Pre-diagnosis plasma immune markers and risk of non-Hodgkin lymphoma in two prospective cohort studies

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Supplementary Materials

Epstein et al., Pre-diagnosis plasma immune markers and risk of non-Hodgkin lymphoma in two prospective cohort studies

This supplementary file includes:

Supplementary Methods

Supplementary Tables 1-8

Supplementary Methods

Study Population

The Nurses' Health Study (NHS) was established in 1976 when 121 700 female nurses aged 30-55 from 11 US states responded to a mailed questionnaire.[1] The Health Professionals Follow-up Study (HPFS) was initiated in 1986 among 51 529 male US health professionals aged 40-75 at baseline. In 1989-90, 32 826 NHS participants contributed blood samples by methods described in detail elsewhere.[2] Between 1993 and 1994, 18 018 men contributed blood samples via similar methods and protocols as for the NHS. Briefly, cohort members received phlebotomy kits, had blood drawn locally, then returned the samples via overnight courier. Upon arrival, samples were centrifuged, aliquotted and stored at -130°C.[2]

Participants from both studies complete biennial questionnaires to update exposures and ascertain new disease diagnoses. Participant deaths are ascertained by next-of-kin, the postal service or routine searches of the National Death Index.[3, 4] Cancer diagnoses identified by self-report or via death follow-up are confirmed by medical record review with participant consent, or by linkage to tumor registries. Follow-up for NHS and HPFS participants submitting a blood sample has consistently been >99% in each cohort.

Informed consent to participate in the cohorts was implied by return of study questionnaires; cohort members who contributed blood samples provided written informed consent at the time of specimen collection. The present study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health.

Case and Control Selection

Among cohort members with archived blood samples we included all with confirmed incident non-Hodgkin lymphoma (NHL) diagnosed at least three months after date of blood draw and prior to December 31, 2010, with no history of other cancer (except non-melanoma skin cancer). NHL histologic subtype was classified as described previously[5] and according to the World Health Organization classification for hematopoietic tumors by study pathologists (JCA, SJR).[6, 7] Subtypes were categorized for analysis according to guidelines from the International Lymphoma Epidemiology (InterLymph) Consortium.[8, 9] Several major B-cell NHL subtypes were analyzed individually, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Other identified, less common subtypes of B-NHL were combined into an "other B-NHL" category. We categorized all T-cell NHLs (T-NHL) together and also defined a category of all B-NHL cases. Confirmed cases that could not be further classified were omitted from subtype-specific analyses.

For each eligible NHL case, we matched one control with an archived blood sample and no history of cancer (other than non-melanoma skin cancer) as of the case's diagnosis date. Matching factors included cohort/sex, age (±1 year), race/ethnicity (Caucasian, other), fasting

status at blood draw (≥8 hours or not), date of blood draw (±1 month), and time of day of blood draw (within 2-hour increments).

Biomarker Assessment

At most, samples had undergone two freeze-thaw cycles prior to immune marker testing. Assays were performed at the University of California, Los Angeles (LM, OMM), using multiplexed assay kits (Fluorokine® MAP, R & D Systems, Minneapolis, MN) according to manufacturer directions, and a Bio-Plex 200 Luminex instrument and Bio-Plex analysis software (Bio-Rad, Hercules, CA). Assay panel A (first panel from the Soluble Receptor Human Panel Multiplex Kit) included sCD30, sIL-2Rα (also known as sCD25), B-cell activating factor of the TNF family (BAFF, a B-cell stimulatory cytokine also known as B lymphocyte stimulator, BLyS) and CXCL13 (also known as B lymphocyte chemoattractant, BLC, or B cell-attracting chemokine 1, BCA-1). Panel B (also from the Soluble Receptor kit) comprised four soluble receptors [soluble CD14 (sCD14), soluble GP130 (sGP130), soluble IL-6 receptor (sIL-6Rα) and sTNF-R2] and C-reactive protein (CRP). Panel C (from the High Sensitivity Human Inflammation Multiplex Kit) included IL-6, IL-8, IL-10, and TNF-α. Specimens from matched cases and controls were handled in the same batches, with pairs of quality control (QC) specimens interspersed randomly in each batch (approximately 10% of samples) to monitor assay performance. Laboratory personnel were blinded to case/control status and the identity of QC specimens.

The overall coefficients of variation (CV) for the immune markers ranged from 3.9% (BAFF) to 14.3% (IL-6); for the three immune markers with overall CVs >10% (IL-6, IL-10, and TNF-α), within-batch CVs were all <8%.

For each plate of samples tested for a given analyte, a biomarker- and plate-specific lower limit of detection (LLD) was defined. Observations below the LLD were assigned a value of one-half the plate-specific LLD for that marker. In addition, extrapolated values ≤0.1 pg/mL were considered unreliable and were similarly assigned a value of one-half the plate-specific LLD for that marker.[10, 11] Biomarkers with recoded values include CRP (N=11), IL-10 (N=193), IL-6 (N=21), and IL-8 (N=5). All analyte concentrations were natural log-transformed to improve normality.

Prior to testing study samples we performed pilot studies to ensure that the pre-processing delays inherent in our blood collection protocols did not compromise biomarker reliability.[2] For all but three analytes, intraclass correlation coefficients (ICC) calculated from samples with 0-, 24- and 48-hour delays indicated good to excellent reproducibility (all ICCs ≥0.55, with most ≥0.80) across the time frame in which the study samples were returned for processing. However, for TNF-α, IL-8 and CXCL13, the reproducibility in samples processed >24 hours after blood draw was poor; thus, in analyses of those three markers we set values to missing for the samples with >24 hour processing delays (NHS: N= 35; HPFS: N=23). We[10] and others[12-14] have previously demonstrated acceptable to excellent within-person temporal stability over a period of up to two years for most biomarkers in the present analysis. Because measured concentrations of biomarkers were similar between cohorts (**Supplementary Table 1**), we

pooled data from the NHS and HPFS to maximize statistical power for subtype-specific and stratified analyses.

Statistical Methods

We implemented the batch calibration methods of Rosner et al. to diminish the potential influence of laboratory batch-related variability on biomarker-NHL associations.[15] Briefly, for each analyte we calculated a "batch effect correction factor" using linear regression models run on natural log-transformed biomarker values and then utilized the batch-specific correction factors to normalize the measured laboratory values across batches.

Outlying immune marker values were identified using the Rosner extreme Studentized deviate method.[16] Records with implausible outlier values were omitted only from analyses of the given marker. We calculated partial Spearman correlation coefficients among the pooled controls with adjustment for age at blood draw and cohort to assess the pairwise correlations between the immune markers.

The primary analysis assessed batch effect-corrected, log-transformed values of each immune marker continuously per standard deviation (SD) increase in concentration based on SD units calculated for the log-transformed variables in the pooled study controls. To permit inclusion of all the controls in subtype-specific analyses, we used unconditional logistic regression models to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association between each immune marker and NHL risk, overall and by major histologic subtype (DLBCL, FL, CLL/SLL, other B-NHL, all B-NHL, all T-NHL). Most models adjusted for all the matching factors; we could not adjust for race in models for T-NHL and certain subgroup analyses due to small numbers. We evaluated additional potential confounding variables, including body mass index at blood draw (<22.5, 22.5-24.9, 25.0-29.9, ≥30 kg/m²) and in young adulthood (<18.5, 18.5-22.4, 22.5-24.9, ≥25 kg/m²) and self-reported history of autoimmune disease (rheumatoid arthritis, ulcerative colitis/Crohn disease, multiple sclerosis, psoriasis, and Sjögren syndrome). However, the addition of these variables to the multivariable model did not meaningfully change the reported associations, and thus only matching factors were retained in the final models. Exclusion of individuals with a history of autoimmune disease also did not influence the observed associations.

