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PROJECT TITLE: Cigarette smoking and socioeconomic status in disease outcomes of systemic lupus erythematosus: results from the 1000 Faces of Lupus cohort

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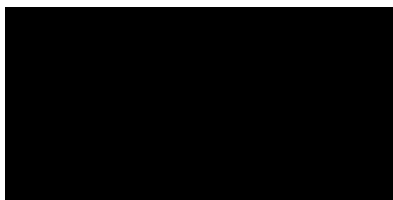
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SUMMARY

Part 1: The effect of smoking on the disease characteristics of systemic lupus erythematosus (SLE) has not been extensively researched in large cohorts to date. Through this study, we aim to examine the relationship between current smoking status, sociodemographic variables, disease activity and organ damage in a large cohort of SLE patients. **Methods:** 1380 adult SLE patients from the 1000 Faces of Lupus cohort were tested for differences in sociodemographic variables, disease activity and organ damage between current smokers and non-smokers. Significant variables from univariate analyses were included in linear regression models examining for predictors of disease outcomes. **Results:** More Caucasians (19%) and Aboriginals (44%) smoked compared to Asians (6%), and Africans (9%) ($p < 0.001$). More smokers had low income compared to non-smokers (27% vs. 11%, $p < 0.001$). Less smokers completed high school (76% vs. 87% of non-smokers, $p < 0.001$). No difference in organ damage was found. Disease activity, measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, trended higher in current smokers (5.5 ± 0.3 vs. 5.0 ± 0.1 in non-smokers). In linear regression, smoking status was the only significant predictor of SLEDAI ($p = 0.024$), other than current treatment with prednisone when controlled for income, education, ethnicity, number of diagnostic criteria met, and age at diagnosis of SLE. **Conclusion:** Current smoking is a predictor of increased disease activity in SLE, and may account for the differences in disease activity seen between ethnic and socioeconomic groups.

Part 2: The relationship between socioeconomic status (SES) and disease outcome is well studied in SLE. Inflammation and immune dysfunction have been proposed as possible mediators. We aim to examine the relationship between SES, autoantibody frequency, and inflammation in SLE patients. **Methods:** A cohort of 273 Winnipeg SLE patients was tested for associations between education, income, autoantibody frequency and inflammation as measured by erythrocyte sedimentation rate (ESR). Linear regression models were developed for predictors of total autoantibody frequency, elevated ESR, and organ damage. **Results:** No associations were found between SES and autoantibody frequency. Less education and low income were associated with increased maximum ESR scores ($p < 0.001$, $p = 0.035$ respectively). Both income and education were predictors of increased mean ESR scores in linear regression ($p = 0.025$ and $p = 0.047$). When total ACR score, age, and income were included in the regression model, mean ESR score and high school completion were predictors of organ damage ($p = 0.032$ and $p = 0.04$). **Conclusion:** Low SES is associated with elevated inflammation, and inflammation may be a mediating factor between low SES and poor disease outcomes in SLE.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown etiology and is associated with the presence of numerous autoantibodies. It is known as the “disease with a thousand faces” because it manifests a diverse range of symptoms. SLE is more common in women than men, with roughly a 9-to-1 ratio¹, and is more prevalent in ethnic minorities and lower socioeconomic groups.¹⁻⁴ SLE disease outcomes are measured in terms of disease activity and organ damage. Disease activity refers to the degree of active inflammation and symptoms as a result of SLE. Organ damage, otherwise known as damage accrual, is permanent and irreversible damage due to SLE, treatment of SLE, or any organ damage that has been present for at least six months after the diagnosis of SLE.⁵ It is common for damage accrual to occur as a result of prolonged or uncontrolled disease activity.⁶

The current model of SLE pathogenesis suggests that genetically-susceptible individuals develop SLE if they are exposed to certain environmental triggers.⁷ Since SLE has poorer outcomes in both ethnic minorities and lower socioeconomic strata, it is greatly debated whether this is a result of genetic factors, environmental factors, or a combination of both (**Figure 1**).^{7,8} Various studies examining both the role of ethnicity and socioeconomic status (SES) in SLE have found conflicting results.^{8,9}

In this study, we will examine the effects of two different environmental factors in SLE. The first is cigarette smoking, a modifiable health behaviour often related to SES.¹⁰ The other is SES, a less quantifiable and more abstract environmental factor.

Cigarette smoking

Cigarette smoking is a risk factor in the development of autoimmune disease. Smoking is strongly associated with the development of autoantibody-positive rheumatoid arthritis (RA), also known as seropositive RA.^{11,12} This pattern is especially significant in individuals with certain genetic signatures, known as shared epitopes.¹³ Smoking is also associated with developing multiple sclerosis and Graves' hyperthyroidism.¹¹ Cigarette smoking is a controversial risk factor for SLE development since conflicting results have been found in multiple studies.^{7,11,14} Smoking has been described as an “instantaneous hazard”¹⁴ for developing SLE by a meta-analysis which concluded that there was an elevated risk of SLE development with current smoking, and no associated risk with past smoking.¹⁴

