

# Smoking associates with increased BAFF and decreased interferon- $\gamma$ levels in patients with systemic lupus erythematosus

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**To cite:** Raymond WD, Hamdorf M, Furfaro M, *et al.* Smoking associates with increased BAFF and decreased interferon- $\gamma$  levels in patients with systemic lupus erythematosus. *Lupus Science & Medicine* 2021;**8**:e000537. doi:10.1136/lupus-2021-000537

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/lupus-2021-000537>).

Received 14 July 2021  
Accepted 9 October 2021



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## ABSTRACT

**Objective** In SLE, smoking increases the burden of cutaneous disease and organ damage, and leads to premature mortality. However, the effect of smoking on disease manifestations and cytokine levels of patients with SLE is unclear. This study compared characteristics of patients with SLE across smoking status, and determined the association of smoking with serum cytokine levels.

**Method** A cross-sectional study of patients with SLE (n=99) during a research visit in which smoking status was ascertained. Smoking status was compared across classification criteria (American College of Rheumatology Classification Criteria for SLE (ACR97)), disease activity (SLE Disease Activity Index), autoantibody levels, accrued damage (Systemic Lupus International Collaborating Clinics/ACR Damage Index), and circulating concentrations of serum interferon-gamma (IFN- $\gamma$ ), interleukin (IL)-1 $\beta$ , IL-4, IL-6, IL-10, IL-12, IL-17, B cell-activating factor (BAFF), tumour necrosis factor-alpha, transforming growth factor beta 1 (TGF- $\beta$ 1), macrophage inflammatory protein 1 alpha (MIP-1 $\alpha$ ), MIP-1 $\beta$  and monocyte chemoattractant protein 1. Linear regression models determined the association between smoking and cytokine levels, adjusting for age and sex, clinical characteristics (model 1), and anti-inflammatory (IL-4, IL-10 and TGF- $\beta$ 1) and regulatory (IL-1 $\beta$ ) cytokines (model 2).

**Results** Among patients with SLE (97.9% ANA+; mean 48.48 years old; 86.9% female; mean 10 years of disease duration), 35.4% (n=35 of 99) were smoking (an average of 7 cigarettes/day for 24 years). Smokers had increased odds of prevalent ACR97 malar rash (OR 3.40, 95% CI 1.23 to 9.34) and mucosal ulcers (OR 3.31, 95% CI 1.36 to 8.05). Smokers had more arthritis (OR 3.19, 95% CI 1.19 to 8.60), migraine (OR 2.82, 95% CI 1.07 to 7.44), Raynaud's phenomenon (OR 5.15, 95% CI 1.95 to 13.56) and increased non-steroidal anti-inflammatory drug use (OR 6.88, 95% CI 1.99 to 23.72). Smoking associated with 27% increased BAFF levels (95% CI 6% to 48%) and 42% decreased IFN- $\gamma$  levels (95% CI -79% to -5%) in model 2.

**Conclusion** In patients with SLE, smoking independently associated with increased BAFF and decreased IFN- $\gamma$  levels, and an increased frequency of arthritis, migraine and Raynaud's phenomenon. Smoking cessation is

## Key messages

### What is already known about this subject?

► Patients with SLE who smoke have more cutaneous disease, organ damage and premature mortality, as well as reduced medication efficacy. However, the effects of smoking on SLE disease activity and circulating cytokine levels are unclear.

### What does this study add?

► This study shows that patients with SLE who smoke have increased odds of arthritis, migraine (lupus headache) and secondary Raynaud's phenomenon, which necessitated additional non-steroidal anti-inflammatory drug use.  
► This study showed that while smoking had a broadly immunosuppressive effect on cytokine levels in patients with SLE, it was independently associated with increased B cell-activating levels and decreased interferon-gamma (IFN- $\gamma$ ) levels.

### How might this impact on clinical practice or future developments?

► Smoking cessation should be advised to reduce systemic inflammation (B cell-activating factor levels) and disease activity, that is, arthritis, vasospasm (Raynaud's phenomenon), vasoconstriction (migraine/headache), and global disease activity scores [patient/physician visual analogue scale (VAS)], as well as improve host defence (IFN- $\gamma$ ) in patients with SLE.

advisable to reduce systemic inflammation, reduce disease activity and improve host defence.

## INTRODUCTION

SLE is the prototypical autoimmune disease characterised by chronic, multisystem inflammation.<sup>1</sup> Patients experience an unpredictable disease course, which leads to end-stage organ damage and premature mortality.<sup>1,2</sup> Epidemiological evidence suggests that smoking contributes to the development of ANA and

dsDNA autoantibody formation, which are central to the pathogenesis of SLE, particularly lupus nephritis (LN)<sup>3</sup>; and smoking has been linked to an increased risk of developing a range of autoimmune diseases, including SLE.<sup>4-6</sup> In patients with SLE, smoking is linked to cutaneous manifestations,<sup>7</sup> damage accrual, including the earlier onset of end-stage renal disease in those with LN,<sup>8</sup> and premature mortality.<sup>9-10</sup> However, the association between smoking and SLE disease activity is relatively understudied.<sup>11</sup>

Cigarette smoke exposes the epithelial cells of the larynx, bronchi and lung to more than 60 chemical carcinogens, which each has the potential to cause DNA damage.<sup>12</sup> Furthermore, smoking has been shown to increase and decrease many proinflammatory and anti-inflammatory cytokines in the general population, with<sup>13</sup> and without SARS-CoV-2 (COVID-19),<sup>14</sup> and in a cohort with Sjogren's syndrome.<sup>15</sup> Yet, there are (very) limited data on the impact of smoking on serum cytokines in patients with SLE, especially in the context of medication use and organ damage.<sup>5</sup> In SLE, cytokines such as B-cell activating factor (BAFF),<sup>16</sup> transforming growth factor beta 1 (TGF- $\beta$ 1)<sup>17</sup> and interferons (IFNs)<sup>18</sup> are associated with disease activity and severity. Therefore, if smoking were to exacerbate abnormal levels of these cytokines, it would have implications on the treatment and management of SLE. Thus, in this study, we aimed to describe the impact of smoking with a range of clinical, serological and immunological characteristics in a cohort of patients with SLE; and to determine the association between smoking and cytokine levels adjusting for age, sex, medication use, disease activity and organ damage.

