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Alcohol consumption is inversely associated with risk and severity of rheumatoid arthritis

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Abstract

Objective. To investigate the association between frequency of alcohol consumption and the risk and severity of RA.

Methods. Frequency of alcohol consumption was recorded by patients and controls in a self-completed questionnaire. Odds ratios (ORs) for RA risk were calculated according to alcohol consumption, adjusted for age, gender and smoking status. Median values of all RA severity measures were then calculated according to the frequency of alcohol consumption, and the non-parametric trend test was used to assess association. A negative binomial regression model was used to adjust for potential confounding.

Results. Eight hundred and seventy-three patients with erosive RA, and 1004 healthy controls were included in the study. Risk of RA decreased according to frequency of alcohol consumption, such that non-drinkers had an OR for RA of 4.17 (3.01–5.77) compared with subjects consuming alcohol on >10 days per month (*P* for trend <0.0001). All measures of RA severity including CRP, 28-joint DAS, pain visual analogue scale, modified HAQ (mHAQ) and modified Larsen score were inversely associated with increasing frequency of alcohol consumption (*P* for trend, each <0.0001). After adjustment for potential confounding in a multivariate regression model, frequency of alcohol consumption remained significantly and inversely associated with X-ray damage and mHAQ.

Conclusion. Although there are some limitations to this study, our data suggest that alcohol consumption has an inverse and dose-related association with both risk and severity of RA.

Key words: Rheumatoid arthritis, Alcohol, Severity, Susceptibility, Environment.

Introduction

RA is a complex and chronic disorder, which affects ~1% of Caucasians. Untreated, it causes persistent joint inflammation, irreversible joint damage and premature mortality. The heterogeneous nature of the disease has hampered attempts to elucidate the interacting genetic and environmental factors that are likely to contribute to its aetiology, but recent studies have demonstrated that subsets of RA defined by the presence or absence of anti-CCP antibodies have quite differing associations with genetic and environmental risks [1, 2]. In particular, smoking is also strongly associated with both anti-CCP and RF-positive RA, and has elegantly been shown to interact with HLA–DRB1 shared epitope alleles in a multiplicative fashion [3], whereas in anti-CCP-negative disease the association is weak if it exists at all [4].

Somewhat surprisingly, given the prevalence of alcohol consumption, relatively few studies have examined the association of alcohol with RA, but available evidence suggests a protective effect. A recent case–control study of two large Scandinavian cohorts has convincingly demonstrated a dose-dependent reduction in RA risk in subjects consuming alcohol regularly in comparison with non-drinkers, independent of gender and CCP status [5]. A previous study in a Scandinavian cohort also showed a dose-dependent reduction in RA risk, but only in anti-CCP-positive disease [2], whereas earlier studies demonstrated protective effects in female-only cohorts [6, 7]. No effect of alcohol on risk of RA was demonstrated, however, in a cohort of older women [8].

Compared with susceptibility, investigation of genetic and environmental association with RA disease severity is less advanced. A number of studies have identified genetic markers associated with radiological joint damage in

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RA, and as with susceptibility it appears that established genetic risk markers associate with severity predominantly in anti-CCP-positive disease [9]. Unlike susceptibility studies, however, smoking appears not to associate with radiographic progression [10], and few other environmental exposures have been studied in association with RA severity. No human studies of RA severity and alcohol exist, but in a mouse model of collagen Type II arthritis, ethanol exposure abrogated the development of destructive arthritis, and interestingly this effect appeared to be testosterone mediated, as testosterone levels increased in the ethanol group and the influence of ethanol treatment diminished in orchidectomized mice [11].

In this study involving a large cohort of UK-based Caucasian RA patients and controls, we have further examined the effect of alcohol consumption on susceptibility to RA, and for the first time in humans, the effect of alcohol on disease severity assessed by clinical, radiological and questionnaire-based methods. We hypothesized that consumption of alcohol would reduce both the risk of RA and disease severity.

Methods

Study design

The influence of alcohol consumption on RA susceptibility was investigated in cases and controls by calculation of odds ratios (ORs) adjusted for potential confounding variables. Further analyses were performed after stratification for gender and autoantibody status. The association of alcohol consumption with RA severity measured by clinical, radiographic and questionnaire-based assessment criteria was then analysed in a cross-sectional cohort of RA cases, and a multivariate regression model was constructed to adjust for potential confounding variables.

