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cohort studies

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Abstract

Inflammation and B-cell hyperactivation have been associated with non-Hodgkin lymphoma development. This prospective analysis aimed to further elucidate pre-diagnosis plasma immune marker profiles associated with non-Hodgkin lymphoma risk.

We identified 598 incident lymphoma cases and 601 matched controls in Nurses' Health Study and Health Professionals Follow-up Study participants with archived pre-diagnosis plasma samples and measured 13 immune marker levels with multiplexed immunoassays. Using multivariable logistic regression we calculated odds ratios and 95% confidence intervals per standard deviation unit increase in biomarker concentration for risk of non-Hodgkin lymphoma and major histologic subtype, stratifying additional models by years (<5, 5 to <10, ≥10) after blood draw.

Soluble interleukin-2 receptor-α, CXC chemokine ligand 13, soluble CD30, and soluble tumor necrosis factor receptor-2 were individually positively associated, and B-cell activating factor of the tumor necrosis factor family inversely associated, with all non-Hodgkin lymphoma and one or more subtypes. The biomarker combinations associated independently with lymphoma varied somewhat by subtype and years after blood draw. Of note, the unexpected inverse association between B-cell activating factor and chronic lymphocytic leukemia/small lymphocytic lymphoma risk (odds ratio: 95% confidence interval: 0.51, 0.43-0.62) persisted more than 10 years after blood draw (odds ratio: 0.70; 95% confidence interval: 0.52-0.93).

In conclusion, immune activation precedes non-Hodgkin lymphoma diagnosis by several years. Decreased B-cell activating factor levels may denote nascent chronic lymphocytic leukemia many years pre-diagnosis.

Introduction

Severe immune compromise is a strong risk factor for non-Hodgkin lymphoma (NHL), and B-cell activation and inflammation have been associated with an increased risk of AIDS-related NHL. Elevated pre-diagnosis plasma levels of markers of B-cell stimulation including CXC chemokine ligand 13 (CXCL13; a B-cell attracting chemokine),[1] interleukin (IL)-6 (a B-cell stimulatory cytokine), and soluble (s) CD30 (sCD30; a soluble receptor indicative of B- and T-cell activation) predicted risk of an AIDS-NHL diagnosis in HIV-positive persons,[2-4] in some instances as early as five years pre-diagnosis.[5] Several of these markers have also demonstrated an association with NHL risk in immunocompetent people in prospective studies.[6-13] Of interest, plasma sCD30 levels were positively associated with NHL risk at 6-10 years[9] and even 15-23 years pre-diagnosis.[11] Another small nested case-control study reported a significant 2.5-fold increase in NHL risk in women with elevated soluble IL-2 receptor-α levels (sIL-2Rα; a marker of T-cell activation and IL-2 upregulation), and marginally significant increases in NHL risk in women with higher pre-diagnosis tumor necrosis factor (TNF)-α and soluble TNF-receptor-2 (sTNF-R2) levels.[14] These findings collectively suggest that chronic B-cell stimulation has a role in lymphomagenesis in immunocompetent persons.

Our study aimed to further characterize pre-diagnosis plasma immune marker profiles associated with risk of HIV-unrelated NHL and its major histologic subtypes in two large US cohorts. This study represents one of the largest populations with prospectively collected pre-diagnosis blood samples to investigate the association between numerous immune markers and NHL risk, including with specific NHL subtypes that are often precluded due to small sample

size, and to assess the independence of biomarker-NHL associations for multiple immune markers.[11, 12] The long-term follow-up of the study population also allowed for examination of the influence of time since blood draw on observed immune marker-NHL associations—including an assessment of potential early markers of lymphomagenesis present ≥10 years prior to diagnosis. The choice of immune markers was guided in part by the immune deregulation we sought to characterize and by reported findings in AIDS- or HIV-unrelated NHL. We hypothesized that pre-diagnosis levels of immune markers indicative of B-cell activation or inflammation would be positively associated with risk of developing NHL and major NHL subtypes, and that the use of multi-marker models will enhance characterization of the immune milieu associated with NHL risk and suggest subtle differences by histologic subtype.

Methods

Study Population

The study population comprised Nurses' Health Study (NHS, all female) and Health Professionals Follow-up Study (HPFS, all male) participants with archived plasma (**Supplementary Methods**).[15, 16] Cancer diagnoses were identified via routine questionnaires or death follow-up[17, 18] and confirmed by medical record review or tumor registry linkage.

Participants provided written informed consent at blood collection. The 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

We included all participants with confirmed incident NHL diagnosed ≥3 months after blood draw through December 31, 2010, with no other cancer history. Study pathologists (JCA, SJR) classified NHL histologic subtype[19] according to World Health Organization[20, 21] and International Lymphoma Epidemiology (InterLymph) Consortium guidelines.[22, 23] We analyzed common B-cell (B-) NHL subtypes individually [diffuse large B-cell (DLBCL), follicular (FL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)], combined less common B-NHLs ("other B-NHL") and defined additional categories by cell type (T-NHL, B-NHL). We matched one control per case by sex (cohort), age, race and blood draw details (**Supplementary Methods**).

Biomarker Assessment

Assays were performed at the University of California, Los Angeles (LM, OMM), using multiplexed kits (Fluorokine® MAP, R & D Systems, Minneapolis, MN), a Bio-Plex 200 Luminex instrument and Bio-Plex analysis software (Bio-Rad, Hercules, CA). Blinded laboratory personnel measured sCD30, sIL-2Rα, B-cell activating factor of the TNF family (BAFF, a B-cell stimulatory cytokine), CXCL13, sIL-6Rα, sGP130, sCD14, sTNF-R2, C-reactive protein (CRP), IL-6, IL-8, IL-10, and TNF-α concentration according to manufacturer directions (**Supplementary Methods**). We set TNF-α, IL-8 and CXCL13 values to missing for samples with >24-hour processing delays (NHS: N= 35; HPFS: N=23). Analyte concentrations were natural log-transformed for all analyses. We observed similar measured biomarker concentrations for the NHS and HPFS (**Supplementary Table 1**) and pooled the data.