Additional analyses explored associations between NHL risk and multiple immune markers. Our *a priori* approach to identifying multi-marker profiles consisted of mutual adjustment of markers that were individually associated with NHL risk (sTNF-R2, sIL-2Rα, CXCL13, sCD30, BAFF), with further adjustment for matching factors. We investigated these 5-marker models for risk of all NHL and each major NHL subtype. For comparison we decided *post hoc* to explore multivariable, multi-marker models constructed using the automated stepwise regression procedure, with the matching factors forced in and the significance level set to p=0.10, as well as a multivariable model mutually adjusted for all 13 immune markers.

We also examined models stratified by the time interval between blood draw and diagnosis (0 to <5, 5 to <10, and ≥10 years) to explore whether any immune biomarker

associations suggested only earlier or later influence on NHL pathogenesis. We assessed heterogeneity in associations by time period using the contrast test method.[17]

Secondary analyses that we added *post hoc* included an examination of possible non-linear relationships between NHL risk and immune markers, which we assessed non-parametrically with restricted cubic splines,[18] looking at risk of all NHL, B-NHL, T-NHL, and the four histologic subtypes of B-NHL (DLBCL, FL, CLL/SLL, other B-NHL). The unconditional logistic regression models included the five immune markers from the main multi-marker models (sTNFR2, sIL2-Rα, CXCL13, sCD30, BAFF), and were additionally adjusted for age at blood draw, time of blood draw, cohort and race.

In another *post hoc* exploratory analysis to compare with unconditional logistic regression, we utilized polytomous logistic regression (PLR) to better account for potential heterogeneity between strata, looking at all B-NHL and all T-NHL in one model, and the four histologic subtypes of B-NHL noted previously in a second model. Models examined the association between NHL and the same five immune markers (sTNF-R2, sIL-2Rα, CXCL13, sCD30, BAFF) as in the unconditional logistic regression multi-marker models for the total time period, and then stratified by time between blood draw and diagnosis/index date (0 to <5, 5 to <10, and ≥10 years). We created a semi-continuous variable with three levels, taking the value of the median of each time period, and constructed an interaction term between this variable and levels of each of the five main biomarkers (per-SD, natural log scale), which we included with the corresponding main effect terms to assess heterogeneity of the biomarker-endpoint associations across time periods. The PLR models were adjusted for age at blood draw (continuous), cohort, and time of blood draw (continuous). We could not adjust the PLR models for race due to small numbers in certain categories (T-NHL and earliest time period).

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Supplementary Tables 1-8

Supplementary Table 1. Description of immune markers by cohort (pg/mL)

Supplementary Table 2. Pairwise Spearman correlation coefficients between immune markers among controls only, adjusted for age and cohort (sex)

Supplementary Table 3. Associations of individual pre-diagnosis plasma immune markers with NHL risk, overall and by major histologic subtype, separately for the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) participants

Supplementary Table 4. Independent associations of multiple pre-diagnosis plasma immune markers with risk of NHL, overall and by B or T cell type of origin, for the complete follow-up period and stratified by years of follow-up, using polytomous logistic regression

Supplementary Table 5. Independent associations of multiple pre-diagnosis plasma immune markers with risk of NHL by major histologic subtype of B-cell NHL for the complete follow-up period and stratified by years of follow-up, using polytomous logistic regression

Supplementary Table 6. Associations of pre-diagnosis plasma immune marker profiles created through stepwise selection with risk of NHL, overall and by major histologic subtype of NHL, for the complete follow-up period and stratified by years from blood draw to diagnosis/index date

Supplementary Table 7. Associations of individual pre-diagnosis plasma immune markers with risk of all NHL, stratified by years of follow-up

Supplementary Table 8. Associations of individual plasma immune markers and risk of major histologic subtypes of NHL in the combined cohorts, stratified by years of follow-up

Supplementary Table 1. Description of immune markers by cohort (pg/mL)

	NHS				HPFS				
Marker	N	Mean	Median	Minimum	Maximum	N	Mean	Median	Minimum	Maximum
					Original values*					
IL-6	689	9.84	7.47	0.53	792.64	510	8.51	7.19	1.19	57.24
IL-8	654	30.23	8.76	1.54	6259.12	487	11.14	5.85	0.63	1132.53
IL-10	687	2.80	2.19	0.04	23.00	507	2.85	2.21	0.20	13.05
TNF-α	654	28.66	26.68	5.09	178.69	487	29.74	28.45	7.36	65.86
CRP†	689	11003967.73	4559642.35	209329.56	462764529.00	510	8699651.28	2348826.14	11800.65	504457100.00
sCD14	689	2142644.13	2025343.98	1080204.24	9922244.05	510	1789479.58	1751751.90	1089323.23	3761290.34
sGP130	689	370953.04	332034.91	223577.85	1986314.93	510	316457.54	311519.56	161432.46	525071.11
sTNF-R2	689	4290.46	3808.80	1722.62	22624.52	510	4419.16	3869.31	1933.82	80532.09
sIL-6Rα	689	80997.67	74227.80	26418.37	390419.22	510	71172.14	68642.09	34127.68	157703.21
BAFF	689	1432.82	1401.83	461.43	3159.70	510	1234.76	1194.76	289.66	6083.44
sIL-2Rα	689	1295.80	1136.68	492.48	8818.70	510	1404.08	1191.71	376.05	12544.05
CXCL13	654	57.85	37.81	7.57	3915.66	487	102.73	37.19	6.41	21732.23
sCD30	689	1532.96	1267.16	497.92	27976.35	510	1435.95	1189.95	431.53	9573.50
					Batch effect-corrected‡, LN-transformed values					
IL-6	687	1.98	1.98	0.02	4.10	510	2.00	1.99	0.18	4.01
IL-8	644	2.19	2.16	0.46	4.35	480	1.77	1.76	0.05	3.55
IL-10	686	0.75	0.78	-1.95	3.43	507	0.82	0.83	-1.58	2.56
TNF-α	650	3.26	3.27	2.13	4.37	487	3.34	3.36	1.94	4.17
CRP	689	15.31	15.29	12.41	19.82	506	14.76	14.66	11.51	18.86
sCD14	679	14.53	14.52	13.94	15.30	509	14.39	14.38	13.90	14.88
sGP130	689	12.76	12.72	12.33	14.41	510	12.66	12.65	12.08	13.17
sTNF-R2	688	8.29	8.26	7.46	9.55	505	8.31	8.28	7.55	9.43
sIL-6Rα	681	11.23	11.22	10.18	12.28	510	11.16	11.15	10.49	11.97
BAFF	686	7.25	7.25	6.36	8.07	507	7.08	7.08	6.19	8.06
sIL-2Rα	680	7.06	7.03	6.20	8.24	505	7.12	7.08	5.93	8.47
CXCL13	645	3.66	3.62	1.99	5.33	480	3.67	3.61	1.85	5.62
sCD30	684	7.19	7.14	6.31	8.76	506	7.15	7.09	6.03	8.59

Abbreviations: NHS indicates Nurses' Health Study; HPFS, Health Professionals Follow-up Study; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; sCD14, soluble CD14; sGP130, soluble GP130; sTNF-R2, soluble tumor necrosis factor receptor-2; sIL-6Rα, soluble interleukin-6 receptor-α; BAFF, B-cell activating factor of the TNF family; sIL-2Rα, soluble interleukin-2 receptor-α; CXCL13, CXC chemokine ligand 13; sCD30, soluble CD30.

* Original values including extrapolated values, but excluding observations with processing delays.

