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

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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 RA patients 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 by the Disease Activity Score examined in 28 commonly affected joints (DAS28-CRP3) and Modified Health Assessment Questionnaire (MHAQ) assessed annually. 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 follow-up time of the cohort was 4 years. Current smoking was not associated with DAS28-CRP3 in this study, but was associated with a higher MHAQ than non-smokers in seropositive RA (p=0.05). Alcohol consumption showed an approximate J-shaped relationship with MHAQ, with the minima occurring at 5.1–10.0 grams/day. Compared to no alcohol use, alcohol consumption of 5.1–10.0 grams/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.

Keywords

Smoking; Alcohol Consumption; Rheumatoid Arthritis; *HLA* Shared Epitope; DAS28; MHAQ; Gene-Environment Interaction

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Introduction

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 smoking is the strongest environmental risk factor for RA [2]. Smoking is also associated with increased disease activity in several cohort studies[3–5], mainly describing it as a predictor for poor tumor necrosis factor alpha (TNF-a)-blocker 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 CRP in the general population[7]. There could be a relationship between alcohol consumption and risk of RA since RA is a chronic, inflammatory disease. Indeed, there has been a recent report that in women with pre-clinical 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[9–15].

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[18–20]. 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 decrease the risk of anti-CCP-antibody positive RA, the first to show a gene-environment interaction between alcohol consumption and *HLA-SE*[10].

The relationships between smoking, alcohol consumption and the disease course of RA assessed by disease activity and functional status in RA patients are not well understood, especially with consideration of genetic factors and gene-environment interaction. 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*.

Methods

The Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) is a large, single-center, prospective and observational cohort of 1100 RA patients. Enrolment 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 due to its access to patient electronic medical records for follow-up interviews and medical record review. Data were collected on medications, smoking, alcohol use, disease activity and functional status yearly[21]. We included 662 patients who had *HLA-SE* genotype, and have been followed up annually, up to 7 years. This 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 based cohort in the United States. A recent report indicated that approximately 80% of CORRONA patients had a disease duration greater than 24 months and almost 90% had an MHAQ score less than 1[24, 25]. The relatively low MHAQ scores indicate that this is a high-functioning group of RA patients which may be the result of healthier patients enrolling compared to non-participants [21]. The exposures were smoking status (current, past or never smokers, or pack-years, more or less than 10 pack-years, cut-offs based on previous literature[18, 26]) and alcohol consumption (none, 0.1–5.0, 5.1–10.0 and >10 grams per day, or gm/day). Alcohol consumption was initially measured as drinks per day and then translated into grams per day. As smoking status had about 7% less data than alcohol consumption due to missingness, we imputed the time-varying smoking status as last observation carried forward (LOCF) and/or backward (LOCB) limited to 1 year. The *HLA-SE* was determined based on two steps: a) 2 digit level then b) sequencing for the subtypes that contain SE motif to determine 4 digits types [27].

To assess the prospective effects of smoking and alcohol consumption, general linear mixed models (GLMM) were used to analyze the repeated measurements ranging from 1 to 7 years of follow-up. 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 was modeled to predict the future DAS28-CRP3 or MHAQ measured 1 year later. We adjusted for baseline DAS28-CRP3 or MHAQ, gender, age, race, education, seropositivity (anti-CCP antibody and/or rheumatoid factor positive), disease duration and body mass index (BMI). Current drug treatments including corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), non-biologic disease-modifying anti-rheumatic drugs (DMARDs) such as antimalarials and methotrexate (MTX), and biologic DMARDs, such as anti-TNF blockers, anti-IL-1 or anti-B cell agents, were also adjusted as time-varying covariates. The different covariance models were evaluated using Akaike's information criterion (AIC) and Bayesian information criterion (BIC). Separate models were developed for seropositive and seronegative RA patients. Multivariable adjusted means of DAS28-CRP3 and MHAQ were compared across smoking or alcohol consumption categories. To assess gene-environment interaction, we stratified the model 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 gender by smoking and alcohol consumption were also evaluated as secondary analyses. SAS 9.2 for Windows (Cary, NC, USA) was used for statistical analysis. A p value of <0.05 was used to determine statistical significance.

