Published in final edited form as:
Ann Rheum Dis. 2009 March ; 68(3): 345–348. doi:10.1136/ard.2007.084582.

Alcohol consumption is not protective for systemic lupus erythematosus

J Wang, **AB Kay**, **J Fletcher**, **MK Formica**, and **TE McAlindon**
Division of Rheumatology, Tufts Medical Center, Boston, Massachusetts, USA

Abstract

Objective—Several studies have suggested that alcohol drinking is protective for the development and progression of systemic lupus erythematosus (SLE). However, a protopathic bias might also explain this apparent association. Our objective was to investigate the association between alcohol consumption and incidence of SLE in a data set that has information on both current and pre-diagnostic alcohol consumption.

Methods—We performed an Internet-based case–control study of SLE. Cases were diagnosed within 5 years of the study and met ≥4 American College of Rheumatology criteria for SLE. The control participants were tightly matched to cases on demographic and socio-economic characteristics using a propensity score. Participants completed an online exposure assessment. We used conditional logistic regression analyses to test the association of current and pre-diagnostic alcohol consumption with SLE.

Results—The sample comprised 114 cases with SLE and 228 matched controls. Current drinking (>2 days per week) was inversely associated with SLE (OR 0.35, 95% CI 0.13 to 0.98). Having more than two drinks per day was also inversely associated with SLE (OR 0.41, 95% CI 0.18 to 0.93). However, alcohol consumption before SLE diagnosis was not associated with the risk of SLE (p≥0.4). Analysis of the change in drinking habits showed that people with lupus were more likely to quit drinking before (OR 2.25, 95% CI 0.96 to 5.28) or after (OR 2.38, 95% CI 0.88 to 6.49) being given the SLE diagnosis.

Conclusions—Our results show that alcohol consumption before SLE diagnosis is not associated with the risk for SLE, and that individuals who develop SLE are more likely to quit.

The aetiology of systemic lupus erythematosus (SLE) involves both genetic predisposition and environmental risk factors yet to be identified.[1] Several epidemiological studies have reported an inverse association between alcohol consumption and SLE, suggesting that alcohol may be protective against the development of SLE.[2–4] However, these findings were constrained by the use of cross-sectional data,[2] prevalent cases[3] and/or the scarcity of exposure.[4] Because there is little biological rationale to support a protective effect of alcohol in the development of SLE, we hypothesised that the associations seen in previous studies may have resulted from some form of protopathic bias, which is an effect of disease on the exposure leading to a false perception of association. The development of intolerance for alcohol in individuals with early SLE is an example of how this might occur. The fact that there are other studies that did not find any significant associations between alcohol consumption and SLE[56] supports this hypothesis.

Correspondence to: Dr J Wang, Division of Rheumatology, Tufts Medical Center, Boston, MA 02111, USA; jwang1@tuftsmedicalcenter.org.

Competing interests: None.

In order to further explore our hypothesis, we analysed the relationship between SLE and alcohol exposure using detailed alcohol exposure data from an Internet-based case–control study of recent-onset SLE. To explore whether the post-diagnosis behaviour change may influence the association between alcohol consumption and SLE, we analysed the association using both current alcohol consumption data and alcohol consumption before lupus diagnosis.

METHODS

Study design

We performed an Internet-based case–control study of SLE. The details of design and validation of this approach has been previously described.[7] Briefly, we constructed a study website to solicit participants and conduct the study. We placed sponsored links on the Google search engine web page, which appeared when a user entered one of a set of pre-specified key-terms in the search field. The sponsored link pointed towards our study website. The homepage of the study website provided information about the study and links to the consent form, eligibility screening and questionnaires. We authenticated the identity and diagnosis for participants with SLE through contact with their physicians and by medical record review. The study received approval from the Institutional Review Board at Tufts Medical Center.

Study population

The source population of the study comprised individuals living within the USA, aged over 18 years, searching on Google using medical key terms.