† CRP is presented in pg/mL for consistency; divide by $1X10^9$ to convert to mg/dL. For example, 11003967.73 pg/mL = 0.01100396773 mg/dL.

‡ Batch effect correction conducted per methods of Rosner, *et al.* (Am J Epidemiol 2008;167:653-66); batch-corrected Ns reflect exclusion of participants missing age at blood draw.

Supplementary Table 2. Pairwise Spearman correlation coefficients between immune markers among controls only, adjusted for age and cohort (sex)*

	IL-6	IL-8	IL-10	TNF-α	CRP	sCD14	sGP130	sTNF-R2	sIL-6Rα	BAFF	sIL2-Rα	CXCL13	sCD30
IL-6	1.00	0.10	0.15	**0.33**	0.14	0.15	0.06	0.11	0.03	0.03	0.12	0.05	-0.01
IL-8		1.00	0.13	**0.22**	-0.03	0.13	0.05	0.10	0.002	0.05	0.15	**0.17**	0.10
IL-10			1.00	**0.23**	0.04	0.02	0.05	0.06	0.03	0.03	0.02	-0.03	0.04
TNF-α				1.00	0.0001	0.14	0.13	0.13	0.01	0.04	0.04	0.06	0.14
CRP					1.00	**0.22**	0.04	**0.25**	0.09	0.07	**0.19**	0.07	-0.04
sCD14						1.00	**0.38**	**0.42**	**0.21**	**0.18**	**0.24**	0.11	0.12
sGP130							1.00	**0.40**	**0.34**	**0.18**	**0.17**	0.10	**0.19**
sTNF-R2								1.00	**0.33**	**0.24**	**0.49**	**0.23**	**0.53**
sIL-6Rα									1.00	0.03	0.12	0.06	0.10
BAFF										1.00	**0.28**	0.13	**0.26**
sIL2-Rα											1.00	**0.26**	**0.58**
CXCL13												1.00	**0.32**
sCD30													1.00

Abbreviations: NHL, non-Hodgkin lymphoma; B-NHL, all B-cell NHL; T-NHL, all T-cell NHL; OR, odds ratio; CI, confidence interval; SD, standard deviation; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; sCD14, soluble CD14; sGP130, soluble GP130; sTNF-R2, soluble tumor necrosis factor receptor-2; sIL-6Rα, soluble interleukin-6 receptor-α; BAFF, B-cell activating factor of the TNF family; sIL-2Rα, soluble interleukin-2 receptor-α; CXCL13, CXC chemokine ligand 13; sCD30, soluble CD30.

* Bold type signifies $p < 0.0001$.

Supplementary Table 3. Associations of individual pre-diagnosis plasma immune markers with NHL risk, overall and by major histologic subtype, separately for the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) participants

	Cohort			
	NHS		HPFS	
Marker	N cases/ controls	OR (95% CI) per 1-SD*	N cases/ controls	OR (95% CI) per 1-SD*
All NHL				
IL-6	343/344	1.01 (0.87,1.17)	254/256	0.93 (0.79,1.09)
IL-8	319/325	1.03 (0.88,1.20)	239/241	0.96 (0.81,1.15)
IL-10	343/343	1.00 (0.87,1.16)	253/254	0.99 (0.83,1.17)
TNF-α	323/327	1.01 (0.87,1.17)	243/244	1.03 (0.86,1.23)
CRP	344/345	1.07 (0.92,1.25)	252/254	1.04 (0.87,1.23)
sCD14	338/341	0.94 (0.81,1.09)	254/255	1.14 (0.96,1.35)
sGP130	338/341	0.94 (0.78,1.14)	254/255	**1.17 (0.98,1.40)**
sTNF-R2	343/345	**1.20 (1.04,1.39)**	249/256	**1.34 (1.12,1.62)**
sIL-6Rα	338/343	1.08 (0.93,1.26)	254/256	1.11 (0.95,1.30)
BAFF	341/345	0.88 (0.78,1.00)	251/256	**0.79 (0.68,0.91)**
sIL-2Rα	335/345	**1.31 (1.14,1.52)**	250/255	**1.45 (1.23,1.71)**
CXCL13	315/330	**1.32 (1.15,1.51)**	239/241	**1.30 (1.10,1.54)**
sCD30	339/345	**1.29 (1.12,1.49)**	251/255	**1.48 (1.26,1.74)**
B-NHL Subtypes				
All B-NHL	N cases		N cases	
IL-6	290	1.03 (0.89,1.21)	212	0.91 (0.77,1.07)
IL-8	267	1.07 (0.91,1.26)	199	0.97 (0.81.1.16)
IL-10	290	1.00 (0.86,1.16)	211	0.96 (0.80,1.14)
TNF-α	271	0.99 (0.85,1.17)	202	0.98 (0.81,1.19)
CRP	291	1.08 (0.92,1.27)	210	1.02 (0.85,1.23)
sCD14	286	0.89 (0.76,1.05)	212	1.13 (0.94,1.35)
sGP130	286	0.92 (0.75,1.12)	212	1.14 (0.95,1.37)
sTNF-R2	290	**1.20 (1.03,1.40)**	207	**1.36 (1.12,1.65)**
sIL-6Rα	286	1.07 (0.91,1.25)	212	1.10 (0.93,1.30)
BAFF	288	**0.86 (0.76,0.99)**	209	**0.75 (0.64,0.88)**
sIL-2Rα	285	**1.31 (1.12,1.52)**	208	**1.48 (1.25,1.77)**
CXCL13	266	**1.30 (1.12,1.50)**	199	**1.26 (1.06,1.50)**
sCD30	288	**1.31 (1.12,1.52)**	210	**1.45 (1.22,1.72)**
DLBCL				
IL-6	70	1.14 (0.87,1.49)	44	1.08 (0.79,1.49)
IL-8	63	0.97 (0.73,1.29)	43	0.97 (0.70,1.34)
IL-10	69	1.08 (0.83,1.40)	44	1.26 (0.91,1.76)
TNF-α	65	0.94 (0.72,1.24)	43	1.02 (0.73,1.42)
CRP	70	1.00 (0.77,1.30)	44	1.34 (0.98,1.84)
sCD14	70	0.80 (0.61,1.06)	44	1.15 (0.84,1.58)
sGP130	70	0.78 (0.53,1.14)	44	1.03 (0.73,1.44)

