Associations of Smoking and Alcohol Consumption with Disease Activity and Functional Status in Rheumatoid Arthritis

Bing Lu, Young Hee Rho, Jing Cui, Christine K. Iannaccone, Michelle L. Frits, Elizabeth W. Karlson, and Nancy A. Shadick

ABSTRACT. ***Objective.*** To investigate the associations of smoking and alcohol consumption with disease activity and functional status in rheumatoid arthritis (RA).

Methods. We conducted a prospective study consisting of 662 patients with RA who were followed up to 7 years from the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study. Smoking and alcohol consumption were assessed through yearly questionnaires. The disease activity and functional status were measured annually by the Disease Activity Score examined in 28 commonly affected joints using C-reactive protein (DAS28-CRP3) and the Modified Health Assessment Questionnaire (MHAQ). Linear mixed models were developed to assess the longitudinal effects of smoking and alcohol consumption on DAS28-CRP3 and MHAQ after adjustment for potential confounders. The HLA-DRB1 shared epitope (HLA-SE) by smoking and alcohol interactions were also evaluated in the analysis.

Results. The median followup time of the cohort was 4 years. Current smoking was not associated with DAS28-CRP3 in our study, but was associated with a higher MHAQ than nonsmokers with seropositive RA ($p = 0.05$). Alcohol consumption showed an approximate J-shaped relationship with MHAQ, with the minima occurring at 5.1-10.0 g/day. Compared to no alcohol use, alcohol consumption of 5.1–10.0 g/day was associated with a significant decrease of MHAQ ($p = 0.02$). When stratified by HLA-SE, the effect of alcohol consumption appeared to be stronger in HLA-SE–positive RA than HLA-SE–negative RA.

Conclusion. We found that current smoking was associated with a worse functional status, while moderate alcohol consumption was associated with a better functional status in RA. Replications of these findings in other prospective studies are needed. (J Rheumatol First Release Dec 1 2013; doi:10.3899/jrheum.130074)

Key Indexing Terms:
SMOKING ALCOHOL CONSUMPTION RHEUMATOID ARTHRITIS
HLA SHARED EPITOPE MODIFIED HEALTH ASSESSMENT QUESTIONNAIRE
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Rheumatoid arthritis (RA) is a chronic, inflammatory arthritis leading to progressive joint and organ system damage and increasing disability[1]. Both genetic and environmental factors have been shown to play a role in the risk of developing RA. It has been reported that smoking is the strongest environmental risk factor for RA[2]. Smoking is also associated with increased disease activity in several cohort studies[3,4,5], which mainly describe it as a predictor for poor tumor necrosis factor-α (TNF-α)-inhibitor response.

The association between alcohol consumption and RA has recently gained interest. Alcohol consumption has a known U-shaped relationship with cardiovascular mortality[6]. Also, such a relationship exists with inflammatory markers such as C-reactive protein (CRP) in the general population[7]. There could be a relationship between alcohol consumption and risk of RA because RA is a chronic, inflammatory disease. It was reported that in women with preclinical RA, alcohol consumption was

associated with inflammatory biomarkers in either a U-shaped pattern or a negative linear pattern[8]. In addition, there are several studies showing that alcohol consumption attenuated the risk of RA[9,10,11,12,13,14,15].

The strongest confirmed genetic risk factor for RA is HLA-DRB1, or the "shared epitope" (HLA-SE)[16,17]. People who have HLA-SE alleles have greatly increased risk for incident RA. Interestingly, it has also been found that such risk increases synergistically when HLA-SE–positive subjects smoke[18,19,20]. Thus, a gene-environment interaction may exist between smoking and HLA-SE on the risk of incident RA. A dual case-control study has also shown that alcohol consumption modifies the effects of HLA-SE to lower the risk of anticyclic citrullinated peptide antibodies (anti-CCP)–positive RA[10]. To our knowledge, it was the first study to show a gene-environment interaction between alcohol consumption and HLA-SE.