Results

In this study, 662 RA patients with *HLA-SE* data from BRASS were followed up to 7 years. The median follow-up time was 4 years (interquartile range (IQR) 2–4 years) 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 2. The cohort was a mainly middle-aged female Caucasian population with mean disease duration of 15 years. Compared to non-smokers, 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, tended to be a seronegative RA case and use prednisone and methotrexate. Alcohol consumption showed approximate J or U-shaped relationship with age, disease duration, DAS28-CRP3 and MHAQ, with the minima occurring at 5.1–10.0 grams/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 one year later in RA. However, current smoking was found to increase MHAQ one 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 pack-years to measure cumulative smoking (results are 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 grams/day. Compared to no alcohol use, patients with alcohol consumption of 5.1–10.0 grams/day have lower level of MHAQ one 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 gender by smoking and gender by alcohol consumption were observed in the analysis.

The DAS28-CRP3 and MHAQ were significantly higher in *HLA-SE* positive patients than 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 this 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 probability for a EULAR response or remission after 12 months in early RA patients[29]. However, a recent Spanish study with a similar setting did not show a significant effect of smoking[30]. Also, 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]. Since 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 since our cohort experienced attrition that may not be completely random[32] and it is also possible that smokers who had worse disease activity may have selectively dropped out. Therefore, the association of smoking with disease activity may be underestimated due to 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 one year later in seropositive RA. One report, using HAQ, had shown that dose-dependent smoking (≥20 pack-years vs. < 20 pack-years) in RA was associated with higher HAQ, but smoking status (smoking vs. non-smoking at disease onset) was not[33], suggesting 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-years vs. < 10 pack-years, results not shown). This could be due to the fact that we used time-varying smoking status to best represent long-term smoking exposure, while they used one 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.

Recent research about alcohol consumption and DAS28-CRP3 has reported a linear inverse relationship[11], while our results suggested a non-significant 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, one 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 grams of pure alcohol), heavy drinking is typically defined as consuming an average of more than 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 methotrexate and NSAIDs, and increase adverse events [35]. For this reason, we would not recommend alcohol consumption for 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 long-term trend compared to one-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, 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 no drinkers. 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, as uncorrected behavior (such as to keep smoking in spite of worse disease) can lead to more intensive treatment, leading to attenuation of the effects of smoking. We adjusted for medication use as time-varying covariates, but did not adjusted for the dose. Uncorrected behavior can also lead to less treatment, such as the physician may rather 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. However, 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 non-drinkers, however our results did not show that case.

Conclusion

In conclusion, 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 non-drinkers. Replication of these findings in other prospective studies is needed.

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Table 1

Baseline characteristics of the study sample from BRASS Cohort by Smoking Status *

Smoking Status	Never (N=353)	Past (N=250)	Current (N=56)	p value
Age (years)	54.6±14.3	61.2±11.0	54.5±11.4	<0.001
Gender (Female)	83.0%	82.4%	78.6%	0.72
Race (White)	93.1%	97.2%	89.1%	0.02
Education (Tech school graduate or higher)	67.3%	57.3%	55.4%	0.02
Smoking Pack-years	0	19.2±21.4	29.6±22.1	<0.001
Alcohol consumption (gm/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 (years)	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)	26.2±5.6	27.3±5.2	26.9±6.1	0.004
Anti-CCP positive status	64.4%	71.8%	71.7%	0.13
Prednisone use	29.7%	30.0%	30.4%	0.99
Methotrexate use	47.0%	52.0%	42.9%	0.33
Antimalarial use	17.6%	14.0%	16.1%	0.50
Other DMARD use	17.6%	19.2%	19.6%	0.85
Biologic DMARD use	37.7%	40.8%	35.7%	0.66
NSAID use	63.5%	63.2%	66.1%	0.92

* Total sample size was 659 after excluded 3 patients without smoking data.