sTNF-R2	70	0.84 (0.63,1.12)	44	1.36 (0.98,1.89)
sIL-6Rα	70	0.82 (0.62,1.09)	44	1.01 (0.74,1.40)
BAFF	70	0.97 (0.76,1.24)	44	1.02 (0.75,1.38)
sIL-2Rα	70	1.05 (0.80,1.37)	44	**1.61 (1.19,2.19)**
CXCL13	65	1.21 (0.95,1.55)	42	1.31 (0.96,1.78)
sCD30	70	1.14 (0.88,1.48)	44	**1.51 (1.14,2.01)**
FL				
IL-6	63	1.04 (0.80,1.45)	29	**0.63 (0.41,0.97)**
IL-8	58	1.16 (0.89,1.52)	26	0.84 (0.56,1.26)
IL-10	63	1.03 (0.79,1.34)	28	0.90 (0.61,1.33)
TNF-α	60	1.12 (0.84,1.48)	27	1.23 (0.80,1.88)
CRP	63	1.23 (0.94,1.61)	29	0.87 (0.57,1.32)
sCD14	61	0.82 (0.61,1.11)	29	1.30 (0.88,1.91)
sGP130	62	1.11 (0.81,1.53)	29	1.34 (0.88,2.05)
sTNF-R2	62	**1.45 (1.11,1.90)**	28	1.19 (0.78,1.84)
sIL-6Rα	62	1.18 (0.90,1.55)	29	1.09 (0.74,1.60)
BAFF	63	0.93 (0.72,1.21)	29	0.91 (0.61,1.36)
sIL-2Rα	62	**1.65 (1.26,2.17)**	29	1.34 (0.92,1.96)
CXCL13	59	**1.66 (1.29,2.14)**	27	**1.46 (1.00,2.14)**
sCD30	62	**1.86 (1.44,2.40)**	28	**1.51 (1.06,2.14)**
CLL/SLL				
IL-6	84	1.03 (0.80,1.31)	81	0.96 (0.76,1.21)
IL-8	79	0.95 (0.74,1.23)†	77	1.03 (0.79,1.34)
IL-10	84	0.83 (0.66,1.05)	81	0.87 (0.68,1.12)
TNF-α	79	1.03 (0.80,1.32)†	79	1.10 (0.85,1.42)
CRP	84	0.94 (0.73,1.20)	81	0.92 (0.71,1.19)
sCD14	83	0.82 (0.63,1.06)	81	1.06 (0.82,1.35)
sGP130	82	0.85 (0.60,1.20)	81	1.22 (0.95,1.56)
sTNF-R2	84	1.16 (0.92,1.45)	80	**1.49 (1.14,1.95)**
sIL-6Rα	84	1.19 (0.94,1.51)	81	1.11 (0.88,1.39)
BAFF	84	**0.58 (0.46,0.73)**	79	**0.48 (0.37,0.63)**
sIL-2Rα	82	**1.40 (1.11,1.77)**	80	**1.61 (1.26,2.05)**
CXCL13	78	1.02 (0.80,1.30)†	78	1.19 (0.93,1.52)
sCD30	83	1.19 (0.95,1.49)	80	**1.56 (1.22,1.99)**
Other B-NHL‡				
IL-6	73	0.96 (0.75, 1.23)	58	0.80 (0.60, 1.07)
IL-8	67	1.23 (0.96, 1.57)	53	0.93 (0.69, 1.26)
IL-10	74	1.15 (0.89, 1.48)	53	0.92 (0.70, 1.21)
TNF-α	67	0.92 (0.71, 1.19)	58	**0.72 (0.54, 0.96)**
CRP	74	1.23 (0.95, 1.59)	56	1.02 (0.75, 1.39)
sCD14	72	1.13 (0.88, 1.44)	58	1.15 (0.86, 1.53)
sGP130	72	0.94 (0.68, 1.29)	58	1.09 (0.81, 1.46)
sTNF-R2	74	**1.41 (1.12, 1.78)**	55	1.25 (0.93, 1.68)

sIL-6Rα	70	1.07 (0.83, 1.39)	58	1.21 (0.92, 1.60)
BAFF	71	1.02 (0.80, 1.29)	57	**0.77 (0.60, 0.99)**
sIL-2Rα	71	**1.35 (1.05, 1.73)**	55	**1.48 (1.13, 1.95)**
CXCL13	64	**1.61 (1.28, 2.03)**	52	**1.34 (1.02, 1.76)**
sCD30	73	1.24 (0.98, 1.59)	58	**1.35 (1.06, 1.71)**
All T-NHL§				
IL-6	18	1.09 (0.68,1.74)	12	1.19 (0.65, 2.18)
IL-8	18	0.61 (0.35, 1.08)	11	1.31 (0.66, 2.64)
IL-10	18	1.00 (0.62, 1.61)	12	1.64 (0.87, 3.09)
TNF-α	18	1.00 (0.61, 1.65)	11	1.37 (0.74, 2.54)
CRP	18	0.87 (0.54, 1.41)	12	1.16 (0.63, 2.14)
sCD14	18	0.78 (0.46, 1.34)	12	1.31 (0.65, 2.64)
sGP130	18	0.70 (0.35, 1.37)	12	1.16 (0.42, 3.22)
sTNF-R2	18	0.89 (0.54, 1.47)	12	1.30 (0.70, 2.41)
sIL-6Rα	18	0.93 (0.59,1.46)	12	1.23 (0.61, 2.47)
BAFF	18	1.15 (0.69, 1.92)	12	1.38 (0.83, 2.32)
sIL-2Rα	18	**1.79 (1.10, 2.92)**	12	**2.24 (1.28, 3.91)**
CXCL13	18	1.33 (0.83, 2.13)	10	1.12 (0.64, 1.97)
sCD30	18	1.25 (0.81,1.92)	11	**1.87 (1.12, 3.12)**

Abbreviations: NHL, non-Hodgkin lymphoma; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; B-NHL, all B-cell NHL; T-NHL, all T-cell NHL; OR, odds ratio; CI, confidence interval; SD, standard deviation; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; sCD14, soluble CD14; sGP130, soluble GP130; sTNF-R2, soluble tumor necrosis factor receptor-2; sIL-6Rα, soluble interleukin-6 receptor-α; BAFF, B-cell activating factor of the TNF family; sIL-2Rα, soluble interleukin-2 receptor-α; CXCL13, CXC chemokine ligand 13; sCD30, soluble CD30.

* All models were adjusted for age at blood draw, time of day of blood draw and race unless otherwise noted.

† Models were adjusted for age at blood draw and time of day of blood draw.

‡ Other B-cell subtypes included Burkitt lymphoma (N=4), lymphoplasmacytic lymphoma (N=19), mantle cell lymphoma (N=20), marginal zone lymphoma (N=44), other B-NHL (N=20), and unclassified B-NHL (N=25).

§ Models were adjusted for age at blood draw only.

Supplementary Table 4. Independent associations of multiple pre-diagnosis plasma immune markers with risk of NHL, overall and by B or T cell type of origin, for the complete follow-up period and stratified by years of follow-up, using polytomous logistic regression

			Years from blood draw to diagnosis/index date						
	Complete follow-up period¶		0 to less than 5		5 to less than 10		10 or more		
Marker*	N cases†	OR (95% CI) per 1-SD ‡,^	N cases†	OR (95% CI) per 1-SD ‡,^	N cases†	OR (95% CI) per 1-SD ‡,^	N cases†	OR (95% CI) per 1-SD ‡,^	P-value§
All NHLǁ									
sTNF-R2	*542*	*1.05 (0.91, 1.21)*	*133*	*0.83 (0.60, 1.14)*	*149*	*1.02 (0.77, 1.35)*	*260*	*1.18 (0.95, 1.46)*	*0.20*
sIL-2Rα	*542*	***1.20 (1.03, 1.39)***	*133*	***1.52 (1.09, 2.11)***	*149*	*1.16 (0.88, 1.53)*	*260*	*1.11 (0.88, 1.39)*	*0.28*
CXCL13	*542*	***1.17 (1.03, 1.32)***	*133*	*1.00 (0.78, 1.29)*	*149*	***1.30 (1.03, 1.62)***	*260*	***1.21 (1.01, 1.46)***	*0.32*
sCD30	*542*	***1.24 (1.06, 1.45)***	*133*	***1.52 (1.09, 2.13)***	*149*	***1.43 (1.07, 1.90)***	*260*	*0.98 (0.78, 1.23)*	*0.02*
BAFF	*542*	***0.74 (0.66, 0.83)***	*133*	***0.73 (0.59, 0.91)***	*149*	***0.61 (0.48, 0.78)***	*260*	*0.83 (0.69, 1.00)*	*0.15*
All B-NHL									
sTNF-R2	454	1.08 (0.93, 1.26)	110	0.91 (0.65, 1.25)	118	1.14 (0.85, 1.53)	226	1.14 (0.91, 1.44)	0.04
sIL-2Rα	454	**1.20 (1.03, 1.40)**	110	**1.46 (1.03, 2.07)**	118	1.16 (0.87, 1.54)	226	1.14 (0.91, 1.44)	0.06
CXCL13	454	**1.14 (1.00, 1.29)**	110	0.99 (0.75, 1.30)	118	1.19 (0.93, 1.51)	226	**1.22 (1.02, 1.47)**	0.46
sCD30	454	**1.24 (1.05, 1.46)**	110	**1.55 (1.09, 2.21)**	118	**1.57 (1.14, 2.16)**	226	0.96 (0.75, 1.23)	0.03
BAFF	454	**0.74 (0.66, 0.83)**	110	0.70 (0.56, 0.87)	118	**0.64 (0.51, 0.81)**	226	0.85 (0.71, 1.02)	0.30
All T-NHL									
sTNF-R2	28	0.64 (0.39, 1.04)	11	0.54 (0.24, 1.22)	10	0.60 (0.26, 1.39)	7	0.74 (0.25, 2.21)	0.94
sIL-2Rα	28	**1.73 (1.11, 2.69)**	11	2.10 (0.97, 4.53)	10	1.79 (0.90, 3.54)	7	0.96 (0.35, 2.62)	0.33
CXCL13	28	1.03 (0.72, 1.47)	11	0.84 (0.46, 1.55)	10	1.48 (0.85, 2.58)	7	0.66 (0.32, 1.37)	0.64
sCD30	28	1.30 (0.83, 2.03)	11	1.47 (0.69, 3.14)	10	1.16 (0.53, 2.53)	7	1.90 (0.73, 4.93)	0.77
BAFF	28	0.96 (0.70, 1.32)	11	1.00 (0.62, 1.60)	10	0.74 (0.43, 1.27)	7	1.32 (0.61, 2.86)	0.36

