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Associations between Perfluoroalkyl Substances and Systemic Lupus Erythematosus in Gullah African Americans

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ABSTRACT

Associations between Perfluoroalkyl Substances and Systemic Lupus Erythematosus in Gullah African Americans

By Jacob W. Hojnacki

Objective: To assess associations between perfluoroalkyl substances (PFAS) and systemic lupus erythematosus (SLE) incidence in Gullah African Americans.

Methods: We analyzed a cross-sectional sample of 42 prevalent SLE cases and 104 persons without SLE at time of enrollment in the Systemic Lupus Erythematosus in Gullah Health (SLEIGH) study as a nested case-control study, with some measurement error on historical exposures and confounders since measures were from a time period after the etiologically relevant time window. PFAS biomarkers, disease status, and potential confounders were measured at the SLEIGH baseline visit. Taking into consideration age at diagnosis, we re-conceptualized this cross-sectional sample as a cohort using age as our time axis, with follow-up of cases ending at age of SLE diagnosis, and disease-free participants' follow-up censored at age at the SLEIGH baseline visit. We then used risk-set sampling of that cohort, matching 3 participants of the same sex as the case, who had not yet developed SLE (thus, older), to each case. We used conditional logistic regression to estimate the odds ratios of lupus as a function of each PFAS, controlling for baseline visit age, family history of SLE, ever/never smoking, educational attainment, and serum albumin. Conditioning on albumin was intended to block the path from disease to measured PFAS as surrogate of past PFAS. Baseline education was a proxy for unmeasured socioeconomic factors.

Results: A 1 ng/mL serum increase PFHxS was positively associated with lupus (Odds Ratio = 1.70, 95% Confidence Interval 1.00, 2.89), as was a 1 ng/mL serum increase in PFOA (OR=1.30, 95% CI 1.00, 1.68).

Conclusion: This observational study suggests that some PFAS may be positively associated with SLE incidence, after controlling for albumin and measured confounders, and making several strong assumptions. This analysis should be viewed as exploratory and tested for replication in a larger sample with prospective exposure assessment.

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune disorder that affects multiple systems of the body including the skin, joints, kidney, and brain.[1] In the United States, the estimated incidence of SLE is approximately 5.5 per 100,000-person years;[2,3] however, these rates are not equal across sex or racial categories. Incidence of SLE is 5-6 times higher in females compared to males, and 2-3 times higher in African American women compared to white women.[2,3] Geographically, in a study of Medicare enrollees, the incidence rate of SLE was highest in the southern US (28 per 100,000-person years) and lowest in the Midwest (21 per 100,000-person years).[4]

The etiology of SLE is unknown, but it is thought that a combination of genetic and environmental factors contribute to disease risk.[5,6] Studying the etiology of SLE in African Americans is difficult due to the highly heterogeneous genetic and environmental characteristics of individuals within the population. Gullah African Americans, descendants of enslaved West Africans brought to the United States,[7] who traditionally have resided in isolation off the Sea Islands of South Carolina and Georgia, offer a unique population to study factors that lead to the development of SLE. Gullah African Americans genetically and culturally have preserved much of their African heritage; they have a low degree of non-African genetic admixture;[8] and have retained linguistic, artistic, dietary, and spiritual aspects of African culture,[8-10] which has likely led to more environmental exposure homogeneity within the population.

Genetic factors have been associated with the development of SLE. First degree relatives of those who have SLE are 2-3.5 times more likely to develop the disease,[6] and more than 30 susceptibility genes have been associated with SLE.[11] The odds of

developing SLE before the age of 18 increases by an average of 48% per identified risk allele in Gullah African Americans with SLE, and 25% in African-American patients.[12]

Despite these findings, genetics may only play a moderate role in a person's risk for developing SLE. Twin studies have found SLE concordance in monozygotic twins is only 20%-40%,[6] and in the Systemic Lupus Erythematosus in Gullah Health (SLEIGH) study, 35% of participants with no family history of SLE had autoantibody positivity at dilution levels of $\geq$1:40.[13] Furthermore, although SLE remains a rare disease in Africa, the prevalence of the disease has increased in African Americans in the United States over the past 20 years.[13,14] Therefore, it is necessary to evaluate the role of environmental exposures in the etiology of SLE in Gullah African Americans.

