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Moderate alcohol consumption is associated with increased radiological progression in women, but not in men, with early rheumatoid arthritis: results from the ESPOIR cohort (Étude et Suivi des Polyarthrites Indifférenciées Récentes)

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Objective: We conducted this study to determine whether alcohol consumption influences radiological progression in early rheumatoid arthritis (RA).
Method: Patients fulfilling the European League Against Rheumatism/American College of Rheumatology 2010 criteria in the early arthritis cohort ESPOIR (Étude et Suivi des Polyarthrites Indifférenciées Récentes) were included in this study. Alcohol consumption was collected at baseline and at each visit. We classified alcohol consumption into three groups: abstinent (0 g/day), moderate (≤ 20 g/day for women, ≤ 30 g/day for men), and abuse (> 20 g/day for women, > 30 g/day for men). The primary outcome was the occurrence of radiological progression, defined as an increase ≥ 5 points in the total Sharp/van der Heijde score. We investigated whether alcohol consumption is predictive of radiological progression at 1, 3, and 5 years by univariate and multivariate analysis adjusted for age, baseline erosion, rheumatoid factor, anti-citrullinated peptide antibody, smoking status, body mass index, and treatment with leflunomide or methotrexate and biologics.
Results: The study included 596 patients. When considering the influence of gender on the interaction between alcohol consumption and radiological progression, we showed a deleterious effect of moderate consumption in women [odds ratio (OR) = 1.73, 95% confidence interval (CI) 1.01; 2.96, p = 0.045] and a trend towards a protective effect of moderate consumption in men (OR = 0.50, 95% CI 0.21; 1.16, p = 0.106) in multivariate analysis.
Conclusion: Our data suggest a deleterious effect of moderate consumption of alcohol on radiological progression in women, but not in men, with early RA.

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that causes cartilage breakdown, bony erosion, and eventually disability. Genetic and environmental factors such as genes coding for human leucocyte antigen (HLA-DR shared epitope), tobacco, infectious agents, food, hormonal and cellular factors, and pro-inflammatory cytokines [tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-1 degradation] are involved in the mechanisms of the disease.

A systematic literature review suggested that alcohol is a protective factor against the occurrence of RA (1, 2) and several authors have suggested an inverse association between the activity of RA and alcohol (3). However, the impact of alcohol consumption on the radiological evolution of RA by radiological studies has only been studied in a small number of patients, with conflicting results (3–6). Other authors (6) have previously suggested an interaction between alcohol and gender on radiological progression. Therefore, we conducted this study to determine whether alcohol consumption influences radiological evolution during the first 60 months of early RA evolution.

Method

The ESPOIR cohort

The ESPOIR cohort is a French national observational cohort of patients with at least two joints affected by synovitis for more than 6 weeks and less than 6 months at baseline, and not undergoing treatment with synthetic

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or biological disease-modifying anti-rheumatic drugs (bDMARDs) at inclusion (7). Patients were enrolled from 2002 to 2005, in hospitals or in private practice, and followed every 6 months in the first 2 years and then every year, with an expected follow-up of 10 years. Multiple clinical and biological data were collected at each visit (at baseline and 6, 12, 18, 24, 36, 48, and 60 months). The Montpellier Ethics Committee approved the study protocol. Written consent forms were obtained from each patient before inclusion.

Study population

We collected the data from the ESPOIR cohort available up to 60 months of follow-up. In this cohort, we included patients fulfilling European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2010 criteria within the first 7 years of follow-up, the last visit available for the ESPOIR cohort.

Objectives and outcome measures

We investigated whether alcohol consumption is an independent predictor of radiological progression. Our primary outcome was the occurrence of radiological disease progression, defined by an increase to 5 points of the Sharp/van der Heijde score (SvHS) at 12 months of follow-up. We also investigated the radiological progression defined as an increase to 5 points of the SvHS at 3 and 5 years. We chose this radiological progression by 5 points of the SvHS as this has been found in the literature to be a clinically significant change (8). Patients with missing data during follow-up or at baseline were excluded.

Alcohol consumption

The self-declared consumption of alcohol was collected in grams/day at all visits up to 60 months. We classified the population into three categories according to the French recommendations of consumption thresholds [abstinent; moderate consumption, defined as ≤ 20 g/day for women and ≤ 30 g/day for men; and abuse, i.e. > 20 g/day for women and > 30 g/day for men (9)]. The initial consumption was used for evaluation of the primary outcome at 1 year. An average value of the alcohol consumption throughout the follow-up was used for the analyses to 3 and 5 years.