Several theories exist for the role of smoking in the development and course of SLE. Smoking may increase the risk of self-antigen exposure to the immune system, leading to autoantibody production. The interaction of free radicals and toxins from cigarette smoke with DNA may cause gene mutations or the formation of DNA adduct products.^{6,11} Anti-double stranded DNA (anti-dsDNA) antibodies titres have been found to be elevated in SLE smokers compared to non-smokers, which may possibly be explained by the highly antigenic nature of these DNA adducts.^{6,15} As well, smoking has been found to elevate the rate of cell apoptosis.¹¹ Increased apoptosis may also explain the elevation of anti-dsDNA titres in smokers due to a greater risk of self-antigens being presented inappropriately to the immune system.¹²

The role of smoking and SLE disease characteristics has not been extensively studied. A cross-sectional study of 111 patients found higher disease activity in current smokers compared to

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former and non-smokers, with a dose response relationship.⁶ Smoking is associated with heart disease, venous thrombosis, and various types of cancer in SLE patients.¹⁶⁻¹⁸ Smoking is also known to reduce the effectiveness of antimalarial drugs¹⁹ which are used, in part, to treat cutaneous manifestations of SLE. Consequently, smoking is associated with higher cutaneous damage.²⁰ Currently no large cohort studies have investigated the effects of smoking in SLE.

Socioeconomic status

The concept of SES is complex and can be described as being comprised of various facets including income, occupational status, neighbourhood of residence, and education.¹⁰ At the same time, each of these components further influences health behaviours, diet and nutrition, and psychological factors, all of which have their own separate effect on health.¹⁰ SES also affects the access, quality and compliance to health care.³

Ethnicity is frequently linked to SES. Though ethnicity also influences susceptibility to disease through genetic factors^{3,8}, ethnic minorities in Western countries are also more likely to belong to lower socioeconomic groups.^{3,10} Thus, like SES, ethnicity plays a multifaceted role in disease and health.

The role of SES has been well-studied in many diseases, including SLE. In SLE there is an increased prevalence in lower SES groups, even after controlling for ethnicity.^{1,3} At the same time, low SES is associated with increased damage accrual², higher disease activity¹, and poorer physical functioning.²¹ Low SES is also associated with increased mortality.¹ Hence, SES has been found to play an influential role in the development and progression of SLE.

The mechanism of SES in disease pathogenesis is unknown and likely complex. Various studies have found that low SES is associated with elevated inflammatory markers.²²⁻²⁴ As well, several theories provide possible explanations of the link between SES and health. Baum et al. proposed that low SES contributes to poorer health outcomes through causing chronic stress.¹⁰ A low SES is associated with a higher risk of an individual experiencing discrimination and limited access to resources, and living in environments that are crowded, noisy, polluted, and have higher rates of crime.¹⁰ Thus, total stress is proposed to be elevated in people of low SES.¹⁰ This chronic stress, in turn, can influence health. Stress has been shown to cause glucocorticoid release.²⁵⁻²⁷ In a separate model of psychoneuroimmunology, Kemeny suggests that chronic stress is experienced by individuals facing discrimination, as well as those from low SES.²⁸ This leads to a chronically activated hypothalamic-pituitary-adrenal system and increased glucocorticoid release by the neuroendocrine system. The chronically elevated glucocorticoid leads to glucocorticoid resistance in cells. The resulting lack of negative feedback via glucocorticoid leads to the elevation of proinflammatory signalling molecules. This in turn may predispose an individual to inflammatory disease.²⁸

The relationship between the neuroendocrine and immune systems has been well-documented and can be described as bidirectional.^{25,28} Products of the neuroendocrine system modify the functions of immune cells and vice versa.²⁵ In normal physiology, a balance of proinflammatory and anti-inflammatory signalling molecules are secreted by different types of T helper cells.²⁶ Glucocorticoid, a neuroendocrine product, has been shown to suppress proinflammatory cytokines and cause a shift towards humoral immunity as opposed to cellular immunity.²⁶ This type of shift has been associated with the development of SLE, as evidenced by dysfunction in

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humoral immune response and the formation of autoantibodies.²⁶ Thus, it is possible that environmental factors such as SES and stress may contribute to the development of autoimmune disease through dysregulation of the immune system via the effects of the neuroendocrine system. It is also possible that immune system dysregulation may lead to the production of autoantibodies. Autoantibodies have been linked to SLE pathogenesis and are known to be present for years before the development of SLE.²⁹ Autoantibodies also play a role in different patterns of organ damage in SLE.³⁰⁻³²

Based on current evidence and models of interaction between the neuroendocrine system, the immune system, SES, and inflammation, we aim to investigate whether SLE patients from low SES have increased autoantibody production and inflammation.

OBJECTIVES

This study has four aims:

- 1) To determine the association between smoking and disease activity in SLE patients
- 2) To determine the association between smoking and organ damage in SLE patients
- 3) To determine the association between SES and autoantibody frequency in SLE patients
- 4) To determine the association between SES and inflammation in SLE patients

This study has been divided into two separate parts. **Part 1** examines aims 1 and 2, and **Part 2** examines aims 3 and 4.

MATERIAL AND METHODS

1000 Canadian Faces of Lupus Cohort. Data was extracted from the 1000 Faces of Lupus study, a prospective and longitudinal multicentre study of SLE in Canada. Patients with a clinical diagnosis of SLE were enrolled from July 2005 to August 2009. Over 95% of enrolled patients met the American College of Rheumatology (ACR) diagnostic criteria for SLE.²

Annual questionnaires completed by the enrolled participants included data regarding sociodemographic variables such as gender, age, ethnicity, marital status, education, occupation, and household income. Information about health-related habits, medication history including lupus and non-lupus related drugs, access to health care, sunlight and ultraviolet radiation exposure, and family history were also self-reported by the patients. Patients completed questionnaires regarding disease activity and overall health.

