Red blood cell membrane *trans* fatty acid levels and risk of non-Hodgkin lymphoma: a prospective nested case–control study

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ABSTRACT

Background: *Trans* fatty acid (TFA) intake persists in much of the world, posing ongoing threats to public health that warrant further elucidation. Published evidence suggests a positive association of self-reported TFA intake with non-Hodgkin lymphoma (NHL) risk.

Objectives: To confirm those reports, we conducted a prospective study of prediagnosis RBC membrane TFA levels and risk of NHL and common NHL histologic subtypes.

Methods: We conducted a nested case–control study in Nurses' Health Study and Health Professionals Follow-Up Study participants with archived RBC specimens and no history of cancer at blood draw (1989–1090 and 1994–1995, respectively). We confirmed 583 incident NHL cases (332 women and 251 men) and individually matched 583 controls on cohort (sex), age, race, and blood draw date/time. We analyzed RBC membrane TFA using GLC (in 2013–2014) and expressed individual TFA levels as a percentage of total fatty acids. We used unconditional logistic regression adjusted for the matching factors to estimate ORs and 95% CIs for overall NHL risk per 1 SD increase in TFA level and assessed histologic subtype-specific associations with multivariable polytomous logistic regression.

Results: Total and individual TFA levels were not associated with risk of all NHL or most subtypes. We observed a positive association of total TFA levels with diffuse large B cell lymphoma (DLBCL) risk [$n = 98$ cases; OR (95% CI) per 1 SD increase: 1.30 (1.05, 1.61); $P = 0.015$], driven by *trans* 18:1n–9(ω-9)/elaidic acid [OR (95% CI): 1.34 (1.08, 1.66); $P = 0.007$], *trans* 18:1n–7/vaccenic acid [OR (95% CI): 1.28 (1.04, 1.58); $P = 0.023$], and *trans* 18:2n–6*t,t* [OR (95% CI): 1.26 (1.01, 1.57); $P = 0.037$].

Conclusions: Our findings extended evidence for TFA intake and DLBCL risk but not for other NHL subtypes. Reduced TFA consumption through dietary choices or health policy measures may support prevention of DLBCL, an aggressive NHL subtype. *Am J Clin Nutr* 2020;112:1576–1583.

Keywords: *trans* fatty acids, non-Hodgkin lymphoma, nutritional epidemiology, risk factor, etiology, Nurses' Health Study, Health Professionals Follow-Up Study

Introduction

Non-Hodgkin lymphoma (NHL) includes >40 distinct histologic types of lymphoid neoplasms arising from B (B-NHL) and T lymphocytes (T-NHL) (1), the most common of which are diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). In the United States, 98,280 new NHL cases and 24,000 deaths were expected in 2020 (2). Few modifiable risk factors for NHL are known; evidence to date supports etiologic heterogeneity by subtype (3). Severe immune compromise is considered the strongest and most consistent NHL risk factor but explains only a small proportion of cases (4). Many other risk factors, including a history of autoimmune disease, certain oncogenic infections, occupational solvent and pesticide exposure, and family history of lymphoid malignancies (4), have immune-modulating properties, suggesting that other immune-modulating exposures are also plausible candidate NHL risk factors.

Diet, and dietary fats in particular, could influence NHL risk through several mechanisms, including the modulation of inflammatory pathways and of cell differentiation and apoptotic processes (5, 6). In the Multi-Ethnic Cohort, prediagnosis RBC membrane levels of various SFAs were positively associated with NHL risk, whereas MUFA and PUFA were not significantly associated with risk of NHL or its subtypes (7). The Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS) recently reported an inverse association of prediagnosis RBC membrane very-long-chain SFA levels with risk of all B-NHL except CLL/SLL and of T-NHL (8). The current study focuses on *trans* fatty acids (TFAs) because prior

studies showed a positive association of dietary TFAs with NHL; those included findings for all NHL (in aggregate) in the NHS based on follow-up through 1994 (9, 10) and for all NHL, DLBCL, and CLL/SLL in a clinic-based case–control study (11). In addition, a prospective study (77,568 participants, 431 NHL cases) reported mixed associations depending on the corresponding food sources (12).

Of interest, dietary TFAs have been correlated with markers of chronic inflammation and immune activation (13–17). In addition, multiple studies (18), including the NHS and HPFS (19), have shown associations of heightened inflammation and immune dysregulation with future risk of NHL, supporting the biologic plausibility of TFA as a NHL risk factor. To our knowledge, the association between RBC membrane TFA levels and NHL risk remains unexamined. RBC membrane TFA levels represent an integrated measure of dietary intake and metabolic processes that collectively influence internal exposure to these fats (20). In this prospective analysis, we aimed to confirm the dietary TFA findings by examining prediagnosis RBC membrane levels of total TFA, *trans* 18:1, *trans* 18:2, and *trans* 16:1n–7 in relation to risk of all NHL and common histologic subtypes. We hypothesized that RBC membrane TFA levels would be positively associated with NHL risk.