Radiological damage

Two trained rheumatologists scored radiographs of the wrists and feet, taken at baseline and 6, 12, 24, 36, and 60 months, using the SvHS. Readers were blinded from each other and had no information about the patients. Intraobserver and interobserver reliabilities were good (7).

Statistical analysis

Baseline demographics and laboratory parameters were compared using the chi-squared test for categorical variables or Fisher's exact test if necessary, and Student's t-tests or Mann–Whitney U-test for quantitative variables. Univariate logistic regression analyses were performed to assess the influence of predictive factors of radiological progression at 12, 36, and 60 months in both men and women with early RA. Where univariate analysis showed a significant impact of alcohol on radiological progression, we conducted a multivariate analysis adjusted for age, baseline erosion, rheumatoid factor (RF), anti-citrullinated peptide antibody (ACPA), smoking status, body mass index (BMI), treatment with leflunomide or methotrexate, and bDMARDs. The interaction of gender × alcohol was analysed by logistic regression. Multivariate stepwise logistic regression analysis using backward selection was performed to identify independent predictive factors of radiological progression ($p < 0.05$ for model entry and $p < 0.15$ for model retention) and the alcohol parameter. Statistical analysis was performed using Stata software, version 13 (StataCorp, College Station, TX, USA) in the Clinical Investigation Center of the Grenoble Alpes University Hospital. The statistician was blinded with regard to clinical information.

Results

Population analysis

In total, 596 of the 813 patients were assessed for the primary outcome at 12 months, 524 patients at 36 months, and 417 patients at 60 months. A total of 103 patients did not fulfil the EULAR/ACR 2010 criteria. A total of 114, 289, and 396 patients were excluded because of missing data at 12, 36, and 60 months, respectively. Characteristics of the excluded patients are described in the Supplementary Table S1. At baseline, significant differences were found between non-consumers, moderate consumers, and abusers (Table 1). The mean ± sd values of SvHS progression of non-consumers, moderate consumers, and abusers were, respectively, 3.5 ± 5.0, 2.9 ± 4.0, and 2.4 ± 3.1 at 1 year and 6.2 ± 10.7, 5.9 ± 8.3, and 3.2 ± 4.7 at 5 years. The proportion of patients with erosive disease (i.e. SvHS > 0) in non-consumers, moderate consumers, and abusers was, respectively, 33.9%, 48.7%, and 39.1% at baseline, 45.2%, 50.7%, and 50.0% at 1 year, and 43.3%, 48.1%, and 55.5% at 5 years. Very few patients had changed their alcohol consumption within 60 months: we found that only 9.2% of patients did so.

Alcohol consumption is not predictive of radiological progression at 1 and 3 years

Alcohol consumption was not a significant predictor of radiological progression at 12 and 36 months in the univariate and multivariate analyses.

Table 1. Baseline demographic characteristics of the population included in the analysis of the primary outcome.

		Consumers		
N = 596*	Non-consumers (n = 493)	Moderate consumers (n = 80)	Abusers (n = 23)	p†
Gender, female	399 (80.9)	50 (62.5)	13 (56.5)	< 0.001
Age (years)	50.1 (38.9; 56.9)	53.7 (44.7; 59.4)	56.1 (51.5; 57.0)	0.002
Active smoking	96 (19.5)	17 (21.2)	12 (52.2)	0.152
BMI (kg/m^2)	25.3	25.5	26.9	0.097
DAS28-ESR (0–9.55)	5.2 (4.5; 6.1)	5.0 (4.1; 5.7)	5.6 (4.9; 6.5)	0.017
HAQ (0–3)	1.0 (0.5; 1.5)	0.6 (0.2; 1.4)	1.2 (0.9; 1.7)	0.003
SvHS (0–448)	2.0 (0.0; 6,5)	5.5 (2.0; 10.0)	6.0 (2.0; 8.0)	< 0.001
RF positivity	239 (48.5)	44 (55.0)	5 (21.7)	0.019
ACPA positivity	206 (41.8)	42 (52.5)	5 (21.7)	0.026
ESR (mm/h)	22.0 (11.0; 38.0)	22.0 (12.0; 36.0)	19.0 (15.0; 38.0)	0.761
CRP (mg/dL)	9.0 (5.0; 23.0)	11.5 (4.0; 28.0)	9.0 (5.0; 14.0)	0.812
At least one bone erosion	167 (33.9)	39 (48.7)	9 (39.1)	0.035