Investigators completed forms regarding lupus flares and management, care barriers, ACR diagnostic criteria, lupus manifestations, renal biopsy findings, detailed medication history, disease activity as measured by the Systemic Lupus Activity Measure-2 (SLAM-2) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores³³, organ damage as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index scores⁵, and the Charlson Co-morbidity Index (CCI) scores. SLEDAI and SLAM-2 scores measured active lupus disease in various organ systems.³⁴ The SLICC/ACR damage index measured permanent damage to organs present for at least six months after the diagnosis of SLE.⁵

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Autoantibody status was determined using annual serologic testing. Autoantibodies included in the study were antinuclear antibodies (ANA), anti-double stranded DNA (DNA), anti-Sm (Sm), anti-ribonucleoprotein (RNP), anti-La (La), anti-Ro (Ro), and antiphospholipid (aPL) antibodies including anticardiolipin antibody and lupus inhibitor.

Study data. **Part 1: Cigarette smoking and disease outcome.** A total of 1380 adult participants with a known smoking status were included in this cross-sectional study. This cohort contained both new and prevalent cases of SLE. 217 patients were excluded because their smoking status could not be determined. Participants were grouped into either current smokers or non-current smokers based on whether they self-reported smoking at the time of their baseline visit. Disease activity was assessed using the SLEDAI scale, while organ damage was assessed using the SLICC/ACR damage index. The percentage of patients with no damage on the SLICC/ACR index was also assessed. Sociodemographic variables examined in the study were age, gender, ethnicity, completion of high school, and total annual household income. Education and income were used to describe SES. Annual household income was divided into four tiers: <\$15 000 (1), \$15 000 - \$29 000 (2), \$30 000 - 49 999 (3) and \geq \$50 000 (4). High school completion was used as a marker of education level. Clinical characteristics examined were age at SLE diagnosis and disease duration at the time of first study visit.

Part 2: The role of SES in autoantibody frequency and inflammation. A subset of the 1000 Faces of Lupus cohort was included in the study because it the most complete in terms of autoantibody and SLAM-2 data. A total of 273 adult patients from the Winnipeg site of the cohort were analyzed. All patients were prevalent cases of SLE. For each autoantibody (ANA, DNA, Sm, RNP, La, Ro, and aPL), we determined if patients were ever tested positive. The total number of autoantibodies present in each patient was calculated. The erythrocyte sedimentation rate (ESR) component of the SLAM-2 form was used as a marker of inflammation. In SLAM-2, ESR is assigned a value from 0 to 3 based on the following four tiers: <25 (0), 25-50 (1), 51-75 (2), and >75 mm/hr (3). Maximum ESR score at any visit was determined for each patient. Mean ESR was calculated by averaging the ESR scores from each visit. It was a numerical value unlike maximum ESR score. Total annual household income and high school completion at last visit were used to describe SES. Sociodemographic and clinical characteristics examined were age, ethnicity defined as either Caucasian or non-Caucasian, number of ACR criteria met, age at diagnosis of SLE and disease duration.

Statistical analysis. SPSS 18 software (PASW, Chicago, IL, USA) was used for all statistical analyses. **Part 1: Cigarette smoking and disease outcome.** Baseline data was analyzed, testing for differences in sociodemographic variables, disease activity and damage accrual between smokers and non-smokers in univariate analyses. Categorical variables were analyzed using χ^2 tests, and continuous variables were analyzed using independent t-tests. Data was expressed as mean \pm SEM. Significant variables from univariate analyses were then included in linear regression models examining for predictors of disease activity. A probability value of <0.05 was considered significant.

Part 2: The role of SES in autoantibody frequency and inflammation. χ^2 tests were used to analyze categorical variables. One-way analysis of variance (ANOVA) and independent t-tests were used to analyze continuous variables. Significant variables were included in linear regression models examining for predictors of total number of autoantibodies, mean ESR, and

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organ damage via the SLICC score. Data was expressed as mean \pm SEM. A probability value of <0.05 was considered significant.

RESULTS

Part 1: Cigarette smoking and disease outcome

Baseline demographics and disease characteristics of smoking classification groups (Table 1)

Of the 1380 patients, 1139 (83%) were classified as non-current smokers and 241 (17%) were current smokers at baseline. The mean age of non-smokers was 43.9 ± 0.4 years. The mean age of smokers was 43.4 ± 0.8 years. 91% of non-smokers and 88% of smokers were female. There were no significant differences in the mean age at diagnosis of SLE or mean disease duration. There was a trend of higher SLEDAI scores in smokers (5.5 ± 0.3) compared to non-smokers (5.0 ± 0.1). The SLICC index was 1.4 ± 0.1 and 1.3 ± 0.1 in non-smokers and smokers respectively. 42% of both non-smokers and smokers had no damage on the SLICC index. None of the above differences were significant.

In terms of ethnicity (**Figure 2**), 19% of Caucasians, 44% of Aboriginals, 6% of Asians and 9% of Africans were current smokers ($p < 0.001$). Income differences between smoking groups are summarized in **Table 2** and **Figure 3**. Current smokers were more likely to have the lowest income (27% vs. 11% in non-smokers) and fewer smokers had the highest income (34% vs. 47% in non-smokers, $p < 0.001$). Smokers were also less likely to complete high school (76% vs. 87% of non-smokers) (**Table 2**, $p < 0.001$).

