Alcohol consumption is associated with decreased risk of rheumatoid arthritis: results from two Scandinavian case–control studies

H Källberg, S Jacobsen, C Bengtsson, M Pedersen, L Padyukov, P Garred, M Frisch, E W Karlson, L Klareskog, L Alfredsson

ABSTRACT

Objectives: To determine the association between risk of rheumatoid arthritis (RA) and alcohol consumption in combination with smoking and HLA-DRB1 shared epitope (SE).

Methods: Data from two independent case–control studies of RA, the Swedish EIRA (1204 cases and 871 controls) and the Danish CACORA (444 cases and 533 controls), were used to estimate ORs of developing RA for different amounts of alcohol consumed.

Results: Alcohol consumption was significantly more common in controls (p<0.05) and dose-dependently associated with reduced risk of RA (p for trend <0.001) in both studies. Among alcohol consumers, the quarter with the highest consumption had a decreased risk of RA of the order of 40–50% compared with the half with the lowest consumption [EIRA, OR = 0.5 (95% CI 0.4 to 0.6); CACORA, OR = 0.6 (95% CI 0.4 to 0.9)]. For the subset of RA that is seropositive for antibodies to citrullinated peptide antigens, alcohol consumption reduced the risk most in smokers carrying HLA-DRB1 SE alleles.

Conclusions: The observed inverse association between alcohol intake and risk of RA and the recent demonstration of a preventive effect of alcohol in experimental arthritis indicate that alcohol may protect against RA. This highlights the potential role of lifestyle in determining the risk of developing RA, and emphasises the advice to stop smoking, but not necessarily to abstain from alcohol in order to diminish risk of RA. The evidence of potential RA prevention should prompt additional studies on how this can be achieved.

Rheumatoid arthritis (RA) is a common, complex disease which seems to develop as a result of an interplay between inducing and protective environmental and genetic factors. Recently, evidence for a possible interaction between lifestyle factors and genetic factors was provided by studies showing how smoking interacts with the shared epitope (SE) alleles of the HLA-DRB1 gene in providing a very high risk of developing RA. Furthermore, the effect of both these risk factors was confined to one subset of RA, characterised by the presence of antibodies to citrullinated peptide antigens (ACPA). These findings are of interest not only for public health, but also from a biological perspective, as they provide leads to a possible aetiology of RA.

Our interest in the role of alcohol consumption was triggered by several reports suggesting that alcohol influences inflammation in general and arthritis in particular; alcohol has been shown to diminish the response to immunogens in animals as well as in humans. Alcohol can downregulate the production of proinflammatory molecules through its influence on innate immunity. Notably, addition of alcohol to the drinking water of mice was recently shown to reduce clinical signs of arthritis as well as joint destruction.

An indication that alcohol consumption may also influence the risk of human RA has come from four studies on environmental factors in RA development, whereas other studies found no alcohol–RA association. No studies have been published that quantify the possible influence of alcohol consumption on the risk of RA and relate the effect of alcohol to genetic risk factors and the effects of smoking.

We combined information from two independent population-based case–control studies on environmental and genetic risk factors for RA, to determine the influence of alcohol consumption on RA taking into account potential interactions between alcohol consumption, smoking and the presence of HLA-DRB1 SE alleles.

METHODS

Two population-based case–control studies on environmental and genetic risk factors for RA were used. The first was the Swedish EIRA (Epidemiological Investigation of Rheumatoid Arthritis). The EIRA material used in this study comprised 1419 incident cases of RA (age 18–70 years; recruited from 19 clinics in the south and middle of Sweden during the period between May 1996 and December 2003). All patients were diagnosed by rheumatologists according to the criteria of the American College of Rheumatology (ACR) in 1987. A total of 1674 controls were randomly selected from the general population matching for age, sex and residential area to the RA cases. More details on the study design and methods used are given elsewhere. The second study used was the Danish CACORA (Case–Control Study on Rheumatoid Arthritis). This material comprised 515 prevalent cases of RA fulfilling the ACR 1987 classification criteria for RA (mean disease duration 2.3 years, range 0–5 years) and 769 controls recruited between August 1998 and July 2003. Patients with RA were identified in rheumatology and internal medicine.
Exenad report