Abbreviations: NHL, Non-Hodgkin lymphoma; B-NHL, all B-cell NHL; T-NHL, all T-cell NHL; OR, Odds Ratio; CI, Confidence Interval; SD, Standard Deviation; sTNF-R2, soluble tumor necrosis factor receptor-2; sIL-2Rα, soluble interleukin-2 receptor-α; CXCL13, CXC chemokine ligand 13; sCD30, soluble CD30; BAFF, B-cell activating factor of the TNF family.

* Values are batch effect-corrected and exclude cohort-specific outliers.

† The models for the full follow-up period included 571 controls. Each of the models for 0 to <5 year, 5 to <10 year and 10 or more year intervals after blood draw included 140, 162 and 267 controls, respectively.

‡ Unstratified models adjusted for age at blood draw (continuous), cohort (HPFS, NHS), time of blood draw (continuous) and race/ethnicity (Caucasian, non-Caucasian). The time-stratified models were not adjusted for race. The models were mutually adjusted for all immune markers listed.

^ Odds Ratios and 95% Confidence Intervals were calculated per standard deviation of natural log-transformed values, in HPFS and NHS combined.

¶ In unstratified analyses, only sTNF-R2 demonstrated significant heterogeneity by tumor cell type (p=0.04); all other p-values for heterogeneity by tumor cell type were ≥0.10.

§ P-values from tests for heterogeneity comparing effect estimates for each immune marker-endpoint association across time strata, based on inclusion of an interaction term for biomarker* time period in the corresponding model for the complete time period.

‖ The all NHL models in italics are included for comparison purposes. These models used unconditional logistic regression, and were not compared statistically with any subtypes.

Supplementary Table 5. Independent associations of multiple pre-diagnosis plasma immune markers with risk of NHL by major histologic subtype of B-cell NHL for the complete follow-up period and stratified by years of follow-up, using polytomous logistic regression

			Years from blood draw to diagnosis/index date						
	Complete follow-up period*		0 to less than 5		5 to less than 10		10 or more		
Marker	N cases†	OR (95% CI) per 1-SD‡, §	N cases†	OR (95% CI) per 1-SD‡, §	N cases†	OR (95% CI) per 1-SD‡, §	N cases†	OR (95% CI) per 1-SD‡, §	P-value¶
DLBCL									
sTNF-R2	107	0.83 (0.64, 1.08)	25	0.65 (0.37, 1.15)	25	0.99 (0.58, 1.69)	57	0.85 (0.56, 1.28)	0.20
sIL-2Rα	107	1.13 (0.87, 1.45)	25	1.65 (0.91, 2.99)	25	1.01 (0.61, 1.65)	57	1.07 (0.73, 1.57)	0.20
CXCL13	107	1.14 (0.93, 1.40)	25	0.76 (0.47, 1.21)	25	1.40 (0.95, 2.07)	57	1.27 (0.95, 1.71)	0.21
sCD30	107	1.24 (0.96, 1.62)	25	0.99 (0.53, 1.83)	25	**1.93 (1.18, 3.18)**	57	1.10 (0.75, 1.62)	0.98
BAFF	107	0.94 (0.78, 1.14)	25	0.98 (0.66, 1.46)	25	**0.68 (0.47, 0.97)**	57	1.11 (0.83, 1.48)	0.47
FL									
sTNF-R2	83	1.04 (0.78, 1.38)	18	0.65 (0.30, 1.42)	22	0.91 (0.52, 1.59)	43	1.45 (0.99, 2.10)	0.0007
sIL-2Rα	83	1.01 (0.76, 1.34)	18	0.74 (0.35, 1.56)	22	1.12 (0.67, 1.87)	43	1.03 (0.68, 1.55)	0.95
CXCL13	83	1.21 (0.97, 1.51)	18	0.86 (0.53, 1.41)	22	1.14 (0.74, 1.75)	43	**1.42 (1.03, 1.97)**	0.15
sCD30	83	**1.65 (1.24, 2.19)**	18	**4.34 (2.13, 8.85)**	22	1.67 (0.96, 2.90)	43	1.08 (0.70, 1.67)	0.001
BAFF	83	**0.81 (0.66, 0.99)**	18	0.79 (0.50, 1.24)	22	0.83 (0.55, 1.23)	43	0.78 (0.57, 1.06)	0.40
CLL/SLL									
sTNF-R2	153	1.23 (0.99, 1.53)	36	1.03 (0.61, 1.71)	44	1.33 (0.88, 2.02)	73	1.20 (0.86, 1.66)	0.29
sIL-2Rα	153	**1.40 (1.12, 1.74)**	36	**2.43 (1.40, 4.23)**	44	1.34 (0.90, 2.00)	73	1.19 (0.85, 1.67)	0.008
CXCL13	153	0.88 (0.73, 1.06)	36	0.79 (0.50, 1.22)	44	0.75 (0.51, 1.11)	73	1.00 (0.76, 1.30)	0.30
sCD30	153	1.20 (0.94, 1.52)	36	1.42 (0.82, 2.47)	44	**1.59 (1.01, 2.53)**	73	0.93 (0.65, 1.34)	0.18
BAFF	153	**0.55 (0.46, 0.65)**	36	**0.46 (0.33, 0.65)**	44	**0.48 (0.34, 0.67)**	73	**0.70 (0.54, 0.91)**	0.10
Other B-NHL‖									
sTNF-R2	111	1.17 (0.92, 1.49)	31	1.16 (0.72, 1.86)	27	1.19 (0.73, 1.94)	53	1.13 (0.78, 1.66)	0.69
sIL-2Rα	111	1.16 (0.91, 1.48)	31	1.19 (0.71, 2.00)	27	1.03 (0.64, 1.64)	53	1.28 (0.87, 1.87)	0.74
CXCL13	111	**1.45 (1.19, 1.75)**	31	1.41 (0.95, 2.09)	27	**1.66 (1.16, 2.37)**	53	1.32 (0.97, 1.80)	0.46

sCD30	111	1.05 (0.81, 1.37)	31	1.47 (0.86, 2.50)	27	1.26 (0.76, 2.10)	53	0.80 (0.52, 1.21)	0.13
BAFF	111	**0.81 (0.68, 0.97)**	31	0.72 (0.52, 1.00)	27	0.74 (0.53, 1.06)	53	0.92 (0.69, 1.23)	0.56

Abbreviations: NHL, Non-Hodgkin lymphoma; B-NHL, all B-cell NHL; T-NHL, all T-cell NHL; OR, Odds Ratio; CI, Confidence Interval; SD, Standard Deviation; sTNF-R2, soluble tumor necrosis factor receptor-2; sIL-2Rα, soluble interleukin-2 receptor-α; CXCL13, CXC chemokine ligand 13; sCD30, soluble CD30; BAFF, B-cell activating factor of the TNF family.

