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Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis

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SUMMARY

Background
Liver cirrhosis is a large burden on global health, causing over one million deaths per year. Observational studies have reported an inverse association between coffee and cirrhosis.

Aims
To perform a systematic review and meta-analysis to characterise the relationship between coffee consumption and cirrhosis.

Methods
We searched for studies published until July 2015 that reported odds ratios, relative risks (RR) or hazard ratios for cirrhosis stratified by coffee consumption. We calculated RRs of cirrhosis for an increase in daily coffee consumption of two cups for each study and overall. We performed analyses by study design, type of cirrhosis and mortality. We assessed the risk of bias in each study and the overall quality of evidence for the effect of coffee on cirrhosis.

Results
We identified five cohort studies and four case–control studies involving 1990 cases and 432 133 participants. We observed a dose–response in most studies and overall. The pooled RR of cirrhosis for a daily increase in coffee consumption of two cups was 0.56 (95% CI 0.44–0.68; I^2 83.3%). The RR pooled from cohort studies for a daily increase of two cups was 0.58 (95% CI 0.41–0.76; I^2 91.1%) and from case–control studies it was 0.52 (95% CI 0.40–0.63; I^2 0.0%). The pooled RR of alcoholic cirrhosis for a daily increase of two cups was 0.62 (95% CI 0.51–0.73; I^2 0%) and of death from cirrhosis it was 0.55 (95% CI 0.35–0.74; I^2 90.3%).

Conclusion
This meta-analysis suggests that increasing coffee consumption may substantially reduce the risk of cirrhosis.

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INTRODUCTION

Liver cirrhosis is a significant burden on global health. Between 1980 and 2010, the number of deaths worldwide from cirrhosis increased from around 676 000 (1.54% of total) to over one million (1.95% of total).[1] Cirrhosis is also an important cause of disability and morbidity, and in 2010 was responsible for 31 million disability-adjusted life years (1.2% of the total). Although the absolute number of deaths from cirrhosis has increased, the global age-adjusted mortality rate decreased by 22% between 1980 and 2010. Trends in mortality rates vary markedly between countries, however, due to varying exposure to risk factors and the availability of vaccinations and treatments. In some countries, such as India and the UK, mortality rates are increasing.[1] The risk factors and aetiologies of cirrhosis are diverse, but those traditionally considered as important include alcohol-related liver disease and chronic viral hepatitis. More recently, and as a result of increases in obesity and diabetes mellitus, non-alcoholic fatty liver disease (NAFLD) has also emerged as a significant aetiological factor.[2, 3] Irrespective of aetiology, cirrhosis develops by a common mechanistic pathway involving chronic inflammation of the liver, followed by fibrosis, leading to end-stage liver disease (cirrhosis), which can be fatal either due to complications related to portal hypertension (decompensation) or to hepatocellular carcinoma (HCC).

Coffee is ubiquitous in most societies. Coffee comprises over a thousand compounds, many of which are biologically active and may affect human health. These include caffeine, chlorogenic acid, melanoids and the pentacyclic diterpenes, kahweol and cafestol.[4] The biological effects of coffee include stimulation of the central nervous system, primarily by caffeine, the attenuation of oxidative stress and inflammation, and anti-carcinogenesis.[5] Due to its widespread consumption, coffee and its effects on health have been studied extensively. In the context of liver disease, coffee appears to confer a number of protective effects. Animal studies and human observational studies suggest that coffee consumption reduces the frequency of abnormal liver function tests, fibrosis, cirrhosis and HCC.[6–10] In addition, a randomised-controlled trial (RCT) showed that patients with hepatitis C who drank more coffee had lower serum levels of liver enzymes.[11] The aim of this meta-analysis was to summarise the evidence from studies on the effect of coffee on cirrhosis.

METHODS

We followed the Prisma guidelines; a protocol is shown in Table S1.

Study searches and selection

We searched for titles of articles in PubMed, Embase (using Ovid) and Web of Science using the term: (coffee OR caffeine) AND (*liver* OR *hepat* OR *cirrh* OR *fibro*). We performed the search in July 2015 and did not restrict publication date. We also performed manual searches of reference lists of relevant studies returned by the initial search.

