MRI in the earliest phases of rheumatoid arthritis

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Chapter 6: Moderate use of alcohol is associated with lower levels of C-reactive protein but not with less severe joint inflammation; a cross-sectional study in early RA and healthy volunteers

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Abstract

Introduction: Moderate alcohol consumption is protective against rheumatoid arthritis (RA)-development and associated with lower levels of systemic inflammation in RA and in the general population. We therefore hypothesized that moderate alcohol consumption is associated with less severe local inflammation in joints in RA, detected by MRI. Since asymptomatic persons can have low-grade MRI-detected inflammation [1,2], we also hypothesized that alcohol consumption is associated with the extent of MRI-inflammation in asymptomatic volunteers.

Methods: 188 newly presenting RA-patients and192 asymptomatic volunteers underwent a unilateral contrast-enhanced 1.5T MRI of MCP, wrist and MTP-joints. The MRIs were scored on synovitis, bone marrow edema and tenosynovitis; the sum of these yielded the MRI-inflammation score. MRI-data was evaluated in relation to current alcohol consumption, categorized: non-drinkers, consuming 1-7 drinks/week, 8-14 drinks/week, and›14 drinks/week. Association between C-reactive protein-level and alcohol was studied in 1070 newly presenting RA-patients.

Results: Alcohol consumption was not associated with the severity of MRI-detected inflammation in hand and foot joints of RA-patients ($p = 0.55$) and asymptomatic volunteers ($p = 0.33$). A J-shaped curve was observed in the association between alcohol consumption and CRP-level, with the lowest levels in patients consuming 1-7 drinks/week ($p = 0.037$).

Conclusion: Despite the fact that moderate alcohol consumption has been shown protective against RA, and our data confirm a J-shaped association of alcohol consumption with CRP-levels in RA, alcohol was not associated with the severity of joint inflammation. The present data suggest that the pathophysiological mechanism underlying the effect of alcohol consists of a systemic effect that might not involve joints.

Introduction

In the general population moderate alcohol consumption has been associated with lower levels of systemic inflammation, as several studies have shown that alcohol consumption is associated with levels of C-reactive protein (CRP) in a J-shaped or U-shaped manner.[1,2] Individuals with an alcohol consumption of 1-2 drinks daily had the lowest CRP-levels.

In rheumatoid arthritis (RA), the influence of alcohol consumption on the risk of developing RA has been studied extensively. Moderate alcohol consumption has been associated with a decreased risk on developing RA.[3-5] The risk of developing RA was lowest in persons who consumed approximately 1 unit of alcohol per day.[3] In RA-patients, alcohol consumption was associated with lower levels of inflammatory markers (e.g., CRP and erythrocyte sedimentation rate (ESR) soluble tumor necrosis factor receptor II, Interleukin-6 (IL-6)).[6-8] For IL-6 levels a U-shaped association was also observed, with the lowest IL-6 levels in RA-patients that consumed 1 unit of alcohol per day.[6]

Within RA the effect of alcohol on local inflammation in joints has been studied once using the swollen joint count (SJC) and no evident association between alcohol consumption and the number of swollen joints was observed in 1238 RA-patients.[9] Because magnetic resonance imaging (MRI) is more sensitive than the swollen joint count to detect local inflammation [10], we anticipated that MRI is useful to detect an effect of alcohol on the severity of local inflammation in RA.

Furthermore, as the effect of alcohol on markers of systemic inflammation is also present in the general population [1] and since some asymptomatic persons of the general population also have low-graded MRI-detected inflammation [11,12], an association between alcohol and joint inflammation might not be confined to RA-patients, but even be present in asymptomatic volunteers.

Therefore, we hypothesized that moderate alcohol consumption is associated with less inflammation in hand and foot joints, visualized by MRI, both in patients with RA and in asymptomatic volunteers. The present study evaluated these two hypotheses.

