymphoma; RBC, red blood cell; SD, standard deviation

¹ Unconditional logistic regression adjusting for age at blood draw, cohort, race, fasting status at blood draw, date of blood draw was used for assessing the associations with all B cell, all B cell except CLL, and all NHL. For the analysis of major subtype, race was not included due to model instability.

² OR (95%CI) per SD: the odds ratio per 1 standard deviation increased in biomarker levels excluding outliers.

³ Sum of 16:1n-7C, 18:1n-9C, 18:1n-7C, 20:1n-9C, 24: 1n-9C