We included studies in this meta-analysis if they: (i) involved a case–control study, cohort study or RCT; and (ii) provided relative risks (RRs), odds ratios (ORs) or hazard ratios (HRs), including 95% confidence intervals (95% CIs), for cirrhosis stratified by coffee consumption in adults aged 18 or older. We excluded studies if they did not provide a summary dose–effect size or allow one to be calculated, which required individual effect sizes for three or more consumption categories. We also excluded studies if they were not in English. We assumed a diagnosis of cirrhosis where studies reported hospitalisation for chronic liver disease (CLD) or death from CLD but without a diagnosis of HCC. If two or more studies reported the same data, we used the most recent study. OJK screened titles and abstracts to remove duplicates. OJK and RB independently reviewed the remaining studies.

Data extraction and quality assessment

The data extraction was performed by OJK and checked by RB. The following data were extracted from each study in a standardised manner: (i) the publication date, the first author's surname and the country of origin; (ii) the study characteristics, including the design, the inclusion and exclusion criteria, the sample size, the measurement of coffee consumption, the outcome measures, and the adjustments for confounding variables and (iii) the number of events (or cases) and non-events (or controls) and the corresponding effect size and 95% CIs for different categories of coffee consumption. For cohorts, we also extracted information concerning whether CLD was excluded at baseline, the follow-up time and the loss to follow-up. Where studies provided multiple effect sizes for a single category of coffee consumption, we extracted the effect size most comprehensively adjusted for confounders. Where studies reported effect sizes for caffeinated and decaffeinated coffee consumption separately,

but not total coffee consumption, we extracted the effect sizes for caffeinated coffee. The case–control studies reported ORs, while the cohort studies reported either RRs [9, 12, 13] or HRs.[8, 14] As the incidence rate of cirrhosis was low, we assumed the ORs, RRs, HRs were equivalent, and from herein we refer to all three as RR for simplicity. We worked form published data only and without contacting study authors.

We assessed the risk of bias in individual studies using the Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI),[15] as has been used previously.[16] We included the following domains of bias: confounding, selection, measurement of exposure at baseline, changing exposure during follow-up, missing data (including loss to follow-up), outcome measurement and selective reporting. In accordance with the Cochrane tool, we judged each domain of bias as 'low', 'high' or 'unknown' risk. We made a single judgement for the risk of bias from 'measurement of exposure', which combined the domains 'measurement of exposure at baseline' and 'changing exposure during follow-up'. We made an overall judgement of the risk of bias for each study. We judged there to be a 'high' overall risk of bias where there was plausibility that individual domain bias would lead to bias in the reported effect estimates. We determined the overall quality of evidence supporting the effect of coffee on cirrhosis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[17] OJK and PJR performed the risk of bias analysis and overall quality of evidence assessment separately and then discussed the results for consensus.

Statistical analysis

Eight studies reported RRs and 95% CIs for cirrhosis. The other, Klatsky *et al.*, reported RRs and 95% CIs for alcoholic and non-alcoholic cirrhosis separately, but not total cirrhosis. For this study, we calculated a RR and 95% CI for total cirrhosis using the method described by Hamling *et al.*[18]

We consider the RRs as reported in the different studies below. However, because the reported categories of coffee consumption varied between the studies, a direct comparison was not initially possible. Thus, we calculated for each study a summary RR and 95% CI for an increase in coffee consumption of two cups per day. For each study, this involved estimating the median coffee consumption in each of the reported categories. Where the consumption category was an integer (e.g. one cup per day), we used the integer as the median. Where the category was a closed range, (e.g. one to three cups per day), we used the mid-point as the median. For the highest ranges, which were open-ended (e.g. >two cups per day), we used the lower end of the range plus the width of the preceding closed range for the median. If there was no preceding closed range, we used the lower end of the open-ended range plus the difference between the two preceding integers. This method was similar to those used for estimating median exposure in ranges in other meta-analyses.[19, 20] After calculating median consumptions, we performed a summary dose–response analysis following the method of Greenland and Longnecker.[21] We tested for nonlinearity of the dose–response across the range of consumption reported in the studies (from 0 to four and above cups per day) using a restricted cubic spline model.[22] This used data from eight studies that provided RRs for different categories of coffee consumption (Tverdal and Skurtveit did not report category-specific RRs). The *P*-value for nonlinearity was 0.34. We also used the cubic spline model to calculate RRs of cirrhosis for one to four cups per day compared to none.