Ethnicity and SES

Significant differences in income levels and education between ethnicities were present in this cohort. Income differences between ethnic groups are summarized in **Figure 4** ($p = 0.001$). 66% of Aboriginals, 92% of Asians, 90% of Afro-Caribbeans and 84% of Caucasians completed high school ($p < 0.001$).

Linear regression (Table 3)

Current smoking and current prednisone use were predictors of disease activity ($p = 0.024$ and $p < 0.001$ respectively) in linear regression models when ethnicity, education, income, ACR score, and age at diagnosis were included. The regression model R^2 value was 0.056.

Part 2: The role of SES in autoantibody frequency and inflammation

Cohort demographics, autoantibody status and ESR scores (Table 4)

The cohort ($n = 273$) had a mean age of 48.5 ± 0.8 years. 91% were female. 32% of the cohort was non-Caucasian. The mean age at SLE diagnosis was 34.3 ± 0.8 years, mean disease duration was 13.7 ± 0.6 years, and mean number of ACR diagnostic criteria met was 5.6 ± 0.1 . The percentage of patients positive for each autoantibody is summarized in **Table 5**. The percentage of patients belonging to each tier of the maximum ESR score at any visit is summarized in **Table 6**.

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Univariate analysis of autoantibody status and SES (Table 7)

In χ^2 analyses, no associations were found between autoantibody status and income or education.

Univariate analyses of inflammation and SES

Lower income was associated with higher maximum ESR scores at any visit as summarized in **Figure 5** ($p = 0.035$). A larger proportion of the lowest income group had a maximum ESR >75 mm/hr compared to the \$30 000 - \$49 999 group (17.9% vs. 3.6%). A larger proportion of the \$30 000 - \$49 999 group had a maximum ESR of <25 mm/hr compared to the lowest income group (69.1% vs. 38.5%). High school graduates had the lowest maximum ESR score (**Figure 6**, $p < 0.001$). 55.2% of graduates had a maximum ESR of <25 mm/hr compared to 37.0% of non-graduates. 7.6% of graduates and 27.8% of non-graduates had a maximum score of 51-75 mm/hr.

Mean ESR was significantly higher in lower income groups (**Table 8**, $p = 0.039$). The $< \$15\ 000$ group had a mean ESR of 0.51 ± 0.09 compared to the \$30 000 - \$49 999 group with a score of 0.20 ± 0.06 ($p = 0.025$). Mean ESR was also higher in high school non-graduates (0.44 ± 0.07) versus graduates (0.27 ± 0.03) (**Table 8**, $p = 0.012$).

Univariate analysis of SES and autoantibody frequency between ethnic groups

Only RNP and Sm autoantibodies were higher in non-Caucasians (**Table 7**, $p = 0.001$, $p = 0.003$ respectively). More Caucasians (84.4%) completed high school compared to 69.4% of non-Caucasians (**Table 9**, $p = 0.005$). In terms of income (**Table 9**, $p < 0.001$), more Caucasians were in the highest income group compared to non-Caucasians. Caucasians had an average of 3.5 ± 0.1 autoantibodies compared to 3.9 ± 0.2 in non-Caucasians ($p = 0.067$). There was no difference in the maximum ESR score (results not shown). The mean ESR was significantly higher in non-Caucasians (0.41 ± 0.05) compared to Caucasians (0.26 ± 0.03) (**Table 9**, $p = 0.017$).

Linear regression

Education and income were not found to be predictors of autoantibody frequency while ACR score was (**Table 10**). High school completion ($p = 0.047$), income ($p = 0.025$) and ACR score ($p = 0.006$) were predictors of mean ESR score in linear regression (**Table 11**, regression model $R^2 = 0.068$). Predictors of SLICC scores (**Table 12**, regression model $R^2 = 0.108$) included high school completion ($p = 0.045$), total ACR score ($p < 0.001$), mean ESR ($p = 0.032$), and age ($p = 0.040$). Household income per number of dependents was also included in the model and was not significant.

DISCUSSION

Part 1: Cigarette smoking and disease outcome

We have found no significant differences between current smokers and non-smokers in terms of organ damage, but a trend towards higher disease activity in smokers in our large cohort study. Since higher disease activity is associated with more organ damage⁶, it is surprising that the SLICC/ACR scores in smokers were slightly lower than in non-smokers. This finding may be due to the fact that our study could not take into account smoking history prior to study

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enrolment and our inability to quantify smoking into pack years due to insufficient data. As well, this study is cross-sectional and thus could not examine organ damage over time.

Our findings regarding organ damage are similar to one study which found no difference in organ damage (SLICC/ACR) and disease activity (SLEDAI) between current smokers and non-smokers.²⁰ Another cross-sectional study found a trend towards more organ damage (SLICC/ACR) and significantly higher disease activity (SLEDAI) in current smokers compared to past and non-smokers, with a dose response relationship.⁶ The elevated SLEDAI score remained significant after adjusting for variables including ethnicity, education, high school grades, and income level.⁶ It is hypothesized that smoking may cause the formation of DNA adducts and anti-dsDNA antibodies.¹⁴ Anti-dsDNA antibodies are associated with elevated disease activity and may predict flares in some patients, though the mechanism has not been fully elucidated.³⁵ Thus, it is possible that increased exposure to cigarette smoke may contribute to higher rates of anti-dsDNA formation in SLE patients and possibly greater disease activity.