Statistical Methods

We conducted batch calibration to diminish the potential influence of laboratory batch-related variability on biomarker-NHL associations.[24] Outlying biomarker values were identified using the Rosner extreme Studentized deviate method[25] and omitted from analyses of the marker.

The primary analysis assessed batch effect-corrected, log-transformed biomarker values continuously per standard deviation (SD) increase in concentration, with SD units calculated for log-transformed values in the pooled controls. We calculated odds ratios (OR) and 95% confidence intervals (CI) for the association of each biomarker with NHL risk (overall and for DLBCL, FL, CLL/SLL, other B-NHL, all B-NHL and all T-NHL) using unconditional logistic regression. Models adjusted for all matching factors unless small cell counts precluded adjustment for race. We evaluated but did not observe confounding by body mass index and autoimmune disease history.

We intended *a priori* to identify multi-marker profiles associated with NHL risk via mutual adjustment of models for biomarkers that were individually associated. We also examined models stratified by follow-up interval (0 to <5, 5 to <10, ≥10 years) and assessed heterogeneity by time period using the contrast test.[26] The **Supplementary Methods** describes additional analyses designed *post hoc*.

Results

In total, 601 cases of NHL (345 NHS and 256 HPFS) were identified and individually matched to controls. Three cases were later excluded due to unconfirmed lymphoma status. The final analysis thus included 598 cases, including 114 DLBCL, 92 FL, 165 CLL/SLL, 132 other B-NHL (4 Burkitt lymphoma, 19 lymphoplasmacytic lymphoma, 20 mantle cell lymphoma, 44 marginal zone lymphoma, 20 other B-NHL, and 25 unclassified B-NHL) and 30 T-NHL, and

601 controls. The study population was 96% Caucasian and 58% female. Cases and controls had similar covariable distributions, due in part to the matched design (**Table 1**).

We omitted 109 individual biomarker measurements (<1% of all measurements) with implausible outlying values (NHS: 72; HPFS: 37), the majority (90%) of which were implausibly high for the particular marker. Omitted values ranged from one measure of IL-10 to 17 measures of IL-8. Spearman correlation coefficients ranged from -0.03 (IL-10 and CXCL13) to 0.58 (sIL-2Rα and sCD30; **Supplementary Table 2**).

Individual immune marker models. Multivariable analyses of individual log-transformed immune markers revealed significant associations for all NHL per SD increment of log-transformed sTNF-R2, sIL-2Rα, CXCL13, sCD30 (all positive) and BAFF (inverse; **Table 2**). In subtype-specific analyses, sTNF-R2 levels were also positively associated with risk of all B-NHL, FL and CLL/SLL, while CXCL13 was positively associated with risk of all B-NHL, DLBCL and FL (**Table 2**). Levels of sIL-2Rα and sCD30 were positively associated with every NHL subtype, including T-NHL. Of interest, the association of BAFF with a 17% decreased risk of all NHL appeared to be driven by CLL/SLL, for which risk decreased by 49% per SD increase in log-transformed BAFF levels (OR: 0.51; 95% CI: 0.43, 0.62; p<0.001); BAFF was not associated with other NHL subtypes in single-marker models. We did not observe significant or consistent associations for the remaining immune markers with risk of any NHL endpoint. Results from cohort-specific models did not suggest marked differences by sex for these associations (**Supplementary Table 3**).

Multi-marker profiles. In the model that mutually adjusted for the five log-transformed immune markers that had significant individual associations with NHL endpoints (sTNF-R2, sIL-2Rα, CXCL13, sCD30, BAFF), sIL-2Rα, CXCL13 and sCD30 remained significantly

associated with a 17-24% increased risk, and BAFF with a 26% decreased risk of all NHL per SD increase in log concentration, while sTNF-R2 was no longer significantly associated (**Table 3**). Results for all B-NHL risk were similar to those for all NHL, whereas mutual adjustment attenuated all the immune marker associations with DLBCL. In the multi-marker model of FL risk, sCD30 and BAFF remained independently associated, with a borderline association noted for CXCL13 (**Table 4**). In the multi-marker model of CLL/SLL risk, sIL-2Rα was significantly associated with a 50% increase (95% CI: 1.18-1.90), and BAFF with a significant 53% reduction (95% CI: 0.38, 0.58), per SD increase in log concentration. Lastly, only sIL-2Rα was independently associated with T-NHL risk (OR per SD increase in log concentration: 1.96; 95% CI: 1.22, 3.13) in mutually adjusted models.

The five-marker models using the PLR approach yielded essentially the same effect estimates as described above for biomarker associations with the NHL endpoints for the full follow-up period (**Supplementary Tables 4 and 5**). sTNF-R2 had significantly different associations with B-NHL and T-NHL (p-value for heterogeneity by subtype=0.04; **Supplementary Table 4**); the associations of CXCL13 and BAFF with individual B-NHL subtypes also showed evidence of significant heterogeneity (p-values for heterogeneity by subtype=0.007 and <0.0001, respectively; **Supplementary Table 5**).

In the covariable-adjusted multi-marker models containing restricted cubic splines, there was evidence of non-linearity for two biomarkers, CXCL13 and BAFF, in their associations with risk of aggregated endpoints (all NHL, B-NHL and other B-NHL; p-values, tests for significance of the curve <0.05), but not for biomarker associations with individual B-NHL subtypes or T-NHLs.