Using the RRs and 95% CIs for an increase of two cups of coffee per day, we calculated a pooled RR and 95% CI of cirrhosis. We used a random effects model to incorporate between study heterogeneity, assuming the biological effects of coffee in different populations would vary randomly, at least by type, processing and measurement of coffee.[23] We examined statistical heterogeneity by performing Cochran's Q and I^2 tests. In accordance with the Cochrane Handbook,[24] Chapter 9.5.2, we used a *P*-value of <0.1 to signify statistically significant heterogeneity and we interpreted the I^2 values as follows: '0–40% heterogeneity might not be important; 30–60% may represent moderate heterogeneity; 50–90% may represent substantial heterogeneity; 75–100%: considerable heterogeneity'. We also examined heterogeneity by performing a sensitivity analysis, in which we calculated pooled RRs and 95% CIs while excluding studies one at a time from the analysis.[25] To examine potential publication bias, we used Egger's regression test. We did not test funnel plot symmetry to assess for publication bias due to the low power of that test when less than ten studies are available.[26] We performed sub-analyses to calculate the pooled RRs for cohort studies and case–control studies separately, the RR of alcoholic cirrhosis and the RR of death (i.e. with a diagnosis of cirrhosis or CLD). In order to assess confounding and the direction and magnitude of overall adjustment, we meta-analysed the crude effect sizes and compared them with the adjusted values.

For this purpose, we used the reported crude effect sizes or, where not reported, we calculated crude effect sizes from the published data. We used STATA (Release 13, StataCorp LP, College Station, TX) and Mathematica (Version 10, Wolfram Research, Inc., Champaign, IL) to perform the analyses, and we used a two-sided $P > 0.05$ for statistical significance.

RESULTS

Details of the study selection process and the included studies

Figure 1 illustrates the process for selecting the studies for inclusion in this meta-analysis. The searches returned 2023 studies. After OJK first excluded 1290 duplicates, OJK and RB separately reviewed titles and abstracts and excluded 646 irrelevant studies. OJK and RB then examined the full text of the remaining studies and excluded a further 78 studies for not meeting the eligibility criteria described above. Nine studies remained and we included all in this meta-analysis.[7–9, 12–14, 27–29]

Table 1 summarises the characteristics of the nine included studies, which included eight journal articles and one conference abstract.[27] The studies were published between 1994 and 2015 and involved 1990 cases and 432 133 participants. Five were cohort studies, involving 1364 cases and 429 202 participants, and four were case–control studies, involving 626 cases and 2305 controls (2931 participants in total). Two of the studies were in the USA, six in Europe and one in Singapore. Seven studies included men and women. One case–control study included males only.[27] One cohort study included only male smokers without a history of malignancy, alcoholism or major health problems.[13] The other cohort studies all involved men and women recruited as summarised in Table 1. The cohort studies measured outcomes using death and/or hospitalisation records and, thus, lost few participants to follow-up. Participants in the case–control studies were recruited from hospital records (i.e. both cases and controls). The studies adjusted for a variable mix of relevant confounders, but all adjusted for alcohol (the exact adjustments used in the conference abstract were unclear[27]). All the studies measured coffee consumption by means of a self-completion questionnaire or interview, in which participants selected a pre-defined category of consumption. All measurements were in cups. One study asked about the type of coffee preparation (e.g. boiled, filtered, etc.) and cup size.[13] Another study asked whether the coffee was caffeinated or decaffeinated.[8] For that study, we used the RRs for caffeinated coffee consumption in our analysis, whereas for the other studies we used the RRs for total coffee consumption.

Figure S1 illustrates the results of the risk of bias assessment for the individual studies. In summary, we found a high risk of bias for the following domains: confounding, selection and outcome measurement. We performed an assessment of the overall quality of evidence for the effect of coffee on cirrhosis using the GRADE system. We rated the quality of evidence based on risk of bias, inconsistency, indirectness, imprecision, publica-