## METHOD

This is a cross-sectional study of 99 patients with SLE fulfilling the American College of Rheumatology's (ACR) classification criteria for SLE.<sup>19-20</sup> Smoking was defined as the current consumption of either prefabricated or hand-rolled cigarettes at the research visit. Ex-smokers (median 10 years since quitting and a median 3.5 pack-year exposure) were counted as non-smoking. This was done to align with the stronger association of current smoking rather than ex-smoking or non-smoking behaviours with disease activity and severity in patients with SLE.<sup>21-22</sup>

Clinical data including disease activity and laboratory results were collected at a research visit, where serums taken were stored within 2 hours at  $-70^{\circ}\text{C}$ . Cytokine assays were performed for all participants at the same time. Serological, immunological and biochemistry levels were measured in an accredited laboratory on samples taken at the time of research visit. Disease activity was recorded using the SLE Disease Activity Index-2K (SLEDAI-2K).<sup>23</sup> We calculated Lupus Low Disease Activity State (LLDAS) scores over time,<sup>24</sup> and presented these data as either  $>30\%$ ,  $>50\%$ ,  $>70\%$  of their time spent in an LLDAS as per Sharma *et al.*<sup>25</sup>

Damage accrual was captured prospectively for each participant with the Systemic Lupus International Collaborating Clinics/ACR Damage Index for SLE (SDI) during a median follow-up of 10 years from date of SLE diagnosis through to the research visit.<sup>26</sup> Medication data were collected at the research visit, which documented the use of prednisone (oral or intravenous methylprednisone), cytostatic agents (azathioprine, cyclophosphamide or mycophenolate) or immunomodulators (hydroxychloroquine or rituximab).

Cytokines (IFN-gamma (IFN- $\gamma$ ), interleukin (IL)-1 $\beta$  (IL-1 $\beta$ ), IL-4, IL-6, IL-10, IL-12, IL-17A, BAFF, macrophage inflammatory protein 1 alpha (MIP-1 $\alpha$ ) (patients with SLE only), MIP 1 beta (MIP-1 $\beta$ ) (patients with SLE only), monocyte chemoattractant protein 1 (MCP-1), tumour necrosis factor-alpha (TNF- $\alpha$ ) and TGF- $\beta$ 1) were measured in stored ( $-70^{\circ}\text{C}$ ) serum samples by a quantitative sandwich immunoassay (Single Analyte ELISArray kit; SuperArray Bioscience Corp, Frederick, Maryland, USA). All assays were run in duplicate and the results averaged. The manufacturer's recommendations were followed throughout, and the same lot was used for each cytokine. For statistical purposes, values below the limit of detection (LOD) were replaced by the LOD value.

## Statistical methods

Continuous clinical, serological, and immunological variables are described as a mean $\pm$ SD or median and IQR depending on the data distribution. Continuous data were compared across smoking status with t-test, Mann-Whitney U test, one-way analysis of variance (ANOVA) or Kruskal-Wallis test. Categorical clinical, serological, and immunological variables are described as frequency (n) and proportion (%), and compared across smoking status with logistic regression (presented as an OR with 95% CIs or a Fisher's exact test). Cytokine levels were described with a geometric mean and 95% CI after undergoing log-transformed to improve normality and then back-transformed with Euler's number.

The associations between smoking and proinflammatory cytokines were determined using Spearman correlation coefficients (Rs) and age-adjusted and sex-adjusted linear regression models. Additional multiple regression modelling of the association between smoking and cytokine levels included clinical characteristics (age, sex, prednisone use, immunosuppressant use, SLEDAI score and SDI score) which are known to influence cytokine levels (model 1). Finally, we performed an ad-hoc multiple regression model which determined the association of smoking with serum BAFF, IFN- $\gamma$ , IL-12, IL-17, TNF- $\alpha$  or MIP-1 $\beta$ , adjusted for model 1 plus anti-inflammatory cytokines (IL-4, IL-10, TGF- $\beta$ 1) and the regulatory cytokine (IL-1 $\beta$ ). This was to determine whether the minimally adjusted association(s) between smoking and cytokine levels held after accounting for known lower TGF- $\beta$ 1 levels in patients with SLE,<sup>17</sup> and to account for the

immunosuppressive effects of smoking on key regulatory and anti-inflammatory cytokines IL-1 $\beta$ , IL-4 and IL-10.<sup>27–30</sup>

## RESULTS

### Clinical characteristics of patients with SLE at the research visit compared across smoking status

At the research visit, patients with SLE (97.9% ANA+) were on average 48 years old, 86.9% female and had been followed up for an average of 10 years. At the research visit, 35.4% (n=35 of 99) were currently smoking (average of 7 cigarettes per day for 24 years) (table 1). Within non-smokers, 39.1% (n=25 of 64) were ex-smokers (average of 9 cigarettes per day for 15 years), with cessation occurring on average 10 years prior to the research visit. Current smokers had a significantly higher pack-year smoking exposure than ex-smokers (9 vs 3.5 pack-years, p=0.003). Within current smokers, 57.1% (n=20 of 35) had a <10 pack-year smoking exposure. A total of 34.3% (n=12 of 35) had a 10–20 pack-year smoking exposure, and 8.6% (n=3 of 35) had a  $\geq$ 20 pack-year smoking exposure. Current and non-smokers had an equivalent burden of comorbid vascular, pulmonary, malignancy and metabolic pathology, as well as accrued damage (SDI >0) and total SDI scores. However, patients with any smoking exposure (current and/or ex-smokers) had higher accrued damage (69.0% vs 46.3%; OR 2.57, 95% CI 1.12 to 5.89; p=0.025) and malignancy (20.7% vs 4.9%; OR 5.09, 95% CI 1.07 to 24.13; p=0.041).