Cases—We advertised for individuals with SLE using sponsored links on Google triggered by lupus-related terms (eg, lupus, SLE and systemic lupus erythematosus). We asked individuals who came to the study website via these links to answer a set of SLE screening questions, used to identify people likely to meet criteria for SLE. The questions solicited a recent physician diagnosis of SLE (defined as a clinical diagnosis of SLE made less than 5 years previously), use of appropriate SLE medications (corticosteroids, antimalarials, azathioprine, cyclophosphamide and methotrexate), and non-use of other rheumatic disease medications (gold, sulphasalazine and penicillamine). In previous research we found this algorithm to have a positive predictive value for SLE of 0.84.[8] We asked case candidates that passed the screen to sign a release form to obtain medical records from their physicians/rheumatologists. An individual whose combined chart review and physician's checklist documented the presence of ≥4 criteria for American College of Rheumatology criterion classification of SLE[9,10] was classified as a SLE case.

Controls—We recruited control participants through the study website over the same period as the case recruitment, using terms derived from a list of medical disorders most frequently searched through Google. Initially, we selected the nine most commonly entered terms for diseases not known to share risk factors with SLE and not exclusive to men (eg, migraine, hypertension, sinusitis and fibroids). Later we changed the approach to one in which we randomly selected 10 key terms every 4 weeks from a list of 80 common medical key terms. Using the reservoir of eligible controls, we performed a 1 to 2 case–control match on gender, age, race, ethnicity, region of residence, reference year, education and household income to create a matched case–control data set.

Data collection

Participants completed an online questionnaire that included standardised questions derived from previous studies[8,11] and covered detailed information on demographics, socio-

economic status, medications, comorbidities, disease epiphenomena and common environmental exposures, such as smoking and alcohol consumption. Questions were constructed to ascertain lifetime exposure, current exposure and exposure before diagnosis (cases) or before the reference year (controls). Ever drinking was defined as having more than 20 drinks in their lifetime. We standardised the definition of a drink, where one drink is equal to one can or bottle of beer, a glass of wine, or a shot of liquor straight or in a mixed drink. For each new control participant, a computational subroutine was applied to assign a reference year in lieu of date of diagnosis from the real-time frequency distribution of diagnosis year among currently enrolled cases.

Data analysis

We used the propensity score matching method[12] to generate a matched case–control data set. We first used the multivariate logistic regression model, including gender, age, race, ethnicity, region of residence, reference year, education and household income as independent variables to compute each applicant's propensity score. We then performed a 1 to 2 case–control match on propensity score using five-digit greedy match algorithm. This matching procedure was performed using a modified user-written SAS Macro.[13] The associations between alcohol consumption and prevalent SLE were examined using conditional logistic regression models. We defined four categories for days of drinking per week (0, less than 1 day, 1–2 days and >2 days), number of drinks per day (0, 1, 2–3, >3 drinks), with the cut-points chosen to result in similar number of controls in each category. Smoking was adjusted as a potential confounder. All analyses were performed using SAS (v9.1, SAS Institute Inc., Cary, North Carolina, USA). A two-sided test with $p<0.05$ was considered statistically significant.

RESULTS

During the 25-month recruitment phase, 1727 people applied to join as cases and 1379 as controls, from whom 402 cases and 693 controls were screened eligible and finished the online questionnaires. One-hundred twenty-four cases had documentation of ≥4 American College of Rheumatology criteria for definite SLE, among whom 114 provided information on alcohol consumption and were included in further analyses. Thirty per cent of the cases had been diagnosed within 1 year, and 66% within 3 years. The median of disease duration was 2 years. Two hundred and twenty-eight controls were matched to the cases. The majority of the study subjects were female (95%), white (82%) and non-Hispanic (92%). The mean age was 41 years. Subjects with SLE and their matched controls exhibited highly concordant distributions for demographic and socio-economic characteristics (table 1). Chart review showed a broad representation of SLE clinical manifestations among cases, including severe disease (table 2).

Forty-five per cent of the cases and 50% of the controls reported drinking alcohol in the past month (current drinkers). There was a non-significant negative association between current drinking and SLE (OR 0.81, 95% CI 0.52 to 1.27) (table 3). This association appeared to be dose-dependent—compared with no drinking, drinking for more than 2 days per week was inversely associated with SLE (OR 0.35, 95% CI 0.13 to 0.98). Consumption of more than 2 drinks per day was also inversely associated with SLE (OR 0.41, 95% CI 0.18 to 0.93).

