Alcohol consumption and the risk of mortality and myocardial infarction in patients with rheumatoid arthritis

I.D. Smith[1,2], N. Lu[3,4], J. Wei[3,4], Y. Zhang[3,4], HK. Choi[3,4], M.B. Bolster[3,4]

[1]Department of Medicine, [2]Division of Rheumatology and Immunology, Duke University Hospital, Duke University School of Medicine, Durham, NC, USA;
[3]Department of Medicine, [4]Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

Abstract

Objective

Many studies have found that moderate alcohol consumption is associated with lower risks of mortality and myocardial infarction (MI). Our aim was to examine the potential effects of alcohol on all-cause mortality and MI in rheumatoid arthritis (RA), a risk factor condition.

Methods

A cohort study (1995-2017) was conducted using medical records of RA patients from The Health Improvement Network in the United Kingdom (UK). Alcohol exposure was divided into non-drinkers, mild (1-7 UK units/week), moderate (8–14 UK units/week), moderate-high (15–21 UK units/week), and high (>21 UK units/week) consumption levels. We calculated hazard ratios (HRs) for the relation of alcohol consumption to all-cause mortality and MI, adjusting for covariates.

Results

Of 30,320 RA patients, 5,994 deaths and 1,098 MI cases occurred over 236,188 person-years. Mild-to-moderate alcohol use was associated with lower all-cause mortality in RA patients, including those taking methotrexate. The multivariable HRs (95% CI) for mortality by alcohol use category were non-drinkers 1.0, mild 0.80 (0.75–0.85), moderate 0.74 (0.67–0.82), moderate-high 0.84 (0.72–0.98), and high 0.99 (0.86–1.15). Mild, moderate-high, and high levels of alcohol use were associated with lower risk of MI among RA patients. The HRs MI risk by alcohol use category were non-drinkers 1.0, mild 0.81 (0.70–0.94), moderate 0.84 (0.68–1.04), moderate-high 0.51 (0.35–0.74), and high 0.59 (0.42–0.84).

Conclusion

These findings suggest that mild-to-moderate alcohol use is associated with a lower mortality risk and overall alcohol use is associated with a lower MI risk in RA patients, similar to the general population.

Key words
rheumatoid arthritis, alcohol drinking, mortality, myocardial infarction

Isaac D. Smith, MD
Na Lu, MPH
Jie Wei, PhD
Yuqing Zhang, DSc
*Hyon K. Choi, MD, DrPH**
*Marcy B. Bolster, MD**

**These authors contributed equally.*

Please address correspondence to:
Isaac D. Smith,
Division of Rheumatology and Immunology,
Duke University Hospital,
2301 Erwin Road,
Durham, NC 27710, USA.
E-mail: isaac.smith063@duke.edu

ORCID iD: 0000-0003-3313-4825

Received on August 5, 2021; accepted in revised form on October 27, 2021.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2022.

Data availability statement: the data underlying this article were provided by The Health Improvement Network under license. Data will be shared on reasonable request to the corresponding author if permissible by The Health Improvement Network.

Funding: this project was funded through the Resident Preceptorship Grant from the Rheumatology Research Foundation in Atlanta, GA.

Competing interests: H. Choi has received research grants from Pfizer and AstraZeneca to Massachusetts General Hospital (MGH) for unrelated studies and served as a consultant for Takeda Pharmaceuticals, Selecta, Horizon, and Ironwood. M. Bolster has received research grants from Abbvie and Pfizer to MGH for unrelated studies, participated in the Cumberland and Corbus clinical trials, has served on an advisory board for Gilead, and has investments with Johnson and Johnson. The other authors have declared no competing interests.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory condition associated with an increased risk of cardiovascular disease and premature mortality (1-7). The incidence of myocardial infarction (MI) is significantly increased in individuals with RA, despite controlling for traditional risk factors (2, 3), and cardiovascular mortality is significantly higher in patients with RA compared to the general population (1, 4).

It has been well-described that mild-to-moderate alcohol consumption (women 1–7 drinks per week, men 1–14 drinks per week, by US standards) is associated with a 25–40% reduced risk of all-cause mortality and acute MI in the general population (8-13). These cardioprotective benefits are observed for all types of alcohol (wine, beer, liquor) (12, 13), and this may be relevant for patients with an increased risk of cardiovascular morality, such as patients with RA. Alcohol consumption generally starts at a young adult age in the UK before the onset of most chronic cardiometabolic conditions and is known to affect blood pressure, lipid profiles, and insulin sensitivity (14-16), likely mediating the pathway to cardiovascular and mortality risk.

Alcohol use has been traditionally discouraged in patients with RA due to concern for increased risk of liver toxicity in patients taking methotrexate (MTX) (17), the first-line disease-modifying anti-rheumatic drug (DMARD) for patients with RA (18, 19). However, a recent cohort study in the UK found mild-to-moderate alcohol consumption (1–14 UK units, or 0.5–8 US drinks per week) was not associated with a significant increase in alanine transaminase (ALT) or aspartate aminotransferase (AST) levels among patients with RA taking MTX (20).