Methods

Study population

We conducted the current study in the NHS, which was established in 1976 with 121,700 female nurses aged 30—55 y at baseline, and the HPFS, which started in 1986 with 51,529 male health professionals aged 40—75 y at recruitment (21). Participants completed enrollment and biennial follow-up questionnaires about lifestyle and health status, with follow-up rates >90% in most cycles. NHL diagnoses first identified via self-report were confirmed by review of medical records and pathology reports. Histologic subtypes were determined according to the WHO classification of lymphomas and categorized as recommended by the International Lymphoma Epidemiology (InterLymph) Consortium Pathology Working Group (22, 23), as described previously (24). Deaths were identified by next of kin, the postal service, or routine searches of the National Death Index (25, 26). A subset of participants (the "blood subcohorts"), whose lifestyle and dietary variable distributions were similar to those of the complete cohorts, provided blood samples in 1989–1990 (n = 32,286, NHS) and 1993–1994 (n = 18,018, HPFS) using protocols reported in detail elsewhere (27). The current study protocol was approved by and conducted in accordance with the ethical standards of the institutional review boards of the Brigham and Women's Hospital and Harvard TH Chan School of Public Health and those of participating cancer registries as required. Participant informed consent was implied by return of the baseline questionnaire; blood subcohort participants provided written informed consent at time of blood collection.

Selection of cases and controls

From the blood subcohort participants with archived RBC samples and no history of other cancer (except nonmelanoma skin cancer), we included all with confirmed incident diagnoses of NHL (International Classification of Diseases, 8th revision, codes 200, 202, and 204.1) diagnosed at least 3 mo after blood draw and through 2010. We matched each case to 1 control by cohort (sex), date of birth (±1 y), race/ethnicity, fasting status at blood draw (≥8 h or not), date of blood draw (±1 mo), and time of day of blood draw (within 2-h intervals) as described previously (8).

Exposure assessment

The analytical procedures to measure fatty acids in RBC membranes by GLC have been described previously in detail (8, 28). The level of an individual fatty acid was expressed as a percentage of total fatty acids. RBC samples for case–control pairs were assayed in the same analytic run by a technician blinded to case status. All the samples were analyzed between 2013 and 2014. Reproducibility of the RBC membrane TFA was assessed from pairs of blinded quality control samples (resembling study matched sets) distributed throughout the study sample batches. Within-batch CVs ranged from 6% for *trans* 16:1n–7 to 37% for *trans* 18:2n–6*t,t*. Between-batch CVs ranged from 12% for *trans* 16:n–7 to 41% for *trans* 18:1n–9 (**Supplemental Table 1**).

Statistical analysis

To assess correlations among individual RBC membrane TFA levels, we calculated Spearman partial correlation coefficients among control participants adjusted for age and sex/cohort. We also calculated Spearman partial correlations with other fatty

This work was supported by the American Cancer Society (Research Scholar Grant RSG-11-020-01-CNE) and by NIH grants UM1 CA186107, P01 CA87969, R01 CA49449, U01 CA167552, R01 CA149445, R01 CA098122, 1U54 CA155626, P30 DK46200, and KL2 TR001455 (to MME) and T32 CA009001 (to AVAK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Neither the American Cancer Society nor any Institute at the NIH had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Data described in the manuscript, code book, and analytic code will not be made available because of participant confidentiality and privacy concerns. Further information including the procedures to obtain and access data from the Nurses' Health Studies and Health Professionals Follow-Up Study is described at https://www.nurseshealthstudy.org/researchers (contact e-mail: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators/.

Supplemental Tables 1–6 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: CLL, chronic lymphocytic leukemia; CRP, C-reactive protein; DLBCL, diffuse large B cell lymphoma; EDII, empirical dietary inflammatory index; FL, follicular lymphoma; HPFS, Health Professionals Follow-Up Study; NHL, non-Hodgkin lymphoma; NHS, Nurses' Health Study; SLL, small lymphocytic lymphoma; TFA, *trans* fatty acid; VLCSFA, very-long-chain SFA.

Received March 26, 2020. Accepted for publication August 11, 2020.

First published online October 6, 2020; doi: https://doi.org/10.1093/ajcn/nqaa251.

acid categories, such as VLCSFA (8), total SFA, MUFA, and PUFA. We performed analysis for all NHL and separately by histologic subtypes (DLBCL, FL, CLL/SLL, other B-NHL, and all T-NHL). We used the Rosner extreme Student deviate method to identify and exclude outlying values for each type of fatty acid ($n = 10$) (29). We modeled each summed and individual TFA variable categorically in quartiles and continuously per 1 SD increase in the relative level. To allow the inclusion of all controls in the subtype-specific analysis, we used unconditional logistic regression adjusted for all matching factors to calculate the ORs and 95% CIs for associations between RBC membrane TFA levels and risk of all NHL. We assessed the association between RBC membrane TFA levels and specific histologic subtypes using unconditional polytomous logistic regression, and we used a contrast test to evaluate heterogeneity in the associations by histologic subtype (30).