Patients

A total of 873 white Caucasian individuals with RA and 1004 unrelated healthy controls were included in the study. The South Sheffield Ethics Committee approved this study (SSREC protocol number 02/186) and written informed consent was obtained from all the participants. All RA patients were recruited from the rheumatology department of the Royal Hallamshire Hospital in Sheffield between 1999 and 2006 and met the ACR criteria for a diagnosis of RA [12]. In addition, all patients had disease duration of at least 3 years (mean 14.1 years) and at least one radiographic erosion of hands or feet on X-rays taken at study entry. The control group was recruited from the Sheffield area and each individual was $\geqslant$18 years of age. Advertisements were placed in local businesses and community centres inviting individuals to participate in the study, and all respondents were carefully screened by an experienced research nurse to ensure that they had no evidence of inflammatory joint disease before enrolment.

Smoking and alcohol exposure

Information on smoking and alcohol exposure was obtained via an extensive self-completed questionnaire, given to patients at study entry. Participants were asked to record the number of days on which they had at least one alcoholic drink over the previous month to one of the four categories (no alcohol, 1–5 days, 6–10 days and $>$10 days), and were also asked to define their previous drinking behaviour between never- and ever-regular drinker. Smoking status was recorded as current smoker, previous smoker and never smoker.

Autoantibody measurement and genotyping

Anti-CCP levels were measured using the DIASTAT anti-CCP ELISA (Axis-Shield, Cambridgeshire, UK). The semi-quantitative protocol was used as recommended by the manufacturer and a cut-off of 5.5 U/ml was established based on mean plus 3 S.D.s of values obtained from 100 age-matched control individuals. RF was measured using a nephelometric method on the Dade Behring BN2 nephelometer (Dade Behring, Marburg, Germany).

Clinical and questionnaire-based measures of RA severity

CRP measurements were available for all patients, and 28-joint DAS using CRP (DAS-28CRP) in addition to a specific visual analogue scale (VAS) for pain were recorded by two experienced research nurses at study entry. All patients also completed the modified HAQ (mHAQ), which is a measure of functional capacity.

Radiographic scoring

Radiographs of hands and feet were scored blind at study entry by a single musculoskeletal radiologist (D.J.M.) using a modification to Larsen score (LS), which provides an integrated measure of bone and cartilage damage in RA [13], with higher scores indicating increased severity of joint damage. To check whether scoring was consistent, 10% of films were selected at random and returned for repeat blinded analysis. A weighted κ score was calculated to quantify the intra-observer variation in the modified LS. The weighted κ score was 0.83, indicating very good agreement between the initial and repeat scores.

Statistical analysis

ORs for RA were calculated for regular drinkers compared with never-regular drinkers using a logistic regression model, adjusted for age, gender and smoking status, as these factors differed significantly between cases and controls. Repeat analyses were performed after stratification by anti-CCP and RF status, and also separately according to gender. Subjects with missing data were omitted from this analysis. Dose effect of alcohol on RA susceptibility was then investigated, by calculating ORs for RA by frequency of alcohol consumption, referent to the highest alcohol consumption group.

Severity of RA was assessed by laboratory, clinical and patient-completed questionnaire criteria. Modified LS (mLS), DAS-28CRP, CRP, pain VAS scores and

mHAQ scores were not normally distributed across the cohort (assessed by the skewness/kurtosis test for normality), and therefore median values for each criterion were tabulated according to frequency of alcohol consumption. The non-parametric trend test (an extension of the Wilcoxon rank-sum test) was used to assess trend across the alcohol consumption groups. In order to assess the influence of potential confounders, binomial regression models (chosen due to the distribution of the total Larsen and mHAQ scores) were constructed with mLS and mHAQ as the dependent variables. The Clinical and laboratory parameters previously shown to influence RA severity were included in the models. All statistical analyses were performed using Stata statistical software (Release 9.2; Stata Corporation, College Station, TX, USA).