The relationships between smoking, alcohol consumption, and the disease course of RA assessed by disease activity and functional status in patients with RA are not well understood, especially with consideration of genetic factors and gene-environment interactions. Thus, we sought to evaluate whether there is an association between smoking or alcohol consumption and subsequent RA disease activity and functional status in RA, and whether such association differs by seropositivity and genetic factors such as HLA-SE.

MATERIALS AND METHODS

The Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) is a large, single-center, prospective, and observational cohort of 1100 patients with RA. Enrollment for the registry began in March of 2003 in the Brigham and Women's Arthritis Center, which averages over 3700 RA visits per year and has minimal turnover in the patient population. The Arthritis Center provides an ideal setting for a registry because of its access to patient electronic medical records for followup interviews and medical record review. Data were collected annually on medications, smoking, alcohol use, disease activity, and functional status[21]. We included 662 patients who had the HLA-SE genotype and have been followed annually, up to 7 years. Our study was approved by the Brigham and Women's Hospital and Boston University Institutional Review Board, and all subjects gave written informed consent.

The disease activity was measured using DAS28-CRP3 (Disease Activity Score examined in 28 commonly affected joints as a function of swollen joints, tender joints, and serum CRP levels)[22]. The functional health status was evaluated by a Modified Health Assessment Questionnaire (MHAQ)[23]. In BRASS, the baseline mean MHAQ score may seem low for a population with established disease, but it is comparable to the Consortium of Rheumatology Researchers of North America (CORRONA), another RA patient registry cohort based in the United States. One report indicated that about 80% of CORRONA patients had a disease duration > 24 months and almost 90% had an MHAQ score < 1[24,25]. The relatively low MHAQ scores indicate that this is a high-functioning group of patients with RA, a situation that may be the result of healthier patients enrolling compared to nonparticipants[21]. The exposures were smoking status (current, past, or never smokers; or more or less than 10 pack-yrs; cutoffs based on previous literature[18,26]) and alcohol consumption (none, 0.1–5.0, 5.1–10.0, and > 10 g/day). Alcohol consumption was initially measured as drinks per day and then translated into grams per day. Because there was about 7% less data on smoking status than alcohol consumption owing to missingness, we imputed the time-varying smoking status as last observation carried forward and/or backward, limited to 1 year. The HLA-SE was determined based on 2 steps: first, the 2-digit level, then sequencing to determine SE motif status (present or absent)[27].

To assess the prospective effects of smoking and alcohol consumption, general linear mixed models were used to analyze the repeated measurements ranging from 1 to 7 years of followup. We used DAS28-CRP3 or MHAQ outcomes lagged by 1 year after the time-varying exposures to reduce the possibility of reverse-causality bias. In other words, smoking or alcohol consumption were modeled to predict the future DAS28-CRP3 or MHAQ measured 1 year later. We adjusted for baseline DAS28-CRP3 or MHAQ, sex, age, race, education, seropositivity (anti-CCP antibody and/or rheumatoid factor–positive), disease duration, and body mass index (BMI). Current drug treatments were also adjusted as time-varying covariates, including corticosteroids, nonsteroidal antiinflammatory drugs (NSAID), nonbiologic disease-modifying antirheumatic drugs (DMARD) such as antimalarials and methotrexate (MTX), and biologic DMARD such as anti-TNF blockers, anti-interleukin 1, or anti-B cell agents. The different covariance models were evaluated using Akaike's information criterion and Bayesian information criterion. Separate models were developed for seropositive and seronegative patients with RA. Multivariable adjusted means of DAS28-CRP3 and MHAQ were compared across smoking or alcohol consumption categories. To assess gene-environment interaction, we stratified by HLA-SE status, and tested interaction terms of HLA-SE by smoking and HLA-SE by alcohol consumption in the multivariable models. In addition, interactions of sex by smoking and alcohol consumption were also evaluated as secondary analyses. SAS 9.2 for Windows was used for statistical analysis. A p value of < 0.05 was used to determine statistical significance.