We evaluated potential nonlinearity in the relations between levels of each RBC membrane TFA and risk of NHL by fitting restricted cubic splines to the multivariable-adjusted unconditional logistic regression models (31) but did not observe nonlinearity. Therefore, we focused on models of continuous TFA levels (per 1 SD increase) as the primary analyses. We conducted analyses separately for each cohort and assessed heterogeneity by cohort using random-effects meta-analysis and the Cochran Q test (32). We did not observe significant heterogeneity by cohort (all Q statistics $\leq$1.5 and all P values for heterogeneity $\geq$0.1) and thus conducted the primary analysis in the pooled study sample. We evaluated several additional potential confounding variables with known associations with chronic inflammation. These included alcohol consumption, usual and young adult BMI (in kg/m^2), smoking history, the empirical dietary inflammatory index (EDII) (33), and the main individual dietary variables utilized to derive the EDII (intakes of fruits and vegetables, red and processed red meat, fish, whole grains, refined grains, coffee, beer, red wine, and sugar-sweetened beverages). Because the inclusion of these covariates did not materially change the estimates (data tables available upon request), the final models excluded them. We imputed cohort-specific medians to address missing values for age ($n = 1$) and time at blood draw ($n = 92$). We evaluated the independence of observed associations by running additional multivariable models with mutual adjustment for each RBC membrane TFA variable that demonstrated an individual association. We also conducted analyses with further adjustment for total RBC membrane VLCSFA, total RBC membrane MUFA, or both (8). We examined models stratified by age at blood draw (<60 y, $\geq$60 y) and by follow-up time after blood draw (<10 y, $\geq$10 y) to explore questions of potential acceleration of lymphomagenesis [most NHL diagnoses occur after age 60 y (34)] and latency. Last, in additional sensitivity analyses, we excluded NHL cases diagnosed in the first year and in the first 3 y after blood draw to assess the potential influence of misclassified case status due to clinically undetected, nascent disease.

In secondary analyses designed post hoc to explore the unexpected subtype restriction of observed associations of RBC membrane TFA levels with NHL (see Results), we evaluated the association of self-reported dietary intake of total TFA and of total *trans* 18, *trans* 18:1, *trans* 18:2, and *trans* 16:1n–7 fatty acids with risk of NHL and its most common subtypes. We utilized data from FFQs administered prior to blood draw—for example, those administered to NHS participants in 1984, 1986, and 1990 and to HPFS participants in 1986, 1990, and 1994. Validation studies have compared FFQ-estimated intakes of various types of fatty acids with intakes observed from 7-d diet records and measurements of adipose tissue fatty acid levels and have demonstrated the validity and reproducibility of the FFQ-derived intakes (35–37). Briefly, the deattenuated correlation between TFA intakes assessed by FFQ and diet records was >0.80 (36), and the correlation between TFA intake assessed by FFQ and adipose tissue TFA level was 0.46 (35). TFA intake was derived from its consumption frequency using information extracted from the Harvard University Food Composition Database and expressed as percentage of total energy. We calculated Spearman partial correlation coefficients for each TFA intake variable and RBC membrane TFA isomer among control participants, adjusted for age, cohort, and total energy intake.

All statistical analyses were performed using SAS version 9.4 (SAS Institute). Results were considered to be statistically significant when $P < 0.05$ (2-tailed).

Results

The current analysis included 583 confirmed incident cases of NHL (332 women and 251 men), including 98 DLBCL, 87 FL, 160 CLL/SLL, 120 other B-NHL, and 25 T-NHL, as well as 583 controls. Due to the matched design, the distributions of age, sex, race, and factors related to the timing of blood draw were similar across cases and controls, with small variability in these variables across NHL subtypes (**Table 1**). Overall, 43% of participants were men and 96% were white; the median age at blood draw was 61 y. Other characteristics, such as smoking status, BMI (at blood draw and in young adulthood), and alcohol intake, did not vary notably by case status, other than modest variability across NHL histologic subtypes for alcohol intake. We observed moderate correlations (Spearman r's of 0.25–0.30) between *trans* 16:1n–7 and all types of *trans* 18 fatty acids and stronger correlations for total *trans* 18 with *trans* 18:1 ($r_s = 0.99$) and *trans* 18:2 ($r_s = 0.75$) and for *trans* 18:1 with *trans* 18:2 fatty acids ($r_s = 0.67$) (**Table 2**). Correlations of individual TFAs with other classes of fatty acid were weak and mostly inverse (Table 2).