Results

Baseline characteristics

The baseline characteristics of the subjects included in the study are shown in Tables 1 and 2. RA patients were significantly older, more likely to smoke than the controls and were more likely to be females. Alcohol consumption differed significantly between cases and controls, with 36.7% of cases compared with only 10.9% of controls reporting no regular alcohol intake and 30% of controls compared with 16% of cases consuming alcohol on >10 days per month. Age, gender, disease duration and smoking exposure ($P < 0.008$ for each) but not autoantibody status differed significantly in RA patients across the alcohol consumption categories. Disease-modifying treatment also differed according to alcohol

Table 1 Characteristics of RA cases and controls

Characteristic	Cases	Controls	OR (95% CI) or *P*-value
n	873	1004	–
Age, mean (S.D.), years	61.4 (12.2)	48.0 (13.9)	$P \leqslant 0.0001$
Gender: women (%)	72.2	65.2	1.32 (1.13, 1.67)
Ever-smokers, *n* (%)	519 (59.4)	418 (41.6)	2.05 (1.70, 2.47)
SE alleles, *n* (%)	815 (93.3)	950 (94.6)	–
0	147 (18.0)	417 (43.9)	Ref.
1	370 (45.4)	388 (40.8)	3.34 (2.63, 4.22)
2	298 (36.6)	145 (15.3)	9.88 (6.96, 14.02)
Alcohol frequency, *n* (%), days per month	873 (100)	1004 (100)	–
0	36.7	10.9	Ref.
1–5	32.8	32.3	0.30 (0.23, 0.40)
6–10	14.7	26.3	0.17 (0.12, 0.23)
>10	15.8	30.4	0.15 (0.11, 0.21)
Ever-regular drinker, *n* (%)	618 (70.8)	908 (90.5)	0.25 (0.19, 0.32)

P-value shown for *t*-test. SE: shared epitope.

Table 2 Baseline characteristics of RA patients categorized by alcohol consumption frequency

Variable	Alcohol frequency, days/month				*P*-value
	0	1–5	6–10	>10	
Age, mean (S.D.), years	64.5 (10.7)	59.1 (13.7)	59.3 (11.4)	60.5 (11.2)	0.001
Gender: female, %	79.6	72.4	61.2	63.8	0.001
Anti-CCP positive, *n* (%)	262 (83.4)	226 (80.1)	99 (81.8)	103 (75.1)	0.226
RF positive, *n* (%)	230 (75.7)	188 (72.3)	81 (65.8)	87 (65.9)	0.08
Disease duration, mean (S.D.), years	16.9 (11.3)	15.4 (10.9)	15.4 (10.6)	14.7 (9.5)	0.008
Smoking, mean (S.D.), pack-years	12.1 (17.7)	12.2 (18.9)	13.4 (12.7)	16.2 (16.5)	0.001
DMARD treatment					
No DMARD, *n* (%)	40 (40.8)	27 (27.6)	11 (11.2)	20 (20.4)	–
Non-MTX DMARD, *n* (%)	74 (31.1)	65 (27.3)	46 (19.3)	53 (22.2)	–
MTX alone/comb, *n* (%)	188 (39.7)	171 (36.2)	61 (12.9)	53 (11.2)	–
Anti-TNF alone/comb, *n* (%)	18 (28.0)	22 (34.4)	12 (18.8)	12 (18.8)	0.002
Mean prednisolone dose (S.D.)	3.75 (4.05)	3.48 (5.36)	3.29 (4.02)	2.25 (3.24)	0.001

P-values stated are for chi-square test (proportions) and Cuzick's test for trend (disease duration and age). Comb: combination.

consumption, with more patients treated with MTX (alone or in combination with other DMARDS) consuming alcohol infrequently or not at all, compared with other treatment groups. With the stated sample size, this study has >99% power to demonstrate a risk ratio for RA of 2.0 for non-drinkers compared with drinkers.

RA susceptibility

Table 3 outlines the influence of alcohol consumption (ever-regular *vs* never drinker) on risk of RA, before and after stratification for anti-CCP and gender. After adjustment for age, smoking status and gender, non-regular drinkers had an OR for RA of 2.31 (1.73–3.07) compared with regular drinkers ($P < 0.0001$). The ORs remained significant in both groups after stratification for gender and anti-CCP status, but the protective effect of alcohol consumption appeared stronger in the anti-CCP-positive group. An almost identical effect was demonstrated after stratification for RF status (data not shown).