In alternative models using semi-automatic stepwise selection, the final models for all

NHL and all B-NHL included sIL-2Rα, CXCL13 and sCD30, which were positively associated

with risk, as well as BAFF, which was inversely associated (**Supplementary Table 6**). In

comparison, for DLBCL and FL, the stepwise procedure selected only sCD30 (p=0.004 and

<0.0001, respectively), and for T-NHL the procedure selected only sIL-2Rα (p=0.002) as

independently (positively) associated with risk. Of interest, the stepwise procedure identified

four immune markers independently associated with risk of CLL/SLL, including BAFF and IL-

10 with significant inverse associations and sIL-2Rα with a significant positive association. The

stepwise procedure identified three immune markers associated with the combined category of

other B-NHL subtypes, including significant positive associations for CXCL13 and sIL-2Rα, and

a significant inverse association for BAFF.

In the model that included all 13 immune markers, sIL-2Rα, CXCL13, and sCD30 again

had strong positive associations with risk of all NHL and all B-NHL (**Table 5**). In the CLL/SLL-

specific model, we observed a significant inverse association with risk for BAFF and also for

sCD14 and IL-10, and a positive association with sIL2-Rα. BAFF was also significantly

inversely associated with FL risk, while sCD30 was significantly positively associated with FL

risk. Only sIL-2Rα was significantly associated with an increased risk of T-NHL. We observed

suggestive positive associations of DLBCL risk with IL-6, CXCL13 and sCD30 in this 13-

marker model.

Time-stratified analyses. The analyses stratified by time between blood draw and

diagnosis/index date suggested that the individual biomarker associations with all NHL

(**Supplementary Table 7**) and with NHL subtypes (**Supplementary Table 8**) varied somewhat

by length of time after blood draw but did not strongly implicate any additional immune marker-

NHL associations. The time-stratified five-marker models (**Table 3**) also suggested variability by follow-up interval in the independent associations of those immune markers with future NHL risk. For example, the association of sIL-2Rα with risk of all NHL appeared to be restricted to a shorter-term interval, specifically within five years of blood draw (OR: 1.52, 95% CI: 1.09, 2.11; **Table 3**), whereas significant associations of CXCL13 with risk of all NHL were evident only five or more years after blood collection (5-<10 years; OR: 1.23, 95% CI: 1.00, 1.52; and >10 years; OR: 1.21, 95% CI: 1.01, 1.45). sCD30 was most strongly associated with all NHL risk within 10 years of blood draw, while BAFF was consistently inversely associated with all NHL across time periods. Of note, in subtype-specific time-stratified analyses, sCD30 levels were strongly positively associated with risk of FL within five years of blood draw (OR: 4.85, 95% CI: 2.02, 11.61), and the association decreased in magnitude with increasing follow-up time. In CLL/SLL-specific models, elevated sIL-2Rα was associated with a nearly four-fold increased risk within five years of blood draw (OR: 3.71, 95% CI: 1.77, 7.76) but had no clear association with longer-term CLL/SLL risk. In contrast, BAFF had significant inverse associations with risk of CLL/SLL in all pre-diagnosis time periods, albeit with particularly strong associations with risk of CLL/SLL within five or 10 years of blood draw (**Table 4**). When modeled using PLR, the effect estimates were virtually the same for time period-specific biomarker associations, both for the aggregated and the individual NHL endpoints (**Supplementary Tables 4 and 5**). The most prominent differences between the two approaches for assessing heterogeneity by time period (PLR with interaction terms vs. time-stratified unconditional logistic regression) pertained to the statistical significance of apparent heterogeneity by follow-up period for the associations of sTNF-R2 with all B-NHL and FL. For example, for the association of sTNF-R2 with all B-NHL, the p-value for heterogeneity by follow-up time was 0.04 for the cross-product term in

PLR (**Supplementary Table 4**) and 0.40 for the main model contrast test (**Table 3**). For the association of sTNF-R2 with FL, the p-value for heterogeneity by time period was 0.0007 for the cross-product term in PLR (**Supplementary Table 5**) and 0.11 for the main model contrast test (**Table 4**). Time-stratified results for the multi-marker models identified with stepwise selection largely agreed with the main results described above (**Supplementary Table 6**).

Discussion

In this pooled analysis within the NHS and HPFS cohorts, we observed significant associations between NHL risk and pre-diagnosis levels of specific plasma immune markers, including a novel, inverse association between levels of BAFF and risk of CLL/SLL. Positive associations between levels of sIL-2Rα, CXCL13, and sCD30 and risk of all NHL and all B-NHL, as well as the inverse association of BAFF with risk of all NHL and CLL/SLL, were consistent and independent across several analytic approaches to constructing a multi-marker profile associated with risk. In contrast, the individual positive associations noted for sTNF-R2 with risk of all NHL and some B-NHL endpoints were attenuated upon adjustment for other immune markers, suggesting a lack of independence in the association between sTNF-R2 levels and NHL risk. Manual selection and automated stepwise-selection of multi-marker profiles yielded fairly consistent results for all NHL, but also some differences for individual histologic subtypes, particularly for CLL/SLL. We also observed some variation in the associations between NHL risk and immune markers by time between blood draw and diagnosis.