There was a higher cumulative prevalence of malar rash (OR 3.40, 95% CI 1.23 to 9.34; p=0.018), mucosal ulcers (OR 3.31, 95% CI 1.36 to 8.05; p=0.008), arthritis (OR 3.19, 95% CI 1.19 to 8.60; p=0.022) and Raynaud's phenomenon (OR 5.15, 95% CI 1.95 to 13.56; p=0.001) in current smokers (online supplemental table 1). SLEDAI-2K scores were equivalent across smoking status, although current smokers had increased odds of migraine (OR 2.82, 95% CI 1.07 to 7.44; p=0.037), with similar representation of other SLEDAI features. Both patient (4 vs 2, p=0.003) and physician (3 vs 2, p=0.046) global disease activity (GDA) visual analogue scale (VAS) scores were however higher. The increased odds of Raynaud's phenomenon in current smokers were higher in male patients (data not shown). Laboratory findings demonstrated that current and non-smokers had similar immunological disease activity, including ANA and anti-dsDNA seropositivity, hypocomplementemia and cytopenias. However, current smokers had higher levels of haemoglobin (13.06 vs 12.99, p=0.036), mean corpuscular volume (MCV) (91.91 vs 88.52, p=0.014) and B cells (0.14 vs 0.08, p=0.037), with lower ApoA 1 lipoprotein levels (1.48 vs 1.61, p=0.039). Smoking was not associated with anti-dsDNA titres (ELIA Rs -0.03, p=0.776), complement protein (C3) (Rs -0.07, p=0.480) or C4 (Rs 0.14, p=0.174) (online supplemental table 4).

The management of SLE required non-steroidal anti-inflammatories in 15.2% (n=15 of 99), prednisone in 50.5% (50 of 99), hydroxychloroquine in 58.6% (n=58

of 99) and immunosuppression in 36.4% (n=36 of 99). Medication requirement for SLE was similar across smoking status with the exception of additional non-steroidal anti-inflammatory drug (NSAID) requirement in smokers (OR 6.88, 95% CI 1.99 to 23.72; p=0.002). Medication requirement for comorbid conditions was equivalent across smoking status (online supplemental table 5).

### Comparison of cytokine levels between patients with SLE and healthy controls

Compared with controls, patients with SLE had higher average levels of BAFF (1.74 vs 0.94 ng/mL, p<0.001) and MCP-1 (137.42 vs 98.22 pg/mL, p=0.028), while having lower levels of IL-1 $\beta$  (26.85 vs 67.86, p<0.001) and TGF- $\beta$ 1 (581.74 vs 733.39, p=0.018). Within patients with SLE, smokers had higher average levels of BAFF (2.01 vs 1.61 ng/mL, p=0.034), yet lower levels of IFN- $\gamma$  (39.37 vs 82.98 pg/mL, p=0.002), TNF- $\alpha$  (35.41 vs 58.37 pg/mL, p=0.024) and MIP-1 $\beta$  (509.26 vs 625.65 pg/mL, p=0.022). Compared with controls, patients with SLE who smoked had higher levels of BAFF (2.01 vs 0.94 ng/mL, p<0.001) and MCP-1 (118.9 vs 98.22 pg/mL, p=0.031), and lower IL-1 $\beta$  (21.85 vs 67.86 pg/mL, p=0.006) but equivalent IFN- $\gamma$  levels (39.37 vs 53.88, p=0.064) (table 2).

### Association of smoking with cytokine levels

Smoking correlated with increased BAFF levels (Rs 0.20, p=0.043) leading to 27% and 28% increased BAFF levels after adjusting for age and sex (95% CI 3% to 57%; p=0.023) and clinical covariates (model 1) (95% CI 5% to 57%, p=0.015), respectively. Smoking inversely correlated with IFN- $\gamma$  levels (Rs -0.32, p=0.001) and a 55% decrease IFN- $\gamma$  in both the age-adjusted and sex-adjusted (95% CI -71% to -27%, p=0.001) and clinical covariate adjusted models (95% CI -72% to -28%; p=0.001). Smoking inversely associated with TNF- $\alpha$  and MIP-1 $\beta$  levels in the univariate, age-adjusted and sex-adjusted model, and model 1. Smoking inversely correlated with IL-4 (Rs -0.25, p=0.015), but was not in the adjusted models. Smoking associated with reduced levels of IL-1 $\beta$  in the age-adjusted and sex-adjusted model only. Smoking associated with decreased IL-12 and IL-17 in the age-adjusted and sex-adjusted model and model 1, but not model 2 (table 3).

### Analysis further adjusting for anti-inflammatory or regulatory cytokines

With further adjustment for anti-inflammatory cytokines (IL-4, IL-10 and TGF- $\beta$ 1) and regulatory cytokine IL-1 $\beta$  (model 2), smoking increased BAFF levels by 27% (95% CI 6% to 48%; p=0.014) and decreased IFN- $\gamma$  levels by 42% (95% CI -79% to -5%; p=0.026); however, smoking no longer associated with changes in IL-12, IL-17, TNF- $\alpha$  or MIP-1 $\beta$  (which were dependent on IL-4 levels) (table 3).