Alcohol dose effect on susceptibility to RA

Risk of RA decreased according to frequency of alcohol consumption, such that non-drinkers had an OR for RA of 4.17 (3.01–5.77) compared with subjects consuming alcohol most frequently (*P* for trend <0.0001). The effect was similar after stratification by gender and again was most marked for risk of anti-CCP-positive RA (data not shown).

RA severity

All measures of RA severity, including CRP, DAS-28CRP, pain VAS, mHAQ and mLS were inversely associated with increasing frequency of alcohol consumption (*P* for trend <0.0001 for all; Table 4). After stratification for gender and

Table 3 Risk of RA by never- *vs* ever-regular alcohol consumption, stratified by gender and anti-CCP status

RA group	Regular drinker	Cases	Controls	Crude OR (95% CI)	Adjusted OR[a] (95% CI)	*P*-value
All	Yes	617	909	1.00	1.00	–
	No	256	95	3.97 (3.04, 5.18)	2.31 (1.73, 3.07)	<0.0001
Gender						
Women	Yes	419	579	1.00	1.00	–
	No	211	76	3.83 (2.84, 5.19)	2.11 (1.52, 2.93)	<0.0001
Men	Yes	198	330	1.00	1.00	–
	No	45	19	3.95 (2.22, 7.03)	2.89 (1.55, 5.40)	<0.001
Anti-CCP positive	Yes	481	909	1.00	1.00	–
	No	209	95	4.16 (3.15, 5.48)	2.36 (1.74, 3.19)	<0.0001
Anti-CCP negative	Yes	122	909	1.00	1.00	–
	No	42	95	3.29 (2.17, 4.99)	1.83 (1.17, 2.88)	0.008

Analysis stratified by gender compares female cases with female controls and the opposite in males. Analysis stratified by anti-CCP status compares anti-CCP-positive or -negative cases with all controls. *P*-values stated for adjusted logistic regression analysis. [a]Adjusted by age, smoking status and gender (except where stratified by gender, then only age and smoking status).

Table 4 RA severity by frequency of alcohol consumption

Severity marker	Frequency of alcohol, days/month				*P* for trend
	0	1–5	6–10	>10	
LS					
All	38 (54)	33 (47)	29 (45)	27 (47)	<0.0001
Gender					
Men	41 (44)	30 (46)	21 (45)	19.5 (34)	0.004
Women	37 (57)	33 (47.5)	32 (52)	30 (54)	0.03
Anti-CCP positive	40 (56)	36.5 (50)	32 (56)	33 (53)	0.02
Anti-CCP negative	27 (52)	22.5 (39.5)	17.5 (23)	16 (35)	0.02
DAS-28CRP	4.29 (1.66)	4.01 (1.50)	3.82 (1.63)	3.72 (1.41)	<0.0001
CRP, mg/l	13 (18.6)	10 (14.7)	8.7 (9.5)	8.0 (8.8)	<0.0001
mHAQ	1.0 (0.94)	0.75 (0.75)	0.5 (0.88)	0.63 (0.75)	<0.0001
Pain VAS, cm	4.1 (4.5)	3.0 (4)	3.1 (3.5)	2.75 (3.5)	<0.0001

The values stated are the median for each severity marker with interquartile range given in parentheses. *P*-values are for the non-parametric trend test.

anti-CCP status, the trend for reduction of median mLS remained significant in all groups ($P < 0.05$). In order to better assess the effect of drinking behaviour over time, measures of severity were also compared according to self-reported ever/never drinking status. In those patients reporting regular alcohol consumption, all severity measures were significantly reduced compared with those not consuming alcohol regularly ($P < 0.003$ for all; Table 5). In a stratified analysis according to MTX treatment status, all severity markers were negatively associated with a history of regular alcohol consumption in both the MTX and non-MTX groups ($P < 0.05$).

In the binomial multiple regression model (Table 6), frequency of alcohol consumption remained negatively and significantly associated with mLS after adjustment for disease duration, DMARD treatment, prednisolone dose, RF and anti-CCP titre, smoking exposure (pack-years) gender and age. Similarly alcohol consumption frequency was significantly associated with mHAQ.