In light of evidence that mild-to-moderate alcohol use may be safe for patients with RA taking MTX, we proposed to investigate the effect of alcohol intake on all-cause mortality and risk of MI among patients with RA, including those taking MTX and other non-MTX DMARDs.

Materials and methods

A cohort study was conducted using electronic medical records (EMR) from The Health Improvement Network (THIN) database between 1995 and 2017. THIN is a large database comprised of fully anonymised EMR data collected by primary care practices from more than 17 million patients (3.1 million active) across the UK (21). Patient consent is obtained at the level of each patient's general practitioner office, and patients can withdraw their consent at any time. Health information is recorded on site at each practice using a computerised system with quality control procedures to maintain high data completion rates and accuracy. The information includes socio-demographics, anthropometrics, lifestyle factors, details from general practitioner visits, diagnoses from specialist referrals and hospital admissions, and results of laboratory tests. The Read classification system is used to code specific diagnoses, and a drug dictionary based on data from the Multilex classification system is used to code medications. Approximately 95% of the UK population is registered with a general practice, and prior research has shown that THIN is representative of the UK population, in terms of patient demographics and the prevalence of common illnesses (22).

The study population consisted of patients with RA in the UK. Patients were identified from the THIN database using Read codes derived from UK medical diagnoses and were then evaluated for DMARD exposure at any point during the study period. The combined RA cohort included all patients with a diagnostic Read code for RA, regardless of DMARD exposure. Read codes for RA have been previously validated in the UK General Practice Research Database, with a positive predictive value (PPV) of approximately 80% (23, 24).

The combined RA cohort was further divided into patients taking MTX and patients taking only other non-MTX DMARDs. To improve the accuracy of RA diagnosis, the definition of RA was further refined for these groups. Only individuals who had their first Read code for RA in the THIN database, followed by a DMARD prescription after this first diagnostic code with no alternative indication for that DMARD, were included in the MTX and non-

MTX DMARD cohorts. This definition has been shown to have a specificity of 96% against the 1987 American College of Rheumatology Criteria for RA (25).

Assessment of exposure

In the combined RA cohort, alcohol exposure was defined as the first recorded alcohol use after the initial diagnostic Read code for RA was filed during the study period. In patients taking MTX or only non-MTX DMARDs, alcohol exposure was defined as the first recorded use after DMARD therapy was initiated. If this information regarding alcohol use was not available, patients recorded as non-drinkers prior to receiving DMARD therapy were considered non-drinkers, and all other patients with an incomplete alcohol exposure history were excluded. Amount of alcohol consumption was measured in UK units per week, where 1 UK unit = 10mL, or 8g of alcohol. All types of alcohol (wine, beer, liquor) were included, and total alcohol consumption in UK units/week was determined by the general practitioner and entered into the THIN database based on the relative alcohol content of the beverages consumed. Patients were then grouped into 5 categories: non-drinkers, mild 1-7 units/week (0.5–4 US drinks/week), moderate 8–14 units/week (4.5–8 US drinks/week), moderate-high 15–21 units/week (8.5–12 US drinks/week), and high >21 units/week (>12 US drinks/week) according to the 2016 alcohol use guidelines from the UK Department of Health (26).

Assessment of covariates

Demographic data including age, sex, body mass index (BMI), smoking status (current, past, and never-smokers), and Townsend deprivation index were assessed at the time of recorded alcohol exposure. Our primary analysis intentionally did not include hypertension, hyperlipidaemia, and diabetes status in order to avoid adjusting for causal intermediates in the relation between alcohol use, all-cause mortality, and the risk of MI. However, we did extract these diagnoses from the THIN database using READ codes, and we then adjusted for the presence of these comorbidities in our secondary analyses.

Assessment of outcome

The primary outcomes were all-cause mortality and incident MI. Specifically, all-cause mortality was defined by the death date recorded in THIN, which is linked to data from the National Health Service. Incident MI was defined as the occurrence of any of the following events: myocardial infarction, heart attack, specified pattern on electrocardiogram, or diagnostic codes describing ischaemic damage to a specific myocardial territory (27). Previous validation studies in the THIN database have found diagnostic Read codes for MI have a PPV >90% (28). Patients with pre-existing coronary heart disease before the first recorded alcohol intake or prior to RA diagnosis were excluded from the incident MI analysis.

Statistical analysis

We compared the baseline characteristics of patients with RA according to categories of alcohol consumption. For each participant, person-years of follow-up were calculated from the time of first recorded alcohol exposure to the first of the following events: death, disenrolment from the THIN database, or the end of the follow-up period. Mortality rates were calculated according to each category of alcohol consumption and compared using Cox proportional hazards models with age as the time-scale. The multivariable Cox proportional hazards model was adjusted for age, sex, BMI, smoking status, and Townsend deprivation index. When examining the relation of alcohol consumption to the risk of MI, a cause-specific Cox proportional hazards model was used to account for competing risk of death.