* In unstratified analyses, CXCL13 ($p=0.0007$) and BAFF ($p<0.0001$) demonstrated significant heterogeneity by B-NHL histologic subtype; all other p-values for heterogeneity by B-NHL histologic subtype were ≥0.08.

† Each model for the complete follow-up period included 571 controls. Each model for the 0 to <5, 5 to <10 and 10 or more year intervals after blood draw included 140, 162 and 267 controls, respectively.

‡ Unstratified models adjusted for age at blood draw (continuous), cohort (sex), time of blood draw (continuous) and race/ethnicity (Caucasian, non-Caucasian); time-stratified models were not adjusted for race. Models were mutually adjusted for all immune markers listed.

§ Odds ratios and 95% confidence intervals were calculated per standard deviation of batch effect-corrected, log-transformed values from the combined Nurses' Health Study and Health Professionals Follow-up Study cohorts.

¶ P-values from test for heterogeneity comparing immune marker-specific effect estimates across time strata, based on inclusion of interaction terms for biomarker*time period in the PLR model for the complete follow-up period.

‖ Other B-NHL subtypes include Burkitt lymphoma (N=4), lymphoplasmacytic lymphoma (N=19), mantle cell lymphoma (N=20), marginal zone lymphoma (N=39), other B-NHL (N=20), and unclassified B-NHL (N=25).

Supplementary Table 6. Associations of pre-diagnosis plasma immune marker profiles created through stepwise selection with risk of NHL, overall and by major histologic subtype of NHL, for the complete follow-up period and stratified by years from blood draw to diagnosis/index date

			Years from blood draw to diagnosis/index date					
	Complete Follow-up Period		0 to less than 5		5 to less than 10		10 or more	
Marker*	N cases/ controls	OR per 1-SD (95% CI)†,‡	N cases/ controls	OR per 1-SD (95% CI)†,‡	N cases/ controls	OR per 1-SD (95% CI)†,‡	N cases/ controls	OR per 1-SD (95% CI)†,‡
All NHL								
sCD30	544/571	**1.26 (1.08, 1.46)**	134/140	**1.48 (1.06, 2.05)**	149/162	**1.59 (1.19, 2.12)**	261/267	1.03 (0.83, 1.28)
BAFF	544/571	**0.74 (0.66, 0.83)**	134/140	**0.72 (0.58, 0.90)**	149/162	**0.61 (0.48, 0.78)**	261/267	0.85 (0.70, 1.02)
CXCL13	544/571	**1.17 (1.04, 1.32)**	134/140	1.00 (0.78, 1.28)	149/162	**1.30 (1.03, 1.63)**	261/267	**1.22 (1.01, 1.46)**
sIL-2Rα	544/571	**1.21 (1.05, 1.40)**	134/140	**1.41 (1.05, 1.89)**	149/162	1.16 (0.89, 1.53)	261/267	1.15 (0.92, 1.43)
B-NHL Subtypes								
DLBCL								
sCD30	114/599	**1.29 (1.06, 1.56)**	26/154	0.96 (0.62, 1.49)	27/165	**1.92 (1.30, 2.84)**	61/278	1.18 (0.90, 1.54)
FL§								
sCD30	90/598	**1.76 (1.43, 2.15)**	21/154	**3.10 (1.93, 4.98)**	22/164	**1.75 (1.15, 2.67)**	47/278	1.32 (0.98, 1.76)
CLL/SLL§								
sCD30	160/594	1.20 (0.96, 1.51)	37/153	1.46 (0.78, 2.74)	46/163	**1.59 (1.06, 2.40)**	77/276	0.98 (0.70, 1.36)
BAFF	160/594	**0.48 (0.39, 0.59)**	37/153	**0.32 (0.20, 0.53)**	46/163	**0.40 (0.26, 0.61)**	77/276	**0.67 (0.49, 0.92)**
IL-10	160/594	**0.83 (0.69, 0.99)**	37/153	0.99 (0.63, 1.56)	46/163	0.78 (0.53, 1.13)	77/276	**0.77 (0.60, 0.99)**
sIL-2Rα	160/594	**1.52 (1.22, 1.90)**	37/153	**3.07 (1.68, 5.62)**	46/163	1.36 (0.89, 2.08)	77/276	1.21 (0.85, 1.71)
Other B-NHL‖								
CXCL13	111/569	**1.48 (1.22, 1.79)**	31/140	**1.64 (1.13, 2.38)**	27/160	**1.56 (1.11, 2.19)**	53/267	1.30 (0.95, 1.76)
BAFF	111/569	**0.80 (0.67, 0.97)**	31/140	0.80 (0.59, 1.09)	27/160	0.78 (0.53, 1.15)	53/267	0.87 (0.62, 1.20)
sIL-2Rα	111/569	**1.25 (1.02, 1.53)**	31/140	1.41 (0.97, 2.05)	27/160	1.27 (0.82, 1.95)	53/267	1.19 (0.86, 1.65)
T-cell NHL§								
sIL-2Rα	30/598	**1.97 (1.37, 2.85)**	13/154	**2.26 (1.31, 3.89)**	10/164	1.91 (0.93, 3.92)	7/278	1.30 (0.59, 2.85)

Abbreviations: NHL, non-Hodgkin lymphoma; OR, odds ratio; CI, confidence interval; SD, standard deviation; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; IL, interleukin; sTNF-R2, soluble tumor necrosis factor receptor-2; sIL-2Rα, soluble interleukin-2 receptor-α; CXCL13, CXC chemokine ligand 13; sCD30, soluble CD30; BAFF, B-cell activating factor of the TNF family.
* Immune markers are listed in the order in which they were selected through the stepwise selection procedure.

† Odds ratios and 95% confidence intervals were calculated per 1 standard deviation increase in biomarker concentration, based on batch effect-corrected, log-transformed values with outliers removed, for Nurses' Health Study and Health Professionals Follow-up Study cohorts combined.

‡ All models were adjusted for age at blood draw, race, time of blood draw, cohort, and the other listed biomarkers unless otherwise noted.

§ T-NHL models were not adjusted for race due to sparse cell counts.

‖ Other B-cell subtypes included Burkitt lymphoma (N=4), lymphoplasmacytic lymphoma (N=19), mantle cell lymphoma (N=20), marginal zone lymphoma (N=44), other B-NHL (N=20), and unclassified B-NHL (N=25); time-stratified models for other B-NHL not adjusted for race due to sparse cell counts.