RESULTS

In our study, 662 RA patients with HLA-SE data from BRASS were followed for up to 7 years. The median followup time was 4 years [interquartile range (IQR) 2–4 yrs] for DAS28-CRP3 and 4 years (IQR 2–5) for MHAQ. The baseline characteristics of study participants by smoking and alcohol consumption are shown in Table 1 and Table 2. The cohort was a mainly middle-aged female white population with mean disease duration of 15 years. Compared to nonsmokers, past or current smokers tended to have lower education, higher alcohol consumption, higher BMI, and higher levels of DAS28-CRP3 and MHAQ. In contrast, compared to no alcohol use, patients with higher alcohol consumption were more likely to be women, white, ever smokers, more educated, lower BMI, seronegative RA, and to use prednisone and MTX. Alcohol consumption showed approximate J or U-shaped relationships with age, disease duration, DAS28-CRP3, and MHAQ, with the minima occurring at 5.1–10.0 g/day.

The multivariable adjusted associations of smoking and alcohol consumption with DAS28-CRP3 and MHAQ stratified by serologic status are shown in Table 3. No significant associations were found between current smoking and DAS28-CRP3 1 year later in RA. However, current smoking was found to increase MHAQ 1 year later compared to never smoking (0.46 ± 0.04 vs 0.37 ± 0.02, p = 0.05) in seropositive RA. Consistent results were observed using

Table 1. Baseline characteristics of the study sample from the BRASS cohort by smoking status. Total sample size was 659 after 3 patients were excluded for lack of smoking status.

Characteristics	Smoking Status Never, n = 353	Past, n = 250	Current, n = 56	p
Age, yrs, mean ± SD	54.6 ± 14.3	61.2 ± 11.0	54.5 ± 11.4	< 0.001
Sex (female), %	83.0	82.4	78.6	0.72
Race (white), %	93.1	97.2	89.1	0.02
Education (high school graduate or higher), %	67.3	57.3	55.4	0.02
Smoking pack-yrs	0	19.2 ± 21.4	29.6 ± 22.1	< 0.001
Alcohol consumption, g/day	4.8 ± 10.1	7.7 ± 14.9	6.2 ± 11.1	0.02
DAS28-CRP3	3.97 ± 1.56	4.07 ± 1.50	4.45 ± 1.48	0.06
MHAQ	0.41 ± 0.45	0.40 ± 0.46	0.56 ± 0.53	0.13
Disease duration, yrs	14.8 ± 12.2	15.7 ± 12.2	14.9 ± 12.3	0.63
HLA-SE carrier, %	61.5	66.0	67.9	0.42
BMI, kg/m^2, mean ± SD	26.2 ± 5.6	27.3 ± 5.2	26.9 ± 6.1	0.004
Anti-CCP–positive, %	64.4	71.8	71.7	0.13
Prednisone, %	29.7	30.0	30.4	0.99
Methotrexate, %	47.0	52.0	42.9	0.33
Antimalarial, %	17.6	14.0	16.1	0.50
Other DMARD, %	17.6	19.2	19.6	0.85
Biologic DMARD, %	37.7	40.8	35.7	0.66
NSAID, %	63.5	63.2	66.1	0.92

Some measurements were missing at baseline (race, n = 653; education, n = 656; and anti-CCP, n = 649). P values were based on Kruskal-Wallis test for continuous variables or chi-squared test for categorical variables. DAS28-CRP3: Disease Activity Score using 28 joints with high-sensitivity C-reactive protein; MHAQ: Modified Health Assessment Questionnaire; BMI: body mass index; DMARD: disease-modifying antirheumatic drug (biologic DMARD refers to all kinds of anti-tumor necrosis factor, anti-interleukin 1, or anti-B cell agents); NSAID: nonsteroidal antiinflammatory drug; anti-CCP: anticyclic citrullinated peptide.

Table 2. Baseline characteristics of the study sample from the BRASS Cohort by alcohol consumption. Total sample size was 615 after 47 patients without alcohol intake data were excluded.