Discussion

Our study has demonstrated that consumption of alcohol is associated with a significant and dose-dependent reduction in susceptibility to RA. For the first time we have also shown a dose-dependent inverse association between frequency of alcohol consumption and severity of RA, measured by a range of clinical, laboratory and radiological parameters. The associations with both

Table 5 RA severity according to ever/never-regular alcohol consumption status and stratified by MTX treatment status

RA Patient Group	Severity marker	Alcohol ever, *n* (%)		*P*-value
		No	Yes	
All	Total LS	38 (256)	31 (617)	0.002
	mHAQ	1.0 (256)	0.75 (617)	<0.001
	DAS-28CRP	4.29 (249)	4.00 (583)	<0.001
	CRP	13.0 (249)	9.6 (583)	<0.001
	pVAS	42 (256)	30 (583)	<0.001
Non-MTX treated	Total LS	41.5 (104)	30.5 (264)	0.009
	mHAQ	1.13 (104)	0.63 (264)	<0.001
	DAS-28CRP	4.42 (103)	4.07 (250)	0.002
	CRP	13.0 (103)	9.4 (250)	0.005
	pVAS	45 (104)	30.5 (264)	<0.001
MTX treated	Total LS	34 (152)	31 (351)	0.04
	mHAQ	0.88 (152)	0.75 (351)	<0.001
	DAS-28CRP	4.21 (146)	3.96 (331)	0.03
	CRP	13.0 (146)	9.9 (331)	0.01
	pVAS	40 (152)	30 (351)	0.02

Values are expressed as median (*n*). pVAS: pain VAS (mm). *P*-values stated are for Mann–Whitney U-test.

Table 6 Binomial multivariate regression model with mLS and mHAQ as dependent variables

Variable	LS			mHAQ		
	Coeff.	S.E.	*P*-value	Coeff.	S.E.	*P*-value
Alcohol 1–5 days/month[a]	−0.105	0.066	0.114	−0.244	0.096	0.011
Alcohol 6–10 days/month[a]	−0.255	0.086	0.003	−0.475	0.139	0.001
Alcohol >10 days/month[a]	−0.214	0.083	0.008	−0.346	0.126	0.006
Disease duration	0.042	0.003	<0.0001	0.013	0.004	<0.0001
RF titre	0.001	0.000	0.021	0.000	0.000	0.142
Anti-CCP titre	0.003	0.001	<0.001	0.000	0.001	0.946
Smoking status	−0.053	0.037	0.177	0.044	0.055	0.422
Age, years	−0.007	0.002	0.004	−0.001	0.004	0.928
Sex	−0.038	0.063	0.540	0.010	0.095	0.916
DMARD treatment[b]	−0.011	0.036	0.753	−0.055	0.052	0.294
Prednisolone dose	0.005	0.006	0.390	0.009	0.007	0.208
Intercept	3.399	0.199	–	−0.226	−0.289	–

[a]Each category of alcohol consumption compared with non-drinkers. [b]Categorized—no DMARD, non-MTX DMARD, MTX alone/combination, anti-TNF. Coeff: coefficient.

susceptibility and severity remain significant after stratification for gender and autoantibody status.

Our findings in relation to the association of alcohol consumption with RA susceptibility are largely in agreement with the previous literature. In contrast to a study reporting the results of two Scandinavian case–control cohorts in which alcohol consumption was recorded as the number of alcohol drinks consumed per week [5], the frequency rather than quantity of alcohol consumption was recorded in our study. We cannot therefore draw any direct comparisons regarding the amount of alcohol consumed by cases or controls in our cohort relative to the Scandinavian cohorts, but it is notable that the association effect size and dose effect sizes for alcohol consumption on RA risk in both studies are similar. As with the Scandinavian study, but unlike a previously reported investigation [2], we have found that the protective association with alcohol consumption is present in both anti-CCP and RF-positive and -negative disease, and is unaltered by gender.