Comorbidities were not included in our primary model, as they would likely have occurred after the initiation of alcohol drinking (making them causal intermediates for mortality or MI outcomes), rather than being a cause of alcohol drinking (to qualify as a confounder). For example, individuals usually start drinking alcohol during young adulthood, which can contribute to the development of cardiovascular-renal-metabolic comorbidities. Nevertheless, our extended model additionally included key comorbidities such as hypertension, hyperlipidaemia, and diabetes status. Furthermore, while our primary exposure of interest was current drinking, we examined the potential impact of the "sick quitter" effect (RA activity leading to discontinuation of drinking) by evaluating the mortality risk among past drinkers (those who ceased alcohol consumption prior to our study baseline).

We used restricted quadratic splines to describe the shape of the dose-response relationship between alcohol consumption and all-cause mortality and MI events (29). All p-values were two-sided and $p<0.05$ was considered significant for all tests. All statistical analyses were conducted using SAS V.9.4.

Institutional Review Board

This research was determined to be exempt from review by the Partners Healthcare Institutional Review Board (IRB) at Massachusetts General Hospital, as it is an observational study that involves the use of fully anonymised patient data not collected by the authors. Permission to perform epidemiologic studies for patients with RA was obtained from the THIN Scientific Review Committee (reference no. 12-005).

Results

We identified a total of 43,214 patients with RA from the THIN database. Of these patients, the 30,320 individuals with complete demographic information were included in the combined RA cohort. Approximately half (50.3%) of these patients received MTX during the study period (Fig. 1). Additional baseline demographic data are shown in Supplementary Table S1. Most patients in the study population either abstained from alcohol (57.2%) or reported mild alcohol intake (26.4%, 1–7 UK units/week). Approximately 7.1% of patients consumed moderate-high (15-21 UK units/week) or high (>21 units/week) levels of alcohol use. These amounts exceed current UK recommendations to limit alcohol use to 14 units per week (22). Men were more likely than women to drink >14 units per week,

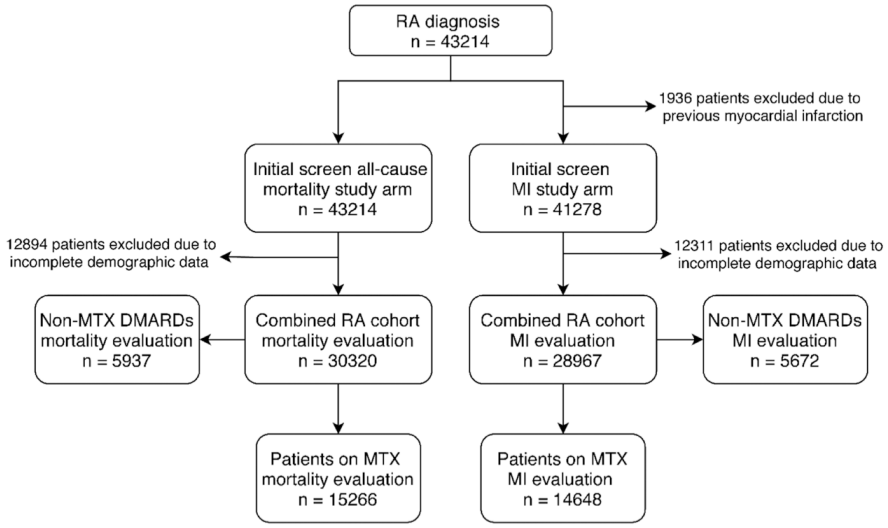

Fig. 1. Flowchart of patient selection for the study. Patients with pre-existing MI (1936) were excluded from the MI arm of the study. Patients with incomplete demographic data (12894) were also excluded. RA: rheumatoid arthritis; n: number of patients; MI: myocardial infarction; MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs.

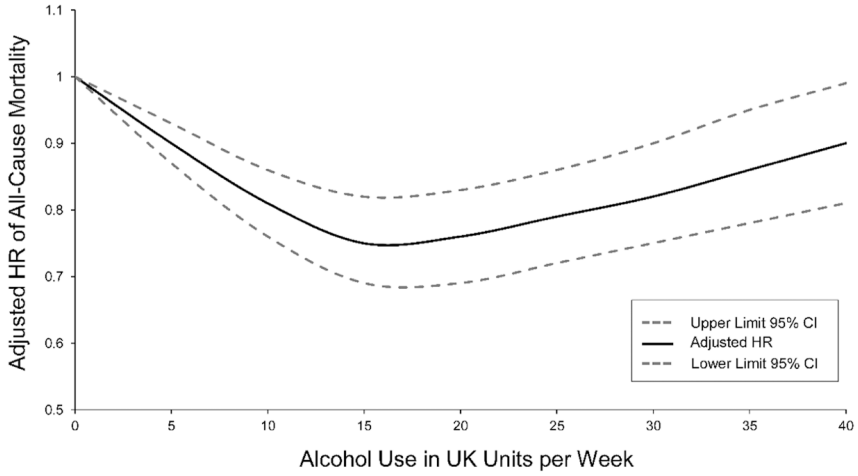

Fig. 2. The relation of alcohol consumption to all-cause mortality among patients with RA. Spline graph of the adjusted hazard ratio (HR) including the upper and lower bounds of the 95% confidence interval (CI). Alcohol consumption is measured in UK units per week, and this model was adjusted for age, sex, BMI, smoking status, and Townsend deprivation index.
BMI: body mass index; CI: confidence interval; HR: hazard ratio; UK: United Kingdom

and heavier alcohol use was more common in younger patients. Past or current smoking was also associated with increased alcohol consumption. BMI and Townsend deprivation index were comparable among the different categories of alcohol use.