Characteristics	Alcohol Intake, g/day None, n = 205	0.1–5.0 g/day, n = 239	5.1–10.0 g/day, n = 63	> 10 g/day, n = 108	p
Age, yrs, mean ± SD	60.2 ± 13.1	55.0 ± 12.7	52.0 ± 14.1	60.0 ± 13.0	< 0.001
Sex (female), %	87.3	85.4	81.0	70.4	< 0.001
Race (white), %	88.1	97.0	98.4	98.2	< 0.001
Education (high school graduate or higher), %	48.3	64.4	76.2	73.8	< 0.001
Smoking status, %					
Never smokers	55.1	53.6	50.8	38.0	0.02
Past smokers	36.6	39.3	36.5	52.8	
Current smokers	8.3	7.1	12.7	9.3	
Smoking pack-yrs, mean ± SD	9.9 ± 16.7	10.5 ± 21.4	6.4 ± 12.5	12.5 ± 17.7	0.04
DAS28-CRP3, mean ± SD	4.33 ± 1.61	3.93 ± 1.44	3.84 ± 1.70	3.97 ± 1.50	0.02
MHAQ, mean ± SD	0.56 ± 0.54	0.36 ± 0.40	0.31 ± 0.44	0.36 ± 0.38	< 0.001
Disease duration, yrs, mean ± SD	17.6 ± 12.5	14.7 ± 12.4	11.1 ± 11.0	14.2 ± 12.0	< 0.001
HLA-SE carrier, %	61.0	69.0	63.5	57.4	0.52
BMI, kg/m^2, mean ± SD	28.1 ± 6.3	26.5 ± 5.3	25.8 ± 5.3	25.1 ± 3.9	< 0.001
Seropositive, %	80.1	72.8	66.7	65.7	0.003
Prednisone, %	36.1	31.0	23.8	23.2	0.01
Methotrexate, %	52.7	53.1	38.1	34.3	< 0.001
Antimalarial, %	16.6	14.6	19.0	15.7	0.98
Other DMARD, %	20.5	14.2	23.8	20.4	0.74
Biologic DMARD, %	36.1	41.8	44.4	36.1	0.82
NSAID, %	62.0	61.1	81.0	63.0	0.03

Some measurements were missing at baseline (race, n = 609; education, n = 612; and anti-CCP, n = 605). DAS28-CRP3: Disease Activity Score using 28 joints with high-sensitivity C-reactive protein; MHAQ: Modified Health Assessment Questionnaire; BMI: body mass index; DMARD: disease-modifying antirheumatic drug (biologic DMARD refers to all kinds of anti-tumor necrosis factor, anti-interleukin 1, or anti-B cell agents); NSAID: nonsteroidal anti-inflammatory drug; anti-CCP: anticyclic citrullinated peptide.

Table 3. Adjusted estimated means (SE) of DAS28-CRP3 and MHAQ by smoking and alcohol consumption. Data were adjusted for age, sex, race, education, disease duration, baseline DAS28-CRP3 or MHAQ, body mass index, and use of prednisolone, DMARD (biologic and nonbiologic), and NSAID. The estimates of smoking and alcohol use were adjusted for each other.