Data are shown as median (interquartile range) for quantitative variables and as numbers and percentages for categorical variables, n (%).
BMI, body mass index; DAS28-ESR, Disease Activity Score based on 28-joint count–erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; SvHS, total Sharp/van der Heijde score; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
*Of the 813 initial patients, 103 patients without a diagnosis of RA for 7 years (ACR/EULAR 2010 criteria) and 114 patients who did not have the necessary data for assessing the primary endpoint (radiological missing data or missing data on alcohol consumption) were excluded.
†Kruskal–Wallis test/chi-squared test as appropriate.

No significant difference in radiological progression according to the different drinker groups (abstinent, moderate, abuse) was found (Table 2). At 36 months, we found a trend towards radiological progression in female consumers (OR = 1.17, 95% CI 0.72; 1.91, p = 0.532) and a trend towards no radiological progression in male consumers (OR = 0.57, 95% CI 0.26; 1.24, p = 0.159). Faced with these conflicting trends, we looked for an interaction between gender and being a consumer, using a multivariate logistic regression model, but could not demonstrate this at 1 year or 3 years (p = 0.096). There was no effect of gender on radiological progression at 12 or 36 months.

Moderate alcohol consumption prevents radiological progression in men and increases radiological progression in women at 5 years

We showed a significant deleterious effect of moderate consumption in women (OR = 1.89, 95% CI 1.14; 3.15, p = 0.014) and a trend towards a decrease in structural progression with moderate consumption in men in univariate analysis at 60 months (OR = 0.51, 95% CI 0.23; 1.16, p = 0.108). We looked for an interaction using a multivariate stepwise logistic regression analysis including gender, alcohol, and cons of the interaction term 'gender × alcohol'.

We found a significant interaction between gender and alcohol consumption (p = 0.002), which means that there is an effect of gender on progression at 60 months. When considering the influence of gender on the interaction between alcohol consumption and radiological progression, we showed a deleterious effect of moderate consumption in women (OR = 1.73, 95% CI 1.01; 2.96, p = 0.045) and a trend towards a protective effect of moderate consumption in men (OR = 0.50, 95% CI 0.21; 1.16, p = 0.106) in multivariate analysis (Table 3).

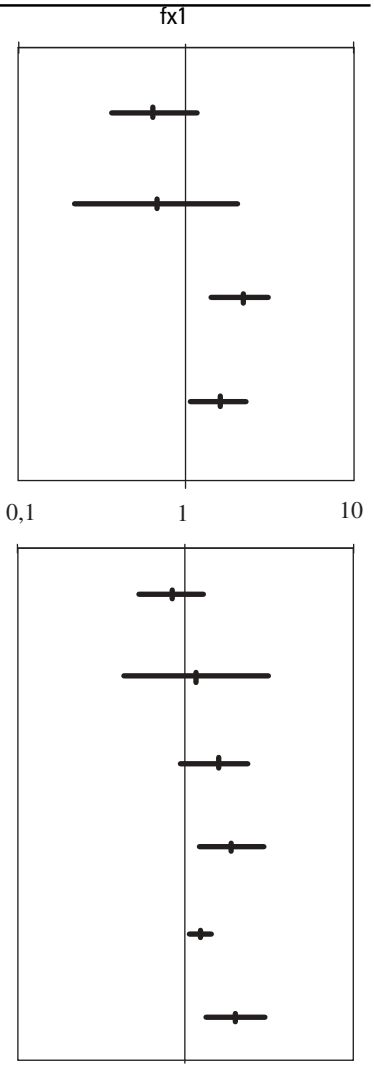
Discussion

We report the first study assessing the impact of alcohol consumption in early RA patients fulfilling the EULAR/ACR 2010 criteria, with a disease duration shorter than 6 months, in contrast to previous studies including RA patients fulfilling the ACR 1987 criteria, with variable disease durations ranging from less than 2 years (3, 4) to 14 years (2). We showed a gender effect on progression to 60 months in moderate consumer groups, with a protective trend of moderate consumption of alcohol on radiological progression at 5 years in men and a deleterious effect on radiological progression in women.