An association of alcohol with severity of RA has not been previously reported in humans, but our results extend the findings of a study in a mouse model of collagen Type II arthritis, in which the initiation and severity of destructive arthritis was significantly reduced by the supplementation of drinking water with 10% ethanol [11]. The authors studied male mice only and demonstrated an effect on NFκB (nuclear factor κ light chain enhancer of activated B cell) signalling, likely to be mediated by testosterone. In our cohort, the association of radiographic RA severity appeared stronger in male patients than females, although the association was significant in both groups. While focal bone loss has not been studied in association with alcohol intake, low-dose alcohol has been shown to be beneficial to fracture risk and BMD in post-menopausal women [14, 15]. The effect of alcohol consumption on inflammatory markers in RA has not been previously investigated, but in studies involving healthy subjects, those consuming moderate quantities of alcohol had lower levels of CRP compared with either non-drinkers or heavy drinkers [16], suggesting an immunomodulatory effect of alcohol. Similarly, in healthy individuals, alcohol has been shown to have anti-nociceptive effects [17], suggesting that the observed correlation between pain VAS and frequency of alcohol consumption in our cohort may be as a consequence of both anti-inflammatory and analgesic effects. With relevance to the reduction in X-ray severity, NFκB signalling plays a central role in the mediation of bone erosion in RA and it has been shown that blocking NFκB attenuates osteoclastogenesis [18]. While the exact mechanisms of action of alcohol in the context of autoimmunity remain to be discovered, a substantial body of experimental and clinical data implicate alcohol as a powerful immunomodulating agent.

Clearly, disease-modifying treatment is one of the most important potential confounders of the results demonstrated in our cohort, as alcohol consumption has the potential to influence choice of DMARD therapy, and conversely the choice of DMARD can influence drinking behaviour. Table 2 demonstrates that as expected, frequency of alcohol consumption in patients treated with MTX was lower than for other DMARD/non-DMARD treated groups. We therefore investigated the influence of alcohol consumption frequency on disease severity measures separately in MTX- and non-MTX-treated patients, demonstrating that all severity measures aside from pain VAS remained significant in both the groups, but with slightly reduced effect size in the MTX-treated patients, perhaps as a consequence of the small number of MTX-treated patients in the higher alcohol consumption groups. Furthermore, alcohol consumption frequency remained significantly associated with radiological damage in a multivariate model including specific DMARD treatment suggesting that the observed associations between severity and frequency of alcohol consumption are not primarily as a consequence of treatment selection.

There are limitations to the design of this study, which necessitate some caution in the interpretation of the results presented. First, there are marked gender and age differences between the RA and control groups in this cohort. All analyses have therefore been adjusted for these factors, but we appreciate that this remains a weakness. Secondly, the study is retrospective in design and there is therefore a risk that recall bias may have influenced the participants reporting their alcohol consumption, and also a significant risk that drinking behaviour in patients with RA may have been influenced by the diagnosis of RA or their subsequent treatment. Furthermore, the alcohol consumption data on which this study is based represent a snapshot of drinking behaviour at one point in time. Some outcome measures of the study, such as mHAQ, pain VAS, CRP and DAS-28CRP, are also single time-point measurements recorded concordantly with drinking behaviour, and we can therefore have reasonable confidence in the validity of the associations demonstrated. Other outcome measures, however, such as the radiographic scores and the presence or absence of RA, reflect biological processes that have occurred over a period of many years, which have potentially been influenced by a variety of genetic, environmental and treatment effects in addition to disease duration. We have attempted to control for these factors by including them in a multivariate regression model in which the frequency of alcohol consumption was significantly associated with radiographic damage ($P = 0.005$). Thirdly, the observational nature of this study means that we have not been able to accurately describe the inevitable fluctuation in alcohol intake over a long period of time, but the strong inverse association with severity demonstrated in patients' self-reported ever/never-regular drinking status does provide further support to the associations demonstrated with frequency of alcohol consumption. Added to this the uniform inverse association between frequency of alcohol consumption and all RA severity markers studied, do suggest the likelihood of a genuine alcohol-mediated effect on RA severity.

Fourthly, frequency rather than quantity of alcohol consumption has been recorded. We cannot therefore draw any conclusions about the actual dose of alcohol required to influence RA severity, although it could be argued that the frequency of alcohol exposure may have greater relevance to the modulation of a chronic disease than exact quantity of exposure. It is also possible that constituents of different alcoholic beverages other than the alcohol itself may have varying effects on RA but this was not investigated in our study. Finally, it should be noted that this study and previously published papers in this area have investigated the association of alcohol consumption with RA risk only in a Caucasian population. Without further investigation, it is not possible therefore to generalize our findings to other ethnic groups.