Our findings are in agreement with previous studies reporting associations between elevated CXCL13 and/or sCD30 levels and increased NHL risk in HIV-positive and immunocompetent populations, including several reports analyzing blood samples taken many

years prior to NHL diagnosis.[2, 3, 8-13] In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Purdue and colleagues[11] prospectively investigated multi-marker models similar to those in our analysis and observed independent positive associations for sCD30 with risk of NHL and DLBCL when adjusted for other biomarkers. Those observations were detectable more than 15 years prior to diagnosis. Also similar to our findings, positive associations observed for sTNF-R2 with NHL did not persist upon adjustment for other immune markers.[11] In a prospective analysis in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, individual associations of CXCL13 and sTNF-R2 with NHL both remained significant with mutual adjustment, with correction for multiple comparisons and with restriction to samples collected 8-13 years prior to diagnosis.[10]

We observed an unexpected yet consistently strong inverse association between BAFF levels and CLL/SLL risk. BAFF is a member of the TNF family involved with B cell survival and maturation.[27] Pre-diagnosis serum BAFF concentrations were positively associated with AIDS-NHL, and BAFF overproduction has been associated with systemic autoimmune diseases, including systemic lupus erythematosus and Sjögren syndrome,[28, 29] which are associated with an increased risk of NHL in HIV-negative persons.[30, 31] However, systemic autoimmune disorders in HIV-negative individuals appear to be preferentially associated with NHL subtypes with a different natural history than CLL/SLL.[30, 32] Nonetheless, CLL cells are known to express multiple BAFF receptors (including TNFRSF13B, TNFRS13C and TNFRSF17),[33] and the inverse association that we observed is biologically plausible if considered indicative of rapid uptake of circulating BAFF by nascent CLL/SLL clones,[34] reflecting subclinical progression of an indolent tumor whose natural course may extend multiple decades. Consistent with this interpretation, several clinical studies have observed lower levels of BAFF in sera from

CLL/SLL patients than in healthy controls.[35-37] The mechanism for the latter findings is unknown; our observation suggests that those underlying physiologic processes may commence early in CLL pathogenesis, even 10 or more years pre-diagnosis. Concurrent measurement of soluble BAFF receptors and study of cell surface expression of those molecules and classification of cases into prognostic subgroups were not feasible for the present study. Confirmation of the present findings is warranted in larger populations with specimens suitable for determining cell surface marker or gene/protein expression. Additionally, prospective studies in patients with monoclonal B-lymphocytosis would be informative to evaluate whether circulating BAFF levels can enhance risk stratification for progression to malignancy.[38]

We also observed significant associations of elevated sIL-2Rα levels with increased risks of all NHL, B-NHL, DLBCL, CLL/SLL and T-NHL, primarily within five years of blood draw. One other study reported a positive association between sIL-2Rα levels and NHL risk in an HIV-negative population with prospective blood collection that persisted after incorporating lag-time greater than two years.[14] Of note, comparatively high sIL-2Rα levels at diagnosis were also associated with poor prognosis in patients with NHL.[39-41] Biologically, sIL-2Rα and sCD30 are highly correlated (r=0.58 in this study), and both can indicate B and T cell activation;[42] in the present analysis, both markers remained independently associated with a significant increased risk of all NHL and all B-NHL after mutual adjustment. In contrast, only sIL-2Rα was significantly associated with an increased risk of T-NHL in the multi-marker models, although small sample size (N=30 cases) limited statistical power to detect significant independent associations for more strongly correlated biomarkers. Of interest, we observed the strongest positive associations of sIL-2Rα with T-NHL risk within 10 years of blood draw, a novel observation that requires confirmation in other populations.

We observed significant positive associations between CXCL13 and risk of all NHL, B-NHL, and FL, as well as borderline associations with DLBCL and other B-NHL, more than 10 years after blood draw, suggesting an early role for an immune environment characterized by B-cell stimulation and aberrant B-cell trafficking. Consistent with this interpretation, a recent, large-scale genome-wide association study of FL identified CXCR5, which is the receptor for CXCL13, as a potential FL susceptibility locus.[43] Further, genetic variation in *CXCR5* and *CXCL13* was associated with serum CXCL13 levels in a study of AIDS-NHL, and elevated serum CXCL13 levels were observed in AIDS-NHL cases >3 years prior to diagnosis.[2] In contrast, elevated sCD30 levels were more strongly associated with increased risk of all NHL, B-NHL and FL within 10 years of blood draw, with a particularly strong association with FL within five years of blood draw. These findings suggest sCD30 may be capturing a more proximal pre-diagnosis increase in immune activation.

When assessed with multivariable PLR models rather than the main unconditional logistic regression analysis, the associations between immune markers and NHL endpoints did not change substantially, whether for aggregated endpoints or the individual B-NHL endpoints. The minor discrepancies suggested somewhat improved precision in the PLR models, which yielded slightly narrower confidence intervals and slightly stronger p-values for heterogeneity by follow-up period for a few of the comparisons. None of the discrepant findings would suggest a different interpretation of the time- or subtype-specific model findings, however, and thus we retained the unconditional logistic regression models as our primary analysis for methodologic consistency across the full series of analyses we conducted.

In the analyses with restricted cubic splines, we observed evidence of significant non-linearity for associations of CXCL13 and BAFF with aggregated NHL endpoints. Of note, those

endpoints comprise small numbers of diverse histologic subtypes of NHL which may have different etiologies. Thus, we believe that the observed non-linear associations more likely reflect sampling variability and/or an artifact of potentially heterogeneous subtype-specific associations for the subtypes in the endpoint groups than a true biological effect.

Together, our findings add new insight to previous publications on both AIDS-NHL and HIV-unrelated NHL risk, collectively suggesting that higher levels of immune activation, and in particular heightened B-cell stimulation, may affect B-cell lymphomagenesis. Interestingly, several markers of immune activation appear to be elevated many years prior to NHL diagnosis and thus could help identify populations at higher risk for developing NHL. It is important to note that some reported associations between immune markers and all NHL risk were not replicated in analyses of individual histologic subtypes; this may be due in part to subtype-specific sample sizes that limited statistical power. Significant associations between immune markers and risk of all NHL may reflect commonalities in subtype etiologies; however, these findings may also conceal a more specific association with one or more of the less common subtypes, as illustrated by the present findings for BAFF and CLL/SLL.