A systematic analysis of the literature suggested that alcohol is a protective factor against the occurrence of RA (1). Several authors have also suggested an inverse association between the clinical and biological activity of RA and alcohol consumption (3). The mechanism behind the relationship between alcohol consumption and radiological damage is still unclear and controversial. Alcohol is likely to reduce the immune response in animals and humans, to decrease the production of pro-inflammatory cytokines (10), and to prevent radiological progression (11). Alcohol

Table 2. Radiological progression at 12 and 36 months.

Risk factor	Univariate analysis OR (95% CI) p	Multivariate analysis OR (95% CI) p
At 12 months (n = 596) Alcohol by group		
Moderate vs non-consumers	0.75 (0.42; 1.33) 0.327	0.64 (0.36; 1.16) 0.144
Abusers vs non-consumers	0.59 (0.20; 1.76) 0.340	0.67 (0.22; 2.03) 0.475
ACPA	2.17 (1.49; 3.16) ≤ 0.001	2.15 (1.47; 3.15) ≤ 0.001
Erosion	1.54 (1.06; 2.25) 0.024	1.56 (1.06; 2.30) 0.025
At 36 months (n = 524) Alcohol by group		
Moderate vs non-consumers	0.97 (0.65; 1.45) 0.883	0.84 (0.54; 1.30) 0.432
Abusers vs non-consumers	1.11 (0.43; 2.81) 0.833	1.16 (0.43; 3.12) 0.776
ACPA	2.09 (1.47; 2.99) ≤ 0.001	1.52 (0.97; 2.40) 0.070
RF	2.28 (1.61; 3.25) ≤ 0.001	1.87 (1.19; 2.93) 0.007
Age (10 years*)	1.25 (1.08; 1.46) 0.004	1.22 (1.03; 1.44) 0.023
Erosion	2.26 (1.54; 3.33) ≤ 0.001	1.95 (1.30; 2.94) 0.001



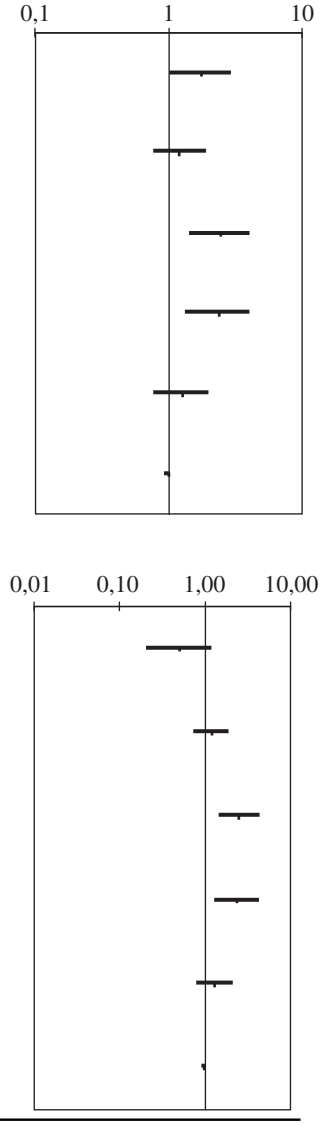
ACPA, anti-citrullinated protein antibody; RF, rheumatoid factor; OR, odds ratio; CI, confidence interval.
*Increase in progression risk every 10 years.

abusers show elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6. However, long-term intake of low to moderate amounts of alcohol has been shown to both reduce levels of TNF-α, IL-1, IL-6, and C-reactive protein (CRP) (12), and to increase levels of anti-inflammatory cytokines(13).

The impact of alcohol consumption on the radiological evolution of RA has been studied in only a few studies, often as a secondary objective with various outcome measures, leading to conflicting results (3–6). Maxwell et al (3) suggested that alcohol consumption was inversely associated with Larsen score. Nissen et al (6) showed a reduction in radiological progression assessed by the Ratingen score in male drinkers compared to male non-drinkers. A dose-dependent relation between alcohol consumption and radiological progression was found in RA patients who consume 15 or more drinks per month (5). Other studies did not find significant associations between alcohol consumption and radiological progression at 7 years (4). The protective effect of alcohol consumption on radiological progression observed in men, but not in women,

Table 3. Analysis of gender (female or male) × moderate alcohol consumption interaction for radiological progression at 60 months.