In univariate analysis, we found significant differences between smoking groups in terms of ethnicity, education, and annual income. More Aboriginals and Caucasians smoked compared to Asians and Africans (**Figure 2**). Smokers were more likely to have the lowest level of annual income, and less likely to have the highest income (**Figure 3**). As well, smokers were less likely to have completed high school (**Table 2**). Thus, a current smoking status was significantly associated with a lower SES. This data is consistent with previous studies examining for differences in health behaviours between SES groups.¹⁰

However, as previously described, ethnicity and SES are also closely linked. In our study population, Aboriginals and Africans were more likely to have the lowest level of income and less likely to have the highest level of income (**Figure 7**). Aboriginals were also less likely to have completed high school. These trends are similar to previous studies.^{2,10} Thus, our results support current data that smoking, ethnicity, and SES are closely interrelated.

In multivariate analysis, only smoking was a significant predictor of higher disease activity, aside from current prednisone use when ethnicity, education, total annual household income, ACR score, and age at diagnosis of SLE were also included in the regression model. Current prednisone use is likely a marker rather than a predictor of disease activity since it is commonly used to treat disease flares and the associated elevated disease activity. We have found significant differences between smokers and non-smokers in terms of education, income, and ethnicity in univariate analysis, but only smoking status was a significant predictor of disease activity when both ethnicity and SES were included in the regression model. Our results contrast findings from past studies^{8,36-38} which found non-Caucasian ethnicity, poverty, and low education levels to be predictors of disease activity. However, these studies did not examine in depth the role of smoking, and smoking was not included in regression analyses. To our knowledge, this is the first study to find smoking as the only significant predictor of disease activity when ethnicity and SES were included in the regression model.

Our findings suggest that smoking contributes to elevated disease activity in SLE and, at the same time, is closely linked with ethnicity and SES. Because smoking has been found to be a predictor of disease activity in this study while ethnicity and SES were not, it is also possible that smoking may account for the differences in disease activity seen between ethnic and

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socioeconomic groups in SLE. Since current smoking is a predictor of disease activity, physicians should aggressively counsel against smoking in SLE patients.

Part 2: The role of SES in autoantibody frequency and inflammation

Our study has found no association between autoantibody frequency and low SES. As well, education and income were not predictors of elevated total autoantibody frequency in linear regression. SLE is associated with a dysfunctional humoral immune response²⁶, and accordingly, nearly all SLE patients are positive for at least one type of autoantibody. Over 95% of SLE patients are ANA positive, and roughly 60% of patients are anti-dsDNA positive.³⁵ Thus, the high prevalence of autoantibodies in SLE patients makes it difficult to elucidate if there is any association between SES and autoantibodies. Number of ACR diagnostic criteria met was a predictor of autoantibody frequency. This is likely because ACR score is an indicator of disease severity and autoantibodies are associated with different organ manifestations³², but also because the ACR score includes two criteria related to autoantibodies. The ACR score excluding these two criteria was still a predictor of the total number of autoantibodies (data not shown).

We have found an association between education, income and inflammation (as assessed by ESR scores). Higher maximum ESR scores were associated with both low income and no high school completion (**Figures 5 and 6**). Furthermore, both low income and less education were predictors of elevated mean ESR scores in linear regression (**Table 11**). To our knowledge, this is the first study to examine the relationship between ESR and SES in SLE patients. Increased damage and higher mortality are well noted in lower socioeconomic groups in SLE.^{2,3,9,39} Thus, it is possible that elevated inflammation may be one intermediary pathway between low SES and poorer outcomes in SLE. This hypothesis is further strengthened by our study's linear regression which found ESR to be a predictor of organ damage (**Table 12**). However, the fact that education was also a predictor for organ damage independent from inflammation suggests that SES also acts through other mechanisms.

Similar parallels have been drawn in the realm of cardiovascular and metabolic disease. Both elevated C reactive protein (CRP) and low SES are markers of increased risk of CVD^{40,41} and diabetes.⁴² At the same time, low SES is associated with elevated inflammatory markers including fibrinogen, CRP^{22,24} and interleukin-6²⁴ which suggests that inflammation may explain the link between low SES and CVD.^{22,24} Though CVD is different from SLE in terms of pathogenesis, both are associated with aberrant inflammation. Thus, past research and results from our study suggest that environmental factors associated with low SES may predispose individuals to increased levels of inflammation and resultantly, poorer disease outcomes such as organ damage.

It is important to note that ethnicity also appears to play a role in inflammation. Low education, low income and higher mean ESR were present in non-Caucasians compared to Caucasians in this cohort (**Table 9**). As mentioned previously, ethnicity and SES are closely connected in SLE. Our findings warrant further investigation into the role of ethnicity and SES in inflammation.

LIMITATIONS

Part 1: This is a cross-sectional study and as a result, there is less predictive value especially with regards to organ damage which typically accumulates over time. Though we did find

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current smoking to be a significant predictor of disease activity, the model R^2 was low, indicating that the model variables only accounted for a small portion of the SLEDAI score. It is likely a prospective inception cohort with detailed smoking history and smoking data would better examine the effects of smoking on disease activity in SLE.

