

## EXTENDED REPORTS

## Smoking history, alcohol consumption, and systemic lupus erythematosus: a case-control study

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**Abstract**

**Objective**—To investigate the effect of smoking on the development of systemic lupus erythematosus (SLE), and the association between alcohol consumption and the disease.

**Methods**—450 subjects (150 SLE patients and 300 controls) from Nottingham, UK were interviewed in a case-control study. Controls were matched to cases for age and sex. All patients met at least four of the American Rheumatology Association criteria for SLE. Controls were randomly selected from the Nottingham Family Health Services Authority register. Information was collected by interview administered questionnaire concerning demographic variables, smoking histories, and drinking habits.

**Results**—Analysis of the data by conditional logistic regression revealed current smokers to have a significantly increased risk of development of SLE compared with never smokers (odds ratio (OR) 1.95, 95% confidence intervals (CI) 1.14, 3.31), although ex-smokers were not at increased risk. There was also suggestion of a marked, highly significant negative association between SLE and alcohol consumption, the magnitude of which increased with units consumed.

**Conclusions**—This study suggests that current smokers are at increased risk of developing SLE compared with non-smokers and ex-smokers. In contrast, alcohol consumption seems to be negatively associated with the disease.

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Although certain genetic factors and sex hormones are known to influence the development of systemic lupus erythematosus (SLE), environmental factors may be paramount.<sup>1</sup> Commonly accepted environmental aetiological factors regarding SLE include ultraviolet light and drugs.<sup>2</sup> Fritzler reviewed various new drug associations linked to the induction of lupus, such as minocycline and sulphasalazine,<sup>3</sup> but more widely acknowledged is the induction of the disease by procainamide and hydralazine, which contain aromatic amines and hydrazine respectively. The development of hydralazine

induced SLE is influenced by the acetylator phenotype of the patient, being more common in slow acetylators. It has therefore been suggested that environmental agents that contain these chemicals, such as tobacco, might induce SLE-like disease.<sup>4</sup>

Epidemiological studies designed to identify host and environmental factors have suggested that smoking tobacco influences certain rheumatological conditions,<sup>5-10</sup> such as SLE. In 1995, a case-control study by Nagata *et al* showed a significantly increased risk of SLE in Japanese women who were current smokers, and this risk was related to the number of cigarettes smoked per day. Drinking habits were also analysed, but the significance of the observed negative association between alcohol consumption and the risk of SLE was constrained by the scarcity of high alcohol consumption among Japanese women.

We undertook a case-control analysis to evaluate the associations between smoking history and current alcohol consumption with the disease in a Western population. The influence of social class was also assessed.

**Methods**

The data for this study were collected by personal interview by a single interviewer (CJH). One hundred and fifty prevalent cases and 300 controls were interviewed between 1993 and 1995, mostly in the interviewee's home (92.9%). One in 20 case and control interviews were taped and subject to external audit to mitigate against non-blinded interviewer bias.

The majority of the patients included in the study were members of a previously identified, geographically complete, cohort of patients in Nottingham, UK,<sup>11</sup> with the remainder comprising additional cases from that area presenting after 1991. The catchment area consists of a central urban zone with a rural fringe. At interview, the diagnosis of SLE was confirmed or refuted on the principles of Fries and Holman<sup>12</sup> and the disease was then classified using the American Rheumatism Association's classification criteria for SLE, revised 1982.<sup>13</sup> Only patients satisfying four or more criteria were included in the study. For each case, two controls, matched for sex and year of birth, were randomly selected from the Nottingham Family Health Services Authority (FHSA)

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register, which listed all residents attached to a general practitioner. Controls who declined to take part were replaced by the next person on the list.

The questionnaire defined demographic details and then sought to determine putative associations with SLE, including medical and menstrual/hormonal histories, and environmental factors such as smoking and alcohol consumption. The questionnaire was based on sections that had been used in other major epidemiological studies, such as the investigation of oral contraceptive use and breast cancer risk,<sup>14</sup> and was successfully piloted on a group of SLE patients living outside the study area. This paper reports the results of the data analysis from the sections relating to smoking and alcohol consumption.