Methods

Participants

The RA-patients studied were consecutively included in the Leiden Early Arthritis Clinic (EAC). This is an inception cohort that includes patients with ≥ 1 swollen joint and a symptom duration of < 2 years. When patients presented at the outpatient clinic, questionnaires were obtained that included a self-reported average number of alcohol consumptions per week (current consumption). Furthermore, physical examination was performed and blood samples were obtained.[13] RA was defined as fulfilling the 1987 ACR-criteria during the first year of follow-up. From 1993 to 2016 1244 RA-patients were included in the EAC cohort. The association between alcohol consumption and CRP was assessed in all RA-patients of whom alcohol consumption was available (1070 RA-patients). From 2010 onwards MRI was added to the study protocol [10] and the association between alcohol and MRI-detected inflammation was assessed in 188 consecutive RA-patients who underwent an MRI at baseline (See Supplementary Figure 1 for a flowchart).

The asymptomatic volunteers were recruited between November 2013 and December 2014, and were described earlier.[12] Volunteers were recruited via advertisements in local newspapers and websites. Volunteers had no history of RA or other inflammatory rheumatic diseases, no joint symptoms during the last month and no clinically detectable arthritis at physical examination. Questionnaires were obtained, including self-reported alcohol consumption. CRP-levels were not assessed in these volunteers. 193 volunteers underwent an MRI; in one of these persons no data on alcohol consumption was obtained. The volunteers received a voucher of 20€ to compensate for their time and travel costs and did not receive a report of the MRI. Therefore, volunteers had no/limited benefit from participating. The medical ethics committee of the Leiden University Medical Center approved this study and all participants have given a written informed consent.

MRI-protocol and scoring

A contrast-enhanced MRI was performed of the unilateral metacarpophalangeal (MCP) 2-5 joints, wrist joints and metatarsophalangeal (MTP) 1-5 joints. In the EAC

the most painful side was scanned or in case of equally severe symptoms at both sides the dominant side was scanned. In asymptomatic volunteers the dominant side was scanned. An ONI-MSK-extreme 1.5T extremity MRI-scanner (GE, Wisconsin, USA) was used. The scan protocol is described in more detail in the Supplementary methods. Briefly, T1-weighted sequences (T1) were acquired. After intravenous contrast administration (gadoteric acid, Guerbet, Paris, 0.1 mmol/kg) T1-weighted sequences with fat saturation (T1Gd) were performed. The foot was scanned with T2-weighted fat saturated (T2) and T1 sequences in the first 106 RA-patients and with T1Gd in the last 82 RA-patients. Scoring of synovitis and bone marrow edema (BME) was done according to the RA MRI score (RAMRIS) method in the MCP, wrist and MTP joints.[14] Tenosynovitis was scored according to Haarvardsholm et al. in the MCP and wrist.[15] The total MRI-inflammation score was calculated by summing the synovitis, BME and tenosynovitis scores, and ranged between 0 and 189. MRI-scoring was done independently by trained readers, the RA-patients were scored by two readers (WPN and ECN) and the asymptomatic volunteers were scored by two readers (HWvS and LM). Readers were blinded for any clinical data. Furthermore, to exclude observer bias introduced by knowledge that persons had no symptoms, MRI images of asymptomatic volunteers were mixed with MRI images of RA-patients and patients with arthralgia without clinical synovitis (n = 99). The within-reader intraclass correlation coefficients (ICC) of the readers were all greater than 0.93 and the between reader ICCs of the four readers were all above 0.91. The mean scores of two readers were used for the analyses.

Analyses

Alcohol consumption was categorized into 4 groups: non-drinkers, participants that consume 1-7 drinks/week, 8-14 drinks/week and >14 drinks/week, this corresponded to no, 1, 2 and more drinks daily as used is some previous studies.[3-6] Groups were compared with the Kruskal Wallis test and the Mann-Whitney U-test when appropriate. The association of alcohol consumption with MRI-detected inflammation was analysed using univariable and multivariable linear regressions adjusted for age, gender, smoking status, and anti-citrullinated protein antibody (ACPA). ACPA was not assessed in asymptomatic volunteers and the multivariable

linear regression in the asymptomatic volunteers was adjusted for age, gender, and smoking status. In the linear regression analyses MRI inflammation scores were log10-transformed (log10(score+1)) to approximate a normal distribution. To analyse whether a J-shape existed in the association between alcohol consumption and CRP-levels, a linear regression with a piecewise linear spline on 1 alcohol consumption per week was used as this fitted the data best. SPSS V23.0.0 was used for analysis.