**Table 1** Characteristics of patients with SLE at the research visit compared across smoking status

	Overall	Current smoker	Not currently smoking	OR (95% CI)	P value
<b>Participants, n</b>	99	35	64		
Age, mean±SD	48.48±15.75	46.91±13.49	49.33±16.89	–	0.941
Male, n (%)	13 (13.1)	7 (20.0)	6 (9.4)	–	0.135
Female, n (%)	86 (86.9)	28 (80.0)	58 (90.6)	–	
Years of follow-up, median (IQR)	10.42 (5.08–17.67)	10.42 (5.08–16.75)	10.46 (4.92–17.67)	–	0.941
<b>Smoking details</b>					
Ex-smoker, n (%)	25 (39.1)	–	25 (39.1)	–	
Cigarettes per day, median (IQR)	7 (3–10)	7 (3–10)	9 (4–10)	–	0.428
Years of consistent daily smoking, median (IQR)	20.0 (13.0–28.00)	24.0 (18.0–30.0)	15.0 (5.0–23.0)	–	0.064
Pack-years, median (IQR)	5.0 (3.0–12.25)	<b>9.00 (3.75–14.00)</b>	<b>3.5 (2.0–5.0)</b>	–	<b>0.003</b>
Years since quit smoking, median (IQR)	10 (6–18)	–	10 (6–18)	–	–
<b>Cumulative ACR97 classification criteria</b>					
Cumulative ACR97 items, median (IQR)	5 (4–7)	6 (4–7)	5 (4–7)	–	0.651
Positive ANA, n (%)	97 (97.9)	35 (100.0)	62 (96.9)	–	–
Mucosal-cutaneous features*, n (%)	95 (96.0)	34 (97.1)	61 (95.3)	1.67 (0.17 to 16.71)	0.662
Malar rash, n (%)	66 (67.3)	<b>29 (82.9)</b>	<b>37 (58.7)</b>	<b>3.40 (1.23 to 9.34)</b>	<b>0.018</b>
Photosensitivity, n (%)	59 (60.2)	23 (65.7)	36 (57.1)	1.44 (0.61 to 3.39)	0.407
Discoid lupus, n (%)	42 (42.9)	18 (51.4)	24 (38.1)	1.72 (0.75 to 3.97)	0.203
Mucosal ulcers, n (%)	31 (31.6)	<b>17 (48.6)</b>	<b>14 (22.2)</b>	<b>3.31 (1.36 to 8.05)</b>	<b>0.008</b>
<b>Disease activity at the research visit (SLEDAI)</b>					
Clinical disease activity, n (%)	84 (84.8)	28 (28.0)	56 (56.5)	0.57 (0.19 to 1.74)	0.324
Migraine, n (%)	22 (22.2)	<b>12 (12.3)</b>	<b>10 (10.6)</b>	<b>2.82 (1.07 to 7.44)</b>	<b>0.037</b>
Arthritis, n (%)	21 (21.2)	<b>12 (34.3)</b>	<b>9 (14.1)</b>	<b>3.19 (1.19 to 8.60)</b>	<b>0.022</b>
Clinical SLEDAI score, median (IQR)	6 (2–12)	6 (2–14)	6 (2–10)	–	0.981
Total SLEDAI score, median (IQR)	8 (2–14)	8 (4–16)	8 (2–11)	–	0.998
Patient GDA VAS, median (IQR)	3 (1–5)	<b>4 (3–6)</b>	<b>2 (1–5)</b>	–	<b>0.003</b>
Physician GDA VAS, median (IQR)	2 (1–4)	<b>3 (2–4)</b>	<b>2 (1–3)</b>	–	<b>0.046</b>
LDAS-50	35 (37.2)	13 (37.1)	22 (37.3)	0.99 (0.42 to 2.36)	0.989
LDAS-30	62 (66.0)	21 (60.0)	41 (69.5)	0.66 (0.28 to 1.58)	0.349
LDAS-70	17 (18.1)	8 (22.9)	9 (15.3)	1.65 (0.57 to 4.78)	0.357
<b>Secondary conditions</b>					
Raynaud's phenomenon, n (%)	25 (25.3)	<b>16 (16.7)</b>	<b>9 (9.1)</b>	<b>5.15 (1.95 to 13.56)</b>	<b>0.001</b>
<b>Medication requirement</b>					
Prednisone, n (%)	50 (50.5)	18 (51.4)	32 (50.0)	1.06 (0.46 to 2.41)	0.892

Continued

Table 1 Continued

	Overall	Current smoker	Not currently smoking	OR (95% CI)	P value
Prednisone dose (mg), median (IQR)	5.00 (5.00–7.50)	5.00 (5.00–7.50)	5.00 (5.00–10.00)		0.898
Non-steroidal anti-inflammatories, n (%)	15 (15.2)	<b>11 (31.4)</b>	<b>4 (6.3)</b>	<b>6.88 (1.99 to 23.72)</b>	<b>0.002</b>
Hydroxychloroquine, n (%)	58 (58.6)	19 (54.3)	39 (60.9)	0.76 (0.33 to 1.75)	0.521
Immunosuppressants, n (%)	36 (36.4)	13 (37.1)	23 (35.9)	1.05 (0.45 to 2.48)	0.905
<b>Comorbidity</b>					
Metabolic disorder, n (%)	61 (61.2)	20 (57.1)	41 (68.3)	0.62 (0.26 to 1.46)	0.274
Dyslipidaemia, n (%)	49 (49.1)	15 (42.9)	34 (57.6)	0.55 (0.24 to 1.28)	0.168
BMI $\geq$ 30, n (%)	12 (12.9)	3 (8.6)	9 (15.5)	0.51 (0.13 to 2.03)	0.340
Diabetes, n (%)	3 (3.2)	3 (8.6)	0 (0.0)	–	–
Hypertension, n (%)	49 (49.6)	15 (42.9)	34 (56.7)	0.57 (0.25 to 1.33)	0.196
Cardiovascular disease, n (%)	31 (31.1)	12 (34.3)	19 (29.7)	1.24 (0.51 to 2.98)	0.637
Heart attack, n (%)	13 (13.8)	6 (17.1)	7 (11.9)	1.54 (0.47 to 5.01)	0.476
Thromboembolic disease, n (%)	13 (13.8)	4 (11.4)	9 (15.3)	0.72 (0.20 to 2.53)	0.605
Stroke, n (%)	5 (5.3)	2 (5.7)	3 (5.1)	1.13 (0.18 to 7.13)	0.895
Cancer, n (%)	11 (11.7)	1 (2.9)	10 (16.9)	0.14 (0.02 to 1.18)	0.071
Pulmonary diseases†, n (%)	13 (13.1)	6 (17.1)	7 (10.9)	1.69 (0.52 to 5.48)	0.386
<b>Damage accrual (SDI &gt;0), n (%)</b>	<b>59 (59.6)</b>	<b>24 (68.6)</b>	<b>35 (54.7)</b>	<b>1.81 (0.76 to 4.30)</b>	<b>0.181</b>
Total SDI score, median (IQR)	2.00 (1.00–3.00)	1.00 (1.00–2.00)	2.00 (2.00–4.00)		0.140
Skin damage, n (%)	3 (3.0)	2 (5.7)	1 (1.6)	3.82 (0.33 to 43.68)	0.281
Pulmonary damage, n (%)	7 (7.1)	4 (11.4)	3 (4.7)	2.62 (0.55 to 12.46)	0.225
Malignancy damage, n (%)	14 (14.1)	3 (8.6)	11 (17.2)	0.45 (0.12 to 1.74)	0.249

Bolded findings are significantly different across current and those not currently smoking.