Regular smoking was defined as smoking at least one cigarette (filter or non-filter) per day for at least three months. Thus, subjects who had ever smoked regularly were asked about their age when they started smoking, the number of cigarettes they smoked per day, and dates of stopping and re-starting, where applicable. Current level of alcohol consumption was also recorded, in terms of both frequency and quantity. Social class was graded by the occupation of the economically active person in the household of the subject, into one of six groups: (I) professional; (II) managerial; (III N) skilled non-manual; (III M) skilled manual; (IV) semi-skilled manual; and (V) unskilled manual.<sup>15</sup>

Data were entered into Epi-Info 5.1 (Center for Disease Control and Prevention (CDC), USA, and the World Health Organisation, Geneva, Switzerland), and analysed in EGRET (Version 1.2.9, SERC and CYTEL) and SPSS for Windows (Version 6.1.1, SPSS Incorporated). The statistical significance of smoking history and consumption of alcohol as associate factors for SLE, after adjusting for social class, was analysed by estimating matched case-control odds ratios and their 95% confidence intervals, using multivariate conditional logistic regression. Mann-Whitney U tests were used to investigate differences in measures of smoking quantity and duration. The interaction between smoking and drinking was also examined.

The retrospective nature of the study necessitated the assignment of a dummy date of SLE diagnosis to each control, taken as the diagnosis date of the case to which that control was originally matched. Thus, for all cases and their matched controls, analysis was restricted to smoking exposures and histories preceding diagnosis. This method concurs with that used by Silman *et al* to provide evidence of a link between cigarette smoking and increased risk of rheumatoid arthritis.<sup>8</sup> Alcohol consumption was, however, measured using intake in the week preceding interview, because of difficulties in recalling past drinking habits.

## Results

Subject recruitment rate was higher for cases (95%) than for controls (39%). The external audit of the interviews detected no difference

Table 1 Distribution of demographic variables in cases of systemic lupus erythematosus and controls

	Cases	Controls
Total number of subjects	150	300
female	138	276
male	12	24
Age (y)		
median	47	47
interquartile range	22	22
Social class, (n) (%) <sup>*</sup>		
I	10 (6.7)	26 (8.7)
II	33 (22.0)	73 (24.3)
III N	21 (14.0)	49 (16.3)
III M	34 (22.7)	90 (30.0)
IV	39 (26.0)	42 (14.0)
V	10 (6.7)	17 (5.7)
missing	3 (2.0)	3 (1.0)
Ethnic group, (n) (%)		
White	122 (81.3)	291 (97.0)
Afro-Caribbean	16 (10.7)	3 (1.0)
Asian	8 (5.3)	3 (1.0)
other	4 (2.7)	3 (1.0)

<sup>\*</sup>Based on the Office of Population Censuses and Surveys classification of occupations (see Methods). N = non-manual; M = manual.

Table 2 Cross tabulation of cases of systemic lupus erythematosus and controls by smoking status

Smoking status	Number of cases (%)	Number of controls (%)
Never smoked	72 (51.8)	163 (58.0)
Ex-smoker	23 (16.5)	58 (20.6)
Current smoker	44 (31.7)	60 (21.4) <sup>†</sup>
Total <sup>*</sup>	139 (100.0)	281 (100.0)

<sup>\*</sup>Missing smoking status data: 11 cases, 19 controls. <sup>†</sup>The Trent Health and Lifestyle Survey reported that the incidence of "current smoking" in the Nottingham area was 22% for the adult population, and for female adults was 21%.<sup>16</sup>

in the interviewer's approach to cases and controls. Characteristics of the cases and controls are compared in table 1. Social class was significantly higher in the control group ( $\chi^2 = 4.06$ ,  $p = 0.04$ ), and there were proportionally more non-white cases (18.7%) than controls (3.0%).

Cases and controls were classified into three smoking status groups, namely never smokers, ex-smokers, and current smokers, where the term "smoker" means a regular smoker as defined in the previous section. Subjects were regarded as ex-smokers if they had stopped smoking regularly for at least one year before either their own diagnosis (cases) or that of the cases to whom they were matched (controls). Table 2 shows the distribution of smoking status among cases and controls.

Table 2 suggests that cases are more disposed to smoking than controls. Additionally, the quantity of cigarettes smoked per day by ever smokers (averaged over their smoking histories) appeared higher for cases (median 15) than controls (median 12) although this was not significant. However, data relating to quantity of cigarettes appeared to be subject to a large degree of digit preference by rounding to the nearest multiple of 5. The median age at which smokers began to smoke was equal for cases and controls (17 years), although cases had been smoking longer than controls (medians 18 and 14 years respectively, difference not significant). The proportion of subjects who had ever smoked regularly was similar for both groups. Pack years (defined as years of smoking multiplied by average packs smoked per day,

Table 3 Cross tabulation of cases of systemic lupus erythematosus and controls by frequency of alcohol consumption

Frequency	Number of cases (%)	Number of controls (%)
At least once a week	69 (46.6)	153 (51.0)
Less than once a week	48 (32.4)	119 (39.7)
Never	31 (20.9)	28 (9.3)
Total*	148 (100)	300 (100)

\*Missing frequency of alcohol consumption data: 2 cases, 0 controls.