Results

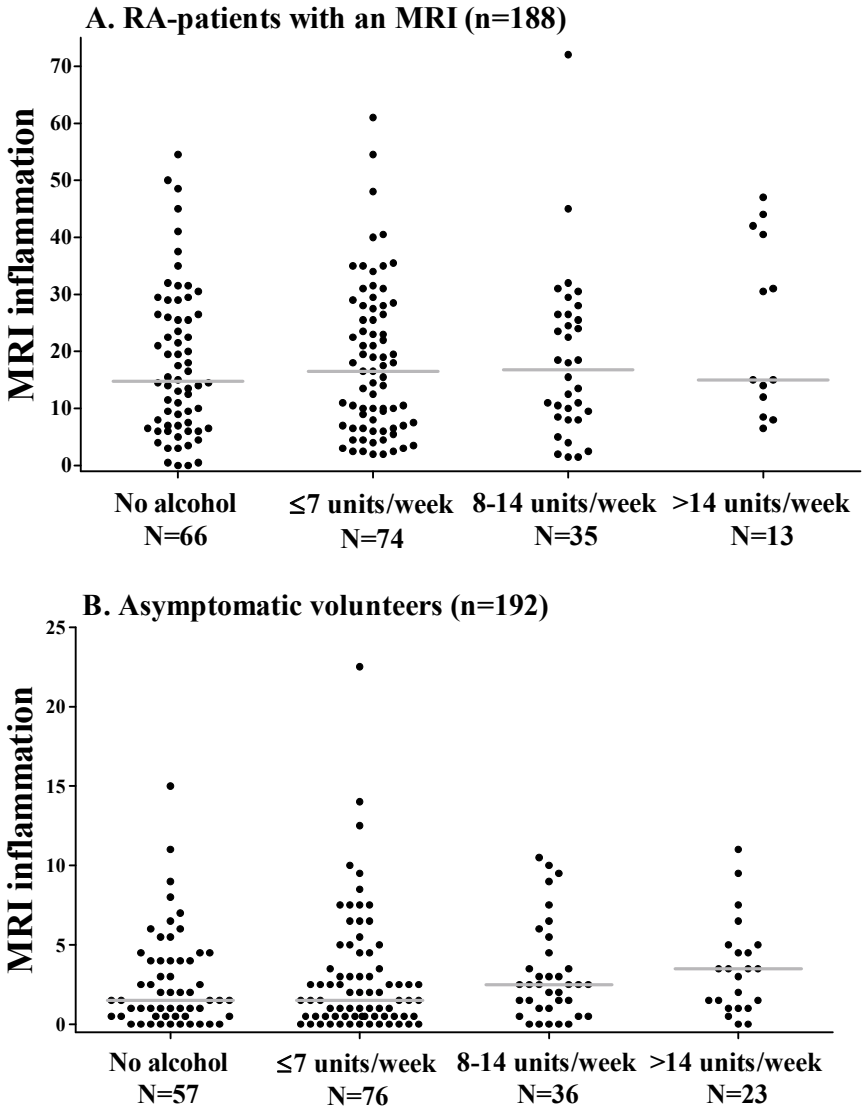
Patients

Baseline characteristics are presented in table 1. Sixty-four % (n = 121) of the RA-patients that underwent MRI (See Supplementary Figure 1 for a flowchart), consumed alcohol at baseline, with a median consumption of 6 drinks/week (IQR 3-11). Of the asymptomatic volunteers, 70% (n = 135) consumed alcohol with a median consumption of 7 drinks/week (IQR 4-14). The RA-patients consumed on average one alcohol consumption less than the asymptomatic volunteers, this difference did not reach statistical significance (p = 0.14).