Perfluoroalkyl substances (PFASs) are environmentally stable chemicals that have surfactant properties appealing for commercial applications.[15] There is an unusual degree of PFAS contamination on the coast near Charleston, South Carolina: estuarine sediments near Charleston have concentrations of PFASs higher than any other reported urban area in the US,[16] and bottlenose dolphins in Charleston Harbor have PFAS levels comparable to occupationally exposed humans.[17] Seafood consumption has shown to be a route of exposure of PFASs in humans.[18,19] Subsistence fishing and a seafood-rich diet are important aspects of Gullah African American culture,[9,10] and Gullah fishermen are not always aware of local fish consumption advisories due to pollution.[9] Seafood consumption from PFAS contaminated waters may put Gullah African Americans at risk of increased PFAS exposure.

There is limited evidence on the potential human toxicological hazards of PFAS other than perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS).[20,21]

PFOA has been associated with high cholesterol, thyroid disease, testicular cancer, kidney cancer, and pregnancy-induced hypertension.[22] Additionally, in a study investigating PFOA's associations with autoimmune disease in the Ohio River Valley, there was a significant positive association of PFOA exposure with the risk of ulcerative colitis.[23] In that population, no association was found between PFOA and SLE.

Gullah African Americans are at increased risk for SLE and many reside in a geographic region with elevated levels of PFAS contamination that may have implications for autoimmunity; therefore, this study aimed to assess associations between PFASs and SLE incidence in Gullah African Americans from Charleston, South Carolina.

METHODS

Source Population

The Systemic Lupus Erythematosus in Gullah Health (SLEIGH) study is a community-engaged[24] observational study of risk factors for SLE in Gullah African Americans.[13] SLE Cases for the SLEIGH study were recruited at Medical University of South Carolina and surrounding private rheumatology clinics. To be eligible to participate in the SLEIGH study, the following inclusion criteria had to be met: 1) age ≥ 2 years; 2) self-identification (or, in the case of minors, parental identification) as African American Gullah from the Sea Islands region of South Carolina, with no known ancestors who were not of Gullah lineage; 3) ability to speak and understand English (or having parents who can communicate in English); 4) ability and willingness to give informed consent (or parental consent). This study population included SLE cases (i.e., persons who met at least 4 of the 11 American College of Rheumatology (ACR) classification criteria for SLE);[25,26] first-degree relatives of SLE cases who did not have SLE; and healthy Gullah African American subjects with no history of autoimmune disease. The majority of SLE cases who were eligible and invited into the SLEIGH study were enrolled: fewer than 5% of eligible participants identified through recruitment refused to participate in the SLEIGH study.[13] Recruitment of patients into the SLEIGH study started in August 2003 and is ongoing.

Outcome Assesment

SLEIGH participants came to the General Clinical Research Center of the Medical University of South Carolina for a comprehensive baseline visit including a blood draw. SLE activity was determined with the Systemic Lupus Erythematosus

Disease Activity Index (SLEDAI) using medical records, laboratory testing and an in-person interview and physical examination.[27]

Exposure Assessment

High performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) was used to measure PFAS concentrations; the analytical methods have been described elsewhere.[28-30] The LOQ (ng/mL) were: 0.20 for PFHxS, 0.18 for PFOS, 0.20 for PFOA, 0.20 for PFNA, 0.16 for PFDA, 0.16 for PFUnDA. Left-censored biomarker values were imputed as the LOQ divided by the square root of 2. The percentage of samples above LOQ was 94% for PFHxS, 99% for PFOA, 99% for PFOS, 97% for PFNA, 91% for PFDA, and 81% for PFUNDA.

Data on Other Variables

Data on smoking history, family history of SLE, and educational attainment were self-reported via questionnaire at SLEIGH baseline visit. Serum albumin levels were measured using the bromcresol green (BCG) albumin reagent method.[31]

Study Sample

For this analysis, we conducted a nested case-control study (**Figure 1**) constructed from a cross-sectional clinical sample of 42 persons with SLE and 104 individuals without disease at time of enrollment in the SLEIGH study, with complete data on exposure, outcome, smoking history, family history of SLE, and educational attainment. Using age at diagnosis data, we re-conceptualized this cross-sectional sample as a birth cohort using age as the time axis, with follow-up of cases ending at age of SLE diagnosis, and disease free participants' follow-up censored at SLEIGH baseline visit age. We then used risk-set sampling of that cohort, matching 3 participants of the same sex as the case,

who had not yet developed SLE (thus, older), to each case. Persons with lupus at baseline were eligible to be controls for other persons who developed lupus at an earlier age. Thus, our study design is an incidence density sampled case control study, along the time axis of year of age. This secondary analysis was designated non-human research by Emory University IRB.

