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TITLE: Comment on: Alcohol consumption is inversely associated with risk and severity of rheumatoid arthritis

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SIR, The recent article by Maxwell et al. [1] addresses a controversial issue that has already attracted considerable international media attention. Maxwell et al. [1] claim that drinking alcohol may reduce the risk and severity of rheumatoid arthritis. But does their evidence really support a protective effect of alcohol against risk and severity of RA?

Maxwell et al. [1] compared alcohol use in two groups of people. One group had a minimum of three years and mean of 14 years duration of RA. The other group comprised healthy volunteers with no history of inflammatory joint disease. Both groups completed a questionnaire at study entry in which they recorded on how many days they had taken alcohol in the previous month. The relationship between alcohol consumption frequency and RA severity was explored by comparing alcohol consumption frequency against markers of disease severity, including anti-CCP antibodies, rheumatoid factor, and radiographic scoring. This research design is a case-control study.

Maxwell et al. [1] are the first to demonstrate an inverse association between alcohol consumption and severity of RA, whilst inverse associations between alcohol consumption frequency and risk of RA have been observed in previous studies [2-5]. However, a well-known limitation of case-control studies is that they cannot determine cause and effect. With such a study design, Maxwell et al. [1] cannot prove whether alcohol consumption affected RA risk and severity, or whether RA risk and severity affected alcohol consumption (or indeed whether an extraneous factor affected both alcohol consumption and RA risk and severity). In short, the cause-effect hypothesis postulated by Maxwell et al. [1] "that the consumption of alcohol

would reduce both the risk of RA and disease severity" cannot be answered by their case-control study.

An inverse association between alcohol consumption and RA risk and severity might simply reflect that patients with RA drink less alcohol after disease onset and that the patients with the most severe disease drink alcohol the least. Several aspects of the disease state in RA might plausibly cause a patient to drink less alcohol – for example, feeling unwell, being socially restricted, and taking anti-inflammatory medications or DMARDs which contraindicate alcohol use [6]. Indeed, Maxwell et al. [1] reported statistically significant inverse associations between alcohol consumption and both disease duration and the use of methotrexate. Multivariate analysis accounting for both radiological damage and specific DMARD treatment were conducted but do not clarify possible cause-effect pathways.

Of particular concern is that age was a confounding variable in the case-control study, with the mean age of cases (61 years) statistically significantly older than controls (48 years). This is a problem, as the severity and duration of RA and use of alcohol are unlikely to be independent of age. How can Maxwell et al. [1] be sure that case-control differences in alcohol consumption were related to differences in disease rather than in age? Although admitting that confounding with age is a weakness of their study, Maxwell et al. [1] did not adjust their conclusions.

The most convincing evidence to date that alcohol consumption might prevent the development of destructive arthritis comes from laboratory studies on mice [e.g. 7]. Epidemiological studies that have investigated relationships between alcohol

consumption and RA in humans appear to have been limited to case-control studies [1-3, 5, 8], a prospective single cohort study [9] and retrospective single cohort studies [4, 10]. Only the prospective cohort study would have been capable of demonstrating a causal relationship between alcohol consumption and risk of RA: alcohol consumption was monitored in a cohort of older women which was followed up to determine who would develop the disease [9]. However, the study authors found no association between alcohol consumption and the risk of RA. A review article published in this journal in 2002 [6] concluded that inverse associations between alcohol intake and the risk of autoimmune diseases are not well understood and require further research.

Of the epidemiological studies mentioned above, only those published in the last four years have claimed causal associations between alcohol consumption and RA [1-3]. Earlier studies did not infer causal relationships, in keeping with the limitations of their study designs. Could this reflect a recent slackening in the rigour of critical interpretation of observational studies?

In summary, the study by Maxwell et al. [1] and other recent case-control studies [1-2] do not support a cause-effect association between alcohol consumption and the risk or severity of RA. More critical consideration should be given to the limitations of case-control studies in this area of research.

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