The association of MRI-detected inflammation with alcohol consumption in RA-patients

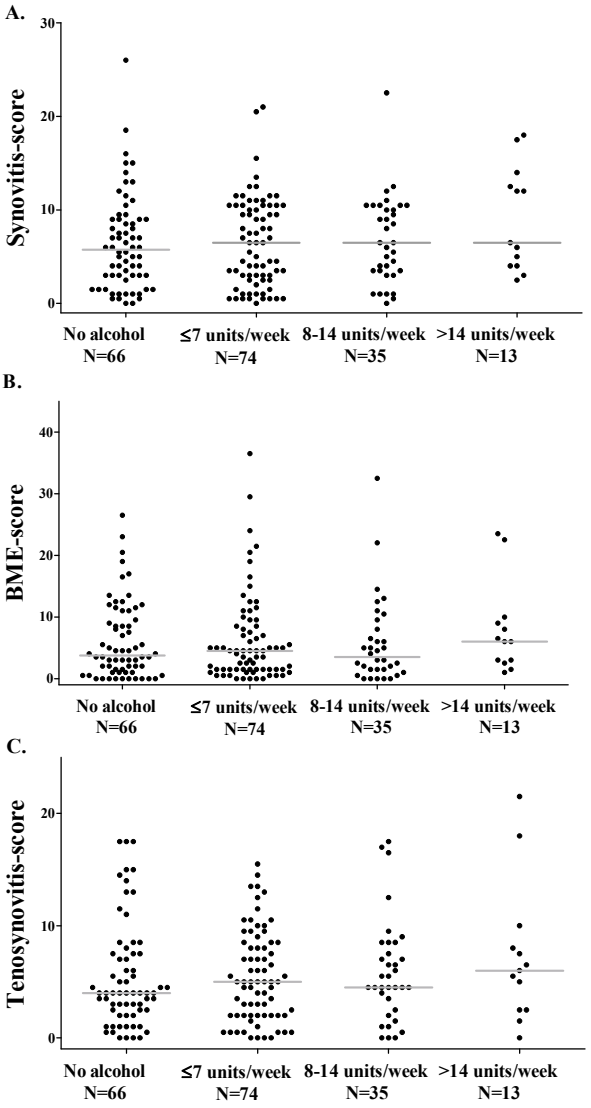
The extent of MRI-detected inflammation was first compared in 4 categories of alcohol consumption. The median MRI-detected inflammation in RA-patients did not significantly differ between the 4 categories; RA-patients who did not drink alcohol had a median MRI inflammation score of 14.8 (IQR = 7.0-26.5), RA-patients consuming ≤ 7 drinks/week had a median of 16.5 (IQR = 7.0-27.5), RA-patients consuming 8-14 drinks/week had a median of 16.8 (IQR = 8.5-26.5),and RA-patients consuming › 14 drinks/week median of median of 15.0 (IQR = 12.0-40.5), p = 0.53 (Figure 1A). When analysing BME, synovitis, and tenosynovitis separately similar results were seen (see Figure 2).

Figure 1 The association between alcohol consumption and the severity of MRI-detected inflammation in hand and foot joints of RA-patients (A), asymptomatic volunteers (B)



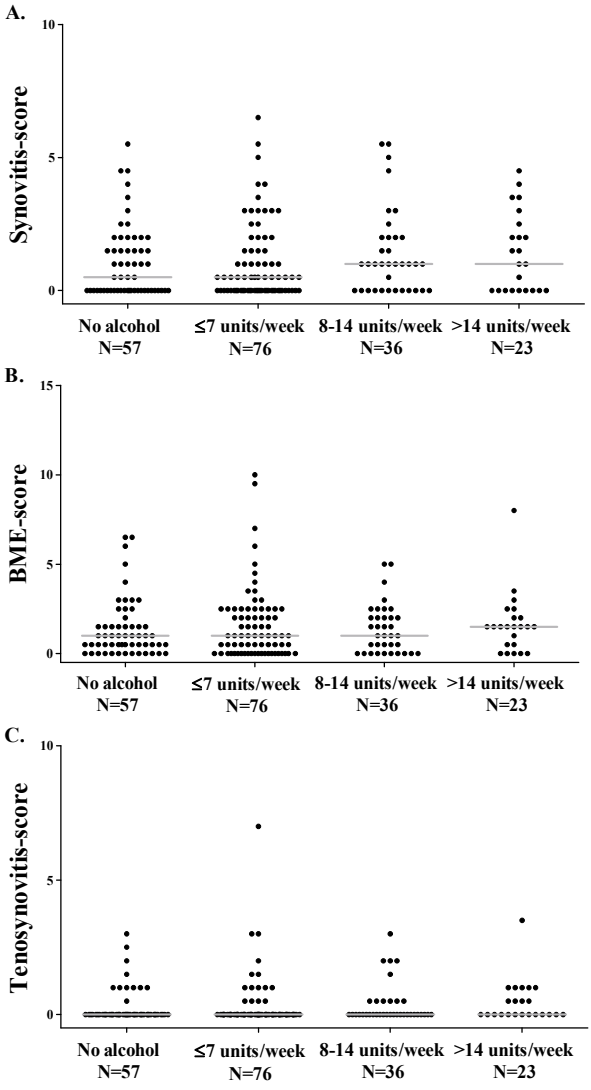
The lines presented in the figure represent median values. MRI-detected inflammation does not differ significantly between the 4 groups in RA-patients and asymptomatic volunteers (respectively $p = 0.53$ and $p = 0.33$)