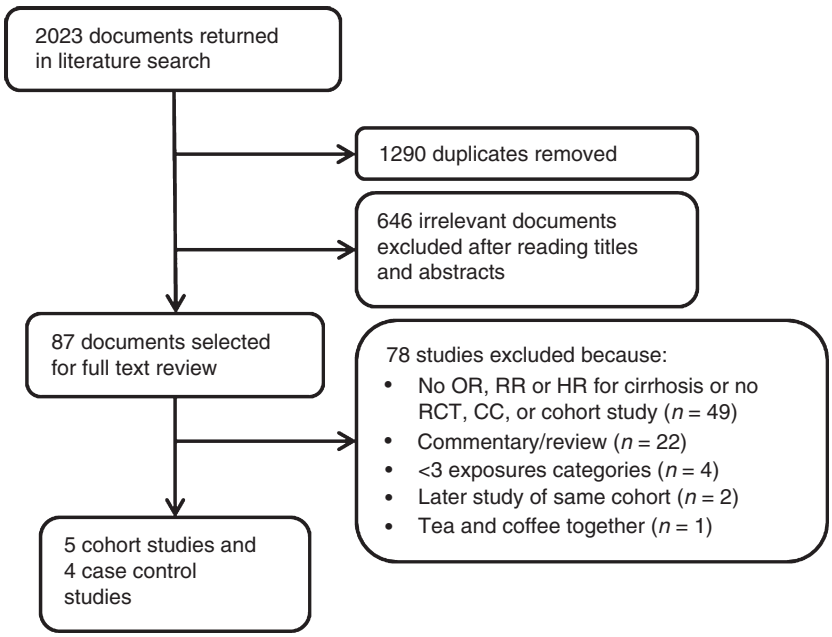

Figure 1 | A schematic showing the selection of relevant studies for inclusion in the meta-analysis.

Table 1 | Summary of the characteristics of the (a) cohort and (b) case–control studies included in this meta-analysis

Cohort study	Country	Follow-up years	Cohort (% men)	Cases (cumulative rate/1000)	Population characteristics (age)	Measurement of coffee consumption	Outcome ascertainment
(a)							
Tverdal and Skurtveit[12]	Norway	16.9 (mean)	51 306 (50)	53 (1.0)	Gen pop (20–55)*	FFQ	Death records (ICD codes)
Klatsky *et al.*[9]	United States	14.1 (mean)	125 580 (44)	330 (2.6)	Gen pop (n/a)†	FFQ	Death/hospital records (ICD codes)‡
Lai *et al.*[13]	Finland	18.2 (median)	27 037 (100)	213 (7.9)	Smokers (50–69)§	FFQ	Death records (ICD codes)
Goh *et al.*[14]	Singapore	14.7 (mean)	63 257 (44)	114 (1.8)	Gen pop (45–74)¶	FFQ	Death records (ICD codes)
Setiawan *et al.*[8]	United States	18 (median)	162 022 (47)	654 (4.0)	Gen pop (45–75)**	FFQ	Death records (ICD codes)

Case–control study	Country	*N* (% men) and age of cases	*N* (%men) and age of controls	Case selection	Control selection	Measurement of coffee consumption
(b)						
Corrao *et al.*[28]	Italy	115 (68) mean age 58	167 (60) mean age 60	Hospital††	Same hospital‡‡	Interview
Corrao *et al.*[7]	Italy	274 (60) mean age 56	458 (60) mean age 55	Hospital§§	Same hospital‡‡	Interview
Gallus *et al.*[29]	Italy	101 (82) median aged 62	1538 (74) median age 56	Hospital¶¶	Same hospital‡‡	FFQ
Stucker *et al.*[27]	France	136 (100) aged <75	142 (100) aged <75	Hospital	Hospital‡‡,***	FFQ

FFQ, Food frequency questionnaire; ICD, International Classification of Diseases; gen pop; general population.

* Recruited from a cardiovascular screening programme.

† Members of a health care programme (CLD excluded at baseline by ICD codes).

‡ Cases identified by ICD codes but confirmed only if (i) histological evidence, (ii) two hospital admissions 12 months apart or 1 admission plus a death certificate diagnosis, (iii) diagnosis by a gastroenterologist or (iv) a compelling clinical picture.

§ Recruited from an earlier trial into the effect of vitamin E supplementation on lung cancer incidence (those who reported cirrhosis excluded at baseline).

¶ Residents in government housing estates.

** Recruited from a driving license database, voter registration lists and health care financing administration data.

†† After exclusion of hepatic encephalopathy, hepatocellular carcinoma and primary biliary cirrhosis.