Supplementary Table 7. Associations of individual pre-diagnosis plasma immune markers with risk of all NHL, stratified by years of follow-up

	Years from blood draw to diagnosis/index date						
	0 to less than 5		5 to less than 10		10 or more		
Marker	N cases/ controls	OR (95% CI) per 1-SD*,†	N cases/ controls	OR (95% CI) per 1-SD*	N cases/ controls	OR (95% CI) per 1-SD*	
IL-6	154/155	1.01 (0.81, 1.24)	165/165	0.87 (0.71, 1.07)	278/278	1.03 (0.88, 1.22)	
IL-8	142/141	1.04 (0.81, 1.33)	154/158	1.09 (0.85, 1.39)	262/265	0.92 (0.77, 1.11)	
IL-10	154/154	1.08 (0.87, 1.34)	165/165	0.98 (0.80, 1.21)	277/276	0.96 (0.82, 1.13)	
TNF-α	145/142	1.09 (0.87, 1.36)	156/159	0.92 (0.73, 1.17)	265/268	1.03 (0.87, 1.22)	
CRP	154/154	1.09 (0.88, 1.35)	164/165	1.08 (0.86, 1.37)	278/278	1.03 (0.87, 1.24)	
sCD14	153/154	1.07 (0.84, 1.37)	166/165	1.07 (0.86, 1.33)	273/275	0.94 (0.78, 1.14)	
sGP130	154/155	0.89 (0.66, 1.20)	165/164	1.28 (0.96, 1.72)	273/275	0.98 (0.80, 1.19)	
sTNF-R2	149/155	**1.29 (1.03, 1.61)**	166/166	**1.27 (1.02, 1.59)**	277/278	**1.22 (1.03, 1.45)**	‡
sIL-6Rα	153/155	0.97 (0.77, 1.21)	164/165	1.20 (0.97, 1.49)	275/277	1.11 (0.94, 1.31)	
BAFF	152/155	**0.79 (0.67, 0.94)**	163/166	**0.73 (0.59, 0.89)**	277/278	0.95 (0.80, 1.12)	‡
sIL-2Rα	147/154	**1.80 (1.45, 2.23)**	163/166	**1.40 (1.14, 1.73)**	275/278	1.14 (0.96, 1.35)	‡
CXCL13	139/140	**1.34 (1.10, 1.64)**	152/162	**1.38 (1.13, 1.69)**	263/267	**1.25 (1.05, 1.48)**	‡
sCD30	150/154	**1.60 (1.30, 1.98)**	164/166	**1.61 (1.29, 2.00)**	276/278	1.13 (0.96, 1.33)	‡

Abbreviations: NHL, non-Hodgkin lymphoma; OR, odds ratio; CI, confidence interval; SD, standard deviation; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; sCD14, soluble CD14; sGP130, soluble GP130; sTNF-R2, soluble tumor necrosis factor receptor-2; sIL-6Rα, soluble interleukin-6 receptor-α; BAFF, B-cell activating factor of the TNF family; sIL-2Rα, soluble interleukin-2 receptor-α; CXCL13, CXC chemokine ligand 13; sCD30, soluble CD30.

* Adjusted for age at blood draw, time of day of blood draw, race, and cohort (sex).

† Odds Ratios (OR) per 1 standard deviation increase in biomarker concentration, based on batch effect-corrected values with outliers removed, for Nurses' Health Study and Health Professionals Follow-up Study cohorts combined.

‡ Statistically significant in non-stratified models (Table 2).

Supplementary Table 8. Associations of individual plasma immune markers and risk of major histologic subtypes of NHL in the combined cohorts, stratified by years of follow-up

Marker	Years from blood draw to diagnosis/index date: 0 to less than 5		5 to less than 10		10 or more	
	N cases/ controls	OR (95% CI) per 1-SD*,†	N cases/ controls	OR (95% CI) per 1-SD*,†	N cases/ controls	OR (95% CI) per 1-SD*,†
B-NHL subtypes						
DLBCL						
IL-6	26/155	1.12 (0.71, 1.78)	27/164	1.01 (0.67, 1.54)	61/278	1.17 (0.88, 1.55)
IL-8	26/141	0.87 (0.54, 1.40)	24/157	1.22 (0.77, 1.93)	56/265	0.89 (0.64, 1.25)
IL-10	26/154	1.05 (0.69, 1.61)	27/164	1.11 (0.75, 1.65)	60/276	1.22 (0.91, 1.65)
TNF-α	26/142	1.07 (0.69, 1.66)	25/158	0.97 (0.62, 1.51)	57/268	0.98 (0.73, 1.31)
CRP	26/154	1.18 (0.79, 1.78)	27/164	1.32 (0.85, 2.06)	61/278	1.03 (0.77, 1.38)
sCD14	26/154	1.10 (0.70, 1.73)	27/164	1.00 (0.65, 1.53)	61/275	0.80 (0.57, 1.12)
sGP130	26/155	0.47 (0.22, 1.01)	27/163	1.03 (0.60, 1.77)	61/275	0.90 (0.62, 1.30)
sTNF-R2	26/155	0.80 (0.51, 1.24)	27/165	1.37 (0.88, 2.14)	61/278	1.04 (0.77, 1.40)
sIL-6Rα	26/155	0.74 (0.45, 1.21)	27/164	1.05 (0.70, 1.58)	61/277	0.87 (0.64, 1.19)
BAFF	26/155	0.86 (0.57, 1.28)	27/165	0.78 (0.51, 1.20)	61/278	1.20 (0.89, 1.61)
sIL-2Rα	26/154	1.33 (0.92, 1.91)	27/165	**1.74 (1.10, 2.76)**	61/278	1.12 (0.85, 1.49)
CXCL13	25/140	0.74 (0.46, 1.18)	25/161	**1.63 (1.14, 2.31)**	57/267	**1.35 (1.01, 1.81)**
sCD30	26/154	0.96 (0.62, 1.49)	27/165	**1.92 (1.30, 2.84)**	61/278	1.18 (0.90, 1.54)
FL						
IL-6	22/155	0.71 (0.44, 1.15)	22/163	0.91 (0.58, 1.41)	48/278	0.99 (0.74, 1.33)
IL-8	20/141	1.23 (0.76, 2.01)	21/156	1.07 (0.66, 1.73)	43/265	1.01 (0.72, 1.41)
IL-10	22/154	0.68 (0.43, 1.06)	21/163	1.02 (0.65, 1.61)	48/276	1.14 (0.83, 1.57)
TNF-α	20/142	1.19 (0.71, 1.97)	22/157	1.32 (0.79, 2.19)	45/268	1.10 (0.80, 1.51)
CRP	22/154	1.02 (0.65, 1.60)	22/163	0.96 (0.58, 1.58)	48/278	1.25 (0.91, 1.73)
sCD14	22/154	1.15 (0.71, 1.85)	22/163	0.59 (0.34, 1.02)	46/275	1.15 (0.79, 1.65)
sGP130	22/155	0.64 (0.31, 1.33)	22/162	1.23 (0.73, 2.10)	47/275	1.29 (0.96, 1.74)
sTNF-R2	21/155	1.34 (0.83, 2.17)	22/164	1.25 (0.78, 2.00)	47/278	**1.45 (1.08, 1.94)**
sIL-6Rα	22/155	1.17 (0.73, 1.88)	22/163	1.06 (0.69, 1.63)	47/277	1.21 (0.90, 1.62)
BAFF	22/155	0.86 (0.56, 1.33)	22/164	0.96 (0.58, 1.59)	48/278	0.92 (0.66, 1.29)