Figure 2 The association between alcohol consumption and the severity of synovitis (A), BME (B) and tenosynovitis (C) in RA-patients



The lines presented in the figure represent median values. Synovitis, BME, and tenosynovitis scores did not differ significantly between the 4 groups in RA-patients (respectively p = 0.60, p = 0.47 and p = 0.85).

Figure 3 The association between alcohol consumption and the severity of synovitis (A), BME (B) and tenosynovitis (C) in asymptomatic volunteers



The lines presented in the figure represent median values. Synovitis, BME, and tenosynovitis scores did not differ significantly between the 4 groups in asymptomatic volunteers (respectively $p = 0.81$, $p = 0.44$ and $p = 0.15$).

The association between alcohol and MRI-detected inflammation was also evaluated with the number of alcohol consumptions on a continuous scale, also showing no association (β = 1.011, 95%CI = 0.992-1.030, p = 0.36). To exclude the possibility of non-significance due to the presence of confounders, the analysis was subsequently adjusted for age, gender, smoking, and ACPA. Also this showed no association between alcohol and inflammation in hand and foot joints. (β = 0.994, 95%CI = 0.975-1.013, p = 0.53).

The association of MRI-detected inflammation with alcohol consumption in asymptomatic volunteers

In asymptomatic volunteers, the extent of MRI-detected inflammation was also compared in 4 categories of alcohol consumption. The median MRI-detected inflammation did not significantly differ between the 4 categories; asymptomatic volunteers who did not drink alcohol had a median MRI inflammation score of 1.5 (IQR = 0.5-4.0), ≤ 7 drinks/week 1.5 (IQR = 0.5-4.0), 8-14 drinks/week 2.5 (IQR = 1.0-4.0), > 14 drinks/week 3.5 (IQR = 1.0-5.0), p = 0.33 (Figure 1B). Analysing BME, synovitis, and tenosynovitis separately revealed similar results (see Figure 3).

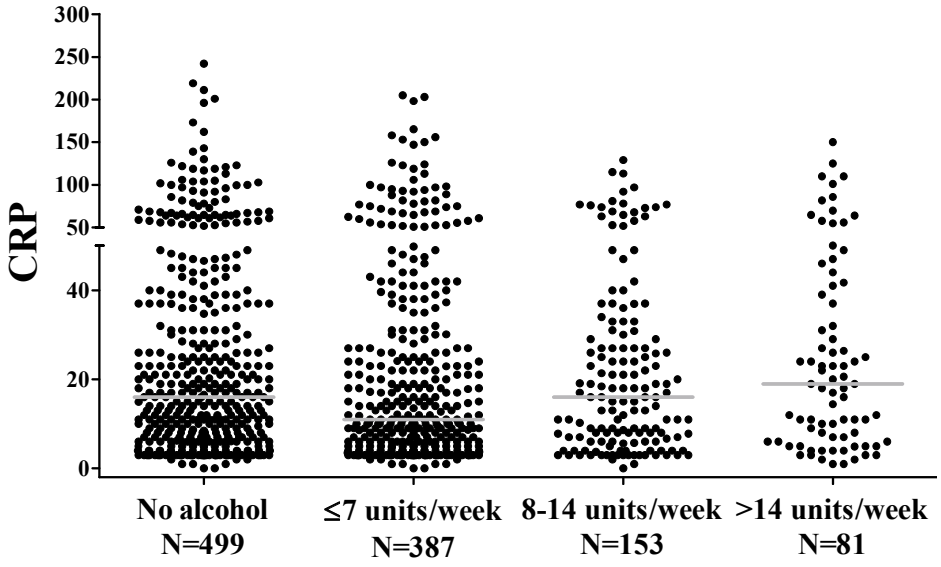
Assessing alcohol consumption on a continuous scale an association was observed in univariable analysis (β = 1.018, 95%CI = 1.002-1.034, p = 0.025). However, after adjusting for age, the association disappeared (β = 1.003, 95%CI = 0.99-1.016, p = 0.62), and also after adjusting for age, gender, and smoking status no association was observed (β = 1.002, 95%CI = 0.99-1.015, p = 0.76).