Data collection and biological analysis

In EIRA, information on alcohol, smoking and other environmental exposures was obtained by means of an extensive self-administered questionnaire given to the patients shortly after they had been informed about their RA diagnosis, and mailed to the controls. The questionnaires were designed to be answered at home, and incomplete questionnaires were completed, by telephone or mail, by appropriately trained people. Each patient and control was asked to give blood samples. The participation rate was 96% for the cases and 82% for the controls (for questionnaires), and 92% and 63% of participating patients and controls, respectively, donated blood. Concomitant genetic and questionnaire information on alcohol and smoking was obtained for 1204 cases (879 female and 325 male) and 871 controls (645 female and 226 male).

In CACORA, information on environmental exposures was obtained by means of a structured telephone interview. All participants were asked to give a blood sample for genotyping and serological analysis. The participation rate was 83% for cases and 64% for controls. Concomitant genetic and questionnaire information was obtained for 444 cases (312 female, 152 male) and 533 controls (327 female, 206 male).

We genotyped participants who gave a blood sample for SE alleles, defined as DRB1*13201 or DRB1*1401 or DRB1*10 in the HLA-DRB1 gene, by using sequence-specific primer PCR (DR low-resolution analysis). Subjects with SE alleles were classified as having single or double SE alleles. For simplicity of evaluation, we assumed a dominant SE allele model. More details on the genotyping procedure are given elsewhere.

Patients were subgrouped according to whether or not they had ACPAs (ACPA-positive RA and ACPA-negative RA), as described elsewhere.

In EIRA, alcohol consumption was detailed by questions about present alcohol consumption during the preceding week as well as previous habitual consumption. In CACORA, the questions on alcohol consumption specified weekly consumption 10 years before inclusion in the study. The questions in EIRA and CACORA allowed quantification of average alcohol consumption in drinks per week (1 drink = 16 g alcohol). We categorised alcohol consumption into four groups, based on the distribution of the sum of consumed alcoholic beverages per week among the controls in each study: non-drinkers (12.5% of all in EIRA, 10.1% of all in CACORA); low consumption (more than zero but below or equal to the median); moderate consumption (more than median but below or equal to the 75th centile); high consumption (above the 75th centile). In both studies, information on tobacco consumption was collected in ways that allowed detailed quantification of smoking habits before disease onset.

Statistical analysis

We calculated odds ratios (ORs) for RA associated with each category of alcohol consumption together with 95% CI by means of unconditional logistic regression models. We performed separate analyses based on sex as well as ACPA status among patients. Biological interaction, defined by departure from additivity of effects as described by Rothman and others, was evaluated between alcohol and smoking and between alcohol and HLA-DRB1 SE alleles. To quantify the interaction, the proportion attributable to interaction (AI) was calculated together with its p value and 95% CI. The proportion attributable to interaction between two interacting factors reflects the joint effect beyond the sum of the independent effects. When analysing interaction between alcohol consumption and HLA-DRB1 SE, we categorised alcohol consumption into three categories: 0, 0.1–4.9, 5 or more alcoholic drinks a week.