This analysis of immune markers measured from prospectively collected blood specimens from two large US cohorts with lengthy follow-up identified several statistically significant associations with the risk of developing NHL, including associations that remained statistically significant for blood samples collected five or more years prior to diagnosis. Although our main results were fairly consistent across analytical approaches, slight variations in markers chosen by *a priori* and secondary analyses emphasize the importance of utilizing diverse panels of immune markers in future studies seeking to characterize conditions conducive to NHL development. Furthermore, our findings suggest that even though an activated immune milieu

may contribute to the development of multiple types of NHL, there is evidence of subtle differences in the pathogenesis of individual NHL subtypes, some of which had not been previously reported. Larger pooled studies will be important to more accurately identify homogeneous and heterogeneous biomarkers of risk or early disease by NHL subtype and to elucidate which are more indicative of earlier or later pathogenic changes to the immune environment.

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Table 1. Characteristics of non-Hodgkin lymphoma cases and matched controls from two prospective cohort studies

Variable	Cases	Controls	P*
Cohort			
NHS	344 (58%)	345 (57%)	0.97
HPFS	254 (42%)	256 (43%)	
Age, years, Mean ± SD	60.8 ± 8.1	60.8 ± 8.1	0.87
Race/ethnicity			
Caucasian	573 (96%)	578 (96%)	0.75
Other	25 (4%)	23 (4%)	
BMI at blood draw, kg/m²			
Less than 22.5	138 (23%)	118 (20%)	0.58
22.5-24.9	139 (23%)	166 (28%)	
25-29.9	217 (36%)	219 (36%)	
30 or greater	74 (12%)	74 (12%)	
Missing	30 (5%)	24 (4%)	
BMI in young adulthood, kg/m²			
Less than 18.5	44 (7%)	54 (9%)	0.31
18.5-22.4	298 (50%)	299 (50%)	
22.5-24.9	126 (21%)	112 (19%)	
25 or greater	106 (18%)	101 (17%)	
Missing	24 (4%)	35 (6%)	
Autoimmune disease†			
Yes	97 (16%)	104 (17%)	0.62
No	501 (84%)	497 (83%)	
Years from blood draw to index date, Mean ± SD	9.6 ± 5.6	9.6 ± 5.6	0.99
Cell type/histologic subtype of NHL‡			
B-NHL	503 (84%)		
DLBCL	114 (19%)		
Follicular lymphoma	92 (15%)		
CLL/SLL	165 (28%)		
Other B-cell subtypes§	132 (22%)		
T-NHL	30 (5%)		

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; BMI, body mass index; NHL, non-Hodgkin lymphoma; B-NHL, B-cell NHL; DLBCL, diffuse large B-cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; and T-NHL, T-cell NHL.

* P-values from a Chi-square test or ANOVA. Tests for BMI at blood draw and BMI in young adulthood did not include individuals missing data for those variables.

† Defined as any self-reported diagnosis of rheumatoid arthritis, ulcerative colitis, multiple sclerosis, psoriasis, or Sjögren syndrome.

‡ Information on cell type was not available for 11% of NHL cases.

§ The other B-NHL 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).

Table 2. Associations between pre-diagnosis concentrations of 13 individual immune markers and risk of Non-Hodgkin Lymphoma (NHL), overall and by major histologic subtype

Marker	All NHL* N cases/controls	All NHL* OR (95% CI)‡	DLBCL N cases	DLBCL OR (95% CI)‡	FL N cases	FL OR (95% CI)‡	CLL/SLL N cases	CLL/SLL OR (95% CI)‡	Other B-NHL† N cases	Other B-NHL† OR (95% CI)‡	All T-NHL N cases	All T-NHL OR (95% CI)‡	P §
IL-6	597/600	0.97(0.87,1.08)	114	1.12(0.91,1.37)	92	0.90(0.73,1.12)	165	0.99(0.84,1.17)	131	0.89(0.74,1.08)	30	1.13(0.78,1.63)	0.46
IL-8	558/566	1.00(0.88,1.13)	106	0.96(0.77,1.22)	84	1.07(0.84,1.36)	156	0.98(0.81,1.20)	120	1.11(0.90,1.37)	29	0.82(0.54,1.26)	0.70
IL-10	596/597	1.00(0.89,1.11)	113	1.14(0.93,1.40)	91	0.98(0.78,1.22)	165	0.85(0.72,1.01)	132	1.04(0.86,1.25)	30	1.21(0.83,1.76)	0.18
TNF-α	566/571	1.02(0.91,1.14)	108	0.98(0.80,1.21)	87	1.16(0.92,1.47)	158	1.06(0.89,1.26)	120	0.82(0.68,1.00)	29	1.14(0.78,1.67)	0.17
CRP	596/599	1.06(0.94,1.19)	114	1.12(0.92,1.38)	92	1.12(0.89,1.40)	165	0.93(0.77,1.12)	130	1.15(0.94,1.40)	30	0.97(0.66,1.42)	0.50
sCD14	592/596	1.01(0.90,1.15)	114	0.90(0.72,1.13)	90	0.97(0.76,1.25)	164	0.91(0.75,1.11)	130	1.14(0.93,1.40)	30	0.94(0.62,1.43)	0.55
sGP130	592/596	1.03(0.89,1.18)	114	0.87(0.66,1.15)	91	1.15(0.90,1.47)	163	1.00(0.80,1.25)	130	0.99(0.79,1.26)	30	0.81(0.48,1.36)	0.57
sTNF-R2	592/601	**1.25(1.12,1.40)**	114	1.02(0.83,1.26)	90	**1.37(1.10,1.70)**	164	**1.28(1.08,1.51)**	129	**1.35(1.13,1.62)**	30	1.03(0.70,1.50)	0.20
sIL-6Rα	592/599	1.10(0.98,1.23)	114	0.89(0.72,1.10)	91	1.16(0.93,1.44)	165	1.15(0.97,1.36)	128	1.13(0.93,1.37)	30	1.01(0.69,1.46)	0.32
BAFF	592/601	**0.83(0.75,0.92)**	114	0.99(0.81,1.21)	92	0.93(0.73,1.17)	163	**0.51(0.43,0.62)**	128	0.87(0.73,1.05)	30	1.26(0.87,1.82)	<0.0001
sIL-2Rα	585/600	**1.37(1.23,1.53)**	114	**1.26(1.04,1.54)**	91	**1.55(1.25,1.94)**	162	**1.49(1.27,1.76)**	126	**1.40(1.16,1.68)**	30	**1.97(1.37,2.85)**	0.26
CXCL13	554/571	**1.31(1.17,1.46)**	107	**1.25(1.03,1.52)**	86	**1.58(1.28,1.95)**	156	1.10(0.93,1.31)	116	**1.48(1.24,1.76)**	28	1.23(0.86,1.76)	0.06
sCD30	590/600	**1.37(1.23,1.52)**	114	**1.29(1.06,1.56)**	90	**1.76(1.44,2.15)**	163	**1.33(1.13,1.57)**	131	**1.29(1.09,1.54)**	29	**1.46(1.05,2.04)**	0.15