		DAS28-CRP3	p	MHAQ	p
	Smoking Status				
All RA, n = 662	Never	3.23 ± 0.06	Referent	0.35 ± 0.02	Referent
	Past	3.36 ± 0.07	0.11	0.37 ± 0.02	0.31
	Current	3.18 ± 0.13	0.70	0.40 ± 0.03	0.13
Seropositive RA, n = 485	Never	3.43 ± 0.07	Referent	0.37 ± 0.02	Referent
	Past	3.55 ± 0.07	0.22	0.40 ± 0.02	0.33
	Current	3.33 ± 0.15	0.54	0.46 ± 0.04	0.05
Seronegative RA, n = 173	Never	2.78 ± 0.09	Referent	0.28 ± 0.03	Referent
	Past	2.95 ± 0.12	0.28	0.29 ± 0.03	0.85
	Current	3.16 ± 0.24	0.14	0.23 ± 0.06	0.40
	Alcohol Intake (g/day)				
All RA, n = 615	None	3.32 ± 0.07	Referent	0.40 ± 0.02	Referent
	0.1–5.0	3.28 ± 0.07	0.55	0.38 ± 0.02	0.16
	5.1–10.0	3.21 ± 0.09	0.24	0.34 ± 0.02	0.02
	> 10.0	3.22 ± 0.09	0.30	0.37 ± 0.02	0.17
	P trend		0.22		0.03
Seropositive RA, n = 448	None	3.53 ± 0.08	Referent	0.44 ± 0.02	Referent
	0.1–5.0	3.43 ± 0.08	0.21	0.40 ± 0.02	0.07
	5.1–10.0	3.33 ± 0.11	0.09	0.38 ± 0.03	0.04
	> 10.0	3.45 ± 0.11	0.53	0.40 ± 0.03	0.17
	P trend		0.30		0.14
Seronegative RA, n = 163	None	2.92 ± 0.13	Referent	0.31 ± 0.04	Referent
	0.1–5.0	3.05 ± 0.12	0.30	0.29 ± 0.03	0.63
	5.1–10.0	3.00 ± 0.15	0.64	0.22 ± 0.04	0.04
	> 10.0	2.88 ± 0.15	0.80	0.25 ± 0.04	0.16
	P trend		0.24		0.07

DAS28-CRP3: Disease Activity Score using 28 joints with high-sensitivity C-reactive protein; MHAQ: Modified Health Assessment Questionnaire; BMI: body mass index; DMARD: disease-modifying antirheumatic drug (biologic DMARD refers to all kinds of anti-tumor necrosis factor, anti-interleukin 1, or anti-B cell agents); NSAID: nonsteroidal antiinflammatory drug; RA: rheumatoid arthritis.

pack-years to measure cumulative smoking (data not shown). For alcohol consumption, it appears that there was a weak J-shaped relationship with DAS28-CRP3 in seropositive RA. Similarly, we found a modest J-shaped association with MHAQ with a minima at alcohol consumption of 5.1–10.0 g/day. Compared to no alcohol use, patients with alcohol consumption of 5.1–10.0 g/day have lower level of MHAQ 1 year later in all RA (0.34 ± 0.02 vs 0.40 ± 0.02, p = 0.02), as well as in seropositive (0.38 ± 0.03 vs 0.44 ± 0.02, p = 0.04) and seronegative RA (0.22 ± 0.04 vs 0.31 ± 0.04, p = 0.04). Additionally, no significant interactions of sex by smoking and sex by alcohol consumption were observed in the analysis.

The DAS28-CRP3 and MHAQ were significantly higher in HLA-SE–positive patients than in negative patients ($p < 0.01$), independent of smoking, alcohol consumption, and other covariates. When stratified by HLA-SE status (Table 4), past smoking was associated with DAS28-CRP3 only in HLA-SE–positive patients, but not in HLA-SE–negative patients (p for interaction = 0.02). Although we did not find a significant interaction between HLA-SE and smoking for MHAQ ($p > 0.05$), the effect of smoking tended to be stronger in HLA-SE–positive patients compared to HLA-SE–negative patients. Similarly, no significant interaction was found between alcohol consumption and HLA-SE, but moderate alcohol consumption tended to reduce MHAQ only in HLA-SE–positive patients, but not in HLA-SE–negative patients. When we used the number of copies for HLA-SE (0, 1, or 2) instead of presence or absence, the results were consistent (data not shown).

DISCUSSION

The results of our prospective study show that current smoking was associated with a worse functional status, and moderate alcohol consumption was associated with a better functional status in RA. In concordance with previous studies[11,28], our findings can contribute to the management of RA and the understanding of the pathophysiology of RA inflammation.