Total and individual RBC membrane TFAs were not associated with risk of all NHL and most histologic subtypes (**Table 3**). However, we observed a positive association between total TFA and DLBCL risk, with a 30% increase in risk per 1 SD increase in level ($P = 0.015$). This association appeared to be explained primarily by *trans* 18 fatty acids (summed; 33% higher DLBCL risk per 1 SD increase in level; $P = 0.008$) and more specifically by *trans* 18:1 fatty acids (summed; 36% higher DLBCL risk per 1 SD increase in level, $P = 0.005$). Among *trans* 18:1 fatty acid isomers, we found positive associations for *trans* 18:1n–9 (elaidic acid; 34% higher risk per 1 SD increase, $P = 0.007$) and *trans* 18:1n–7 (vaccenic acid; 28% higher risk per 1 SD increase, $P = 0.023$) with risk of DLBCL (Table 3). For the *trans* 18:2 fatty acids, we observed a statistically significant positive association for *trans* 18:2n–6*t*,*t* (26% higher risk per 1 SD increase, $P = 0.037$) and risk of DLBCL (Table 3). The categorical analyses yielded similar associations to those described for the continuous TFA measures (**Supplemental Table 2**). In models with mutual adjustment of individual *trans* 18 fatty acids for one another, statistically significant positive associations with DLBCL risk remained for *trans* 18:1, *trans*

TABLE 1 Characteristics of study population at blood draw among 1166 participants in the NHS (1989–1990) and HPFS (1993–1994)[1]

	Cases of NHL ($n = 583$), by major histologic subtype						
Characteristic	DLBCL	FL	CLL/SLL	Other B cell NHL[2]	T cell NHL	Other/unclassified NHL[3]	Controls
n[4]	98	87	160	120	25	72	583
Men, *n* (%)	33 (34)	26 (30)	80 (50)	47 (39)	10 (40)	54 (40)	251 (43)
Age at blood drawn, y	61 (56, 66)	60 (53, 64)	61 (54, 67)	60 (54, 65)	58 (53, 68)	66 (59, 72)	61 (54, 67)
Fasting at blood draw, *n* (%)	61 (62)	62 (72)	98 (61)	56 (47)	17 (68)	41 (57)	359 (62)
Age at diagnosis, y	72 (65, 78)	68 (61, 74)	70 (65, 77)	70 (64, 74)	67 (62, 74)	75 (68, 80)	71 (65, 76)[5]
Time between blood draw and diagnosis, y	11.5 (6.6, 15.3)	10.4 (4.9, 14.6)	9.7 (5.2, 14.9)	8.8 (4.9, 13.7)	5.3 (3.3, 10.3)	5.9 (3.4, 10.3)	9.3 (4.9, 14.3)[5]
Smoking status, *n* (%)							
Current smoker	7 (7)	8 (9)	13 (8)	14 (12)	2 (8)	3 (4)	46 (8)
Past smoker	40 (41)	33 (38)	66 (42)	54 (45)	11 (44)	34 (47)	280 (48)
Never smoker	49 (50)	46 (53)	80 (50)	51 (43)	12 (48)	31 (43)	248 (43)
White/Caucasian, *n* (%)	93 (95)	84 (97)	155 (97)	115 (96)	25 (100)	65 (90)	561 (96)
Height, cm	168 (163, 179)	168 (163, 173)	170 (163, 179)	170 (163, 177)	170 (165, 178)	178 (170, 183)	170 (163, 178)
BMI[6], kg/m^2	25 (22, 29)	24 (21, 27)	25 (22, 27)	25 (22, 27)	22 (21, 25)	24 (22, 28)	24 (22, 27)
Young adult BMI[7], kg/m^2	21 (20, 24)	22 (20, 24)	22 (20, 24)	22 (20, 23)	21 (20, 23)	23 (21, 25)	22 (20, 24)
Alcohol intake[8], g/d	5.4 (2.1, 10.7)	4.4 (1.5, 10.0)	6.4 (1.2, 13.7)	6.6 (1.1, 17.0)	5.3 (2.7, 26.2)	4.3 (1.0, 17.7)	3.4 (0, 12.5)
RBC total *trans* fatty acids[9]	1.99 (1.61, 2.45)	1.92 (1.59, 2.21)	1.85 (1.54, 2.19)	1.84 (1.53, 2.16)	1.96 (1.52, 2.27)	1.86 (1.51, 2.20)	1.87 (1.58, 2.22)
RBC *trans* 18:1 (summed), %[9]	1.52 (1.24, 1.79)	1.45 (1.22, 1.72)	1.43 (1.15, 1.71)	1.42 (1.14, 1.69)	1.56 (1.08, 1.77)	1.45 (1.15, 1.73)	1.45 (1.18, 1.73)
trans 18:1n–12	0.19 (0.15, 0.26)	0.18 (0.15, 0.24)	0.19 (0.14, 0.24)	0.18 (0.14, 0.22)	0.18 (0.14, 0.26)	0.19 (0.16, 0.24)	0.19 (0.14, 0.24)
trans 18:1n–9	0.35 (0.28, 0.48)	0.34 (0.28, 0.42)	0.33 (0.25, 0.41)	0.33 (0.26, 0.40)	0.39 (0.27, 0.44)	0.33 (0.26, 0.40)	0.34 (0.27, 0.42)
trans 18:1n–7	0.40 (0.32, 0.48)	0.37 (0.32, 0.46)	0.36 (0.28, 0.44)	0.37 (0.28, 0.45)	0.39 (0.29, 0.46)	0.38 (0.28, 0.46)	0.37 (0.30, 0.45)
RBC *trans* 18:2 (summed), %[9]	0.31 (0.24, 0.36)	0.29 (0.24, 0.35)	0.29 (0.25, 0.34)	0.30 (0.25, 0.35)	0.27 (0.23, 0.35)	0.29 (0.24, 0.34)	0.29 (0.25, 0.34)
trans 18:2n–6*t,t*	0.02 (0.01, 0.03)	0.02 (0.01, 0.02)	0.02 (0.01, 0.02)	0.02 (0.01, 0.02)	0.02 (0.01, 0.02)	0.02 (0.01, 0.02)	0.02 (0.01, 0.02)
trans 18:2n-6*c,t*	0.16 (0.13, 0.18)	0.15 (0.13, 0.18)	0.15 (0.13, 0.18)	0.15 (0.13, 0.18)	0.15 (0.13, 0.18)	0.15 (0.12, 0.17)	0.15 (0.13, 0.17)
trans 18:2n–6*t,c*	0.12 (0.10, 0.16)	0.12 (0.10, 0.15)	0.12 (0.10, 0.15)	0.12 (0.10, 0.15)	0.11 (0.10, 0.16)	0.12 (0.10, 0.15)	0.12 (0.10, 0.15)
RBC *trans* 16:1n–7, %[9]	0.14 (0.11, 0.16)	0.13 (0.11, 0.16)	0.13 (0.11, 0.15)	0.13 (0.11, 0.15)	0.12 (0.11, 0.15)	0.13 (0.11, 0.15)	0.13 (0.11, 0.15)