Part 2: The smaller sample size limited the power of this study. As well, we had a restricted ability to assess inflammation since only ESR was used as an inflammatory marker. Additionally, ESR may be elevated in non-inflammatory conditions. Since our study population had a high prevalence of autoantibodies, we did not observe any associations between SES and autoantibody frequency. It would be interesting to investigate whether low SES predisposes individuals without autoimmune disease to developing autoantibodies and as a result, places them at a higher risk of developing autoimmune disease.

CONCLUSION

Our study has found that current smoking is a significant predictor of disease activity. As well, smoking appears to play a role in the ethnic and socioeconomic disparities in SLE disease activity. Our study has also found that SES, as represented by low education and income, is a predictor of inflammation, as measured by the ESR score.

FUTURE DIRECTIONS

Our study has demonstrated that ethnicity, SES, smoking and inflammation are closely related. Further investigations into the roles and interactions of smoking, SES, ethnicity, inflammation, disease activity and organ damage are warranted to further elucidate the role of environmental factors in SLE disease progression and outcome.

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TABLES

Table 1. Demographic and SLE characteristics of current smokers and non-smokers.

Variable	Not currently smoking (n = 1139)	Currently smoking (n = 241)	p
Mean age (years ± SEM)	43.9 ± 0.4	43.4 ± 0.8	0.5
Mean age at diagnosis of SLE (years ± SEM)	31.1 ± 0.4	31.3 ± 0.8	0.9
Mean disease duration (years ± SEM)	12.2 ± 0.3	11.2 ± 0.6	0.2
Gender (% female)	91	88	0.1
ACR criteria met (mean ± SEM)	5.8 ± 0.1	5.7 ± 0.1	0.4
SLICC index (mean ± SEM)	1.4 ± 0.1	1.3 ± 0.1	0.2
No damage, SLICC index = 0 (%)	42	42	1.0
SLEDAI score (mean ± SEM)	5.0 ± 0.1	5.5 ± 0.3	0.1

ACR: American College of Rheumatology, SLICC: Systemic Lupus International Collaborating Clinic, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index. All demographics assessed at baseline visit.

Table 2. Total annual household income and high school completion of current smokers and non-smokers.

Variable	Not currently smoking	Current smoking
Yearly total household income, % smoking group (n = 615)		
<\$15 000	11 (55)	27 (34)
\$15 000 - \$29 999	16 (76)	19 (24)
\$30 000 - \$49 999	26 (126)	20 (26)
≥\$50 000	47 (230)	34 (44)
High school completion, % smoking group (n = 1368)	87 (982)	76 (179)

Both income and education had a significant value of $p < 0.001$. Both variables were assessed at baseline visit.

Table 3. Linear regression model of SLE disease activity.

Independent variable	Measure estimate	Standard Error	95% CI for β	p
*Current smoking	1.23	0.54	0.17-2.29	0.024
*Current prednisone use	1.08	0.23	0.62-1.54	<0.001
Ethnicity	0.12	0.10	-0.70-0.31	0.215
High school completion	-0.67	0.65	-1.93-0.60	0.301
Annual total household income	-0.06	0.21	-0.46-0.35	0.782
ACR score	0.02	0.15	-0.28-0.31	0.921
Age at SLE diagnosis	0.008	0.02	-0.23-0.04	0.597

Model $R^2 = 5.6\%$. * indicates significant predictors of high disease activity, as indicated by $p < 0.05$.

Table 4. Sociodemographic and clinical characteristics of Winnipeg cohort.

Variable	Cohort (n = 273)	Variable	Cohort (n = 273)
Mean age (years ± SEM)	48.5 ± 0.8	Mean age at SLE diagnosis (years ± SEM)	34.3 ± 0.8
Gender (% female)	90	Mean disease duration (years ± SEM)	13.7 ± 0.6
High school completion, % completed (n = 264)	77 (210)	ACR criteria met (mean ± SEM)	5.6 ± 0.1
Ethnicity, % (n = 272)		Annual household income, % (n = 271)	
Aboriginal	20 (55)	<\$15 000	14 (39)
Asian	8 (22)	\$15 000 - \$29 999	14 (38)
Afro-Caribbean	3 (8)	\$30 000 - \$49 999	20 (55)
Hispanic	1 (2)	≥\$50 000	51 (139)
Caucasian	68 (185)		
Bi-ethnic grouping, % (n = 272)			
Caucasian	68 (185)		
Non-Caucasian	32 (87)		

All variables assessed at last visit except age at diagnosis and disease duration. ACR: American College of Rheumatology

Table 5. Autoantibody status of Winnipeg cohort.

Variable	Cohort (n = 273)
ANA positive, %	97.4 (265)
Sm positive, %	21.2 (58)
RNP positive, %	25.7 (70)
La positive, %	17.6 (48)
Ro positive, %	40.1 (109)
DNA positive, %	67.6 (184)
APL positive, %	
1 APL positive	27.9 (76)
2 APL positive	16.9 (46)
3 APL positive	9.6 (26)

Autoantibodies assessed as ever or never positive at last visit. n=270 for each antibody

Table 6. ESR characteristics of Winnipeg cohort.