Table 1 Characteristics of cases and controls in EIRA and CACORA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EIRA Cases (n = 1204)</th>
<th>EIRA Controls (n = 871)</th>
<th>p Value</th>
<th>CACORA Cases (n = 644)</th>
<th>CACORA Controls (n = 533)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (%)</td>
<td>73 (n = 879)</td>
<td>74 (n = 645)</td>
<td>0.59</td>
<td>70.3 (n = 312)</td>
<td>61.4 (n = 327)</td>
<td>0.004</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>51.1 (12.5)</td>
<td>52.1 (11.7)</td>
<td>0.07</td>
<td>49.1 (11.1)</td>
<td>49.8 (10.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>RA disease duration (years)</td>
<td>0.8† (0)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ACPA-positive (%)</td>
<td>61.1 (n = 735)</td>
<td>1.9 (n = 16)</td>
<td>&lt;0.001</td>
<td>69.4 (n = 308)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ever smokers (%)</td>
<td>66.1 (n = 796)</td>
<td>60.3 (n = 525)</td>
<td>0.006</td>
<td>69.8 (n = 310)</td>
<td>60.6 (n = 323)</td>
<td>0.003</td>
</tr>
<tr>
<td>HLA-DRB1 SE alleles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterozygous carriers (%)</td>
<td>49.3 (n = 593)</td>
<td>42.8 (n = 373)</td>
<td>&lt;0.001</td>
<td>45.1 (n = 200)</td>
<td>44.5 (n = 237)</td>
<td>0.77</td>
</tr>
<tr>
<td>Homozygous carriers (%)</td>
<td>24.5 (n = 295)</td>
<td>22.9 (n = 85)</td>
<td>&lt;0.001</td>
<td>30.0 (n = 133)</td>
<td>8.4 (n = 45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-drinkers (%)</td>
<td>15.1 (n = 182)</td>
<td>12.5 (n = 109)</td>
<td>0.046</td>
<td>18.0 (n = 80)</td>
<td>10.1 (n = 54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol intake (drinks/week)*</td>
<td>2.9 (4.2)</td>
<td>4.1 (5.6)</td>
<td>&lt;0.001</td>
<td>6.6 (8.9)</td>
<td>9.0 (8.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Median (units/week)</td>
<td>1.9</td>
<td>2.9</td>
<td>–</td>
<td>4</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>75th centile (drinks/week)</td>
<td>3.8</td>
<td>4.9</td>
<td>–</td>
<td>8.5</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>Correlation smoking and alcohol</td>
<td>0.11 (p&lt;0.001)</td>
<td>0.17 (p&lt;0.001)</td>
<td>–</td>
<td>0.22 (p&lt;0.001)</td>
<td>0.17 (p&lt;0.001)</td>
<td>–</td>
</tr>
</tbody>
</table>

*Mean (SD). †Newly diagnosed cases; mean duration between onset of first symptoms and inclusion in the study. *Prevalent cases; mean interval between RA diagnosis and inclusion in the study. †ACPAs not measured in the controls in CACORA.

ACPAs, antibodies to citrullinated peptide antigens; CACORA, Case–Control Study on Rheumatoid Arthritis; EIRA, Epidemiological Investigation of Rheumatoid Arthritis; RA, rheumatoid arthritis; SE, shared epitope.
To estimate if alcohol consumption was associated with smoking, we calculated Pearson's correlation coefficient between smoking and alcohol. Trend test for a dose–response relationship between alcohol consumption and risk of RA was performed by using a continuous variable for units of alcohol consumed in a logistic regression model as suggested by Armitage et al. As the strength of the association between alcohol consumption and RA risk differed significantly between the Swedish and the Danish study, we display the results in parallel.

We used SAS software for windows, V.9.1, to analyse the data.

RESULTS

Alcohol consumption and risk of RA overall and of ACPA-positive RA and ACPA-negative RA

Table 1 shows the sex and age distribution of cases and controls, and alcohol consumption, for both EIRA and CACORA data. A considerably higher consumption of alcohol was reported by the controls in CACORA than the controls in EIRA. The overall relationship between number of drinks a day and RA risk, as estimated by the logistic regression model when alcohol was entered as a continuous variable, was \(-0.068\) (95% CI \(-0.093\) to \(-0.056\)) in EIRA and \(-0.021\) (95% CI \(-0.035\) to \(-0.008\)) in CACORA, corresponding to an average decrease in the odds of RA of 5% per drink per week in EIRA and 2% per drink per week in CACORA (both p values for trend < 0.001).

Table 2 displays the relationship between different categories of alcohol consumption and risk of RA overall as well as for the ACPA-positive and ACPA-negative subsets of RA for each of the two studies. A statistically significant dose-dependent reduction in the odds of RA overall was seen in people with higher alcohol consumption in both datasets. In EIRA, the larger of the studies, the effect was present in both men and women (data not shown) and for ACPA-positive and ACPA-negative RA (table 2). In CACORA, the inverse association between alcohol consumption and RA risk was significant only for the ACPA-positive subset.

Table 3 Risk of ACPA-positive rheumatoid arthritis in subjects exposed to different combinations of alcohol and smoking

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We used SAS software for windows, V.9.1, to analyse the data.
**Extended report**

**Alcohol consumption, smoking and risk of ACPA-positive RA**

We were interested in whether alcohol consumption interacts with smoking behaviour in influencing RA risk. As smoking is known to influence only ACPA-positive disease, this interaction analysis was only carried out for ACPA-positive RA.