[1]Values are medians with IQR or counts with respective percentages. CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HPFS, Health Professionals Follow-Up Study; NHL, non-Hodgkin lymphoma; NHS, Nurses' Health Study; SLL, small lymphocytic lymphoma.

[2]Other B cell NHL subtypes include mantle cell ($n = 17$); marginal zone ($n = 43$); Waldenström macroglobulinemia/lymphoplasmacytic lymphoma ($n = 18$); Burkitt lymphoma ($n = 1$); B cell, other ($n = 19$); and B cell, unclassified ($n = 22$).

[3]Other/unclassified NHL subtypes include unclassified NHL ($n = 72$).

[4]Cases with missing subtype classification represent those for whom a histological subtype could not be assigned based on their available medical record information ($n = 21$).

[5]Age at diagnosis for controls and time between blood draw and diagnosis for controls were estimated as the median values for the respective matched case.

[6]BMI reported in the questionnaire closest to blood draw.

[7]Young adult BMI is BMI at age 18 y for NHS and age 21 y for HPFS.

[8]Cumulative average was calculated up to the report closest to blood draw.

[9]RBC *trans* fatty acid levels are expressed as a percentage of total RBC fatty acids.

TABLE 2 Spearman partial correlations between RBC membrane *trans* fatty acids and other fatty acid categories among controls ($n = 583$)[1,2]

	trans 18[3]	*trans* 18:1	*trans* 18:2	*trans* 16:1n–7	SFA[4]	MUFA[5]	PUFA[6]	VLCSFA[7]
trans 18[3]	1.00							
trans 18:1	0.99[8]	1.00						
trans 18:2	0.75[8]	0.67[8]	1.00					
trans 16:1n–7	0.30[8]	0.30[8]	0.25[8]	1.00				
SFA[4]	–0.25[8]	–0.25[8]	–0.15[8]	0.15[8]	1.00			
MUFA[5]	–0.09[8]	–0.12[8]	0.07[8]	–0.13[8]	–0.19[8]	1.00		
PUFA[6]	–0.08	–0.05	–0.21[8]	–0.17[8]	–0.55[8]	–0.56[8]	1.00	
VLCSFA[7]	–0.02	–0.002	–0.11[8]	–0.07	0.11[8]	–0.11[8]	–0.01	1.00

[1] Spearman correlations were adjusted for age and cohort (sex). VLCSFA, very-long-chain SFA.
[2] RBC *trans* fatty acid levels are expressed as a percentage of total RBC fatty acids.
[3] Sum of *trans* 18:1 and *trans* 18:2.
[4] SFA = sum of 14:0, 15:0, 16:0, 17:0, 18:0, 19:0, 20:0, 22:0, 23:0, and 24:0.
[5] MUFA = sum of 16:1n–7*c*, 18:1n–9*c*, 18:1n–7*c*, 20:1n–9*c*, and 24:1n–9*c*.
[6] PUFA = sum of 18:3n–3*c*, 20:5n–3*c*, 22:5n–3*c*, 22:6n–3*c*, 18:2n–6*c*, 18:3n–6*c*, 20:3n–6*c*, 20:4n–6*c*, and 22:4n–6*c*.
[7] VLCSFA = sum of 20:0, 22:0, 23:0, and 24:0.
[8] P value < 0.05.