	Univariate analysis	Multivariate analysis	Adjusted forest plot
Risk factor (n = 417)	OR (95% CI) p	OR (95% CI) p	Reduced risk of radiological progression / Increased risk of radiological progression
Female × alcohol intake			
Interaction with moderate alcohol intake	1.89 (1.14; 3.15) 0.014	1.73 (1.01; 2.96) 0.045	
RF	1.52 (1.02; 2.27) 0.042	1.17 (0.76; 1.82) 0.472	
Erosion	2.36 (1.45; 3.83) 0.001	2.41 (1.46; 3.99) 0.001	
bDMARD	1.86 (1.02; 3.40) 0.043	2.34 (1.34; 4.08) 0.003	
Methotrexate or leflunomide	1.43 (0.91; 2.25) 0.125	1.24 (0.79; 1.94) 0.356	
BMI	0.98 (0.94; 1.02) 0.363	0.97 (0.93; 1.02) 0.203	
Male × alcohol intake			
Interaction with moderate alcohol intake	0.51 (0.23: 1.16) 0.108	0.50 (0.21; 1.16) 0.106	
RF	1.52 (1.02; 2.27) 0.042	1.19 (0.77; 1.85) 0.435	
Erosion	2.36 (1.45; 3.83) 0.001	2.47 (1.49; 4.10) 0.001	
bDMARD	5.26 (1.59; 17.41) 0.007	2.30 (1.32; 4.02) 0.003	
Methotrexate or leflunomide	1.89 (0.71; 5.00) 0.202	1.28 (0.82; 2.00) 0.279	
BMI	0.89 (0.78; 1.02) 0.082	0.97 (0.93; 1.02) 0.494	



RF, rheumatoid factor; bDMARD, biological disease-modifying anti-rheumatic drug; BMI, body mass index; OR, odds ratio; CI, confidence interval.

may be partly explained by gender differences in RA severity (14). Nevertheless, several other authors have demonstrated no gender differences in terms of radiological outcomes. Moderate alcohol consumption also appears to have a greater influence on systemic markers of inflammation, such as CRP and leucocyte count, in men than in women (15).

One of the main strengths of our study was the use of the largest worldwide prospective cohort of early arthritis, for which the biological, immunological, and radiological data were carefully collected. In our study, the radiological evolution was evaluated prospectively by two reviewers which were double blinded and blinded with respect to clinical information (7). Another strength of this study is the inclusion of the most important predictive factors of radiological progression (7), i.e. baseline erosion, ACPA, and RF, in the multivariate analysis. In contrast to previous studies which assessed the impact of alcohol consumption on radiological score change (3–6), we report here the impact of alcohol consumption on radiological

progression, defined as a clinically significant change in the SvHS (8). We chose not to study radiological progression linearly because this had already been done in the pilot study by Nissen et al (6). Hence, over the course of a lifetime in a chronic disease such as RA, the role of alcohol is likely to be clinically significant.

Some limits to our study should be emphasized. First, the analysis of alcohol consumption in men is based on a limited number of patients because of the gender ratio in the ESPOIR early arthritis cohort and because of the number of patients with missing data. However, the baseline alcohol consumption of these patients was similar to that of the included patients. The lack of statistical significance of the trend towards a protective role against radiological damage at 5 years is probably explained by a lack of statistical power. These data confirmed the trend towards a reduction in radiological progression among casual male drinkers compared to male non-drinkers (6). Secondly, alcohol consumption was recorded as a self-declared outcome, with a possibility of underestimated consumption. Most previous studies (16) also used this proxy reliable outcome. When we adjusted our multivariate model on these parameters at 5 years, it did not change the meaning of our results on the role of alcohol. We found alcohol to be a significant risk factor for structural progression in women and a non-significant protective factor in men. Our analysis does not allow the study of the impact of therapies over time and reveals these as risk factors for structural evolution, whereas the presence of treatments such as biologics is the consequence of more aggressive disease, rather than the cause of structural evolution.

Finally, as chronic abuse of alcohol increases morbidity and mortality, our results should not lead to a recommendation for men to consume alcohol.

Conclusion

Our data suggest a protective effect of moderate consumption of alcohol on radiological progression at 5 years in men and a deleterious effect on radiological progression in women with early RA. Hence, recording alcohol consumption in future studies investigating radiological progression in early RA patients, especially when analysing the effects of gender, appears to be relevant to avoid confusion bias. Further research is required to better understand the impact of alcohol consumption on RA in terms of the type of alcohol, drinking pattern, volume, drug interactions, and the ethnicity of the population, while taking into account the morbidity and mortality of this consumption.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Demographic characteristics of the initial population and of the excluded population from the analysis of the primary outcome.

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