A significant interaction between smoking and no alcohol consumption (table 3) was observed for ACPA-positive RA in both studies. Thus the risk reduction associated with alcohol consumption was more pronounced among ever smokers than never smokers in both studies (table 3).

**Alcohol consumption, HLA-DRB1 SE alleles and risk of ACPA-positive RA**

As the risk of developing ACPA-positive RA is highly dependent on carrying none, one or two copies of the HLA-DRB1 SE alleles, we investigated whether alcohol consumption influenced risk of RA differently according to HLA-DRB1 genotype. In both studies, the absolute risk reduction associated with alcohol consumption was more pronounced among carriers of HLA-DRB1 SE alleles than among non-carriers (fig 1 and supplementary table 1). When formally tested, this gene–environment interaction between HLA-DRB1 SE and alcohol consumption with regard to risk of ACPA-positive RA was found to be significant in both EIRA (p<0.001) and CACORA (p<0.001) when non-drinkers were compared with high consumers of alcohol (at least 5 drinks/week).

![Histograms showing OR of antibodies to citrullinated peptide antigen-positive rheumatoid arthritis for different combinations of alcohol consumption, smoking (never/ever) and presence or absence of HLA-DRB1 shared epitope (SE) alleles compared with never smokers with low alcohol consumption (0.1–4.9 drinks/week) and without SE alleles, by study (A, Epidemiological Investigation of Rheumatoid Arthritis (EIRA); B, Case–Control Study on Rheumatoid Arthritis (CACORA)]. Further details are given in supplementary table 2.

**Alcohol consumption, smoking, HLA-DRB1 SE alleles and risk of ACPA-positive RA**

Figure 1 shows the more complex picture when alcohol, smoking and HLA-DRB1 SE alleles are considered simultaneously (supplementary table 2). The overall pattern can be seen to be fairly similar for the two studies. The risk reduction associated with alcohol consumption seems to be most pronounced among smokers carrying one or two HLA-DRB1 SE alleles (EIRA, p for trend <0.001; CACORA, p for trend <0.01).

**DISCUSSION**

The major finding of this study is that alcohol consumption exhibits a dose-dependent inverse association with RA. Furthermore, alcohol consumption is associated with attenuation of the effect of the best established risk factors for RA, smoking and HLA-DRB1 SE with regard to ACPA-positive RA.

It is methodologically demanding to investigate the relationship between two lifestyle factors (alcohol, smoking) and one genetic factor (HLA-DRB1 SE) in two subsets of RA, as these factors may be inter-related to varying degrees in patients with RA and completeness of information and non-biased recruitment of cases and controls is crucial for the reliability of results. The two studies both used unique features of the Scandinavian healthcare systems in capturing representative and population-based collections of patients and well-matched controls. Alcohol consumption differed between the studies. In the Danish study (CACORA), the average consumption was higher than in the Swedish study (EIRA), a well-known country-specific difference which is in accordance with WHO information on alcohol consumption in Denmark and Sweden.

The high response rates of cases and controls should minimise the risk of selection bias. As always in case–control studies with retrospective exposure information, recall bias is a concern. Recall bias is usually related to the tendency to over-report previous exposure in cases relative to controls. In our study, the situation is the opposite—that is, if our results were explained by recall bias, patients would have systematically understated their previous alcohol consumption compared with controls.

To highlight if patients with RA tend to change their alcohol consumption over time, we studied the association between disease duration and alcohol consumption in EIRA. Alcohol consumption reported by patients with RA duration less than 6 months did not differ from that reported by patients with longer disease duration. On the assumption that recall bias is influenced by disease duration, the lack of such association is reassuring.