18:1n–9, and *trans* 18:2n–6*t,t* fatty acids (**Supplemental Table 3**). For instance, for *trans* 18:1, the increase in DLBCL risk remained 36% per 1 SD after further adjustment ($P = 0.005$) (Supplemental Table 3). With mutual adjustment of TFA variables for total MUFA and/or VLCSFA (8), the TFA-specific results remained virtually unchanged (**Supplemental Table 4**). We did not observe statistically significant heterogeneity by age at blood draw [<60 y, ≥60 y; all P values for interaction > 0.05 (all chi-square values ≤ 1.6)] (**Supplemental Table 5**) or by time from blood draw to diagnosis or index date [<10 y, ≥10 y; all P values for interaction > 0.05 (all chi-square values ≤ 1.6)] (**Supplemental Table 6**) for any associations of RBC membrane TFA levels with NHL endpoints. In the sensitivity analysis to assess potential misclassification of disease due to the presence of subclinical disease at blood draw, the associations remained unchanged regardless of whether we excluded cases diagnosed within the first year or those diagnosed within the first 3 y after blood draw (data tables available upon request). In the *post hoc* sensitivity analysis, the Spearman partial correlation coefficients for RBC membrane TFA levels and dietary TFA intakes among control participants ($n = 559$) were modest ($r_s \leq 0.38$; all $P < 0.05$; **Table 4**) and were slightly stronger for the averaged pre-blood draw dietary TFA variables than for the most recent (e.g., to blood draw) TFA intake. For example, the Spearman correlation coefficients between dietary TFA (averaged pre-blood draw) and their RBC membrane counterparts ranged between 0.19 for *trans* 18:2 fatty acids and 0.38 for *trans* 18:1 fatty acids (Table 4). In models of average dietary TFA intake and risk of NHL endpoints, we did not observe an association of average dietary TFA intake with all NHL or most histologic subtypes. Furthermore, in contrast to the observed associations for RBC membrane TFA levels, we did not observe statistically significant associations for total *trans*, *trans* 18, and *trans* 18:1 fatty acids with DLBCL risk. For example, the ORs (95% CI) for the associations of total average dietary *trans* 18:1 fatty acid intake with all NHL and DLBCL risk were 1.04 (0.89, 1.20) and 1.13 (0.87, 1.48), respectively, per 1 SD increase in intake. We did not observe statistically significant associations of any dietary TFA variable with any NHL endpoint when based on only the most recently reported FFQ to blood draw.

Discussion

Due to adverse health effects, particularly around cardiovascular disease risk, the WHO has recommended the elimination of industrially produced *trans* fats from food products (38). In the United States, intake of total TFA has halved from more than 2% of total calories in 1995 to just >1% in 2009–2010, according to the US Department of Agriculture, mostly due to a gradual phase out of industrially produced partially hydrogenated oils from the diet (39, 40). Despite these decreases, some industrially produced TFAs remained in the US diet (41, 42). More recent evidence has shown that the health effects of TFA can persist for many years, even at lower intake amounts (43). A combination of voluntary and mandatory policies aimed at reducing the use of partially hydrogenated oils and limiting the intake of TFAs in several countries has contributed to decreases in TFA intake in several populations from 1995 to 2010 (39); however, these restrictions are not in effect globally (44). In the current study, we observed significant positive associations of RBC membrane TFA levels with NHL risk, particularly DLBCL. This evidence can help support new and existing food industry and public health initiatives to continue decreasing TFAs in the worldwide food supply.

The current prospective study utilized blood samples collected during the period of relatively high average US TFA consumption, e.g., in the early 1990s. We observed that prediagnosis RBC membrane TFA levels were not associated with all NHL or most histologic subtypes, whereas levels of *trans* 18:1 and, in particular, *trans* 18:1n–9 and *trans* 18:1n–7 fatty acids were associated with a moderately increased risk of DLBCL. Prediagnosis RBC membrane levels of *trans* 18:2n–6*t,t* fatty acids were also positively associated with DLBCL risk. The associations of DLBCL risk with RBC membrane TFA levels were independent of previously reported associations with prediagnosis RBC membrane VLCSFA and MUFA levels (8). The significant associations of *trans* 18:1, *trans* 18:1n–9, *trans* 18:1n–7, and *trans* 18:2n–6*t,t* with DLBCL risk persisted after adjustment for other RBC membrane *trans* 18 isomers despite modest to strong correlations among the various RBC membrane TFAs. To our knowledge, no other studies have examined the

TABLE 3 Adjusted ORs and 95% CIs for risk of NHL and common histologic subtypes of NHL for every 1 SD increase in prediagnosis RBC membrane *trans* fatty acid levels[1]