In conclusion, this study has confirmed a dose-dependent reduction in risk of RA with moderate consumption of alcohol, and for the first time has demonstrated an inverse association between the severity of RA and frequency of alcohol exposure. While there are a number of limitations to the methodology of this study, the results do suggest that the consumption of alcohol may modify RA, influencing both risk and severity. Further research is needed to confirm the results that we have demonstrated, and to investigate the mechanisms by which alcohol influences outcome in RA.

Rheumatology key messages

- Alcohol consumption is associated with reduced risk of RA, confirming the results of a previous study.
- In patients with RA, alcohol consumption is associated with reduced disease severity.

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References

1 Ding B, Padyukov L, Lundstrom E *et al*. Different patterns of associations with anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis in the extended major histocompatibility complex region. Arthritis Rheum 2009;60:30–8.

2 Pedersen M, Jacobsen S, Klarlund M *et al*. Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. Arthritis Res Ther 2006;8:R133.

3 van der Helm-van Mil AH, Verpoort KN, le Cessie S, Huizinga TW, de Vries RR, Toes RE. The HLA-DRB1 shared epitope alleles differ in the interaction with smoking and predisposition to antibodies to cyclic citrullinated peptide. Arthritis Rheum 2007;56:425–32.

4 Klareskog L, Stolt P, Lundberg K *et al*. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38–46.

5 Kallberg H, Jacobsen S, Bengtsson C *et al*. Alcohol consumption is associated with decreased risk of rheumatoid arthritis: results from two Scandinavian case-control studies. Ann Rheum Dis 2009;68:222–7.

6 Hazes JM, Dijkmans BA, Vandenbroucke JP, de Vries RR, Cats A. Lifestyle and the risk of rheumatoid arthritis: cigarette smoking and alcohol consumption. Ann Rheum Dis 1990;49:980–2.

7 Voigt LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. Epidemiology 1994;5:525–32.

8 Cerhan JR, Saag KG, Criswell LA, Merlino LA, Mikuls TR. Blood transfusion, alcohol use, and anthropometric risk factors for rheumatoid arthritis in older women. J Rheumatol 2002;29:246–54.

9 Marinou I, Healy J, Mewar D *et al*. Association of interleukin-6 and interleukin-10 genotypes with radiographic damage in rheumatoid arthritis is dependent on autoantibody status. Arthritis Rheum 2007;56:2549–56.

10 Finckh A, Dehler S, Costenbader KH, Gabay C. Swiss Clinical Quality Management project for RA. Cigarette smoking and radiographic progression in rheumatoid arthritis. Ann Rheum Dis 2007;66:1066–71.

11 Jonsson IM, Verdrengh M, Brisslert M *et al*. Ethanol prevents development of destructive arthritis. Proc Natl Acad Sci USA 2007;104:258–63.

12 Arnett FC, Edworthy SM, Bloch DA *et al*. The American rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

13 Rau R, Herborn G. A modified version of Larsen's scoring method to assess radiologic changes in rheumatoid arthritis. J Rheumatol 1995;22:1976–82.

14 Feskanich D, Korrick SA, Greenspan SL, Rosen HN, Colditz GA. Moderate alcohol consumption and bone density among postmenopausal women. J Womens Health 1999;8:65–73.

15 Holbrook TL, Barrett-Connor E. A prospective study of alcohol consumption and bone mineral density. Br Med J 1993;306:1506–9.

16 Imhof A, Woodward M, Doering A *et al*. Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: results from three Monica samples (Augsburg, Glasgow, Lille). Eur Heart J 2004;25:2092–100.

17 Perrino AC Jr, Ralevski E, Acampora G, Edgecombe J, Limoncelli D, Petrakis IL. Ethanol and pain sensitivity: effects in healthy subjects using an acute pain paradigm. Alcohol Clin Exp Res 2008;32:952–8.

18 Clohisy JC, Roy BC, Biondo C *et al*. Direct inhibition of NF-kappa B blocks bone erosion associated with inflammatory arthritis. J Immunol 2003;171:5547–53.