Abbreviations: NHL, non-Hodgkin lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; T-NHL, all T-cell NHL; OR, Odds Ratio; and CI, Confidence Interval; 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.

* The all B-NHL (N=503 cases) results were similar to the all NHL results.

† Other B-NHL 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).

‡ Odds ratios and 95% confidence intervals were calculated per 1 standard deviation increase in log biomarker concentration, based on batch-corrected values with outliers removed, for NHS and HPFS cohorts combined. All models except those for T-NHL were adjusted for age at blood draw (continuous), cohort, time of blood draw (continuous), race (Caucasian/other); the models for T-NHL were adjusted for age and cohort only.

§ P-values for heterogeneity by subtype from contrast tests comparing immune marker-specific estimates between DLBCL, FL, CLL/SLL, other B-NHL and T-NHL.

Table 3. 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

				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 (95% CI) per 1-SD *,†	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 *,†	p-value‡
All NHL									
sTNF-R2	542/571	1.05 (0.91, 1.21)	133/140	0.83 (0.60, 1.14)	149/162	1.02 (0.77, 1.35)	260/267	1.18 (0.95, 1.46)	0.20
sIL-2Rα	542/571	**1.20 (1.03, 1.39)**	133/140	**1.52 (1.09, 2.11)**	149/162	1.16 (0.88, 1.53)	260/267	1.11 (0.88, 1.39)	0.28
CXCL13	542/571	**1.17 (1.03, 1.32)**	133/140	1.00 (0.78, 1.29)	149/162	**1.30 (1.03, 1.62)**	260/267	**1.21 (1.01, 1.46)**	0.32
sCD30	542/571	**1.24 (1.06, 1.45)**	133/140	**1.52 (1.09, 2.13)**	149/162	**1.43 (1.07, 1.90)**	260/267	0.98 (0.78, 1.23)	0.02
BAFF	542/571	**0.74 (0.66, 0.83)**	133/140	**0.73 (0.59, 0.91)**	149/162	**0.61 (0.48, 0.78)**	260/267	0.83 (0.69, 1.00)	0.15
All B-NHL									
sTNF-R2	454/570	1.07 (0.92, 1.25)	110/140	0.88 (0.63, 1.23)	118/161	1.15 (0.86, 1.54)	226/267	1.13 (0.90, 1.42)	0.40
sIL-2Rα	454/570	**1.20 (1.03, 1.41)**	110/140	**1.51 (1.06, 2.14)**	118/161	1.12 (0.84, 1.49)	226/267	1.15 (0.91, 1.46)	0.38
CXCL13	454/570	**1.13 (1.00, 1.29)**	110/140	0.96 (0.74, 1.25)	118/161	1.17 (0.92, 1.49)	226/267	**1.24 (1.02, 1.50)**	0.31
sCD30	454/570	**1.24 (1.05, 1.46)**	110/140	**1.59 (1.10, 2.28)**	118/161	**1.58 (1.14, 2.20)**	226/267	0.96 (0.75, 1.22)	0.02
BAFF	454/570	**0.73 (0.64, 0.83)**	110/140	0.67 (0.53, 0.84)	118/161	**0.64 (0.50, 0.81)**	226/267	0.84 (0.69, 1.02)	0.14
All T-NHL									
sTNF-R2	28/569	0.62 (0.37, 1.03)	11/140	0.44 (0.17, 1.19)	10/160	0.65 (0.27, 1.58)	7/267	0.73 (0.24, 2.21)	0.78
sIL-2Rα	28/569	**1.96 (1.22, 3.13)**	11/140	2.10 (0.95, 4.68)	10/160	2.20 (0.93, 5.20)	7/267	1.04 (0.36, 3.00)	0.50
CXCL13	28/569	1.11 (0.75, 1.65)	11/140	1.03 (0.48, 2.22)	10/160	1.37 (0.78, 2.42)	7/267	0.57 (0.24, 1.37)	0.26
sCD30	28/569	1.33 (0.84, 2.10)	11/140	1.68 (0.69, 4.08)	10/160	1.34 (0.56, 3.21)	7/267	1.77 (0.70, 4.43)	0.90
BAFF	28/569	0.88 (0.58, 1.32)	11/140	0.93 (0.52, 1.67)	10/160	0.55 (0.24, 1.28)	7/267	1.68 (0.64, 4.44)	0.23

Abbreviations: NHL, non-Hodgkin lymphoma; B-NHL, B-cell NHL; T-NHL, 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.