Table 4 Cross tabulation of cases of systemic lupus erythematosus and controls by units of alcohol consumption\*

Units consumed	Number of cases (%)	Number of controls (%)
0	63 (42.3)	75 (25.2)
1–2	28 (18.8)	50 (16.8)
3–5	19 (12.8)	57 (19.1)
6–10	25 (16.8)	60 (20.1)
more than 10	14 (9.4)	56 (18.8)
Total†	149 (100.0)	298 (100.0)

\*Based on alcohol consumption in the week before interview.

†Missing units of alcohol data: 1 case, 2 controls.

where one pack equals 20 cigarettes) were calculated to provide a combined measure of smoking duration and quantity. Cases had smoked slightly more pack years (median 10.9) than controls (median 9.5), although this difference was not significant.

The “classic” confounding variables associated with smoking are alcohol consumption and social class. Case/control status is cross tabulated by the three levelled frequency of alcohol consumption variable in table 3. As was the case with smoking status, the distribution of frequency of alcohol consumption seems to be associated with case/control status. Interestingly, it is the controls rather than the cases who seem to have the greater exposure to alcohol, which is the reverse of the association between exposure to smoking and disease status.

As a follow up to the analysis of frequency of alcohol consumption, the subjects were questioned about the quantity of alcohol they had consumed in the week before interview. This information was used in the ascertainment of any dose response effect of alcohol consumption. Subjects were asked which alcoholic drinks they had consumed, and thus the number of units of alcohol consumed could be calculated. This variable was categorised by creating a baseline group, consisting of all subjects who had consumed no alcohol in the week prior to interview, and four subsequent groups, each representing one quartile of subjects who had consumed alcohol recently, divided according to the amount consumed. The resulting distribution substantiates the earlier finding that increased exposure to alcohol is more common among the controls than among the cases (table 4).

Multivariate analysis of the data, using conditional logistic regression techniques and adjusting for social class, led to significant odds ratios for smoking status and units of alcohol consumption in the week before interview (table 5). This analysis suggests that current smokers are more likely to have SLE than their

Table 5 Odds ratios of systemic lupus erythematosus for smoking and alcohol drinking patterns

	Odds ratios	95% Confidence intervals
Smoking status		
Never smoked	1.00	
Former smoker	1.23	0.70, 2.17
Current smoker	1.95	1.14, 3.31
Units of alcohol*		
0	1.00	
1–2	0.73	0.39, 1.36
3–5	0.41	0.20, 0.85
6–10	0.47	0.24, 0.91
more than 10	0.30	0.14, 0.63

\*Based on alcohol consumption in the week before interview. Analysis of smoking habits restricted to white subjects only revealed odds ratios of 1.53 for former smokers and 2.30 for current smokers. (95% confidence intervals 0.80, 2.95, and 1.19, 4.45 respectively). Similarly, odds ratios for alcohol intake were not confounded by the different racial composition of case and control groups.

counterparts who have never smoked (OR 1.95, 95% CI 1.14, 3.31). However, ex-smokers are at no more risk of developing the disease than never smokers, according to the data (OR 1.23, 95% CI 0.70, 2.17). Nevertheless, if continuous pack years is included in the model in place of smoking status, each additional pack year carries a small but significant increase in risk (OR 1.03, 95% CI 1.00, 1.05), indicating that a combined measure of smoking history (accounting for duration and quantity, but disregarding whether the subject still smokes or not) is a risk factor for the disease. Furthermore, dichotomising the pack years variable according to whether a subject had smoked at least 20 pack years or not yields an increased risk for subjects falling into the former category (OR 2.15, 95% CI 1.05, 4.41). Increased weekly consumption of alcohol was found to be significantly negatively associated with SLE (table 5). A test for trend of alcohol consumption gave further evidence of a dose response negative association ( $p < 0.001$ ). No evidence was found of a significant interaction effect between smoking and drinking.

## Discussion

Our findings have two principal elements, namely the presentation of further evidence of a link between smoking and susceptibility to SLE, and the identification of a negative association between alcohol consumption and the disease.

The ascertainment of well characterised lupus patients from a previously identified cohort proved to be an effective means of recruiting cases for our study. The use of prevalent cases, however, meant that data collected regarding alcohol referred to dates subsequent to diagnosis—that is, the week before interview. Recruitment of controls was more problematical, with a 61% refusal rate, but this is not unusual in surveys of a non-emotive nature. In fact the comparability of smoking prevalence in our control group and the Nottingham population as a whole<sup>16</sup> suggests that this introduced no major selection bias.