‡‡ Liver disease excluded.

§§ After exclusion of hepatic encephalopathy, hepatocellular carcinoma, primary biliary cirrhosis and other rare forms of cirrhosis, such as Wilson's disease and hemochromatosis.

¶¶ Derived from another case–control study into cancer.

*** Matched for age and birth country.

tion bias and factors that increase the quality of evidence. We rated the quality of evidence as low, as indicated in the Table S2.

To understand better the magnitude and direction of overall confounding across all studies, we compared the pooled adjusted and unadjusted RRs of cirrhosis for an increase in coffee consumption of two cups per day. After adjustment, the pooled RR decreased from 0.66 (95% CI 0.47–0.85) to 0.56 (95% CI 0.44–0.68), indicating the overall effect of adjusting for confounding increase the effect size away from null.

In determining the overall risk of bias in the individual studies, we found a high risk in all the case–control studies because of the potential for selection bias in

Table 2 | Summary of the results of the studies included in this meta-analysis

Study	Coffee (cups per day)	Participants	Cases (cumulative rate/1000)	Adjusted RR (95% CI)	Adjustments
Cohort studies country					
Tverdal and Skurtveit[12] (any cirrhosis)	2	51 306	53 (1.0)	0.6 (0.5–0.8)	Gender, age, alcohol, smoking, BMI, cholesterol, systolic blood pressure, triglycerides
Tverdal and Skurtveit[12] (alcoholic cirrhosis)	2	51 306	36 (0.7)	0.6 (0.5–0.8)	Gender, age, alcohol, smoking, BMI, cholesterol, systolic blood pressure, triglycerides
Klatsky *et al.*[9] (alcoholic cirrhosis)	0*	33 634	54 (1.6)	1 (ref.)	Gender, alcohol, smoking, BMI, race, education
	<1	17 576	24 (1.4)	0.7 (0.4–1.1)	
	1–3	52 351	96 (1.8)	0.6 (0.4–0.8)	
	4+	20 504	22 (1.1)	0.2 (0.1–0.4)	
	Per extra cup			0.8 (0.7–0.9)	
Klatsky *et al.*[9] (non-alcoholic cirrhosis)	0*	33 634	24 (0.7)	1 (ref.)	Gender, alcohol, smoking, BMI, race, education
	<1	17 576	17 (1.0)	1.2 (0.6–2.2)	
	1–3	52 351	68 (1.3)	1.3 (0.8–2.1)	
	4+	20 504	18 (0.9)	0.7 (0.4–1.3)	
	Per extra cup			0.9 (0.8–1.0)	
Lai *et al.*[13]	0	667	10 (15.0)	0.73 (0.38–1.42)	Age, alcohol, smoking, BMI, cholesterol, education, diabetes, tea, marital status, ATBC intervention arm†
	>0 to <1	3094	75 (24.2)	1 (ref.)	
	1 to <2	7204	68 (9.4)	0.44 (0.31–0.62)	
	2 to <3	8086	39 (4.8)	0.23 (0.15–0.35)	
	3 to <4	4515	15 (3.3)	0.15 (0.08–0.26)	
	4+	3471	6 (1.7)	0.08 (0.03–0.18)	
	Per extra cup			0.55 (0.48–0.63)	
Goh *et al.*[14]	0 ‡	18 816	45 (2.4)	1 (ref.)§	Gender, age, alcohol, smoking, BMI, education, diabetes, physical activity, dialect group, year of recruitment
	1	22 803	34 (1.5)	0.62 (0.40–0.97)§	
	2+	21 638	35 (1.6)	0.63 (0.40–1.00)§	
Setiawan *et al.*[8]	0	44 438	184 (4.1)	1 (ref.)§	Gender, age, alcohol, smoking, BMI, race, education, diabetes
	<1	31 056	163 (5.2)	1.14 (0.92–1.41)§	
	1	45 717	202 (4.4)	0.85 (0.69–1.04)§	
	2–3	32 593	91 (2.8)	0.54 (0.42–0.69)§	
	4+	8218	14 (1.7)	0.29 (0.17–0.50)§	
Case–control studies					
Corrao *et al.*[28]	0	60	28	1 (ref.)¶	Gender, age, alcohol, smoking, HBsAg and anti-HCV status
	1	124	49	0.6 (0.2–1.1)¶	
	2+	98	38	0.5 (0.3–1.0)¶	
Corrao *et al.*[7]	0	112	57	1 (ref.)¶	Alcohol, smoking, education, HBsAg and anti-HCV status, energy intake, carbohydrates, lipids and proteins
	>0 to 1**	173	71	0.47 (0.20–1.10)¶	
	>1 to 2**	258	84	0.23 (0.10–0.53)¶	
	>2 to 3**	87	25	0.21 (0.06–0.74)¶	
	3+**	57	20	0.16 (0.05–0.50)¶	
Gallus *et al.*[29]	0	247	28	1 (ref.)¶	Gender, age, alcohol, smoking, BMI, education, diabetes, area of residence, year of interview, history of hepatitis
	1	367	31	0.8 (0.4–1.6)¶	
	2	463	29	0.6 (0.3–1.2)¶	
	3+	562	13	0.3 (0.1–0.7)¶	