Data are expressed as mean ± SD or percentage (%). Some measurements were missing at baseline (race n=653, education, n=656 and anti-CCP n=649). DAS28-CRP3: Disease Activity Score using 28 joints with high sensitivity CRP. MHAQ: Modified Health Assessment Questionnaire. *HLA-SE: HLA-DRB1* shared epitope. BMI: Body mass index. DMARD: Disease-modifying anti-rheumatic drug. Biologic DMARD refers to all kinds of anti-TNF, anti-IL-1 or anti-B cell agents. NSAID: Non-steroidal anti-inflammatory drug. P values were based on Kruskal-Wallis test for continuous variables or Chi-squared test for categorical variables.

Table 2

Baseline characteristics of the study sample from BRASS Cohort by Alcohol Consumption *

Alcohol Intake, gm/day	None (N=205)	0.1–5.0 gm/d (N=239)	5.1–10.0 gm/d (N=63)	>10 gm/d (N=108)	P
Age (years)	60.2±13.1	55.0±12.7	52.0±14.1	60.0±13.0	<0.001
Gender (Female)	87.3%	85.4%	81.0%	70.4%	<0.001
Race (White)	88.1%	97.0%	98.4%	98.2%	<0.001
Education (Tech school graduate or higher)	48.3%	64.4%	76.2%	73.8%	<0.001
Smoking					
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-years	9.9±16.7	10.5±21.4	6.4±12.5	12.5±17.7	0.04
DAS28-CRP3	4.33±1.61	3.93±1.44	3.84±1.70	3.97±1.50	0.02
MHAQ	0.56±0.54	0.36±0.40	0.31±0.44	0.36±0.38	<0.001
Disease Duration (years)	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)	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 use	36.1%	31.0%	23.8%	23.2%	0.01
Methotrexate use	52.7%	53.1%	38.1%	34.3%	<0.001
Antimalarial use	16.6%	14.6%	19.0%	15.7%	0.98
Other DMARD use	20.5%	14.2%	23.8%	20.4%	0.74
Biologic DMARD use	36.1%	41.8%	44.4%	36.1%	0.82
NSAID use	62.0%	61.1%	81.0%	63.0%	0.03

* Total sample size was 615 after excluded 47 patients without alcohol intake data.

Data are expressed as mean ± SD or percentage (%). 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 CRP. MHAQ: Modified Health Assessment Questionnaire. *HLA-SE: HLA-DRB1* shared epitope. BMI: Body mass index. DMARD: Disease-modifying anti-rheumatic drug. Biologic DMARD refers to all kinds of anti-TNF, anti-IL-1 or anti-B cell agents. NSAID: Non-steroidal anti-inflammatory drug. P values were based Kruskal-Wallis test for continuous variables or Chi-squared test for categorical variables.

Table 3

Adjusted Estimated Means (SE) of DAS28-CRP3 and MHAQ by Smoking and Alcohol Consumption *

		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 (gm/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

* Adjusted for age, gender, race, education, disease duration, baseline DAS28-CRP3 or MHAQ, body mass index, prednisolone, DMARD (biologic and non-biologic) and NSAID use. The estimates of smoking and alcohol were adjusted for each other.

Table 4

Adjusted Estimated Means (SE) of DAS28-CRP3 and MHAQ by smoking and alcohol consumption, stratified by *HLA-SE* status*

		DAS28-CRP3				MHAQ			
		HLA-SE+	**p**	***HLA-SE−***	**p**	***HLA-SE+***	**p**	***HLA-SE−***	**p**
Smoking	**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 (gm/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

*Adjusted for age, gender, race, education, disease duration, baseline DAS28CRP3 or MHAQ, body mass index, prednisolone, DM ARD (biologic and non-biologic) and NSAID use. The estimates of smoking and alcohol were adjusted for each other.