Statistical Approach

The median and interquartile range were reported for participant age at study baseline, serum albumin, and PFAS biomarkers. Proportions were estimated for family history of SLE (yes/no), history of smoking (ever/never), and educational attainment (≤ 12 years vs. > 12 years).

Conditional logistic regression models were used to estimate the association of PFASs with SLE within each matched set, adjusting for confounders. Separate models were run for each PFAS biomarker. We first estimated models without confounder adjustment, and then sequentially adjusted for age at baseline, then also family history of SLE, then also smoking history, and then also educational attainment.

Hypoalbuminemia is common among patients with SLE, occurring in 30% to 50% of patients, as the result of kidney damage that can result from lupus nephritis.[32] PFASs are bound to albumin in serum,[33] so it is important to account for serum albumin to calibrate the PFAS biomarker when measuring associations with SLE. Albumin data was only available in a subset of participants. In that subsample, the same sequence of sequentially adjusted models were estimated, and a sixth model was fit with further adjustment for albumin. This allowed for direct comparisons of the associations in the

sub-population with albumin data versus the full sample, as one way to assess potential selection bias in the subsample analysis.

In a risk-set matched case-control study, the odds ratio (OR) from conditional logistic regression provides an unbiased estimate of the source population's incidence rate ratio irrespective of the frequency of the disease.[34] Here, the incidence rate ratios are defined in respect to a time axis of person-year of age since birth. Conducting a risk-set sampled case-control study with respect to age of diagnosis creates an imbalance in age between cases and controls, by design.

All statistical analysis were conducted in STATA SE version 15.1 (StataCorp. College Station, TX, USA). Missing data were handled by listwise deletion.

RESULTS

Participant Characteristics

Demographic details of our study sample are provided in **Table 1:** our analytical study population consisted of 42 cases of physician-confirmed SLE, and 126 controls. There were 33 cases and 30 controls with albumin data available, and 9 cases and 96 controls without albumin data available. The sex distribution was similar across the participants with albumin data available and unavailable: 89% of cases without albumin data and 91% of cases with albumin data were female. There were differences in age between the groups with or without albumin data: among participants with albumin data, the average age of controls was 43 and of cases was 33 years; among participants without albumin data, the average age of controls was 49 and of cases was 38 years. Controls were more educated than cases, and this difference was more pronounced in the study sample with albumin data available. The majority of participants did not have a history of smoking, but the association of smoking status with case/control status differed in direction across the samples with and without albumin data available: among participants without albumin data, 26% of controls and 11% of cases reported a history of smoking, whereas among the sample with albumin data, 18% of cases and 13% of controls reported a history of smoking. Family history of SLE was common in both cases and risk-set matched controls, with 66% cases and 81% of controls having a history of SLE among participants with missing albumin measurements, and 61% of cases and 71% of controls having a history of SLE among participants with albumin measurements data (Table 1).

Associations of PFAS with SLE

The associations of PFAS with lupus from crude and adjusted conditional logistic regression models, in the sample including participants regardless of albumin data availability, are reported in **Table 2.** Model 1 shows the unadjusted association of PFASs with SLE. The odds ratio of SLE per 1 ng/mL serum increase in PFHxS was 0.67 (95% Confidence Interval 0.49, 0.91); per 1ng/mL serum increase in PFOA was 0.76 (95% CI 0.65, 0.89); per 1ng/mL serum increase in PFOS was 0.95 (95% CI 0.92, 0.97); per 1ng/mL serum increase in PFNA was 0.29 (95% CI 0.16, 0.52); per 1ng/mL serum increase in PFDA was 0.34 (95% CI 0.18, 0.64); and per 1ng/mL serum increase in PFunDA was 0.35 (95% CI 0.19, 0.71). Adjusting for age attenuated associations, but the point estimates still suggested negative associations with PFAS. Further adjustment for family history of SLE, history of smoking, and educational attainment did not substantially change association estimates.