choosing cases and controls and for recall bias in determining exposure to confounders. We found an unclear overall risk of bias in the cohort studies. We did not assign a 'low' risk of overall bias to any study even if there was no obvious source of bias that would have affected the results. This was in accordance with the ACROBAT-NRSI, which indicates that only randomised trials should be considered 'low' overall risk of bias.

Coffee consumption and cirrhosis

Table 2 summarises the results as reported by the studies. Figure 2 is a forest plot of the calculated RRs of cir-

Table 2 | (Continued)

Study	Coffee (cups per day)	Participants	Cases (cumulative rate/1000)	Adjusted RR (95% CI)	Adjustments
Stucker *et al.*[27]	0–1	133††	76††	1 (ref.)¶	n/a
	2	70††	33††	0.65 (0.3–1.4)¶	
	2+	75††	27††	0.33 (0.2–0.7)¶	

BMI, body mass index; ATBC, alpha-tocopherol, beta-caroten; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus.

* Never or seldom.

† Participants were taken from another trial investigating vitamin E supplementation in the form of alpha-tocopherol or beta-caroten.

‡ None/less than daily.

§ Hazard ratio.

¶ Odds ratio.

** Reported as caffeine from coffee, with 100 mg being equal to one cup.

†† Calculated from the total number of cases and controls and the percentage of the totals in each consumption category.

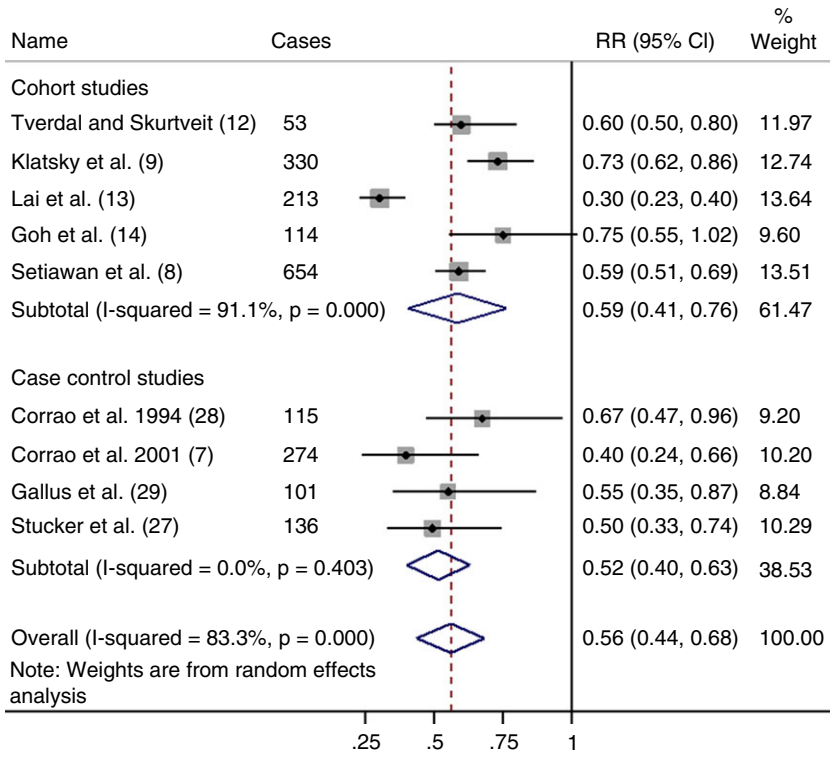

Figure 2 | Forest plot showing the associations of cirrhosis with drinking an additional two cups of coffee per day as reported by the included studies individually and pooled overall. The pooled RRs were calculated by random effects meta-analyses. The sizes of the squares represent the weighting of each study in the calculation and the pooled RRs are represented by diamonds.