All-cause mortality

During the study period, 5,994 deaths occurred among 30,320 patients in the combined RA cohort during 236,188 person-years of follow-up. Level of alcohol consumption was associated with the risk of all-cause mortality in a U-shaped curve (Fig. 2), where the multivariable HRs (95% CI) for mortality were 0.80 (0.75–0.85), 0.74 (0.67–0.82), 0.84 (0.72–0.98), and 0.99 (0.86–1.15) for no use, mild, moderate, moderate-high, and high alcohol use, respectively (Table I). Similar U-shaped relationships between level of alcohol consumption and all-cause mortality were also observed in the patients with RA taking MTX or only other non-MTX DMARDs (Table II). Furthermore, even after adjusting for the presence of hypertension, hyperlipidaemia, and diabetes, the U-shaped relationship persisted (Suppl. Tables S4-6). A subgroup analysis comparing non-drinkers to past drinkers exposed to methotrexate during the study period to evaluate the "sick quitter" effect showed a multivariable HR (95% CI) of 1.10 (0.97–1.25) (Suppl. Table S7).

Myocardial infarction rates

Among patients in the combined RA cohort, 1,098 MI cases were recorded during 222,535 person-years of follow-up. Mild, moderate-high, and high levels of alcohol use were all associated with significantly lower rates of MI. The multivariable HRs (95% CI) for MI were 1.0, 0.81 (0.70–0.94), 0.84 (0.68–1.04), 0.51 (0.35–0.74), and 0.59 (0.42–0.84) for no use, mild, moderate, moderate-high, and high alcohol use, respectively (Table III). The relationship between alcohol use and reduced rates of MI reached significance with moderate-high to high use among patients with RA taking MTX and with mild-to-moderate use in patients with RA taking only non-MTX DMARDs (Table IV). Similar trends persisted after additionally adjusting for the presence of hypertension, hyperlipidaemia, and diabetes (Suppl. Tables S8-10).

Discussion

In this RA cohort study, we found mild-to-moderate alcohol use was associated with lower rates of all-cause mortality in patients with RA, including patients taking MTX and patients taking only other non-MTX DMARDs. We also observed a lower risk for MI with alcohol use in this patient population. Additional model adjustment for the presence of hypertension, hyperlipidaemia, and diabetes yielded similar results. The results of both primary outcomes are consistent with the results of several previous studies conducted in the general population context (8-13), particularly the observed U-shaped dose-risk relationship between amount of alcohol consumed and all-cause mortality.

Patients with RA have traditionally been advised to abstain from alcohol due to concern for an increased risk of hepatotoxicity associated with concomitant MTX use (17), and there are no recent comprehensive recommendations re-

Table I. The relation of alcohol use to all-cause mortality in patients in the combined RA cohort.

Alcohol intake (units/week)†	n	Events	Unadjusted HR (95% CI)	Adjusted HR‡ (95% CI)
0	17331	3757	1.00 (Reference)	1.00 (Reference)
1–7	8012	1423	0.82 (0.77 – 0.87)	0.80 (0.75 – 0.85)
8–14	2821	431	0.84 (0.76 – 0.92)	0.74 (0.67 – 0.82)
15–21	1091	185	1.02 (0.88 – 1.19)	0.84 (0.72 – 0.98)
>21	1065	198	1.34 (1.16 – 1.54)	0.99 (0.86 – 1.15)

†Units based on standard UK measures where 1 unit = 8g alcohol. By US standards, 7 UK units = 4 US drinks.
‡Adjusted for age, sex, BMI, smoking status, and Townsend deprivation index.
*CI: confidence interval; HR: hazard ratio; n: number of patients in each group; RA: rheumatoid arthritis.

Table II. The relation of alcohol use to all-cause mortality in patients taking MTX or only non-MTX DMARDs.