	Adjusted OR (95% CI) per 1 SD increase[2]						
		B cell NHL					
	All NHL	DLBCL	FL	CLL/SLL	Other B cell NHL[3]	T cell NHL	*P*-heterogeneity[4]
Cases, *n*	583	98	87	160	120	25	
Total *trans* fatty acids	1.04 (0.93, 1.18)	1.30 (1.05, 1.61)	1.04 (0.82, 1.32)	0.98 (0.82, 1.17)	0.86 (0.70, 1.07)	1.01 (0.66, 1.53)	0.06
trans 18[5]	1.04 (0.93, 1.17)	1.33 (1.08, 1.65)	1.02 (0.80, 1.30)	0.95 (0.79, 1.14)	0.88 (0.71, 1.09)	1.03 (0.68, 1.56)	0.04
trans 18:1 (summed)	1.03 (0.92, 1.16)	1.36 (1.10, 1.68)	1.02 (0.80, 1.30)	0.93 (0.77, 1.11)	0.87 (0.70, 1.07)	1.05 (0.69, 1.58)	0.04
trans 18:1n–12	0.99 (0.87, 1.14)	1.16 (0.91, 1.50)	0.91 (0.68, 1.21)	0.98 (0.79, 1.20)	0.85 (0.66, 1.08)	0.94 (0.57, 1.53)	0.48
trans 18:1n–9	1.04 (0.93, 1.17)	1.34 (1.08, 1.66)	1.08 (0.85, 1.37)	0.93 (0.77, 1.11)	0.87 (0.70, 1.08)	1.15 (0.77, 1.73)	0.04
trans 18:1n–7	1.02 (0.91, 1.15)	1.28 (1.04, 1.58)	1.09 (0.86, 1.37)	0.91 (0.76, 1.08)	1.00 (0.81, 1.22)	0.93 (0.62, 1.41)	0.16
trans 18:2 (summed)	1.04 (0.92, 1.17)	1.14 (0.91, 1.42)	1.07 (0.84, 1.36)	0.95 (0.79, 1.14)	0.99 (0.81, 1.22)	0.97 (0.63, 1.49)	0.76
trans 18:2n–6*t*	1.04 (0.91, 1.18)	1.26 (1.01, 1.57)	1.05 (0.81, 1.36)	0.93 (0.76, 1.15)	0.99 (0.79, 1.24)	0.84 (0.50, 1.42)	0.30
trans 18:2n–6*c*,*t*	1.04 (0.92, 1.16)	1.11 (0.90, 1.38)	1.02 (0.81, 1.29)	0.98 (0.82, 1.17)	0.98 (0.80, 1.20)	1.01 (0.67, 1.51)	0.91
trans 18:2n–6*t*,*c*	1.04 (0.92, 1.17)	1.10 (0.88, 1.36)	1.05 (0.83, 1.33)	0.97 (0.81, 1.16)	1.00 (0.81, 1.23)	1.00 (0.66, 1.52)	0.93
trans 16:1n–7	0.98 (0.87, 1.11)	1.11 (0.89, 1.39)	0.97 (0.76, 1.23)	1.04 (0.87, 1.25)	0.81 (0.66, 1.00)	0.89 (0.58, 1.37)	0.28

[1] Unconditional logistic regression models were adjusted for matching factors [age at blood draw ± 1 y, cohort/sex, race, fasting status at blood draw (≥8 h vs. not), date of blood draw (±1 mo), and time of day of blood draw (within 2-h intervals)] for all NHL. The analysis of major subtypes utilized the same modeling approach except that race was not included due to model instability. CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; SLL, small lymphocytic lymphoma.

[2] OR (95% CI) per 1 SD increase: the OR per 1 SD increase in biomarker levels excluding outliers by the Rosner extreme Studentized deviate method (29).

[3] Other B cell NHL subtypes include mantle cell (n = 17); marginal zone (n = 43); Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (n = 18); Burkitt lymphoma (n = 1); B cell, other (n = 19); and B cell, unclassified (n = 22).

[4] P values for heterogeneity by subtype from contrast tests comparing TFA isomer-specific estimates between DLBCL, FL, CLL/SLL, other B cell NHL, and T cell NHL.

[5] Sum of *trans* 18:1 and *trans* 18:2.

association between RBC membrane TFA levels and NHL risk. The positive associations observed for DLBCL were generally consistent with published findings for self-reported intake of TFA and all NHL risk in the NHS for follow-up through 1994 (9, 10), as well as with a clinic-based case–control study, although the latter study reported a positive association with a greater variety of NHL endpoints (all NHL, DLBCL, and CLL/SLL) and focused only on total TFA intake.(11) In addition, a cohort study of multiple dietary factors and cancer risk in Norway reported an inverse association of NHL risk with TFA intake from partially hydrogenated vegetable oils, a positive association for ruminant TFA, and no association for TFA from partially hydrogenated fish oils (12). The latter study did not examine individual NHL subtypes.

The mechanisms linking TFA intake and NHL development are not well characterized; a few plausible mechanisms merit consideration. First, several lines of evidence support an etiologic role of TFA in chronic inflammation, particularly for industrially derived TFA isomers (13–15, 17). In observational studies, TFA intake has been positively correlated with markers of chronic inflammation, including C-reactive protein (CRP) and soluble TNF receptors 1 and 2 (14, 15). These markers, in turn, have been associated with tumor growth, angiogenesis, suppression of apoptosis, and metastasis of multiple types of cancer (45). In randomized feeding trials in humans, intake of TFA-rich foods was linked to increased concentrations of CRP, IL-1, IL-6, IL-8, and TNF-α (13, 17), although other trials found no changes in inflammatory biomarkers associated with TFA intake (46). The collective evidence supports heightened inflammation as a plausible mechanism for the observed associations of RBC membrane TFA levels with DLBCL risk, which is consistent with evidence that a milieu of inflammation and heightened immune activation is associated with long-term risk of NHL, including findings in the NHS and HPFS (18, 19). A second plausible mechanism by which TFAs may influence NHL risk is the alteration of cell signaling after TFAs are incorporated into cell membrane phospholipids (47). In particular, TFAs may inhibit the autophagy typically induced by other fatty acids and that normally protects cells against inflammatory responses (48). In addition, TFAs may influence the regulation of apoptosis; for example, cell culture studies have shown that *trans* 18:1n–9 and *trans* 18:1n–7 fatty acid exposure may lead to a buildup of ceramides, which may inhibit apoptosis (49). The current study cannot determine which mechanisms explain the observed associations or the apparent restriction to DLBCL. However, the collective mechanistic and epidemiologic evidence supports the biologic plausibility of the observed positive associations.