* Models were adjusted for age at blood draw (continuous), cohort (sex), time of blood draw (continuous) and race/ethnicity (Caucasian, non-Caucasian) and were mutually adjusted for all markers listed, except that models for all T-NHL were not adjusted for race.

† Odds ratios and 95% confidence intervals were calculated per 1-standard deviation increase in batch effect-corrected, log-transformed values (with cohort-specific outliers excluded) from the Nurses' Health Study and Health Professionals Follow-up Study combined.

‡ P-values from tests for heterogeneity comparing immune marker-specific estimates across time strata.

Table 4. 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

				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 (95% CI) per 1-SD*,†	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*,†	p-value‡
DLBCL									
sTNF-R2	107/570	0.81 (0.62, 1.07)	25/140	0.61 (0.34, 1.10)	25/161	1.05 (0.60, 1.85)	57/267	0.83 (0.56, 1.24)	0.42
sIL-2Rα	107/570	1.18 (0.91, 1.53)	25/140	**1.83 (1.00, 3.37)**	25/161	1.19 (0.67, 2.11)	57/267	1.09 (0.75, 1.58)	0.35
CXCL13	107/570	1.17 (0.95, 1.45)	25/140	0.71 (0.43, 1.19)	25/161	1.42 (0.95, 2.12)	57/267	1.30 (0.95, 1.79)	0.09
sCD30	107/570	1.23 (0.95, 1.59)	25/140	0.90 (0.48, 1.67)	25/161	**1.76 (1.07, 2.89)**	57/267	1.09 (0.75, 1.59)	0.19
BAFF	107/570	0.95 (0.76, 1.18)	25/140	0.96 (0.59, 1.55)	25/161	0.69 (0.44, 1.08)	57/267	1.08 (0.78, 1.50)	0.27
FL									
sTNF-R2	83/569	1.03 (0.77, 1.38)	18/140	0.45 (0.16, 1.25)	22/160	0.95 (0.53, 1.69)	43/267	1.35 (0.93, 1.96)	0.11
sIL-2Rα	83/569	1.06 (0.78, 1.46)	18/140	0.93 (0.35, 2.44)	22/160	1.09 (0.63, 1.89)	43/267	1.09 (0.70, 1.68)	0.95
CXCL13	83/569	1.24 (0.98, 1.58)	18/140	1.10 (0.58, 2.06)	22/160	1.12 (0.72, 1.75)	43/267	**1.48 (1.03, 2.13)**	0.56
sCD30	83/569	**1.69 (1.26, 2.26)**	18/140	**4.85 (2.02, 11.61)**	22/160	**1.88 (1.04, 3.40)**	43/267	1.06 (0.68, 1.64)	0.007
BAFF	83/569	**0.76 (0.59, 0.98)**	18/140	0.70 (0.38, 1.30)	22/160	0.72 (0.41, 1.24)	43/267	0.78 (0.55, 1.12)	0.94
CLL/SLL									
sTNF-R2	153/569	1.21 (0.96, 1.52)	36/140	0.98 (0.49, 1.93)	44/160	1.27 (0.81, 1.98)	73/267	1.16 (0.85, 1.58)	0.82
sIL-2Rα	153/569	**1.50 (1.18, 1.90)**	36/140	**3.71 (1.77, 7.76)**	44/160	1.39 (0.90, 2.15)	73/267	1.26 (0.87, 1.83)	0.04
CXCL13	153/569	0.90 (0.74, 1.10)	36/140	0.78 (0.48, 1.27)	44/160	0.80 (0.54, 1.20)	73/267	1.04 (0.77, 1.41)	0.48
sCD30	153/569	1.15 (0.89, 1.48)	36/140	1.43 (0.71, 2.87)	44/160	1.54 (0.96, 2.46)	73/267	0.90 (0.62, 1.30)	0.17
BAFF	153/569	**0.47 (0.38, 0.58)**	36/140	**0.32 (0.19, 0.53)**	44/160	**0.39 (0.25, 0.61)**	73/267	**0.63 (0.46, 0.86)**	0.05
Other B-NHL^									
sTNF-R2	111/569	1.17 (0.92, 1.49)	31/140	1.28 (0.78, 2.12)	27/160	1.17 (0.73, 1.90)	53/267	1.11 (0.77, 1.61)	0.90
sIL-2Rα	111/569	1.15 (0.89, 1.48)	31/140	1.07 (0.62, 1.83)	27/160	1.05 (0.63, 1.74)	53/267	1.29 (0.87, 1.91)	0.77
CXCL13	111/569	**1.45 (1.19, 1.77)**	31/140	1.50 (0.98, 2.30)	27/160	**1.52 (1.07, 2.17)**	53/267	1.36 (0.98, 1.88)	0.88
sCD30	111/569	1.08 (0.82, 1.41)	31/140	1.28 (0.73, 2.26)	27/160	1.37 (0.81, 2.32)	53/267	0.79 (0.52, 1.21)	0.20
BAFF	111/569	**0.78 (0.64, 0.95)**	31/140	0.74 (0.53, 1.04)	27/160	0.72 (0.48, 1.07)	53/267	0.89 (0.64, 1.24)	0.66

Abbreviations: NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; B-NHL, B-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.