The estimates of association among the subset of participants with serum albumin data are reported in **Table 3**. Model 1 shows the unadjusted association of PFASs with SLE. The odds ratio of SLE per 1 ng/mL serum increase in PFHxS was 1.04 (95% CI 0.71, 1.52); per 1 ng/mL serum increase in PFOA was 0.94 (95% CI 0.80, 1.08); per 1ng/mL serum increase in PFOS was 0.99 (95% CI 0.97, 1.01); per 1 ng/mL serum increase in PFNA was 0.69 (95% CI 0.45, 1.02); per 1 ng/mL serum increase in PFDA was 0.69 (95% CI 0.43, 1.09), and per 1 ng/mL serum increase in PFunDA was 0.69 (95% CI 0.44, 1.07). Adjusting for participant age at baseline (Model 2) produced positive associations between SLE and PFHxS, PFOA, and PFNA. The age-adjusted odds ratio of SLE per 1 ng/mL serum increase in PFHxS was 1.67 (95% CI 1.00, 2.78); per 1

ng/mL serum increase in PFOA was 1.17 (95% CI 0.97, 1.44); and per 1 ng/mL serum increase in PFNA was 1.12 (95% CI 0.68, 1.82). Further adjustment for smoking history and family history of SLE (Model 4) changed the odds ratio of SLE per 1ng/mL serum increase in PFOA to 1.22 (95% CI 0.98, 1.52); and per 1ng/mL serum increase in PFNA to 1.19 (95% CI 0.70, 2.01). Adjustment for age at baseline, history of smoking, family history of SLE, educational attainment, and baseline albumin levels (Model 6) produced odds ratios of SLE per 1ng/mL increase of PFASs of 1.70 (95% CI 1.00, 2.89) for PFHxS, 1.30 (95% CI 1.00, 1.68) for PFOA, 1.00 (95% CI 0.98, 1.03) for PFOS, 1.32 (95% CI 0.75, 2.34) for PFNA, 0.98 (95% CI 0.57, 1.72) for PFDA, and 0.97 (95% CI 0.57, 1.67) for PFunDA (**Table 4**).

DISCUSSION

Among the full set of participants with or without serum albumin data, PFASs were negatively associated with odds of incident SLE, but in the sample with observed serum albumin, the direction of association of PFHxS, PFOA, and PFNA with lupus was positive. We would expect Models 1-5 in the total sample and the subset to produce similar odds ratios if the subset was similar to the total sample. However, we observed differences in estimates between the full sample and the subset starting with unadjusted models, where PFASs associations with SLE were strongly negative in the complete sample, compared to the subset associations, which were negative for PFOA, PFOS, PFNA, PFDA, and PFUNDA; but positive for PFHxS. Additional adjustment for confounders in the full sample was negative for all PFASs, whereas PFHxS, PFOA and PFNA were positively associated with SLE incidence in the subset with albumin data available.

The difference in odds ratios between our full sample and subset with albumin data available when adjusting for the same confounders indicate a possible selection bias. Participants with SLE at the SLEIGH baseline visit were more likely to have albumin data available than controls in our analytical sample who were without SLE at the SLEGH baseline visit. The analysis restricted to participants with album data available retained the majority of cases from the full sample, although those included in the subset had lower serum concentrations of PFHxS, PFOA, and PFOS compared to cases not included into the subset. Many of the controls in our main analysis analytical sample who did not have SLE diagnosis at the baseline SLEIGH visit were excluded from our subset analysis due to missing albumin. Retained controls who did not have diagnosed SLE by

the SLEIGH baseline visit had lower levels of PFHxS, PFOA, PFOS, and PFNA compared to disease free controls excluded from the subset.