\*Also includes alopecia.

†Pulmonary diseases include fibrotic and obstructive diseases (asthma n=6).

ACR97, American College of Rheumatology Classification Criteria for SLE; BMI, body mass index (kg/m<sup>2</sup>); GDA, global disease activity; LDAS-50, Low Disease Activity State-50; SDI, Systemic Lupus International Collaborating Clinics/ACR Damage Index; SLEDAI, SLE Disease Activity Index; VAS, visual analogue scale.

## DISCUSSION

This cross-sectional cohort study demonstrates that in patients with SLE, current smoking associates with increased BAFF levels and decreased IFN- $\gamma$  levels. This was on a background of current smokers having increased joint manifestations necessitating higher NSAID usage, migraine, Raynaud's phenomenon and increased GDA scores. Current smokers had accrued more malar rash and mucosal ulcers over time (ACR97), but not skin damage (OR 3.82, p=0.281). Having ever smoked was associated with increased odds of organ damage and cancer development. However, current smokers and non-smokers were

similar with respect to the remaining ACR97 classification criteria items and scores, cross-sectional SLEDAI-2K scores, damage accrual (SDI >0, 59.6%), comorbidity and other medication requirement.

The harmful effects of cigarette smoking are well established in the general population, and the more recent phenomenon of smoking e-cigarettes (vaping) is gradually being shown to equally so.<sup>31</sup> The 35.4% of patients with SLE smoking and the 25 (39.1%) ex-smokers aligned with Norwegian national survey data on smoking prevalence and cessation at the time of the study.<sup>32</sup> Compared with other studies of patients with SLE, smoking prevalence

**Table 2** Cytokine levels in patients with SLE and 31 healthy controls (reference levels) at the research visit, compared across smoking status

Participants, n	Healthy controls			SLE			SLE non-smokers			ANOVA*		
	31			99			35			64		
	Geometric mean (95% CI)	Geometric mean (95% CI)	P value	Geometric mean (95% CI)	Geometric mean (95% CI)	P value	Geometric mean (95% CI)	Geometric mean (95% CI)	P value	t-test	t-test	P value
BAFF, ng/mL	0.94 (0.84 to 1.04)	1.74 (1.58 to 1.92)	<0.001 *	2.01 (1.72 to 2.34)	1.61 (1.42 to 1.83)	0.034 #	2.01 (1.72 to 2.34)	1.61 (1.42 to 1.83)	0.034 #	0.034 #	0.034 #	<0.001 %
IFN- $\gamma$ , pg/mL	53.88 (35.81 to 81.06)	63.75 (50.51 to 80.47)	0.480	39.37 (27.80 to 55.74)	82.98 (61.96 to 111.13)	0.002 #	39.37 (27.80 to 55.74)	82.98 (61.96 to 111.13)	0.002 #	0.002 #	0.002 #	0.006 %
IL-1 $\beta$ , pg/mL	67.86 (40.08 to 114.90)	26.85 (22.08 to 32.63)	<0.001 *	21.85 (16.80 to 28.43)	30.04 (23.02 to 39.22)	0.123	21.85 (16.80 to 28.43)	30.04 (23.02 to 39.22)	0.123	0.123	0.123	<0.001 %
IL-4, pg/mL	10.98 (7.47 to 16.14)	11.65 (9.23 to 14.70)	0.801	8.99 (6.58 to 12.28)	13.43 (9.78 to 18.44)	0.102	8.99 (6.58 to 12.28)	13.43 (9.78 to 18.44)	0.102	0.102	0.102	0.237
IL-6, pg/mL	19.12 (14.72 to 24.84)	20.84 (17.66 to 24.59)	0.605	18.23 (13.93 to 23.87)	22.42 (18.12 to 27.73)	0.239	18.23 (13.93 to 23.87)	22.42 (18.12 to 27.73)	0.239	0.239	0.239	0.416
IL-10, pg/mL	11.14 (7.82 to 15.86)	13.31 (10.28 to 17.24)	0.481	10.87 (7.56 to 15.65)	14.87 (10.47 to 21.11)	0.253	10.87 (7.56 to 15.65)	14.87 (10.47 to 21.11)	0.253	0.253	0.253	0.374
IL-12, pg/mL	38.92 (27.44 to 55.20)	31.51 (25.58 to 38.81)	0.318	24.18 (17.39 to 33.62)	36.41 (27.88 to 47.55)	0.062	24.18 (17.39 to 33.62)	36.41 (27.88 to 47.55)	0.062	0.062	0.062	0.099
IL-17, pg/mL	51.01 (37.26 to 69.82)	49.65 (41.20 to 59.82)	0.887	40.18 (30.82 to 52.38)	55.74 (43.42 to 71.55)	0.096	40.18 (30.82 to 52.38)	55.74 (43.42 to 71.55)	0.096	0.096	0.096	0.233
MCP-1, pg/mL	98.22 (76.47 to 126.15)	137.42 (118.36 to 159.54)	0.028 *	118.90 (93.40 to 151.37)	148.74 (122.84 to 180.10)	0.156	118.90 (93.40 to 151.37)	148.74 (122.84 to 180.10)	0.156	0.156	0.156	0.031 %
TNF- $\alpha$ , pg/mL	47.91 (33.68 to 68.15)	48.91 (39.58 to 60.45)	0.923	35.41 (26.10 to 48.03)	58.37 (44.20 to 77.07)	0.024 #	35.41 (26.10 to 48.03)	58.37 (44.20 to 77.07)	0.024 #	0.024 #	0.024 #	0.070
TGF- $\beta$ 1, pg/mL	733.39 (663.16 to 811.06)	581.74 (524.97 to 644.65)	0.018 *	509.26 (419.01 to 618.96)	625.65 (556.02 to 703.99)	0.057	509.26 (419.01 to 618.96)	625.65 (556.02 to 703.99)	0.057	0.057	0.057	0.007 %
MIP-1 $\alpha$ , pg/mL	Not available	42.10 (31.65 to 55.99)	-	34.72 (21.44 to 56.22)	47.22 (32.54 to 68.50)	0.319	34.72 (21.44 to 56.22)	47.22 (32.54 to 68.50)	0.319	0.319	0.319	-
MIP-1 $\beta$ , pg/mL	Not available	228.65 (206.54 to 253.13)	-	195.24 (165.18 to 230.78)	249.30 (219.74 to 282.83)	0.022 #	195.24 (165.18 to 230.78)	249.30 (219.74 to 282.83)	0.022 #	0.022 #	0.022 #	-

Bolded findings are significantly different across either \* SLE patients and healthy controls; # SLE patients who were currently smoking vs not currently smoking; and, % healthy controls, SLE non-smokers and SLE current smokers.