Alcohol intake (units/week)†	n	Events	Unadjusted HR (95% CI)	Adjusted HR‡ (95% CI)
Mortality in RA patients taking MTX				
0	8784	1445	1.00 (Reference)	1.00 (Reference)
1–7	4130	623	0.90 (0.82 – 0.99)	0.90 (0.82 – 0.99)
8–14	1394	149	0.75 (0.64 – 0.89)	0.69 (0.58 – 0.82)
15–21	498	65	0.94 (0.73 – 1.20)	0.80 (0.62 – 1.03)
>21	460	72	1.34 (1.05 – 1.70)	1.03 (0.81 – 1.32)
Mortality in RA patients taking only non-MTX DMARDs				
0	3418	934	1.00 (Reference)	1.00 (Reference)
1–7	1500	299	0.72 (0.63 – 0.82)	0.70 (0.61 – 0.80)
8–14	546	99	0.75 (0.61 – 0.93)	0.65 (0.53 – 0.80)
15–21	240	45	0.87 (0.64 – 1.17)	0.70 (0.51 – 0.95)
>21	233	42	1.06 (0.78 – 1.44)	0.78 (0.57 – 1.08)

†Units based on standard UK measures where 1 unit = 8g alcohol. By US standards, 7 UK units = 4 US drinks.
‡Adjusted for age, sex, BMI, smoking status, and Townsend deprivation index.
*CI: confidence interval; DMARD: disease-modifying anti-rheumatic drug; HR: hazard ratio; MTX: methotrexate; n: number of patients in each group; RA: rheumatoid arthritis.

Table III. The relation of alcohol use to myocardial infarction rates in the combined RA cohort.

Alcohol intake (units/week)†	n	Events	Unadjusted HR (95% CI)	Adjusted HR‡ (95% CI)
0	16552	657	1.00 (Reference)	1.00 (Reference)
1–7	7674	270	0.84 (0.73 – 0.96)	0.81 (0.70 – 0.94)
8–14	2685	106	1.07 (0.87 – 1.31)	0.84 (0.68 – 1.04)
15–21	1032	29	0.77 (0.53 – 1.11)	0.51 (0.35 – 0.74)
>21	1024	36	1.05 (0.75 – 1.46)	0.59 (0.42 – 0.84)

†Units based on standard UK measures where 1 unit = 8g alcohol. By US standards, 7 UK units = 4 US drinks.
‡Adjusted for age, sex, BMI, smoking status, and Townsend deprivation index.
*CI: confidence interval; HR: hazard ratio; n: number of patients in each group; RA: rheumatoid arthritis.

garding safe levels of alcohol consumption in patients with RA who are taking MTX (18, 19, 30, 31). Interestingly, we observed lower rates of all-cause mortality with mild-to-moderate alcohol use among patients with RA taking MTX in our study. In order to better counsel patients with RA taking MTX regarding appropriate levels of alcohol use, further studies are needed to better characterise the long-term effects of concurrent alcohol use and MTX.

While several environmental factors have been linked to the risk of developing RA and disease severity (7), alcohol use in patients with RA remains a controversial topic. Some observational studies have reported improved disease activity measures and reduced radiographic progression of RA with mild-to-moderate alcohol use (32-35); however, a recent study from Baker and colleagues (36) found alcohol use did not improve disease activity in RA after adjusting for potential confounding factors (36). The authors did observe slightly lower mortality rates among patients with RA who drank alcohol using multivariable adjusted models. While the authors also adopted marginal structural models (36), a proper application of these causal models requires following patients from initiation of exposure (*i.e.* alcohol), similar to randomised trials, which these models are designed to emulate. As alcohol consumption generally starts at a young adult age, this follow-up was not possible in that study, in our study, or in previous general population studies (8-13). Nevertheless, in contrast to the study from Baker *et al* (36), we did not find a "sick quitter" effect in our past drinker analysis (Suppl. Table S7) and we assessed alcohol intake quantitatively. Furthermore, the observed association between mild-to-moderate alcohol use and all-cause mortality remained significant, even after adjusting for potential causal covariates. Our study also found alcohol use was associated with lower rates of MI in patients with RA, which is relevant for a patient population at increased risk of cardiovascular mortality.

Several mechanisms have been proposed to explain the potential cardioprotective effects of mild to moderate alcohol use in the general population. Alcohol use has been shown to increase high density lipoprotein and apolipoprotein 1 concentrations, which, in theory, may reduce atherosclerosis by increasing reverse cholesterol transport from the peripheral tissues to the liver (37-39). Increased adiponectin concentrations are also seen with alcohol use (37, 40), and in basic science models, adiponectin has been associated with a number of cardioprotective effects, including improved insulin sensitivity,

Table IV. The relation of alcohol use to MI rates in patients taking MTX or only non-MTX DMARDs.

Alcohol intake (units/week)†	n	Events	Unadjusted HR (95% CI)	Adjusted HR‡ (95% CI)
Myocardial infarctions in RA patients taking MTX				
0	8434	318	1.00 (Reference)	1.00 (Reference)
1–7	3965	144	0.89 (0.73 – 1.09)	0.89 (0.73 – 1.09)
8–14	1331	59	1.25 (0.95 – 1.65)	0.98 (0.74 – 1.31)
15–21	473	13	0.74 (0.43 – 1.29)	0.48 (0.28 – 0.85)
>21	445	13	0.86 (0.50 – 1.50)	0.48 (0.28 – 0.85)
Myocardial infarctions in RA patients taking non-MTX DMARDs				
0	3256	153	1.00 (Reference)	1.00 (Reference)
1–7	1435	47	0.66 (0.48 – 0.92)	0.62 (0.44 – 0.86)
8–14	524	17	0.72 (0.43 – 1.18)	0.58 (0.35 – 0.96)
15–21	230	8	0.80 (0.39 – 1.64)	0.56 (0.27 – 1.15)
>21	227	10	1.20 (0.63 – 2.28)	0.74 (0.38 – 1.44)