This study was limited by its sample size in the number of variables that could be controlled for in the analysis, and limited by our study design in its ability to control for potential confounding by age due to non-overlap in age distributions between the cases and the controls.[35-37] The severe differences in risk of SLE by sex were considered especially important, so we matched cases and controls on sex. We adjusted for age at baseline under the assumption that those who were older would have a higher lifetime exposure to PFASs, but this adjustment involved substantial model extrapolation due to the non-overlap in age distributions between cases and controls under our study design. We included history of smoking in our model because smoking is a risk factor for SLE;[38] however, conditioning on smoking status at the SLEIGH baseline visit could have introduced bias if participants changed their reported smoking behavior subsequent to SLE diagnosis. Family history of SLE is a risk factor for developing SLE,[6] and could be a confounder of the association of PFAS with lupus if there are differences between families in PFAS exposure sources. Educational attainment was included as a proxy for unmeasured socio-economic factors earlier in life that may be associated both with developing SLE and exposure to PFAS. Lastly, we controlled for serum albumin levels as they may have influenced our observed PFAS biomarkers.[33,39] The validity of our SLEIGH baseline visit PFAS biomarker as a measure of historical PFAS exposure depends on full mediation of the relationship of prior lupus diagnosis to biomarker levels at the SLEIGH baseline visit, which is a very strong assumption. Seafood consumption is a part of the Gullah culture,[9] and is an exposure route for PFASs.[18,19] Fish oils have

shown to suppress the onset of SLE in mice,[40] and attenuate disease severity in humans.[41,42] Therefore, it is possible that Gullah African Americans with SLE who were aware of the benefits of seafood consumption for lupus control may have consumed greater quantities of seafood after diagnosis, and as a result have had higher post-diagnosis exposures to PFASs than controls.

Epidemiological data on the potential effects of PFASs on the incidence SLE are limited. The C8 cohort study found increased risk of ulcerative colitis in both a community and occupational cohort with elevated PFOA exposure,[23] and an increased risk for rheumatoid arthritis in the same occupational cohort,[43] although no associations were found between PFOA and SLE in either of these studies.[23,43] The C8 study also found that the titer of antinuclear antibodies (ANA) increased with PFOA exposure.[44] The majority of people with SLE have an elevated ANA titer, although not everyone with a high ANA titer develops SLE.[26] Although the C8 study did not detect associations between PFOA and SLE, that research was conducted in a majority predominantly white population;[23,43,45] their findings may not be generalizable to African Americans.

Toxicological studies suggest that PFASs have the ability to activate peroxisome proliferator-activated receptors (PPARs), notably PPAR-α, which is a ligand-activated nuclear hormone receptor protein that helps regulate a number of processes including inflammation.[21] Ligands of PPAR-α have been shown to have anti-inflammatory effects,[21] consistent with the negative associations between PFASs and SLE found in our main analysis including participants regardless of albumin data availability. However, the past associations of PFOA with various autoimmune diseases are consistent with the higher SLE incidence observed in our subset analysis. PFASs may shift the balance of T-

helper cells 1 and 2 (T_H1, T_H2) towards the T_H2 type.[21] T_H1 cells are responsible for promoting immune response towards foreign pathogens, while T_H2 cells are responsible for antibody-mediated immunity and activation of B-cells.[46] A shift in the balance of T_H cells towards T_H2 type could contribute to the development of an autoimmune disease.[21] PFASs also have been demonstrated to stimulate the production of Tumor Necrosis Factor (TNF-α) and interluekin-6 (IL-6) in mouse,[47,48] and IL-6 in human[49] tissue models. TNF-α and IL-6 are important cytokines in stimulating the production of B-cells and are associated in the development of SLE and other autoimmune disease.[50-52] IL-6 and TNF-α increased *ex vivo* in peritoneal, bone marrow, and spleen cells, of male C57Bl/6 mice following *in vivo* exposure to PFOA and PFOS at dose levels ranging from 50 mg/kg of body weight to 400 mg/kg of body weight.[47,48] Brieger et al. (2011) conducted an in *vitro study* where blood from human volunteers was incubated with 0.1 μg/ml to 100 μg/ml of PFOA or PFOS and measured TNF-α and IL-6 after lipopolysaccharide was added. IL-6 concentrations increased with both PFOA and PFOS exposure, however levels of TNF-α significantly decreased at PFOS 100 μg/ml.[49]

CONCLUSIONS

Although limited by its sample size and potential selection and information biases, our study provides preliminary evidence that exposure to PFHxS and PFOA may be associated with higher incidence rates of SLE in Gullah African Americans. These results are some of the earliest to associate PFAS exposure with SLE in a nonwhite population, and demand replication in a larger sample with prospective exposure assessment.