* All models were adjusted for age at blood draw (continuous), cohort (sex), time of blood draw (continuous) and race/ethnicity (Caucasian, non-Caucasian), and were mutually adjusted for all markers listed, except that models for other B-NHL were not adjusted for race.

† Odds ratios and 95% confidence intervals were calculated per 1-standard deviation increase in batch effect-corrected, log-transformed values (with cohort-specific outliers excluded) from the Nurses' Health Study and Health Professionals Follow-up Study combined.

‡ P-values from tests for heterogeneity comparing immune marker-specific estimates across time strata.

§ Other B-NHL subtypes included 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).

Table 5. Associations of pre-diagnosis plasma immune markers with risk of NHL, with mutual adjustment for all thirteen immune markers, for all NHL and by major histologic subtype

Marker	N Cases/ Controls	All NHL OR (95% CI) per 1-SD *,†	N cases	DLBCL OR (95% CI) per 1-SD *,†	N cases	FL OR (95% CI) per 1-SD *,†	N cases	CLL/SLL OR (95% CI) per 1-SD *,†	N cases	Other B-NHL‡ OR (95% CI) per 1-SD *,†	N cases	All T-NHL OR (95% CI) per 1-SD *,†
IL-6	523/550	1.06 (0.93, 1.21)	104	1.22 (0.96, 1.55)	78	0.86 (0.66, 1.12)	150	1.10 (0.89, 1.37)	106	1.03 (0.81, 1.31)	28	1.10 (0.71, 1.73)
IL-8	523/550	0.96 (0.83, 1.10)	104	0.92 (0.72, 1.18)	78	0.94 (0.71, 1.24)	150	1.00 (0.79, 1.26)	106	1.11 (0.88,1.38)	28	0.65 (0.40, 1.07)
IL-10	523/550	0.95 (0.84, 1.07)	104	1.14 (0.91, 1.43)	78	0.93 (0.72, 1.22)	150	**0.80 (0.65, 0.99)**	106	0.99 (0.79, 1.23)	28	1.19 (0.77, 1.82)
TNF-α	523/550	1.00 (0.87, 1.15)	104	0.84 (0.66, 1.08)	78	1.09 (0.81, 1.46)	150	1.09 (0.87, 1.37)	106	0.86 (0.67, 1.10)	28	1.18 (0.74, 1.89)
CRP	523/550	1.00 (0.87, 1.15)	104	1.07 (0.84, 1.37)	78	1.29 (0.96, 1.72)	150	0.82 (0.65, 1.04)	106	1.00 (0.77, 1.29)	28	0.85 (0.54, 1.34)
sCD14	523/550	0.84 (0.71, 1.00)	104	0.82 (0.61, 1.11)	78	0.84 (0.61, 1.18)	150	**0.68 (0.51, 0.89)**	106	0.92 (0.68, 1.24)	28	0.90 (0.51, 1.56)
sGP130	523/550	1.06 (0.85, 1.32)	104	1.05 (0.71, 1.55)	78	1.20 (0.78, 1.86)	150	1.11 (0.78, 1.58)	106	0.84 (0.57, 1.22)	28	0.76 (0.36, 1.60)
sTNF-R2	523/550	1.06 (0.86, 1.31)	104	0.96 (0.67, 1.37)	78	0.88 (0.57, 1.36)	150	1.33 (0.94, 1.87)	106	1.16 (0.81, 1.65)	28	0.75 (0.38, 1.46)
sIL-6Rα	523/550	1.03 (0.89, 1.20)	104	0.86 (0.66, 1.12)	78	1.02 (0.74, 1.40)	150	1.14 (0.90, 1.45)	106	1.19 (0.91, 1.56)	28	1.11 (0.67, 1.84)
BAFF	523/550	**0.73 (0.64, 0.82)**	104	0.98 (0.78, 1.23)	78	**0.74 (0.56, 0.97)**	150	**0.46 (0.37, 0.57)**	106	**0.76 (0.62, 0.94)**	28	0.88 (0.58, 1.34)
sIL-2Rα	523/550	**1.19 (1.02, 1.40)**	104	1.09 (0.82, 1.44)	78	1.09 (0.77, 1.54)	150	**1.59 (1.23, 2.06)**	106	1.10 (0.83, 1.46)	28	**1.95 (1.22, 3.10)**
CXCL13	523/550	**1.18 (1.04, 1.34)**	104	1.20 (0.96, 1.49)	78	1.22 (0.94, 1.59)	150	0.92 (0.74, 1.13)	106	**1.45 (1.18, 1.78)**	28	1.20 (0.80, 1.82)
sCD30	523/550	**1.26 (1.06, 1.48)**	104	1.27 (0.96, 1.66)	78	**1.80 (1.30, 2.50)**	150	1.10 (0.84, 1.45)	106	1.13 (0.85, 1.52)	28	1.25 (0.76, 2.05)

Abbreviations: NHL, non-Hodgkin lymphoma; B-NHL, B-cell NHL; SD, standard deviation; OR, odds ratio; CI, confidence interval; 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.

* From multivariable logistic regression models that include all 13 immune markers in each model, adjusted for age at blood draw, time of day of blood draw, race and cohort. T-NHL models were not adjusted for race due to sparse cell counts.

† 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.

‡ Other B-NHL 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).

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)

Marker	N	Mean	Median	Minimum	Maximum	N	Mean	Median	Minimum	Maximum
			NHS					HPFS		
					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 1×10^9 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

Marker	Cohort			
	NHS		HPFS	
	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)**

Marker	N cases	OR (95% CI) per 1-SD[*]	N cases	OR (95% CI) per 1-SD[*]
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 NHL[‖]									
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.

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¶ 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.

ǁ 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).