Association of alcohol consumption and CRP in RA-patients

Because of the negative findings done thus far, we searched for a positive control and we wished to verify if the previously observed association between alcohol consumption and CRP was present in our cohort of RA-patients. In a total of 1070 RA-patients 58% consumed alcohol with a median consumption of 6 drinks/week (IQR 2-11). The median CRP-level in nondrinkers was 16 mg/L (interquartile range (IQR) = 6-37 mg/L), in patients that consume ≤ 7 drinks/week the median was 11 mg/L (IQR = 5-29 mg/L), in patients that consume 8-14 drinks/week the median was 16 mg/L (IQR = 6-31 mg/L), and in patients that consume > 14 drinks/week the

median was 19 mg/L (IQR = 6-41 mg/L). The median CRP-levels between these four groups differed significantly (p = 0.043). Evaluation by eye suggested the presence of a J-shaped effect with the lowest CRP in the group that consumes ≤ 7 drinks/week. Indeed comparing this group with the non-drinkers revealed a significant difference (p = 0.011, Figure 4). To further confirm this J-shape, a piecewise linear spline regression was used. The regression was divided into 2 regression coefficients of the J-curve (e.g. the left decreasing part and the right increasing part with the lowest CRP-level on 1 drink/week). CRP-level decreased significantly with increasing alcohol consumption up until a maximum of 1 drink/week (β = 0.80, 95%CI = 0.68-0.93, p = 0.003). In patients consuming > 1 drink/week, CRP-levels increased significantly (β = 1.015, 95%CI = 1.004-1.025, p = 0.006). Hereby, the J-shaped association was confirmed. In a multivariable analyse adjusting for

Figure 4 The association between alcohol consumption and the association between alcohol consumption and CRP-levels in RA-patients



The lines presented in the figure represent median values. CRP does not differ significantly between the groups (p = 0.043).

age, gender, smoking and ACPA status, the downward part of the J-curve was still present (β = 0.85, 95%CI = 0.73-0.99, p = 0.039) but the upward part of the J-curve lost its significance (β = 1.007, 95%CI = 1.00-1.017, p = 0.214). A beta of 1.007 indicates that for every drink/week increase in alcohol consumption there is an 1.007-fold increase in CRP-level, thus in patients consuming > 1 drink/week higher alcohol consumption was associated with a higher CRP-level.

Discussion

Moderate alcohol consumption has been associated with less severe systemic inflammation (generally measured using CRP-levels), in the general population. [1,2] Also within RA-patients, it has been shown repeatedly that moderate alcohol consumption lowers the risk of developing RA and is associated with less severe systemic inflammation [3,4] Because of these findings, we hypothesized that moderate alcohol consumption might also be associated with less severe inflammation in joints, which can be sensitively detected with MRI. The current data revealed no association between alcohol consumption and the severity of local inflammation in hand and foot joints on MRI. Thus, though moderate alcohol consumption is associated with lower levels of systemic inflammation and a lower risk to develop RA, based on the present findings it is not associated with less severe inflammation in joints.