Evidence for a significantly increased risk of SLE in current smokers, but not in ex-smokers, when compared with never smokers,

is presented. This confirms the results of Nagata *et al*, who reported an age adjusted odds ratio, for current compared with never smokers, of 2.31 (95% CI 1.34, 3.97).<sup>7</sup> Our finding of an increased risk among all subjects who had smoked at least 20 pack years also compares favourably with Nagata *et al*, who report an odds ratio relating only to current smokers of 4.17 (95% CI 1.09, 16.03). Benoni *et al* also found an association between smoking and SLE but this failed to reach statistical significance, probably because of their smaller sample size.<sup>17</sup> Nagata *et al* stated that although a causal relation between smoking and SLE was unclear, there was enough evidence to conclude smoking provides no protective effect.<sup>7</sup> We suggest that the concordance between our results and previous related studies advances this conclusion, and confirms the existence of a positive association between smoking and SLE.

Several recent epidemiological studies have focused on links between tobacco smoking and rheumatoid arthritis (RA), and as SLE and RA are both inflammatory joint diseases, these findings are pertinent to SLE. Silman *et al* found strong evidence of a positive association between current smoking and RA in combined monozygotic and dizygotic twin pairs (OR 3.71, 95% CI 1.57, 10.1).<sup>8</sup> Voigt *et al* detected a slight, non-significant increase in the risk of RA for both current and former female smokers, and a relative risk of RA of 1.5 (95% CI 1.0, 2.0) for women who had smoked 20 or more pack-years.<sup>9</sup> Vessey *et al* found that there was a strong association between referral to hospital with RA and cigarette smoking (female never smokers: 0.27 per 1000 woman years; women smoking 15 or more cigarettes per day: 0.64 per 1000 woman years).<sup>10</sup> All three papers support a link between cigarettes and RA and compare well with our SLE data.

We observed a significant, negative association between alcohol consumption and SLE, which becomes stronger with higher weekly intake of alcohol. Nagata *et al* also found this inverse association, but could not draw strong conclusions about drinking habits and SLE because of the low alcohol consumption among Japanese women.<sup>7</sup> In our study, 79.0% of cases and 90.7% of controls drank alcohol and the figures for regular drinkers (at least once a week) were 46.6% and 51.0% respectively. It is possible that the observed negative association may result from post-diagnosis changes in alcohol consumption, perhaps as a result of the clinical course of SLE, or by patients acting on medical advice. The possibility that certain medical advisers seeing the patients included in this study may have given advice relating to alcohol cannot be excluded, but their consultants do not regularly give such advice. The prospect of alcohol protecting against SLE should not be dismissed as recent studies have highlighted the cardioprotective effects of moderate alcohol intake,<sup>18 19</sup> and mechanisms leading to these effects may well be acting in the vasculature of patients with SLE. Kannel and Ellison emphasise the well documented increased risk of car-

diovascular mortality presented by excess drinking, citing a U shaped mortality curve cast by the combined protective and harmful influences of alcohol.<sup>18</sup> Our data hint at a deceleration of the negative association between alcohol and SLE in subjects drinking over 30 units of alcohol per week, although subjects falling into this category are too few to analyse statistically.

Standard statistical analysis mitigates against the danger of our findings being due to chance, although we acknowledge the argument that our reliance on self reported data of a potentially sensitive nature (such as alcohol consumption) could introduce a bias. However, we do not consider the subjective collection of the participants' smoking data to have biased our results, as there exists strong evidence that such measures of both past and present smoking habits can provide valid information.<sup>20 23</sup> The recruitment rate of 39% in the control population is probably a reflection of society's lack of awareness of SLE as a public health issue, as control uptake is usually higher in other, more common disease settings such as cancer. We suggest that our findings are unlikely to be biased by the difference between case and control recruitment rates, as such bias usually takes the form of higher overall social class in the control group, which was adjusted for in our analyses. Similarly, the higher social class among controls most probably accounts for the relative lack of ethnic diversity in this group.

We have not attempted to tackle the difficult issue of genetic susceptibility to the disease, or individual exposure thresholds. Moreover, as mentioned earlier, the question of whether or not our findings constitute a genuine, causal relation has not been resolved. Wallace supports the opinion that tobacco smoke should be avoided by SLE patients, although he does not consider alcohol consumption.<sup>24</sup> We report an observed association between SLE and both alcohol consumption and smoking, but prospective studies would be required to determine whether these relations are causal in nature, and hence we have not attempted to speculate on the biological mechanisms underlying the findings presented.

In conclusion, this study provides further evidence of a significant positive association between smoking and SLE, and establishes a significant negative association between alcohol consumption and the disease.

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