We further evaluated the association between drinking habits prior to SLE diagnosis and the risk of SLE. Ever drinking alcohol before SLE diagnosis was not associated with the risk of SLE (OR 1.12, 95% CI 0.63 to 2.00), neither was there an association for days of drinking per week (p trend = 0.9) or number of drinks per day before SLE diagnosis (p trend = 1.0). Further analysis of change of drinking behaviour showed that people with SLE appeared more likely to quit drinking before (OR 2.25, 95% CI 0.96 to 5.28) or after (OR 2.38, 95%

CI 0.88 to 6.49) being given SLE diagnosis. Further adjustment for smoking did not change the results (data not shown).

DISCUSSION

In this Internet-based case–control study using recently diagnosed SLE cases, we found that alcohol consumption before SLE diagnosis was not associated with reduced risk of SLE. However, individuals who developed SLE were more likely to quit drinking before and after diagnosis, which resulted in an apparent negative association between alcohol consumption and SLE. This result suggests that the inverse associations reported in previous studies were due to bias of the disease on the exposure.

Whether alcohol may have any beneficial effects against SLE has drawn researchers' attention,[14,15] as several previous studies have reported an inverse association between alcohol consumption and SLE.[2–5] In a study of 150 prevalent SLE cases and 300 matched controls (Nottingham, UK), Hardy *et al*,[2] reported that current alcohol consumption (measured as intake in the week preceding interview) had a dose–response negative association with SLE (p trend <0.001). While the authors did not dismiss the possible beneficial effects of alcohol through its cardioprotective mechanism, they were more inclined to conclude that the observed negative association resulted from post-diagnosis changes in alcohol consumption, perhaps as a result of the clinical course of SLE, or by patients acting on medical advice. However, the authors did not have appropriate data to examine their conjecture. Results from our study clearly confirmed Hardy *et al*'s observation and supported their speculation of the post-diagnosis change of drinking behaviour causing the negative association between alcohol consumption and SLE.

Two case–control studies of SLE analysed the alcohol consumption before lupus diagnosis. In a study of 282 female patients with incident SLE and 292 age-matched controls (Japan), Nagata *et al*[4] found that alcohol consumption was associated with a non-significant decreased risk of SLE. (Compared with never drinking, weekly drinking, OR = 0.52, 95% CI 0.25 to 1.06; daily drinking, OR = 0.57, 95% CI 0.19 to 1.71; p trend, 0.07.[4]) However, the alcohol intake was very infrequent among this study sample, 92% cases and 87% controls reported never drinking alcohol, making the analysis based on very few drinkers. In another study of 91 female patients with incident SLE retrieved for the period 1981–99 and 205 age-matched controls within a defined area (southern Sweden), Bengtsson *et al*[3] found a dose-dependent inverse association between moderate alcohol use and SLE (compared with use of alcohol, very seldom, 1–150 g/month, OR = 0.4, 95% CI 0.2 to 1.0; >150 g/month, OR = 0.2, 95% CI 0.1 to 0.5). The authors concluded that the concordance of their results with Hardy *et al* and Nagata *et al* studies strongly indicated that the protective effect of alcohol is real. In Bengtsson *et al*'s study, however, the gap between diagnosis and participation in the study could be up to 18 years, with a median time of 9 years, which might have injured the accuracy of recall. It is possible that the participants likely mistook more recent behaviour (after diagnosis among cases) for past behaviour (before diagnosis). If cases were also likely to reduce or quit drinking after diagnosis, then this recall bias would have led to a negative association between alcohol consumption and SLE risk.

A major advantage we had in the study of the association between alcohol and SLE was that our study participants were required to have been recently diagnosed with SLE within the previous 5 years. This would have presumably greatly reduced the misclassification of the behaviours before and after a diagnosis of SLE. In addition, we had sufficient numbers to achieve a close case–control match on demographic and socioeconomic characteristics, minimising the potential for confounding due to these characteristics. Our results are also consistent with two other reports, a prospective analysis of incident SLE in the Black

Women's Health Study[6] and a case–control study in a predominantly Hispanic population,[5] which did not find significant associations between alcohol consumption and SLE. In fact, in a recent report from Japan, alcohol consumption was reported to be associated with increased risk of SLE at one study site, but not another.[16]

While our study shows no overall protective effect of alcohol for the development of SLE, we did not collect information to distinguish the type of alcohol consumed. This could be important in the unlikely circumstances that different types of alcoholic beverages vary in their relationship with SLE and the beverage preferences of Internet-users differ from the general population.