\*One-way ANOVA compared cytokine levels between healthy controls, SLE smokers and SLE non-smokers.

ANOVA, analysis of variance; BAFF, B cell-activating factor; IFN- $\gamma$ , interferon-gamma; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MIP-1 $\alpha$ , macrophage inflammatory protein 1 alpha; MIP-1 $\beta$ , macrophage inflammatory protein 1 beta; TGF- $\beta$ 1, transforming growth factor beta 1; TNF- $\alpha$ , tumour necrosis factor-alpha.

**Table 3** Univariate and multivariate association between smoking and cytokine levels in patients with SLE

	Univariate		Age and sex adjusted		Model 1		Model 2	
	Rs	P value	B (95% CI)	P value	B (95% CI)	P value	B (95% CI)	P value
Ln(BAFF)	0.20	0.043	0.24 (0.03 to 0.45)	0.023	0.25 (0.05 to 0.45)	0.015	0.27 (0.06 to 0.48)	0.014
Ln(IFN- $\gamma$ )	-0.32	0.001	-0.79 (-1.25 to 0.32)	0.001	-0.80 (-1.27 to 0.33)	0.001	-0.42 (-0.79 to 0.05)	0.026
Ln(IL-1 $\beta$ )	-0.19	0.054	-0.42 (-0.82 to 0.02)	0.039	-0.38 (-0.78 to 0.02)	0.062	-*	-
Ln(IL-4)	-0.25	0.015	-0.47 (0.98 to 0.02)	0.060	-0.43 (-0.92 to 0.07)	0.089	-0.03 (-0.27 to 0.20)**	-0.778
Ln(IL-6)	-0.15	0.142	-0.26 (-0.61 to 0.09)	0.088	-0.24 (-0.59 to 0.11)	0.183	-0.06 (-0.35 to 0.23)	0.666
Ln(IL-10)	-0.04	0.725	-0.42 (-0.96 to 0.12)	0.123	-0.35 (-0.89 to 0.18)	0.195	0.03 (-0.28 to 0.35)#	0.832
Ln(IL-12)	-0.19	0.055	-0.51 (-0.93 to 0.08)	0.021	-0.46 (-0.89 to 0.03)	0.038	-0.09 (-0.41 to 0.22)	0.588
Ln(IL-17)	-0.12	0.237	-0.43 (-0.80 to 0.06)	0.022	-0.41 (-0.78 to 0.03)	0.034	-0.20 (-0.46 to 0.07)	0.146
Ln(MCP-1)	-0.16	0.104	-0.24 (-0.55 to 0.07)	0.129	-0.24 (-0.56 to 0.07)	0.124	-0.12 (-0.43 to 0.19)	0.435
Ln(TNF- $\alpha$ )	-0.24	0.016	-0.55 (-0.99 to 0.11)	0.014	-0.54 (-0.98 to 0.09)	0.019	-0.25 (-0.60 to 0.10)	0.155
Ln(TGF- $\beta$ 1)	-0.17	0.1	-0.20 (-0.41 to 0.02)	0.076	-0.21 (-0.43 to 0.01)	0.062	-0.18 (-0.41 to 0.05)%	0.118
Ln(MIP-1 $\alpha$ )	-0.13	0.21	-0.28 (-0.90 to 0.35)	0.381	-0.19 (-0.81 to 0.43)	0.55	0.16 (-0.41 to 0.73)	0.580
Ln(MIP-1 $\beta$ )	-0.27	0.007	-0.27 (-0.49 to 0.06)	0.011	-0.26 (-0.47 to 0.05)	0.014	-0.13 (-0.31 to 0.05)	0.159

Model 1 adjusted for age, sex, prednisone use, immunosuppressant use, SLEDAI score, SDI score.

Model 2 adjusted for model 1 plus (regulatory cytokine) IL-1 $\beta$ \* and anti-inflammatory cytokines (IL-4\*\*, IL-10\* and TGF- $\beta$ %) (\*, \*\*, #, % indicate that this cytokine was dropped from the independent variables of the model).

Bolded findings: current smoking associated with changes (+/-) in the level of the cytokine of interest smoking.

BAFF, B cell-activating factor; IFN- $\gamma$ , interferon-gamma; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MIP-1 $\alpha$ , macrophage inflammatory protein 1 alpha; MIP-1 $\beta$ , macrophage inflammatory protein 1 beta; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI, SLE Disease Activity Index; TGF- $\beta$ 1, transforming growth factor beta 1; TNF- $\alpha$ , tumour necrosis factor-alpha.

was equivalent to studies based in the USA (32% current smokers) and Denmark (51% ever-smoked), but higher than in Canada (14% current smokers) and Brazil (8% current smokers).<sup>7 10 11 21</sup> Similarly, smoking intensity (cigarettes per day and pack-years) in our cohort was equivalent to those who reported it.<sup>7 11 21</sup> Despite the Norwegian effort to promote smoking cessation, the prevalence of smoking is currently around 20%, and it is not expected to fall below 10% until 2029,<sup>32</sup> which indicates that an opportunity still exists for clinicians to encourage smoking cessation in their patients.