As mentioned above, smoking has been shown to be associated with RA disease activity, particularly when assessing response to specific treatments[3,5]; however, when studied in a general setting, the results are conflicting. A Swedish study reported that current smokers had a lower

Table 4. Adjusted estimated means (SE) of DAS28-CRP3 and MHAQ by smoking and alcohol consumption, stratified by HLA-SE status. Data were adjusted for age, sex, race, education, disease duration, baseline DAS28-CRP3 or MHAQ, body mass index, and use of prednisolone, DMARD (biologic and nonbiologic), and NSAID. The estimates of smoking and alcohol were adjusted for each other.

		DAS28-CRP3				MHAQ			
		HLA-SE+	p	HLA-SE–	p	HLA-SE+	p	HLA-SE–	p
Smoking status	Never	3.34 ± 0.08	Referent	3.04 ± 0.09	Referent	0.38 ± 0.02	Referent	0.31 ± 0.02	Referent
	Past	3.56 ± 0.09	0.03	2.98 ± 0.10	0.64	0.41 ± 0.02	0.27	0.32 ± 0.02	0.71
	Current	3.55 ± 0.16	0.20	2.54 ± 0.25	0.05	0.46 ± 0.04	0.09	0.31 ± 0.06	0.98
Alcohol, g/day	None	3.54 ± 0.10	Referent	2.95 ± 0.12	Referent	0.46 ± 0.03	Referent	0.31 ± 0.03	Referent
	0.1–4.9	3.45 ± 0.09	0.30	2.98 ± 0.13	0.79	0.42 ± 0.02	0.10	0.30 ± 0.03	0.65
	5.0–9.9	3.45 ± 0.12	0.41	2.75 ± 0.15	0.21	0.38 ± 0.03	0.01	0.30 ± 0.04	0.77
	≥ 10.0	3.50 ± 0.12	0.72	2.73 ± 0.15	0.18	0.40 ± 0.03	0.07	0.33 ± 0.04	0.76
	P trend		0.73		0.10		0.03		0.77

DAS28-CRP3: Disease Activity Score using 28 joints with high-sensitivity C-reactive protein; MHAQ: Modified Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drug (biologic DMARD refers to all kinds of anti-tumor necrosis factor, anti-interleukin 1, or anti-B cell agents); NSAID: nonsteroidal antiinflammatory drug.

probability for a European League Against Rheumatism response or remission after 12 months in patients with early RA[29]. However, a recent Spanish study with a similar setting did not show a significant effect of smoking[30]. In addition, a study from CORRONA, in which the data structure was similar to ours, has not shown a significant effect of smoking cessation on disease activity[31]. Because baseline smokers had a higher disease activity in CORRONA, we think that more intensive treatment may have attenuated the effects of smoking; however, baseline treatment did not differ in our case. Also, because our cohort experienced attrition that may not be completely random[32], it is possible that smokers who had worse disease activity may have selectively dropped out. Therefore, the association of smoking with disease activity may be underestimated as a result of selection bias.

There are few studies of the association between smoking and MHAQ in RA. Our results showed that current smoking was adversely associated with MHAQ 1 year later in seropositive RA. Masdottir, *et al*, using HAQ, had shown that dose-dependent smoking (≥ 20 pack-yrs vs < 20 pack-yrs) in RA was associated with higher HAQ, but smoking status (smoking vs nonsmoking at disease onset) was not[33]. This finding suggests that cumulative smoking may be more important than smoking status; however, our results showed similar results to current smoking when using cumulative smoking (≥ 10 pack-yrs vs < 10 pack-yrs, results not shown). This could be because we used time-varying smoking status to best represent longterm smoking exposure, while Masdottir, *et al* used 1-time measurement at disease onset. We found a significant interaction between smoking and HLA-SE for DAS28-CRP3. Past smoking was associated with higher DAS28-CRP3 only in HLA-SE carriers. Current smoking appeared to be associated with increased DAS28-CRP3 and MHAQ, but did not reach statistical significance. We did not find these associations in HLA-SE–negative patients. Therefore, smoking may be not only a risk factor for RA but also a poor prognostic factor of disease course in RA. Thus, smoking should be avoided in all circumstances for those who are thought to be at risk for RA as well as those who already have RA.