SUPPLEMENTAL MATERIALS

Figure 1. Outline of incidence density sampling in nested case control study in a reconstructed birth cohort. Unobserved etiologically relevant PFAS exposure occurs before SLE cases are developed. Case-control risk-sets were created at the time of SLE incidence (age at diagnosis). Cases were sex-matched to disease free individuals of equal or greater age than cases. Observed cross-sectional PFAS biomarkers were measured at SLEIGH baseline, after cases had developed.

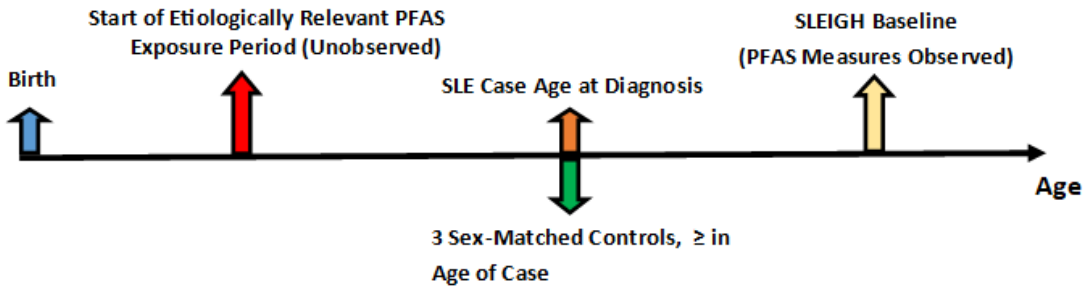


Table 1. Participant characteristics by SLE status

	Participants Without Albumin Data		Participants with Albumin Data	
	Controls (n = 96)	SLE Cases (n=9)	Controls (n=30)	SLE Cases (n=33)
Sex[a]				
Female	85 (89%)	8 (89%)	29 (96%)	30 (91%)
Male	11 (11%)	1 (11%)	1 (4%)	3 (3%)
Baseline Age[b]	49 (40, 56)	38 (21, 41)	43 (35, 57)	33 (20, 42)
Years of Education[a]				
≤ 12 years	39 (41%)	5 (56%)	11 (37%)	20 (61%)
> 12 years	57 (59%)	4 (44%)	19 (73%)	13 (39%)
History of smoking[a]				
No	71 (74%)	8 (89%)	26 (87%)	27 (82%)
Yes	25 (26%)	1 (11%)	4 (13%)	6 (18%)
Family History of SLE[a]				
No	18 (19%)	4 (44%)	9 (30%)	13 (39%)
Yes	78 (81%)	5 (66%)	21 (70%)	20 (61%)
PFAS Exposure (ng/mL)[b]				
PFHxS	2.30 (1.24, 3.6)	2.10 (1.04, 3.86)	1.29 (0.64, 1.81)	0.69 (0.54, 1.66)
PFOA	5.44 (4.36, 8.16)	3.09 (2.61, 6.03)	4.52 (1.51, 5.60)	1.84 (1.35, 5.48)
PFOS	39.84 (27.80, 69.55)	18.86 (11.51, 28.64)	27.00 (7.92, 36.37)	7.92 (4.88,20.72)
PFNA	1.94 (1.46, 3.07)	1.05 (0.80, 1.19)	1.86 (1.33, 2.47)	1.00 (0.54, 1.87)
PFDA	0.89 (0.51, 2.29)	0.41 (0.22, 0.47)	1.05 (0.48, 1.52)	0.50 (0.23, 1.04)
PFunDA	0.89 (0.49, 2.29)	0.41 (0.11, 0.47)	1.04 (0.44, 1.52)	0.50 (0.11, 1.04)
Albumin (g/dl)[b]	-	-	3.90 (3.30, 4.10)	3.50 (3.10, 3.90)

[a] n (%); [b] Median value (IQR)

Table 2. Odds Ratios (95% Confidence Interval) for Systemic Lupus Erythematosus by PFAS in risk sets matched regardless of participants' availability of urine albumin data. Participants were also matched on Sex (3:1 matching, n= 168)