sIL-2Rα	22/154	**2.29 (1.46, 3.60)**	22/164	1.40 (0.90, 2.19)	47/278	1.30 (0.94, 1.79)
CXCL13	20/140	**2.22 (1.41, 3.50)**	22/160	1.22 (0.82, 1.81)	44/267	**1.65 (1.19, 2.29)**
sCD30	21/154	**3.10 (1.93, 4.98)**	22/164	**1.75 (1.15, 2.67)**	47/278	1.32 (0.98, 1.76)
CLL/SLL						
IL-6	41/155	1.20 (0.86, 1.66)	47/163	0.89 (0.64, 1.23)	77/278	0.98 (0.76, 1.27)
IL-8	38/141	1.37 (0.91, 2.06)	45/156	1.17 (0.80, 1.70)	73/265	0.75 (0.56, 1.01)
IL-10	41/154	1.07 (0.75, 1.51)	47/163	0.87 (0.63, 1.19)	77/276	**0.75 (0.58, 0.96)**
TNF-α	40/142	1.17 (0.83, 1.65)	45/157	0.96 (0.67, 1.37)	73/268	1.04 (0.80, 1.35)
CRP	41/154	1.05 (0.76, 1.45)	47/163	0.85 (0.59, 1.24)	77/278	0.89 (0.67, 1.18)
sCD14	41/154	1.03 (0.71, 1.52)	47/163	1.18 (0.84, 1.66)	76/275	**0.69 (0.50, 0.94)**
sGP130	41/155	0.91 (0.55, 1.51)	47/162	**1.57 (1.05, 2.36)**	75/275	0.78 (0.54, 1.12)
sTNF-R2	40/155	**1.66 (1.16, 2.38)**	47/164	**1.44 (1.04, 2.00)**	77/278	1.06 (0.82, 1.36)
sIL-6Rα	41/155	0.97 (0.68, 1.40)	47/163	**1.38 (1.01, 1.89)**	77/277	1.11 (0.87, 1.42)
BAFF	39/155	**0.36 (0.24, 0.53)**	47/164	**0.47 (0.32, 0.68)**	77/278	**0.70 (0.52, 0.93)**
sIL-2Rα	39/154	**2.79 (1.90, 4.09)**	46/164	**1.50 (1.09, 2.07)**	77/278	1.05 (0.80, 1.38)
CXCL13	38/140	**1.35 (1.00, 1.81)**	45/160	0.99 (0.72, 1.37)	73/267	1.02 (0.78, 1.34)
sCD30	40/154	**2.36 (1.59, 3.51)**	46/164	**1.51 (1.11, 2.04)**	77/278	0.96 (0.74, 1.24)
Other B-NHL‡						
IL-6	38/155	1.00 (0.69, 1.45)	37/163	0.76 (0.55, 1.06)	56/278	0.95 (0.71, 1.27)
IL-8	33/141	1.01 (0.68, 1.51)	33/156	1.13 (0.76, 1.68)	54/265	1.15 (0.85, 1.56)
IL-10	38/154	1.22 (0.87, 1.71)	38/163	1.05 (0.75, 1.47)	56/276	0.89 (0.66, 1.20)
TNF-α	33/142	0.98 (0.68, 1.39)	33/157	**0.62 (0.42, 0.92)**	54/268	0.86 (0.64, 1.16)
CRP	38/154	1.22 (0.86, 1.74)	36/163	1.14 (0.76, 1.71)	56/278	1.15 (0.85, 1.57)
sCD14	37/154	1.13 (0.77, 1.68)	38/163	1.30 (0.93, 1.81)	55/275	1.00 (0.70, 1.41)
sGP130	38/155	1.18 (0.76, 1.81)	37/162	1.10 (0.71, 1.71)	55/275	0.87 (0.60, 1.28)
sTNF-R2	35/155	**1.54 (1.09, 2.17)**	38/164	**1.42 (1.01, 1.99)**	56/278	1.20 (0.90, 1.59)
sIL-6Rα	37/155	1.11 (0.76, 1.64)	36/163	1.07 (0.75, 1.52)	55/277	1.18 (0.89, 1.56)
BAFF	38/155	0.85 (0.64, 1.12)	35/164	0.89 (0.65, 1.24)	55/278	0.95 (0.69, 1.29)
sIL-2Rα	34/154	**1.71 (1.23, 2.38)**	36/164	**1.47 (1.01, 2.12)**	56/278	1.19 (0.89, 1.60)
CXCL13	33/140	**1.75 (1.25, 2.44)**	29/160	**1.41 (1.03, 1.94)**	54/267	1.31 (0.98, 1.76)
sCD30	38/154	**1.40 (1.05, 1.87)**	37/164	**1.55 (1.10, 2.19)**	56/278	1.05 (0.79, 1.40)
All T-NHL						

IL-6	13/155	0.98 (0.53, 1.79)	10/163	1.30 (0.67, 2.53)	7/278	1.13 (0.53, 2.39)
IL-8	12/141	0.70 (0.36, 1.35)	10/156	1.18 (0.59, 2.36)	7/265	0.66 (0.27, 1.65)
IL-10	13/154	1.30 (0.73, 2.33)	10/163	0.76 (0.42, 1.39)	7/276	2.21 (0.90, 5.45)
TNF-α	12/142	0.93 (0.52, 1.64)	10/157	1.18 (0.58, 2.41)	7/268	1.56 (0.70, 3.46)
CRP	13/154	0.83 (0.48, 1.45)	10/163	2.05 (0.99, 4.28)	7/278	0.54 (0.22, 1.29)
sCD14	13/154	1.01 (0.54, 1.89)	10/163	0.86 (0.43, 1.73)	7/275	0.93 (0.38, 2.29)
sGP130	13/155	0.98 (0.46, 2.09)	10/162	0.86 (0.33, 2.23)	7/275	0.59 (0.19, 1.84)
sTNF-R2	13/155	1.13 (0.63, 2.01)	10/164	0.85 (0.41, 1.76)	7/278	1.01 (0.47, 2.17)
sIL-6Rα	13/155	0.72 (0.37, 1.37)	10/163	1.17 (0.65, 2.13)	7/277	1.26 (0.65, 2.43)
BAFF	13/155	1.38 (0.86, 2.22)	10/164	0.74 (0.34, 1.60)	7/278	1.63 (0.70, 3.81)
sIL-2Rα	13/154	**2.26 (1.31, 3.89)**	10/164	1.91 (0.93, 3.92)	7/278	1.30 (0.59, 2.85)
CXCL13	11/140	1.23 (0.66, 2.29)	10/160	1.40 (0.85, 2.30)	7/267	0.72 (0.30, 1.70)
sCD30	12/154	**1.74 (1.01, 2.97)**	10/164	1.33 (0.72, 2.45)	7/278	1.49 (0.75, 2.95)

Abbreviations: NHL, non-Hodgkin lymphoma; OR, odds ratio; CI, confidence interval; SD, standard deviation; B-NHL, B-cell NHL; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; and T-NHL, T-cell NHL; IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein; sCD14, soluble CD14; sGP130, soluble GP130; sTNF-R2, soluble tumor necrosis factor receptor-2; sIL-6Rα, soluble interleukin-6 receptor-α; BAFF, B-cell activating factor of the TNF family; sIL-2Rα, soluble interleukin-2 receptor-α; CXCL13, CXC chemokine ligand 13; sCD30, soluble CD30.

* Adjusted for age at blood draw, time of day of blood draw, and cohort (sex).

† Odds Ratios (OR) per 1 standard deviation increase in biomarker concentration, based on batch effect-corrected values with outliers removed, for Nurses' Health Study and Health Professionals Follow-up Study cohorts combined.

‡ Other B-cell subtypes include Burkitt lymphoma (N=4), lymphoplasmacytic lymphoma (N=19), mantle cell lymphoma (N=20), marginal zone lymphoma (N=44), other B-NHL (N=20), and unclassified B-NHL (N=25).