Variable	Cohort (n = 273)
Max ESR at any visit, % (n)	
<25 mm/hr	51.5 (140)
25-50 mm/hr	25.7 (70)
51-75 mm/hr	11.4 (31)
>75 mm/hr	10.7 (29)

ESR: erythrocyte sedimentation rate

Table 7. Autoantibody status associations with income, ethnicity, and education

Variable	p	Variable	p
ANA positive		La positive	
total income	0.476	total income	0.856
bi-ethnicity	0.707	bi-ethnicity	0.874
high school completion	0.980	high school completion	0.341
dsDNA positive		Ro positive	
total income	0.894	total income	0.522
bi-ethnicity	0.110	bi-ethnicity	0.445
high school completion	0.737	high school completion	0.729
RNP positive		Sm positive	
total income	0.477	total income	0.706
*bi-ethnicity	0.001	*bi-ethnicity	0.003
high school completion	0.423	high school completion	0.492

* indicates a significant value with $p < 0.05$. Income, ethnicity and education were assessed at last visit.

Table 8. Univariate analyses of associations between mean ESR score and annual household income and mean ESR score and high school completion.

Variable	Mean ESR	SD	SEM	95% CI	p
*Income					0.039
<\$15 000	0.51	0.55	0.09	(0.33, 0.68)	
\$15 000 – 29 999	0.32	0.44	0.07	(0.18, 0.47)	
\$30 000 – 49 999	0.20	0.43	0.06	(0.09, 0.32)	
≥\$50 000	0.30	0.47	0.04	(0.22, 0.38)	
*High school completion					0.012
Yes	0.27	0.43	0.03	(-0.30, -0.38)	
No	0.44	0.48	0.07	---	

Mean ESR was an average of the SLAM-2 tiers: <25 mm/hr, 25-50 mm/hr, 51-75 mm/hr, >75 mm/hr, which were assigned the value 0, 1, 2 and 3 respectively. SD: standard deviation, SEM: standard error of the mean, CI: confidence interval, SLAM-2: Systemic lupus activity measure. * indicates significant value with $p < 0.05$.

Table 9. Univariate associations between ethnicity, mean ESR and sociodemographic characteristics.

Variable	Caucasian	Non-Caucasian	p
Total # autoantibodies (mean ± SEM)	3.5±0.1	3.9±0.2	0.067
*Mean ESR (mean ± SEM)	0.26±0.03	0.41±0.05	0.017
*High school completion (%)	84.4	69.4	0.005
*Annual household income (%)			<0.001
<\$15 000	8.2	27.6	
\$15 000 - \$29 999	13.6	14.9	
\$30 000 - \$49 999	18.5	24.1	
≥\$50 000	59.8	33.3	

All variables were assessed at last visit. * indicates significant value with $p < 0.05$.

Table 10. Linear regression of associations between clinical and socioeconomic variables, and total number of autoantibodies.

Independent variable	Measure estimate	Standard Error	95% CI for β	p
High school completion	-0.199	0.265	-0.721-0.324	0.455
Annual total household income	-0.086	0.097	-0.276-0.0105	0.377
*ACR score	0.309	0.069	0.173-0.444	<0.001

Model $R^2 = 7.4\%$. * indicates significant predictors of autoantibody frequency, as indicated by $p < 0.05$.

Table 11. Linear regression of associations between clinical and socioeconomic variables, and mean ESR score.

Independent variable	Measure estimate	Standard Error	95% CI for β	p
*High school completion	0.135	0.068	0.002-0.268	0.047
*Annual total household income	-0.056	0.025	-0.104 – -0.007	0.025
*ACR score	0.046	0.017	0.014-0.079	0.006

Model $R^2 = 6.8\%$. * indicates significant predictors of high mean ESR score, as indicated by $p < 0.05$.

Table 12. Linear regression of associations between clinical and socioeconomic variables, and SLICC score.

Independent variable	Measure estimate	Standard Error	95% CI for β	p
*High school completion	0.599	0.297	0.014-1.184	0.045
Household income/#dependents	-0.076	0.148	-0.367-0.216	0.610
*ACR score	0.283	0.076	0.133-0.432	<0.001
*Mean ESR	0.581	0.270	0.049-1.112	0.032
*Age	0.019	0.009	0.001-0.037	0.040

Model $R^2 = 12.6\%$. * indicates significant predictors of high SLICC score, as indicated by $p < 0.05$.

FIGURES

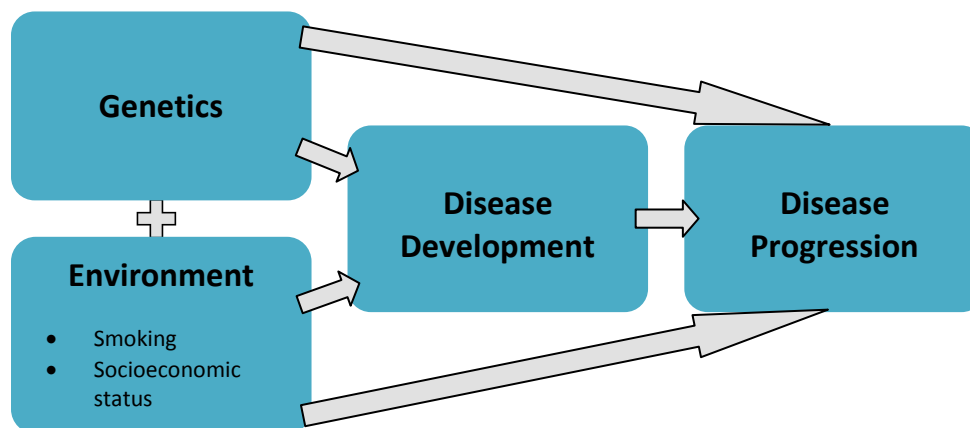


Figure 1. Proposed model of disease pathogenesis. Both genetics and environmental factors contribute to disease.