Substance	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)	Model 3[c] OR (95% CI)	Model 4[d] OR (95% CI)	Model 5[e] OR (95% CI)
PFHxS	0.67 (0.49, 0.91)	0.73 (0.49, 1.07)	0.76 (0.52, 1.11)	0.76 (0.51, 1.12)	0.78 (0.53, 1.16)
PFOA	0.76 (0.65, 0.89)	0.85 (0.72, 1.01)	0.87 (0.73, 1.03)	0.84 (0.70, 1.01)	0.86 (0.71, 1.04)
PFOS	0.95 (0.92, 0.97)	0.96 (0.93, 0.99)	0.96 (0.93, 0.99)	0.96 (0.93, 0.99)	0.96 (0.93, 0.99)
PFNA	0.29 (0.16, 0.52)	0.52 (0.27, 1.01)	0.53 (0.27, 1.02)	0.53 (0.27, 1.02)	0.55 (0.29, 1.06)
PFDA	0.34 (0.18, 0.64)	0.56 (0.29, 1.07)	0.54 (0.27, 1.07)	0.55 (0.28, 1.10)	0.58 (0.30, 1.13)
PFunDA	0.35 (0.19, 0.71)	0.56 (0.29, 1.05)	0.55 (0.28, 1.06)	0.56 (0.29, 1.07)	0.58 (0.31, 1.11)

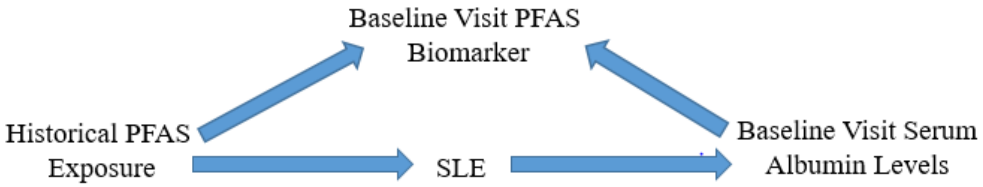
[a] Unadjusted
[b] Adjusted for age at baseline
[c] Adjusted for age at baseline & family history of SLE
[d] Adjusted for age at baseline, family history of SLE & history of smoking
[e] Adjust for age at baseline, family history of SLE, history of smoking & education

Table 3. Odds ratios (95% confidence interval) for Systemic Lupus Erythematosus by PFAS in risk sets matched among participants with measured albumin. Participants were also matched on sex (3:1 matching, n= 126)

Substance	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)	Model 3[c] OR (95% CI)	Model 4[d] OR (95% CI)	Model 5[e] OR (95% CI)	Model 6[f] OR (95% CI)
PFHxS	1.04 (0.71, 1.52)	1.67 (1.00, 2.78)	1.65 (0.98, 2.79)	1.68 (1.00, 2.83)	1.65 (0.98, 2.79)	1.70 (1.00, 2.89)
PFOA	0.94 (0.80, 1.08)	1.17 (0.97, 1.44)	1.17 (0.96, 1.43)	1.22 (0.98, 1.52)	1.22 (0.97, 1.54)	1.30 (1.00, 1.68)
PFOS	0.99 (0.97, 1.01)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.03)
PFNA	0.69 (0.45, 1.02)	1.12 (0.68, 1.82)	1.15 (0.69, 1.90)	1.19 (0.70, 2.01)	1.19 (0.70, 2.02)	1.32 (0.75, 2.34)
PFDA	0.69 (0.43, 1.09)	0.92 (0.56, 1.52)	0.94 (0.56, 1.56)	0.96 (0.57, 1.63)	0.95 (0.55, 1.64)	0.98 (0.57, 1.72)
PFunDA	0.69 (0.44, 1.07)	0.91 (0.56, 1.48)	0.92 (0.56, 1.52)	0.95 (0.57, 1.59)	0.94 (0.55, 1.60)	0.97 (0.57, 1.67)

[a] Unadjusted
[b] Adjusted for age at baseline
[c] Adjusted for age at baseline & family history of SLE
[d] Adjusted for age at baseline, family history of SLE & history of smoking
[e] Adjust for age at baseline, family history of SLE, history of smoking & education
[f] Adjust for age at baseline, family history of SLE, history of smoking, education, and baseline albumin levels

Figure 2. Directed acyclic graph of albumin as a mediator of disease status to SLEIGH baseline visit PFAS biomarkers as a surrogate of historical PFAS exposures.



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