Our cohort was similar to other studies about the impact of smoking on SLE, with respect to participants' age (mean 48 years old),<sup>21</sup> disease duration (an average of 10 years)<sup>21</sup> and sex distribution.<sup>7 11 21 22</sup> The higher odds of prevalent (ACR97) mucosal ulcers in our cohort add to the established link between current smoking and (active) mucocutaneous features in SLE.<sup>21</sup> In spite of the small numbers, we showed a signal of more skin damage in current smokers (OR 3.82;  $p > 0.05$ ), although similar for the over-representation of cumulative cutaneous features in smokers. Our findings differed to others who showed that having ever smoked<sup>7</sup> or having had a >20 pack-year history<sup>11</sup> increased the odds of discoid lesions and photosensitivity. The increased odds of mucosal rather than discoid lesions and photosensitivity may result from differences in the ultraviolet (UV) light exposure at each research setting,<sup>33</sup> with Tromsø (Northern Norway) having lower peak UV (~4) compared with the Canadian and Danish studies (~6 UV index).<sup>7 11</sup> We showed that having ever smoked rather than current smoking alone resulted in proportionally more damage accrual and malignancy. This aligned with Bourré-Tessier *et al* who reported that smoking associated with lung cancer in patients with SLE.<sup>7</sup> Taken together, patients with SLE should be advised to cease smoking to reduce the odds of mucocutaneous disease flares, damage accrual and cancer development.

Similar to other cross-sectional studies, smoking exhibited little influence on total SLEDAI score, rather we showed increased odds of arthritis, migraine and vasculitis (Raynaud's phenomenon).<sup>11 21</sup> In contrast, other studies showed that smoking increased average SLEDAI scores,<sup>21</sup> increased cutaneous-SLE disease activity,<sup>34</sup> and either slowed or prevented the reduction of SLEDAI scores after treatment with belimumab.<sup>35</sup> Herein, the increased odds of arthritis in patients with SLE who smoked contradicted the inverse association between a smoking history of >20 pack-years and with non-erosive arthritis (OR=0.45) reported by Leffers *et al*.<sup>11</sup> However, in the context of the lower IFN- $\gamma$  levels shown herein, our data align with murine models, which showed that smoking can cause a collagen-induced arthritis.<sup>36 37</sup> Patients with SLE who smoked also had more migraine, headache and Raynaud's phenomenon (disproportionately affecting men). This fits with the increased frequency of headache and vasculitis in active smokers, and the increased odds of neurological disorders in those with smoking history

of >20 pack-years reported elsewhere.<sup>10 11 21 38</sup> Patients with SLE who smoked also had increased patient and physician GDA scores (0–10 mm VAS). Yet, similar to Golder *et al*, we found that smoking status (current or ex-smoking) had no influence on LLDAS-30, LLDAS-50 or LLDAS-70 scores (all  $p > 0.30$ ).<sup>39</sup> Thus, in patients with SLE, we suspect that the harmful effects of smoking to health, systemic inflammation and disease activity are not entirely captured by the SLEDAI-2K,<sup>23</sup> which may mean that the impact of smoking is potentially obscured in current treat-to-target indices.<sup>39</sup>

For similar medication profiles, current smokers trended towards a reduction in the prevalence (OR 0.52,  $p = 0.125$ ) and severity of the typical cytopenias seen in SLE, and current smokers had increased levels of haemoglobin and MCV.<sup>40 41</sup> This reflects the increased systemic inflammatory state brought about by smoking-induced damage to the lungs and circulation of smoking by-products throughout the body.<sup>40 41</sup> In spite of the increased systemic inflammatory state, smoking did not influence the proportion with active hypocomplementemia and autoantibody production, which is consistent with the literature.<sup>4 10 42 43</sup> Thus, clinicians should advise their patients that smoking causes acute systemic damage to the body, beyond what is captured within the routine clinical assessment (SLEDAI-2K) or target-to-treat indices of SLE.

The increased (27%) serum BAFF levels in patients with SLE who smoked confirmed the 8.7% and 24% increase seen in (ANA-/ANA+) smokers in the Nurse's Health Study (n=1177), respectively.<sup>5</sup> Smoking has been shown to increase serum BAFF levels in the absence of autoimmune disease.<sup>5 44</sup> The overexpression of BAFF in SLE is hypothesised to be driven by localised inflammation or B cell activation resulting from inherent immune dysregulation in SLE.<sup>30 45</sup> BAFF levels have also been associated with disease activity<sup>46</sup> and organ damage<sup>47 48</sup> in some but not all cohort studies.<sup>45</sup> Yet, the failure of monoclonal anti-BAFF therapy to dampen disease activity<sup>49</sup> suggests that aberrant BAFF production is a feature rather than a direct cause of lupus disease activity.<sup>45</sup> Furthermore, smoking has been shown to reduce the efficacy of belimumab (BAFF inhibition)<sup>35</sup> and antimalarial agents in the management of SLE.<sup>50</sup> Taken together, the independent association between smoking and BAFF levels, on a background of increased physician GDA score arthritis and vasculopathies, suggests that smoking cessation should be a priority in the management of SLE to reduce systemic inflammation and disease activity, which would help to reduce serum BAFF levels.<sup>30</sup>

Innate antiviral immune competence is a major function of many type I IFNs, which along with IL-12, IL-15 and IL-18, can induce type II IFN (IFN- $\gamma$ ) production.<sup>51</sup> Dysregulation of type I IFN, and potentially type II IFN (IFN- $\gamma$ ), can lead to uncontrolled virus replication coupled with uncontrolled inflammation which causes tissue damage.<sup>51</sup> IFN- $\gamma$  in inflammatory and autoimmune pathologies has bidirectional immunoregulatory effects,