In summary, alcohol consumption prior to SLE diagnosis is not associated with the risk for SLE. However, individuals diagnosed with SLE are more likely to quit drinking, which likely explains the inverse association apparent in previous studies.[2–5] Information among patients with SLE, including changes in behaviour before and after diagnosis, should be carefully collected in future studies to reduce recall bias.

Acknowledgments

This work was supported by grant P60 AR47785 from the National Institutes of Health (NIH) and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

REFERENCES

1. Deapen D, Escalante A, Weinrib L, Horwitz D, Bachman B, Roy-Burman P, et al. A revised estimate of twin concordance in systemic lupus erythematosus. Arthritis Rheum. 1992; 35:311–318. [PubMed: 1536669]
2. Hardy CJ, Palmer BP, Muir KR, Sutton AJ, Powell RJ. Smoking history, alcohol consumption, and systemic lupus erythematosus: a case—control study. Ann Rheum Dis. 1998; 57:451–455. [PubMed: 9797548]
3. Bengtsson AA, Rylander L, Hagmar L, Nived O, Sturfelt G. Risk factors for developing systemic lupus erythematosus: a case—control study in southern Sweden. Rheumatology (Oxford). 2002; 41:563–571. [PubMed: 12011382]
4. Nagata C, Fujita S, Iwata H, Kurosawa Y, Kobayashi K, Kobayashi M, et al. Systemic lupus erythematosus: a case—control epidemiologic study in Japan. Int J Dermatol. 1995; 34:333–337. [PubMed: 7607794]
5. Ghaussy NO, Sibbitt WL Jr, Qualls CR. Cigarette smoking, alcohol consumption, and the risk of systemic lupus erythematosus: a case—control study. J Rheumatol. 2001; 28:2449–2453. [PubMed: 11708417]
6. Formica MK, Palmer JR, Rosenberg L, McAlindon TE. Smoking, alcohol consumption, and risk of systemic lupus erythematosus in the Black Women's Health Study. J Rheumatol. 2003; 30:1222–1226. [PubMed: 12784393]
7. McAlindon T, Wang J, Formica M, Kay A, Tighiouart H, Chaisson C, et al. Feasibility and validity were demonstrated of an online case—control study using the prototype of recent-onset systemic lupus erythematosus (SLE). J Clin Epidemiol. 2008; 617:671–678. [PubMed: 18342488]
8. McAlindon TE, Formica M, Palmer JR, Lafyatis R, Rosenberg L. Assessment of strategies for identifying diagnosed cases of systemic lupus erythematosus through self-report. Lupus. 2003; 12:754–759. [PubMed: 14596424]
9. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum. 1997; 40:1725. [PubMed: 9324032]
10. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982; 25:1271–1277. [PubMed: 7138600]

11. Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS. Risk factors for development of systemic lupus erythematosus: allergies, infections, and family history. J Clin Epidemiol. 2002; 55:982–989. [PubMed: 12464374]
12. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998; 17:2265–2281. [PubMed: 9802183]
13. Parsons, LS. Performing a 1:N case—control match on propensity score. Proceedings of the Twenty-ninth Annual SAS Users Group International (SUGI) Conference; 2004; SAS Institute Inc.; Cary, North Carolina. 2004.
14. Sofat N, Keat A. Alcohol intake in rheumatic disease: good or bad? Rheumatology (Oxford). 2002; 41:125–128. [PubMed: 11886958]
15. Simard JF, Costenbader KH. What can epidemiology tell us about systemic lupus erythematosus? Int J Clin Pract. 2007; 61:1170–1180. [PubMed: 17577298]
16. Washio M, Horiuchi T, Kiyohara C, Kodama H, Tada Y, Asami T, et al. Smoking, drinking, sleeping habits, and other lifestyle factors and the risk of systemic lupus erythematosus in Japanese females: findings from the KYSS study. Mod Rheumatol. 2006; 16:143–150. [PubMed: 16767552]