This study has several strengths, including a prospective design, data on individual RBC membrane TFA isomers, a relatively large sample of NHL cases, and long duration of follow-up. Our study also has some limitations, including reliance on a single assessment of RBC membrane TFA levels. RBC membrane fatty acids represent dietary intake or metabolic exposures occurring a few months (50) prior to blood draw and thus may not represent long-term intake of TFAs or reflect the etiologic period most relevant to pathogenesis. Second, we cannot exclude an influence of laboratory measurement error; however, any such error is likely to be nondifferential because cases and controls were analyzed in the same batch. Nonetheless, even nondifferential measurement error could have influenced the observed associations. Third, the

TABLE 4 Spearman correlations between prediagnosis RBC membrane *trans* fatty acid levels and dietary *trans* fatty acids among control participants ($n = 559$)[1]

	Prediagnosis RBC[2] membrane *trans* fatty acids				
Dietary *trans* fatty acids	Total *trans* fatty acids	*trans* 18	*trans* 18:1	*trans* 18:2	*trans* 16:1n–7
Cumulative average[3]					
Total *trans* fatty acids	0.35	0.35	0.36	0.20	0.21
trans 18	0.37	0.37	0.38	0.23	0.24
trans 18:1	0.37	0.37	0.38	0.23	0.24
trans 18:2	0.32	0.31	0.32	0.19	0.21
trans 16:1n–7	0.04	0.01	0.01	–0.01	0.32
Questionnaire closest to blood draw[4]					
Total *trans* fatty acids	0.31	0.32	0.32	0.21	0.22
trans 18	0.32	0.32	0.33	0.22	0.17
trans 18:1	0.33	0.33	0.34	0.23	0.21
trans 18:2	0.25	0.25	0.26	0.15	0.13
trans 16:1n–7	0.01	–0.01	–0.01	–0.03	0.30

[1]Spearman correlations were adjusted for age, cohort, and total energy intake (kilocalories per day).

[2]Continuous measures of RBC *trans* fatty acid levels expressed as a percentage of total RBC fatty acids. HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

[3]Continuous measures of average dietary intake of *trans* fatty acids in 1986, 1990, and 1994 in the HPFS and 1984, 1986, and 1990 in the NHS expressed as a percentage of total energy intake.

[4]Continuous measures of dietary intake of *trans* fatty acids in 1994 in the HPFS and 1990 in the NHS expressed as a percentage of total energy intake.

study participants were adult health professionals of (mostly) European ancestry, which may limit the generalizability of our findings to other populations. We had relatively small numbers for individual NHL subtypes, resulting in imprecise effect estimates and warranting caution in their interpretation, especially regarding the apparent restriction to DLBCL, for which we know of no clear physiologic explanation. We also had limited numbers to examine the associations stratified by age and follow-up time, calling for caution in their interpretation. We examined multiple TFAs simultaneously and did not adjust for multiple comparisons; we acknowledge the possibility of false-positive findings and cannot rule out chance as an explanation for the DLBCL-specific results. Last, although we matched and controlled for several potential NHL risk factors, we cannot rule out an influence of residual or unmeasured confounding.

Our prospective study findings of positive associations between RBC membrane TFA levels and DLBCL risk are consistent with published positive associations for TFA intake and have biologic plausibility. However, they leave the question of associations for other NHL subtypes unclear and require replication in other cohorts. Collectively, the evidence suggests that food industry and public health measures to continue to reduce TFAs in the food supply may help reduce risk of NHL, or specifically of DLBCL, and calls for further elucidation of the role of diet in NHL etiology.

We thank the participants and staff of the NHS and HPFS for their dedication and contribution to the research and the following state cancer registries for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, and Wyoming. We assume full responsibility for analyses and interpretation of the data. We also thank Jeremy Furtado for measurement of the red blood cell membrane fatty acid levels.

The authors' responsibilities were as follows—BMB: designed the research; HC: provided data; AVAK and Y-HC: analyzed the data; AVAK and BMB: interpreted the data and wrote the manuscript; KAB, SZ, MME, BAR, SC, ELG, and JEG: helped with data interpretation and provided critical scientific input; BMB and AVAK: had primary responsibility for the final contents; and all authors: read and approved the final manuscript. The authors report no conflicts of interests.

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