†Units based on standard UK measures where 1 unit = 8g alcohol. By US standards, 7 UK units = 4 US drinks.
‡Adjusted for age, sex, BMI, smoking status, and Townsend deprivation index.
*CI: confidence interval; DMARD: disease-modifying anti-rheumatic drug; HR: hazard ratio; MTX: methotrexate; n: number of patients in each group; RA: rheumatoid arthritis.

anti-inflammatory effects, decreased oxidative stress, improved endothelial function, and decreased atherosclerosis (41-44). However, despite these findings, recent epidemiologic studies have shown an "adiponectin paradox" in which individuals with increased adiponectin levels have a paradoxically increased risk of all-cause and cardiovascular mortality (45). Decreased fibrinogen levels have also been observed with mild-to-moderate alcohol, which may suggest a favourable haemostatic profile and lower levels of systemic inflammation (37, 46). Elevated fibrinogen has been studied as a predictor of future cardiovascular events and may slightly improve predictive risk algorithms in certain populations (47, 48). Several other potential mediators and modifiers of cardiovascular risk with mild-to-moderate alcohol use have also been proposed, including genetic factors, effects on other lipid biomarkers, anti-inflammatory effects, haemostatic factors, and changes in vascular function, though studies have shown mixed results (37, 40, 49-52).

There are important limitations to our observational study. Though all THIN data are validated by Cegedim Strategic Data Medical Research UK, it is possible that some of the patients carrying a diagnosis of RA were misclassified in the database. To limit this effect, we used a more specific RA definition for patients in the MTX and non-MTX DMARD groups that included Read codes and required a prescription for DMARD therapy. This has been shown to have very high specificity for RA diagnosis in previous validation studies of the UK population (25). Additionally, the THIN database does not include RA disease activity measures, but when we separated non-drinkers into past drinkers and lifelong non-drinkers, we did not observe the "sick quitter" phenomenon (53). Alcohol consumption was also only assessed at one time point. We recognise behaviours may change over time; however, notably most of the primary literature concerning the effects of alcohol use on mortality and cardiac risk applies similar methodology (10, 13, 54, 55).

The strengths of this study include a large patient population with longitudinal follow-up and reliable reporting of demographic data. The THIN database is representative of the general UK population (22), and mortality data are linked directly to the National Health Service, providing real-time confirmed death dates for the study population. The observed alcohol behaviour trends in the study population were consistent with the 2005-2016 and 2017 "Adult drinking habits in Great Britain" dataset collected by the Office for National Statistics (56). Additionally, information regarding specific DMARD use was available. Our outcomes were clearly defined, and we adjusted for several potential confounders for risk of MI and all-cause mortality, including age, sex, BMI, Townsend deprivation index, smoking status, hypertension, hyperlipidaemia, and diabetes.

Conclusion

In conclusion, this cohort study of a UK population of patients with RA demonstrated that mild- to-moderate alcohol use was associated with a lower risk of all-cause mortality in patients with RA, including those taking MTX and other non-methotrexate DMARDs. Alcohol use was also associated with a lower risk of MI in patients with RA. While further studies are needed to inform recommendations regarding safe levels of alcohol consumption in this patient population, these findings are similar to trends observed in the general population.

Acknowledgements

This project was funded through the Resident Preceptorship Grant from the Rheumatology Research Foundation in Atlanta, GA.

References

1. SPARKS JA, CHANG S, LIAO KP *et al.*: Rheumatoid arthritis and mortality among women during 36 years of prospective follow-up: results from the Nurses' Health Study. *Arthritis Care Res* 2015; 68: 753-62.
2. SOLOMON DH, KARLSON EW, RIMM EB *et al.*: Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003; 107: 1303-7.
3. DEL RINCÓN I, WILLIAMS K, STERN MP, FREEMAN GL, ESCALANTE A: High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional risk factors. *Arthritis Rheum* 2001; 44: 2737-45.
4. AVIÑA-ZUBIETA JA, CHOI HK, SADATSAFAVI M, ETMINAN M, ESDAILE JM, LACAILLE D: Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis Rheum* 2008; 59: 1690-7.
5. WOLFE F, MITCHELL DM, SIBLEY JT *et al.*: The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 481-94.
6. WIDDIFIELD J, PATERSON JM, HUANG A, BERNATSKY S: Causes of death in rheumatoid arthritis: how do they compare to the general population? *Arthritis Care Res* 2018; 70: 1748-55.
7. TESTA D, CALVACCHI S, PETRELLI F *et al.*:

One year in review 2021: pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol* 2021; 39: 445-52.
8. DI CASTELNUOVO A, COSTANZO S, BAGNARDI V, DONATI MB, IACOVIELLO L, DE GAETANO G: Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies. *Arch Internal Med* 2006; 166: 2437-45.
9. COSTANZO S, DI CASTELNUOVO A, DONATI MB, IACOVIELLO L, DE GAETANO G: Cardiovascular and overall mortality risk in relation to alcohol consumption in patients with cardiovascular disease. *Circulation* 2010; 121: 1951-9.
10. MUKAMAL KJ, CHEN CM, RAO SR, BRESLOW RA: Alcohol consumption and cardiovascular mortality among U.S. adults, 1987 to 2002. *J Am Coll Cardiol* 2010; 55: 1328-35.
11. BELL S, DASKALOPOULOU M, RAPSOMANIKI E *et al*.: Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. *BMJ* 2017; 356: j909.
12. MUKAMAL KJ, CONIGRAVE KM, MITTLEMAN MA *et al*.: Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *N Engl J Med* 2003; 348: 109-18.
13. DJOUSSÉ L, LEE I, BURING JE, GAZIANO M: Alcohol consumption and risk of cardiovascular disease and death in women. *Circulation* 2009; 120: 237-44.
14. BEILIN LJ, PUDDEY IB: Alcohol and hypertension: an update. *Hypertension* 2006; 47: 1035-8.
15. CASTELLI WP, DOYLE JT, GORDON T *et al*.: Alcohol and blood lipids: the Cooperative Lipoprotein Phenotyping Study. *Lancet* 1977; 310: 153-5.
16. GREENFIELD JR, SAMARAS KS, HAYWARD CS, CHISHOLM DJ, CAMPBELL JV: Beneficial postprandial effect of a small amount of alcohol on diabetes and cardiovascular risk factors: modification by insulin resistance. *J Clin Endocrinol Metab* 2005; 90: 661-72.
17. KREMER JM, ALARCON GS, LIGHTFOOT RW *et al*.: Methotrexate for rheumatoid arthritis: suggested guidelines for monitoring liver toxicity. *Arthritis Rheum* 1994; 37: 316-28.
18. SMOLEN JS, LANDEWÉ R, BIJLSMA J *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017; 76: 960-77.
19. SINGH JA, SAAG KG, BRIDGES SL *et al*.: 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2015; 68: 1-26.
20. HUMPHREYS JH, WARNER A, COSTELLO R *et al*.: Quantifying the hepatotoxic risk of alcohol consumption in patients with rheumatoid arthritis taking methotrexate. *Ann Rheum Dis* 2017; 76: 1506-14.
21. The Health Improvement Network (THIN) [Internet]. London: THIN Advisory Committee; [cited 2020 Nov 11]. Available at: https://www.the-health-improvement-network.com.
22. BLAK BT, THOMPSON M, DATTANI H, BOURKE A: Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care* 2011;1 9: 251-5.
23. GARCÍA RODRÍGUEZ LA, TOLOSA LB, RUIGÓMEZ, JOHANSSON S, WALLANDER MA: Rheumatoid arthritis in UK primary care: incidence and prior morbidity. *Scand J Rheumatol* 2009; 38: 173-7.
24. WATSON DJ, RHODES T, CAI B, GUESS HA: Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. *Arch Intern Med* 2002; 162: 1105-10.
25. THOMAS SL, EDWARDS CJ, SMEETH L, COOPER C, HALL AJ: How accurate are diagnoses for rheumatoid arthritis and juvenile idiopathic arthritis in the general practice research database? *Arthritis Car Res* 2008; 59: 1314-21.
26. DEPARTMENT OF HEALTH: Alcohol Guidelines Review – Report from the Guidelines-development group to the UK Chief Medical Officers, 2904568. [Internet]. 2015 [cited 2020 Nov 11]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/545739/GDG_report-Jan2016.pdf.
27. TOMMASSON G, PELOQUIN C, MOHAMMAD A *et al*.: Risk for cardiovascular disease early and late after a diagnosis of giant-cell arteritis: a cohort study. *Ann Intern Med* 2014; 160: 73-80.
28. GARCÍA RODRÍGUEZ LA, TACCONELLI S, PATRIGNANI P: Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *J Am Coll Cardiol* 2008; 52: 1628-36.
29. GREENLANDER S: Dose-response and trend analysis in epidemiology: alternative to categorical analysis. *Epidemiology* 1995; 6: 256-65.
30. CHAKRAVARTY K, MCDONALD H, PULLAR R *et al*.: BSR/BHPR guidelines for disease-modifying anti-rheumatic drugs (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology* (Oxford) 2008; 47: 924-5.
31. VISSER K, KATCHAMART W, LOZA E *et al*.: Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; 68: 1086-93.
32. MAXWELL JR, GOWERS IR, MOORE DJ, WILSON AG: Alcohol consumption is inversely associated with risk and severity of rheumatoid arthritis. *Rheumatology* (Oxford) 2010; 49: 2140-6.
33. BERGMAN S, SYMEONIDOU S, ANDERSSON ML, SODERLIN MK: Alcohol consumption is associated with lower self-reported disease activity and better health-related quality of life in female rheumatoid arthritis patients in Sweden: data from BARFOT, a multicenter study on early RA. *BMC Musculoskelet Disord* 2013; 14: 2018.
34. LU B, RHO YH, CUI J *et al*.: Associations of smoking and alcohol consumption with disease activity and functional status in rheumatoid arthritis. *J Rheumatol* 2014; 41: 24-30.
35. NISSEN MJ, GABAY C, SCHERER A, FINCH A: The effect of alcohol on radiographic progression in rheumatoid arthritis. *Arthritis Rheum* 2010; 62: 1265-72.
36. BAKER JF, ENGLAND BR, MIKULS TR *et al*.: Changes in alcohol use and associations with disease activity, health status, and mortality in rheumatoid arthritis. *Arthritis Care Res* 2020; 72: 301-8.
37. RONKSLEY PE, BRIEN SE, TURNER BJ *et al*.: Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ* 2011; 342: d671.
38. RIMM EB, WILLIAMS P, FOSHER K *et al*.: Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effect on lipids and haemostatic factors. *BMJ* 1999; 319: 1523.
39. OUIMET M, BARRETT TJ, FISHER EA: HDL and reverse cholesterol transport: Basic mechanisms and their roles in vascular health and disease. *Circ Res* 124; 10: 1505-18.
40. SIERKSMA A, PATEL H, OUCHI N *et al*.: Effect of moderate alcohol consumption on adiponectin, tumor necrosis factor alpha, and insulin sensitivity. *Diabetes Care* 2004; 27: 184-9.
41. KADOWAKI T, YAMAUCHI T: Adiponectin and adiponectin receptors. *Endrocr Rev* 2005; 26: 439-51.
42. KOBASHI C, URAKAZE M, KISHIDA M, KIBAYASHI E, KOBAYASHI H, KIHARA S: Adiponectin inhibits endothelial synthesis of interleukin-8. *Circ Res* 2005: 97: 1245-52.
43. WONG WT, TIAN XY, XU A *et al*.: Adiponectin is required for PPARγ-mediated improvement of endothelial function in diabetic mice. *Cell Metab* 2011: 14: 104-15.
44. OUCHI N, KIHARA S, ARITA Y, NISHIDA M, MATSUYAMA A, OKAMOTO Y: Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* 2001; 103: 1057-63.
45. MENZAGHI C, TRISCHITTA V: The adiponectin paradox for all-cause and cardiovascular mortality. *Diabetes* 2018; 67: 12-22.
46. LUYENDYK JP, SCHOENECKER JG, FLICK MJ: The multifaceted role of fibrinogen in tissue injury and inflammation. *Blood* 2019; 133: 511-20.
47. EMERGING RISK FACTORS COLLABORATION: C-reactive protein, fibrinogen, and cardiovascular disease prevention. *N Engl J Med* 2012; 367: 1310-20.
48. LASSÉ M, PILBROW AP, KLEFFMANN T, ÖVERSTRÖM EA, VON ZYCHLINSKI A, FRAMPTON CMA: Fibrinogen and hemoglobin predict near future cardiovascular events in asymptomatic individuals. *Sci Rep* 2021; 11: 2605.
49. HINES LM, STEMPFER MJ, MA J *et al*.: Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. *N Engl J Med* 2001 344: 549-55.
50. LARSSON SC, BURGESS S, MASON AM, MICHAËLSSON: Alcohol consumption and