which often moderate disease severity, and maintains antiviral and microbial defences, among other features.<sup>52–56</sup> We showed increased IFN- $\gamma$  levels in non-smoking patients with SLE compared with healthy controls (82.98 vs 53.88 pg/mL,  $p < 0.001$ ).<sup>18 57</sup> However, patients with SLE who smoked had IFN- $\gamma$  levels similar to and trending lower than those of healthy controls (39.37 vs 53.88 pg/mL,  $p = 0.064$ ). The suppression of IFN- $\gamma$  levels within patients with SLE who smoked (model 2) aligns with the literature about smoking-induced suppression of type I and II IFN cytokines.<sup>58–62</sup> With respect to IFNs, smoking can cause phosphorylation-dependent downregulation of IFN-1A receptor (IFN-1AR) by reactive oxygen species (ROS),<sup>63</sup> which, although unproven as yet, may result from exposure to the major phenolic components of cigarette tar, hydroquinone and catechol.<sup>27</sup> Additionally, the phosphorylation-dependent downregulation of IFN-1AR by ROS was ameliorated by the antioxidant N-acetylcysteine (NAC).<sup>63</sup> Interestingly, in patients with SLE, disease activity was shown to improve within 1 month of administration of NAC (2.4–4.8 g/day),<sup>64</sup> which suggests that perhaps, NAC supplementation may be beneficial in patients with SLE,<sup>65</sup> especially for those struggling with smoking cessation.<sup>66</sup> Nicotine has been recently cited as having beneficial proinflammatory and anti-inflammatory effects<sup>67</sup>; and pertinent to SLE, nicotine was shown to augment TGF- $\beta$  levels and increase expression of FoxP3 in mice.<sup>68</sup> However, in our study, TGF- $\beta$ 1 levels were lowest in patients with SLE who smoked. Thus, while nicotine replacement therapy has its use in smoking cessation, its psychoactive properties (addictive), vasoconstrictive properties (perhaps responsible for the increased odds of headache and Raynaud's phenomenon seen herein) and the significantly reduced levels of TGF- $\beta$ 1 levels of current smokers make its potential use as an immune modulator unlikely.<sup>69</sup> Ultimately, the ability of NAC supplementation and nicotine to influence systemic and immune-mediated inflammation requires further study in patients with SLE. The clinical phenotype of patients with SLE who smoked aligns with murine model data, in which, the absence of IFN- $\gamma$  had a significant reduction in serum immunoglobulins, ANA and anti-dsDNA seropositivity, renal immune deposits and proteinuria.<sup>38</sup> Similarly, in murine models of collagen-induced arthritis, IFN- $\gamma$  was protective against arthritis by inhibiting the development of Th17 cytokines.<sup>36 37</sup> Taken together, smoking in SLE depletes IFN- $\gamma$  to levels similar to or beyond those of healthy controls, with the cost of more arthritis, migraine/headaches and vasculitis, which necessitates increased NSAID use; and while we lacked the data, we suspect that smoking would have a higher prevalence of infection or viral reactivation as well. Future research could investigate the scope for NAC supplementation to help prevent a rebounding effect of type I and II (IFN- $\gamma$ ) IFNs to aberrant levels in patients undergoing smoking cessation.<sup>18 70</sup> Furthermore, use of type I or II IFN inhibitors in patients with SLE who smoke would likely be met with poorer treatment response

and further increase the development and severity of viral infection or reactivation.<sup>70</sup>

Levels of IL-1 $\beta$  are reported to be higher in patients with SLE relative to controls, especially with higher disease activity<sup>17 71 72</sup>; and lower levels of IL-1 $\beta$  have been shown in well-managed,<sup>17</sup> quiescent<sup>72</sup> and now inversely associated with smoking in patients with SLE (age-adjusted and sex-adjusted model). Our data and others indicate that in patients with SLE, the by-products of smoking can reduce the levels of conventionally proinflammatory (TNF- $\alpha$ , IL-12, IL-17 and MIP-1 $\beta$ ) and anti-inflammatory (IL-4) cytokines.<sup>27 73</sup> While the depletion of these cytokines may not be significant enough to cause immune-mediated pathology, in the context of a reduced regulatory capacity of IL-1 $\beta$ ,<sup>30</sup> this may increase the susceptibility of patients with SLE to infections, atherosclerosis, cardiovascular disease and cancer development.<sup>9 74–77</sup> Thus, we speculate that smoking cessation may help normalise levels of IL-1 $\beta$  in patients with SLE, which would help to inhibit undesirable immune responses, possibly by increasing the Treg functionality via Th2 cytokines, and give protection against comorbidity.

The strength of this study is the availability of a large range of disease characteristics in all the patients, the inclusion of longitudinal organ damage data, and the adjustment for a range of cytokines involved in regulating or exacerbating SLE. Some of the limitations of this study lie in the fact that our patients were all of Northern European descent and were mostly in a state of low disease activity, such that results cannot be extrapolated to cohorts with a different genetic or clinical makeup. The smoking exposure was captured prospectively since SLE diagnosis (with the question 'Have you smoked earlier or do you smoke daily?') as well as at the research visit, meaning that the details of ex-smokers' cigarette consumption, including 'cigarettes smoked per day', 'years of continuous smoking' and the 'years since quit smoking' to determine pack-years, was defined retrospectively by self-report. We lacked complete data on socioeconomic status and did not collect data on alcohol consumption, although we suspect these exposures would have minimal effect on the adjusted associations with cytokine levels. While we demonstrated an independent association between smoking and IFN- $\gamma$ , we did not have data on other type I IFNs, thus we cannot determine whether smoking directly influenced IFN- $\gamma$  levels via type I IFNs or other cytokines, such as IL-18, which can stimulate the production of IFN- $\gamma$ . Finally, our results were based on clinical and serological findings and, therefore, cannot confirm the cellular source or causation of effects of smoking on BAFF, IFN- $\gamma$  and IL-1 $\beta$ , for which further experimental studies will be needed.

## CONCLUSION

Smoking independently associated with increased serum BAFF and decreased IFN- $\gamma$  in patients with SLE. Smoking status associated with a clinical phenotype, which

included mucocutaneous features, arthritis, migraine/lupus headaches and secondary Raynaud's phenomenon, and necessitated increased use of NSAIDs. Smoking cessation should be encouraged in SLE with the aim to reduce systemic inflammation (BAFF and physician GDA), arthritis, vasospasticity, cutaneous features and NSAID requirement, while improving medication efficacy (hydroxychloroquine) and innate immune competence (IFN- $\gamma$ ).

**Acknowledgements** Andrea Becker-Merok and Kristen Nilsen.

**Contributors** All authors have contributed to the study design and writing of this manuscript. WDR is responsible (guarantor) of the overall content. WDR conducted the statistical analysis and assures the integrity and accuracy of the data presented in this study.

**Funding** This work was supported by an unrestricted grant from the Arthritis and Osteoporosis Foundation of Western Australia (JN). WR received a PhD scholarship in Memory of John Donald Stewart, the Gabrielle Vitale Memorial Fund Grant from the Lupus Group of Western Australia, and the Australian Rheumatology Association (Western Australia Branch) Research & Training Scholarship.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** Patients provided written informed consent for this study, which was approved by the regional ethics committee (REK: 2015/1400).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplemental information.

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