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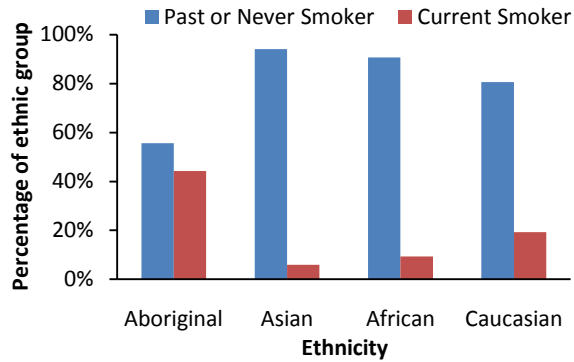


Figure 2. Percentage of ethnic group belonging to non-smoker or current smoker classification. $p < 0.001$.

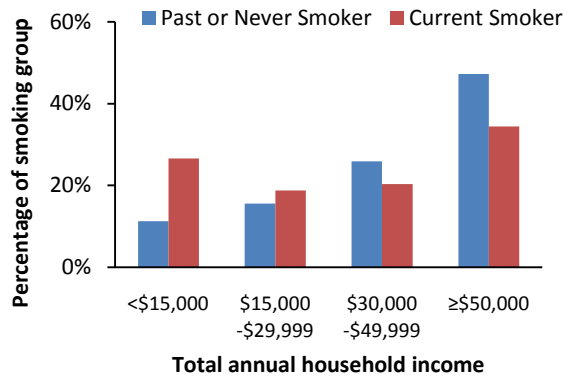


Figure 3. Percentage of members from non-smoking and current smoking groups in each income tier. $p < 0.001$.

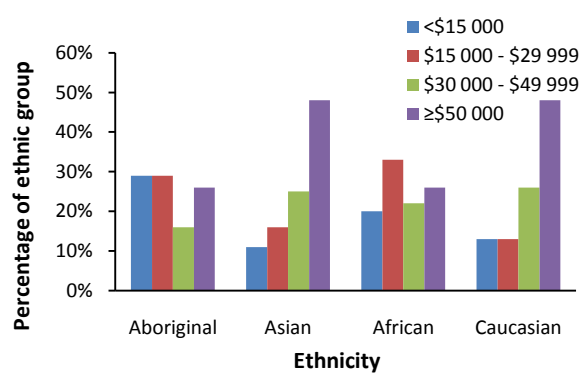


Figure 4. Percentage of ethnic group in each total annual household income tier for Part 1. $p = 0.001$.

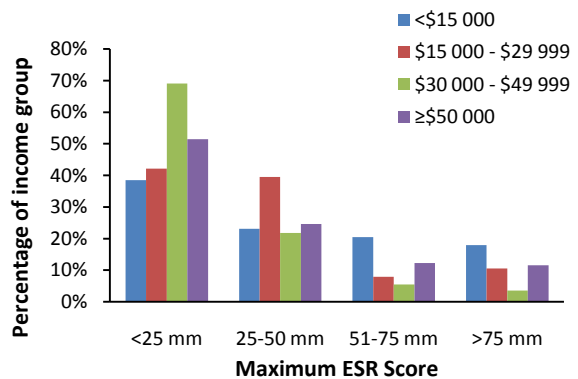


Figure 5. Percentage of annual household income group in each maximum ESR score tier for Part 2. $p = 0.035$.

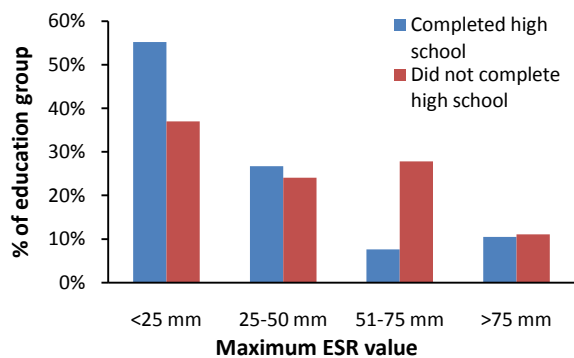


Figure 6. Percentage of education group (did or did not complete high school) in each maximum ESR score tier for Part 2. $p < 0.001$.

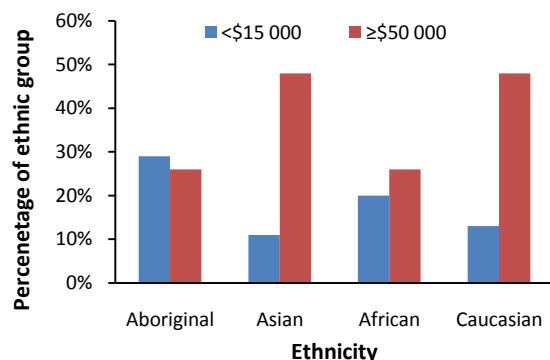


Figure 7. Percentage of ethnic group belonging to the lowest income tier (<\$15,000) and highest income tier (≥\$50,000) for Part 1. $p < 0.001$.