Table 1

Basic characteristics of study participants

	Cases n = 114	Controls n = 228	p Value
Gender			
Female	109 (96%)	217 (95%)	0.7
Male	5 (4%)	11 (5%)	
Race			
White	93 (82%)	186 (82%)	0.8
African American	10 (9%)	24 (11%)	
More than one race	7 (6%)	11 (5%)	
Others*	4 (4%)	1 (0.4%)	
Did not say	0	6 (3%)	
Ethnicity			
Non-Hispanic	105 (92%)	210 (92%)	0.9
Hispanic	5 (4%)	8 (4%)	
Did not say	4 (4%)	10 (4%)	
Age			
Mean (SD)	40.6 (11.5)	40.5 (11.6)	0.9
Region of residence			
Northeast	19 (17%)	41 (18%)	0.9
Midwest	21 (18%)	44 (19%)	
South	46 (40%)	90 (40%)	
West	28 (25%)	53 (23%)	
Education level			
High school graduate or less	14 (12%)	30 (13%)	0.8
Some college	47 (41%)	98 (43%)	
College graduate	30 (26%)	57 (25%)	
Professional or graduate school	21 (18%)	40 (18%)	
Did not say	2 (2%)	3 (1%)	
Household income			
Less than $25K	25 (22%)	52 (23%)	0.9
$25–50K	29 (25%)	61 (27%)	
$50–100K	32 (28%)	62 (27%)	
$100K+	16 (14%)	32 (14%)	
Did not say	12 (11%)	21 (9%)	

*Others included Asians and American Indians.

Table 2

Prevalence of SLE clinical manifestations among cases (n = 114)

Malar rash	64%
Discoid rash	15%
Photosensitivity	63%
Oral ulcers	43%
Arthritis	93%
Serositis	36%
Renal disease	12%
Neurological disorder	6%
Psychosis	4%
Haematological disorder	44%
Immunological disorder	71%
Antinuclear antibodies	96%

Table 3

Association between alcohol consumption and risk of SLE

Alcohol consumption	Cases (%)	Controls (%)	OR (95% CI)
Current drinking (drinking in past month)			
No	63 (55)	114 (50)	1.0 (ref.)
Yes	51 (45)	114 (50)	0.81 (0.52–1.27)
Days of drinking/week			
0	63 (55)	114 (50)	1.0 (ref.)
<1 day	25 (22)	48 (21)	0.94 (0.54–1.63)
1–2 days	21 (18)	41 (18)	0.90 (0.49–1.65)
>2 days	5 (4)	25 (11)	0.35 (0.13–0.98)
			p trend = 0.11
Drinks/day			
0	63 (55)	114 (50)	1.0 (ref.)
1	29 (25)	50 (22)	1.08 (0.6–1.92)
2	14 (12)	28 (12)	0.94 (0.47–1.88)
>2	8 (7)	36 (16)	0.41 (0.18–0.93)
			p trend = 0.07
Drinking before lupus diagnosis			
No	21 (18)	46 (20)	1.0 (ref.)
Yes	93 (82)	182 (80)	1.12 (0.63–2.00)
Days of drinking/week			
0	21 (18)	46 (20)	1.0 (ref.)
<1 day	53 (46)	94 (41)	1.24 (0.67–2.28)
1–2 days	29 (25)	49 (21)	1.35 (0.66–2.76)
>2 days	11 (10)	39 (17)	0.61 (0.26–1.42)
			p trend = 0.4
Drinks/day			
0	21 (18)	46 (20)	1.0 (ref.)
1	37 (32)	74 (32)	1.11 (0.58–2.11)
2	27 (24)	42 (18)	1.44 (0.70–2.96)
>2	29 (25)	66 (29)	0.97 (0.49–1.90)
			p trend = 1.0
Change of drinking behaviour			
Never drank	10 (9)	30 (13)	1.0 (ref.)
Quit before lupus diagnosis	28 (25)	35 (15)	2.25 (0.96–5.28)
Quit after lupus diagnosis	17 (15)	22 (10)	2.38 (0.88–6.49)
Still drinking	59 (52)	141 (62)	1.24 (0.56–2.77)