Another potential bias may stem from patients with RA treated with methotrexate or non-steroidal anti-inflammatory drugs being advised to abstain from alcohol by their doctor. However, in EIRA, we did not find any differences in reported alcohol consumption between patients who were taking methotrexate or non-steroidal anti-inflammatory drugs and those who were not. In CACORA, questions were asked specifically about alcohol consumption 10 years previously, which should minimise the risk of differential recall between cases and controls. Although our findings need replication, we consider our ability to use two parallel but completely independent studies performed in two countries with similar socioeconomic and cultural conditions to be a strength of this study. Similar findings to ours with regard to alcohol consumption and risk of RA from a prospective cohort study conducted in the south of Sweden have recently been presented.
A further concern is that information on interacting exposures such as smoking must be accurate and detailed; replication of these findings is also needed. We are confident that the Swedish and Danish studies on the interaction between smoking and RA are consistent; furthermore, these results have been confirmed in a Dutch study. Why these results were not fully replicated in a recent study from North America is not yet clear, but it may be due to regional differences in the complex interplay between a variety of genetic and environmental factors besides smoking. From this perspective also, our combination of independent studies from culturally and genetically similar environments in Sweden and Denmark is advantageous.

Somewhat unexpectedly, we observed an interaction between lack of alcohol and smoking and between lack of alcohol and presence of HLA-DRB1 SE alleles, respectively, with regard to risk of ACPA-positive RA. The method used to calculate this interaction is based on a calculation of deviation from additivity, and the existence of such interactions is an indication of at least one pathway towards disease in which both risk factors are required. Further research into mechanisms behind the interactions between smoking and alcohol may thus be of value in helping us to understand molecular aspects of RA pathology, similarly to what appears to be the case from our recent studies of interactions between smoking and HLA-DRB1 alleles. Evidence that alcohol intake may protect against development of arthritis has recently also been obtained from studies on experimental arthritis, where administration of alcohol reduced both the incidence and severity of collagen-induced arthritis in mice. Further studies on the mechanisms of this protective effect indicated an effect of alcohol on the NF-kappaB-dependent proinflammatory signalling pathways, but limited effects on the anti-collagen immune response, ie, on adaptive immunity. These data lend support to the notion that alcohol intake may be causatively associated with a reduced risk of RA in humans also. The evidence from the larger of the two studies, EIRA, that alcohol intake is inversely related to both ACPA-positive and ACPA-negative RA is also compatible with an effect on general proinflammatory mechanisms in human disease. We do not, however, have any good biological hypothesis to explain either the interaction between alcohol intake and HLA-DRB1 SE or the observed interaction between smoking and alcohol intake. Together, these findings call for extended studies on biological effects of alcohol and related compounds in relation to arthritis.

Seen in a wider perspective of inflammatory diseases, the currently observed association of alcohol with the risk of developing RA shows similarities to what has long been known for cardiovascular disease: moderate alcohol consumption is dose-dependently associated with a decreased risk of developing cardiovascular disease. However, despite many years of research, no clear-cut mechanism has been identified to explain these relationships. Our current finding of a similar effect in a classic inflammatory disease, RA, may also shed some light on the relationship between alcohol consumption and other inflammatory diseases; these relationships should be subjected to more combined studies in the future.

In summary, this study has several potential medical implications. From a public health perspective, we consider the findings of interest as they provide new information on how a modifiable lifestyle factor may influence the risk of developing RA. The main message remains that cessation of smoking is the most effective way to diminish the risk of RA, irrespective of genetic constitution, but that this recommendation should not necessarily be combined with a recommendation to stop moderate alcohol consumption. Equally interesting are the potential biological implications. The fact that data from both animal and human studies suggest that arthritis risk can be reduced by alcohol—or other agents with similar effects—should encourage further studies on how such prevention can be achieved.

Acknowledgements: All participants and organisations involved in EIRA and CACORA are acknowledged in the supplemental file. The sponsors of the studies did not have any role in study design, data collection, data analysis, data interpretation or writing the report.

Competing interests: None declared.

REFERENCES


Supplementary table 1: Interaction between amount of alcohol consumption and HLA-DRB1 SE genotype regarding risk of ACPA-positive RA, by study.