Research about alcohol consumption and DAS28-CRP3 has reported a linear inverse relationship[11], while our results suggested a nonsignificant association with an approximate J-shape trend. Such discrepancies could probably be explained by the type of measure (drinking frequency vs amount per day). We may not have enough power to detect a modest effect of alcohol intake on disease activity of RA. Few studies have described the effects of alcohol on MHAQ. Consistent with our findings, 1 study indicated that alcohol consumption showed a favorable response in HAQ score compared with no use[28]. Maxwell, *et al* also reported an inverse (favorable) relationship with MHAQ score[11].

According to the Dietary Guidelines for Americans, drinking in moderation is typically defined as having up to 1 standard drink per day (equal to 10-15 g of pure alcohol); heavy drinking is typically defined as consuming an average of > 1 drink per day[34]. However, some medications may interact with alcohol, thereby altering the metabolism or effects of alcohol and/or medications. For example, alcohol may interact with MTX and NSAID and increase adverse events[35]. For this reason, we would not recommend alcohol consumption for the purpose of achieving beneficial RA outcomes.

Prior studies reported a gene-environment interaction between smoking or alcohol consumption and the risk of RA[10,18]. To date, there is no study reporting such interactions predicting disease activity or functional status in RA. We found that past smoking was associated with DAS28-CRP3 only in HLA-SE–positive patients, not in HLA-SE–negative patients. Although we did not find a significant interaction between HLA-SE and alcohol consumption or smoking for MHAQ, it appeared that the

effect of alcohol on MHAQ was stronger in HLA-SE carriers than HLA-SE–negative patients. With our overall sample size, we may not have enough power to detect a significant interaction. Future studies with larger number of patients are needed to confirm our findings.

Our study has several strengths. It is a large, longitudinal cohort study with repeated measurements up to 7 years. The lagged analysis may help determine causal inference in terms of a temporal relationship between the predictors and the outcome. Although self-reported smoking and alcohol use based on questionnaires may be subject to misclassification bias, the repeated measures of outcomes and exposures will increase accuracy and represent a longterm trend compared to 1-time measurement. Also, we have controlled for various covariates including socioeconomic, genetic, and serologic status and time-varying treatments to minimize the chance for confounding bias.

Our study also has several limitations. First, because of the observational nature of the study, patients were not randomly assigned to exposure groups. We cannot prove that the observed associations are truly causal because of possible residual confounding. Second, patients with higher disease activity or poor function status may refrain from drinking, which can equally lead to the same conclusion — alcohol consumption leading to decreased disease activity or improved functional status. However, we have adjusted for baseline values of DAS28-CRP3 or MHAQ and explicitly modeled in the temporal relationship between the predictors and the outcome, so such bias from reverse causality should be minimized. Third, consistent with previous studies[11,28], alcohol drinkers tended to be younger and have shorter disease duration than nondrinkers. It is also possible that the effect of alcohol consumption may be confounded or modified by disease duration. However, after adjusting for age and disease duration, the association with MHAQ remained. We also did not find a mediation effect through disease duration. Thus disease duration may not affect our findings. Another issue is a possibility of confounding by indication, because uncorrected behavior (such as to keep smoking in spite of worse disease) can lead to more intensive treatment, leading in turn to attenuation of the effects of smoking. We adjusted for medication use as time-varying covariates, but did not adjust for the dose. Uncorrected behavior can also lead to less treatment; the physician may prefer to avoid MTX if the patient cannot stop drinking alcohol. As suggested in Table 2, an inverse relationship between alcohol consumption and MTX use was observed. But if such avoidant practice were to be truly influential, then we would expect more severe disease activity or functional status in alcohol drinkers than in nondrinkers, and our results did not show that.

In this prospective, observational cohort, current smoking may be associated with worse functional status in RA. Moderate alcohol consumption may be associated with better functional status than alcohol avoidance. Replication of these findings in other prospective studies is needed.

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