cardiovascular disease: A Mendelian randomization study. *Circ-Genom Precis Med* 2020; 13: e002814.

51. DJOUSSÉ L, LEE I-M, BURING JE, GAZIANO JM: Alcohol consumption and risk of cardiovascular disease and death in women: Potential mediating mechanisms. *Circulation* 2009; 120: 37-44.
52. MATTACE-RASO FU, VAN DER CAMMEN TJ, VAN DEN ELZEN AP *et al*.: Moderate alcohol consumption is associated with reduced arterial stiffness in older adults: the Rotterdam study. *J Gerontol A Biol Sci Med Sci* 2005; 60: 1479-83.
53. FILLMORE KM, GOLDING JM, GRAVES KL *et al*.: Alcohol consumption and mortality. I. Characteristics of drinking groups. *Addiction* 1998; 93: 183-203.
54. MASUNAGA N, KIMURA A, MIYATAKA M *et al*.: Effects of alcohol consumption on cardiovascular events in male patients with healed myocardial infarction. *Circ J* 2006; 70: 1263-68.
55. AGUILAR D, SKALI H, MOYE LA *et al*.: Alcohol consumption and prognosis in patients with left ventricular systolic dysfunction after a myocardial infarction. *J Am Coll Cardiol* 2004; 43: 2015-21.
56. Office for National Statistics: Adult drinking habits in Great Britain (2005-2017) [Internet]. London: Office for National Stastistics; [2018, cited 2020 Nov 11]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/drugusealcoholandsmoking/datasets/adultdrinkinghabits.