### EIRA

<table>
<thead>
<tr>
<th>No. of HLA-DRB1 SE alleles</th>
<th>Alcohol consumption</th>
<th>0.1 - 4.9 drinks/week</th>
<th>Non-drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>exp</td>
<td>OR† 95% CI</td>
<td>exp OR† 95% CI</td>
<td>exp OR† 95% CI</td>
</tr>
<tr>
<td>ca/co*</td>
<td></td>
<td>ca/co*</td>
<td>ca/co*</td>
</tr>
<tr>
<td>0</td>
<td>17/94 1.0‡ Ref</td>
<td>74/273 1.9 1.0 - 3.4</td>
<td>20/46 4.0 1.8 - 8.5</td>
</tr>
<tr>
<td>1 or 2</td>
<td>91/96 5.6 3.2 - 10.6</td>
<td>43/298 10.4 6.0 - 18.1</td>
<td>100/63 13.5 7.1 - 25.6</td>
</tr>
<tr>
<td>p-interaction §</td>
<td>p&lt; 0.0001</td>
<td></td>
<td>p&lt; 0.0001</td>
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</table>

### CACORA

<table>
<thead>
<tr>
<th>No. of HLA-DRB1 SE alleles</th>
<th>Alcohol consumption</th>
<th>0.1 - 4.9 drinks/week</th>
<th>Non-drinkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>exp</td>
<td>OR† 95% CI</td>
<td>exp OR† 95% CI</td>
<td>exp OR† 95% CI</td>
</tr>
<tr>
<td>ca/co*</td>
<td></td>
<td>ca/co*</td>
<td>ca/co*</td>
</tr>
<tr>
<td>0</td>
<td>16/129 1.0‡ Ref</td>
<td>18/90 1.6 0.8 - 3.3</td>
<td>11/32 2.6 1.1 - 6.4</td>
</tr>
<tr>
<td>1 or 2</td>
<td>114/153 6.0 3.4 - 10.7</td>
<td>98/107 7.2 4.0 - 13.1</td>
<td>51/22 17.9 8.5 - 37.5</td>
</tr>
<tr>
<td>p-interaction §</td>
<td>p = 0.33</td>
<td></td>
<td>p&lt; 0.0001</td>
</tr>
</tbody>
</table>

* Number of exposed (exp) cases (ca) and controls (co), † Odds ratio adjusted for sex, age, smoking and residential area (EIRA only). ‡ Reference category. § Attributable proportions due to interaction (AP) between HLA-DR1 SE status and different amounts of alcohol consumption (95 % confidence interval) were: for EIRA, (0.1 - 4.9 drinks/week) AP = 0.4 (0.2 - 0.6), (≥ 5 drinks/week) AP = 0.6 (0.4 - 0.9) and CACORA, (0.1 - 4.9 drinks/week) AP = 0.09 (-0.3 - 0.6), (≥ 5 drinks/week) AP = 0.8 (0.7 - 1.0).
Supplementary table 2: Odds ratio (OR) with 95% confidence interval (95% CI) of ACPA positive rheumatoid arthritis for subjects in different alcohol consumption categories, by smoking and HLA-DRB1 SE status and by study (EIRA and CACORA)

<table>
<thead>
<tr>
<th>Alcohol consumption (Drinks/week)</th>
<th>HLA-DRB1 SE alleles</th>
<th>Smoking</th>
<th>EIRA</th>
<th>Number of cases/controls</th>
<th>OR a</th>
<th>95% CI b</th>
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<tr>
<td>Non-drinkers</td>
<td>No, 0.1 - 4.9</td>
<td>Never</td>
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<td>≥ 5</td>
<td>No, ≥ 5</td>
<td>Never</td>
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<td>Never</td>
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<td>0.4</td>
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<td>Never</td>
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<td>118/116</td>
<td>4.7</td>
<td>2.7 - 7.9</td>
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<td>≥ 5</td>
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<td></td>
<td>7/15</td>
<td>2.3</td>
<td>0.8 - 6.4</td>
</tr>
<tr>
<td>≥ 5</td>
<td>Any, ≥ 5</td>
<td>Ever</td>
<td></td>
<td>51/170</td>
<td>1.4</td>
<td>0.8 - 2.5</td>
</tr>
<tr>
<td>Non-drinkers</td>
<td>Any, 0.1 - 4.9</td>
<td>Ever</td>
<td></td>
<td>15/75</td>
<td>0.9</td>
<td>0.4 - 1.8</td>
</tr>
<tr>
<td>≥ 5</td>
<td>Any, ≥ 5</td>
<td>Ever</td>
<td></td>
<td>66/18</td>
<td>18.6</td>
<td>9.2 - 37.5</td>
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<td>Ever</td>
<td></td>
<td>31/182</td>
<td>8.6</td>
<td>5.2 - 14.1</td>
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<tr>
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<td>Any, ≥ 5</td>
<td>Ever</td>
<td></td>
<td>75/65</td>
<td>5.1</td>
<td>2.8 - 9.1</td>
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<table>
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<th>Alcohol consumption (Drinks/week)</th>
<th>HLA-DRB1 SE alleles</th>
<th>Smoking</th>
<th>CACORA</th>
<th>Number of cases/controls</th>
<th>OR a</th>
<th>95% CI b</th>
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</thead>
<tbody>
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<td>Non-drinkers</td>
<td>No, 0.1 - 4.9</td>
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<td></td>
<td>6/21</td>
<td>1.2</td>
<td>0.4 - 4.2</td>
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<td></td>
<td>8/36</td>
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<td>Reference</td>
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<td>14/8</td>
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<td>2.2 - 22.8</td>
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<td>0.7 - 4.6</td>
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<tr>
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<td>Ever</td>
<td></td>
<td>5/11</td>
<td>2.0</td>
<td>0.5 - 7.4</td>
</tr>
<tr>
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<td>Any, ≥ 5</td>
<td>Ever</td>
<td></td>
<td>10/54</td>
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<td>0.3 - 2.4</td>
</tr>
<tr>
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<td>14/83</td>
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<td>92/99</td>
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<td>2.0 - 10.6</td>
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</tbody>
</table>