The pathophysiological mechanism underlying the association between alcohol consumption and inflammation is unknown. Different studies explored the immunoregulatory effects of alcohol and various results have been observed. High alcohol consumption has been reported to be associated with depleted cell-mediated and humoral immune responses [16], whereas other data suggest that low alcohol consumption has a stimulatory effect on the cellular immune response.[17]

Distinguishing high alcohol consumption from moderate alcohol consumption has several pitfalls. In this study, assessment of alcohol consumption is based on questionnaires and could therefore deviate from the true alcohol consumption. Also, the concentration of alcohol in plasma might significantly differ, depending on the

size and type of the alcohol consumption and variability in the period in which alcohol is used. Nonetheless, the fact that the association of alcohol consumption and CRP-levels in this study resemble the associations found in the literature [1] supports the validity of the data on alcohol consumption.

Alcohol consumption is part of a lifestyle and might therefore be a proxy for other factors associated with lifestyle. So, the association of alcohol on joint inflammation might have been influenced by other factors. Multivariate analyses were performed to adjust for some of these factors (amongst others age, smoking), but this did not majorly influence the study results.

The lack of association between alcohol consumption and the extent of local joint inflammation on MRI found in this study might have been caused by an inadequate power to detect an effect of alcohol on joint inflammation on MRI, especially as the previously observed effect of alcohol on systemic inflammatory markers, such as CRP-levels, was generally observed in very large studies.[1] MRI is more time-consuming and more expensive to perform than e.g. CRP-level measurements; making an MRI-study within thousands of RA-patients infeasible. In our view there was not even a trend towards an association between alcohol and local inflammation, this makes it unlikely that the present finding is falsely negative.

The present study in early RA had a cross-sectional study design. This allowed to perform the measurements before disease modifying treatment was initiated. A longitudinal study is needed to evaluate the association between alcohol and long-term outcome of RA, but current treatments and treat-to-target strategies may mask an effect of alcohol (if it is present) on the course of RA.

According to the European Society of musculoSkeletal Radiology (ESSR) recommendations, BME was evaluated on T1Gd. The RAMRIS method suggest to use T2, but a T2 was omitted from our scan protocol since previous studies have shown that these sequences preform equally well to depict BME [18,19] and a T1Gd has already been used to assess synovitis and tenosynovitis. This allowed a shorter imaging time for the participants.

Healthy, asymptomatic volunteers can also have some subclinical inflammation in hand and foot joints, especially at higher age. The nature of this inflammation is incompletely clear. Immunosenescence or degeneration may play a role. Although

the origin is incompletely known, we speculated that a potential effect of alcohol on joint inflammation might also be present in persons without RA. But similar as to within RA, alcohol did not influence the severity of subclinical inflammation in hand and foot joints of asymptomatic volunteers.

Conclusions

Moderate alcohol consumption has been shown to have a beneficial effect on the risk of RA-development and inflammatory markers, and the present study confirmed a J-shaped association between alcohol and CRP, we observed no association between alcohol and the extent of local inflammation in joints. Therefore the present data suggest that the pathophysiological mechanism underlying the effect of alcohol consists of a systemic effect that might not involve joints.

Supplementary material
Supplementary material is available from the author on request.

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Table 1 Baseline characteristics of RA-patients and asymptomatic volunteers in which hand and foot MRIs were performed and RA-patients in which CRP was analysed

	RA-patients with an MRI n = 188	Asymptomatic volunteers n = 192	RA-patients with CRP measurement n = 1070
Age in years, mean (SD)	56 (14)	50 (16)	56 (15)
Female, n (%)	121 (64.4)	NA	717 (67.0)
Symptom duration in weeks, median (IQR)	15.4 (7.9-29.6)	NA	18.4 (9.1-35.6)
CRP in mg/L, median (IQR)	10.0 (3.8-23.5)	NA	14.0 (6.0-33.0)
ACPA positivity, n (%)	102 (54.3)	NA	550 (52.6)
RF positivity, n (%)	116 (61.7)	NA	604 (56.9)
Curernt smokers, n (%)	50 (28.4)	17 (8.8)	271 (25.7)
Patients consuming alcohol, n (%)	121 (64.4)	135 (69.9)	621 (58.0)
Units/week, median (IQR)	6.0 (3.0-10.5)	7.0 (4.0-14.0)	6.0 (2.0-10.5)

Of RA-patients with an MRI smoking status was missing in 12 RA.
In RA-patients with a CRP measurement smoking status, RF and ACPA status was missing in respectively 17, 9, and 24 RA-patients.
NA, not assessed.