a Odds ratio adjusted for sex, age and residential area (EIRA only).

b 95% confidence interval for the corresponding odds ratio.
Supplemental information acknowledgement:
The EIRA study was supported by grants from the Swedish Medical Research Council, from
Swedish Council for Working life and Social Research, from King Gustaf V:s 80-year
foundation, from the Swedish Rheumatism Foundation, from Stockholm County Council and
from the insurance company AFA..
The CACORA study was supported by grants from The Danish Rheumatism Association,
The Danish Medical Research Council, Apotekerfonden, Hede Nielsen’s Foundation, Aase
and Ejnar Danielsen’s Foundation, and the Frimodt-Heineke Foundation.
We would like to thank following individuals for contributing to this report: all participating
RA patients and controls, in EIRA, for recruiting patients: Ingeli Andréasson, Landvetter;
Eva Baecklund, Akademiska Hospital; Ann Bengtsson and Thomas Skogh, Linköping
hospital; Birgitta Nordmark, Johan Bratt and Ingiäld Hafström, Karolinska University
Hospital; Kjell Huddénius, Rheumatology Clinic in Stockholm City; Shirani Jayawardene,
Bollnäs Hospital; Ann Knight, Hudiksvall Hospital and Uppsala University Hospital; Ido
Leden, Kristianstad Hospital; Göran Lindahl, Danderyd Hospital; Bengt Lindell, Kalmar
Hospital; Christin Lindström and Gun Sandahl, Sophiahemmet; Björn Löfström,
Katrineholm Hospital; Ingmar Petersson, Spenshult Hospital; Christoffer Schaufelberger,
Sahlgrenska University Hospital; Patrik Stolt, Västerås Hospital; Berit Sverdrup, Eskilstuna
Hospital; Olle Svernell, Västervik Hospital; Tomas Weitoft, Gävle Hospital; for excellent
data collection: Marie-Louise Serra and Lena Nise, who provided invaluable contributions to
the collection of data and maintenance of the database.
We also thank the following individuals for providing patients for the CACORA study: J. K.
Pedersen, Kong Christian X’s Gighospital, Gråsten; S. Freiesleben-Sørensen, Bispebjerg
Hospital); A. Rødgaard, Roskilde County Hospital Køge; A. Hansen and M. Sejer Hansen,
Copenhagen County Hospital Glostrup; L. Juul, Frederiksberg Hospital; H. H. Mogensen,
Hørsholm Hospital; B. Unger, Holstebro Hospital; P. Mosborg Petersen, Randers Hospital; J.
Christensen, Næstved Hospital; R. Pelck, Roskilde County Hospital Roskilde; M. Graakjær Nielsen, Aarhus University Hospital; N. Gregersen, Bornholm Hospital); and J. Sylvest, Amager Hospital.
Alcohol consumption is associated with decreased risk of rheumatoid arthritis; Results from two Scandinavian case-control studies

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