rhosis for an increase in coffee consumption of two cups per day for each study and overall. In eight studies, increasing coffee consumption by two cups per day was associated with a statistically significant reduction in the risk of cirrhosis. In the other study, Goh *et al.*, the corresponding RR was 0.75 (95% CI 0.55–1.02). The pooled RR across all studies was 0.56 (95% CI 0.44–0.68). In all but one study, Goh *et al.*, there was evidence of a dose-dependent relationship, with generally lower RRs for higher consumption categories. The data as reported by the studies are illustrated as a semi-log plot in Figure 3. We calculated that compared to no consumption the pooled RRs of cirrhosis were 0.78 (95% CI 0.68–0.90), 0.57 (95% CI 0.50–0.65), 0.43 (95% CI 0.37–0.50) and 0.35 (95% CI 0.30–0.41) for one to four cups of coffee per day respectively.

Egger's regression test gave no indication of statistically significant publication bias ($P > 0.05$). Cochran's Q and I^2 were 48 ($P = 0.0$) and 83.3%, respectively, and showed statistically significant heterogeneity between the

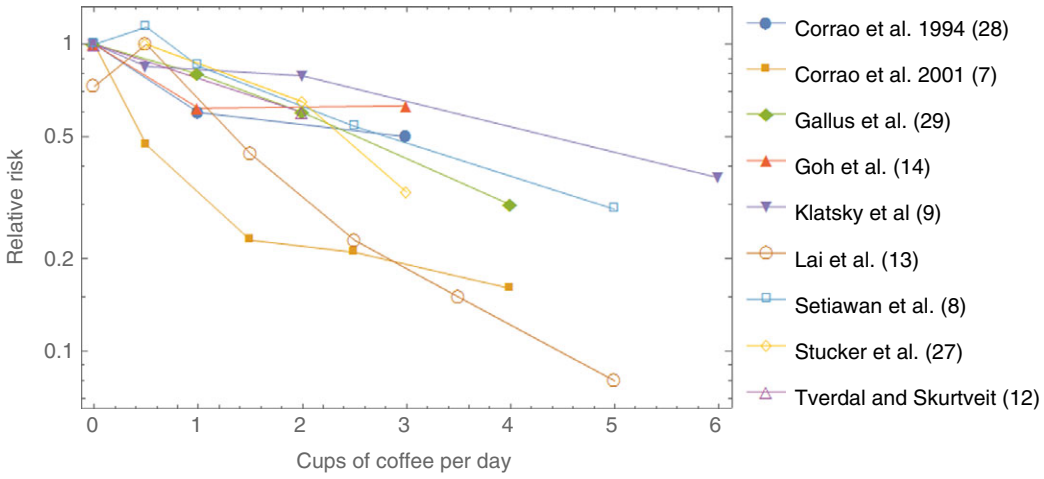

Figure 3 | A semi-log plot of the adjusted study-specific and overall RRs of cirrhosis vs. cups of coffee per day. The study-specific RRs are plotted against the estimated median coffee consumption in each reported category.

studies. We further investigated this heterogeneity by means of a sensitivity analysis, in which we calculated pooled RRs while excluding the studies one at a time. The pooled RRs in the sensitivity analysis and the Q and I^2 varied most substantially when Lai *et al.* was excluded. Without Lai *et al.*, the pooled RR for an increase in coffee consumption of two cups per day was 0.61 (95% CI 0.53–0.68). The corresponding Q and I^2 values were 11 (P = 0.14) and 36.1%, showing markedly reduced heterogeneity compared to when Lai *et al.* was included. The pooled RR of cirrhosis for an increase of two cups per day in cohort studies was 0.58 (95% CI 0.41–0.76; I^2 91.1%) and in case–control studies it was 0.52 (95% CI 0.40–0.63; I^2 0.0%). The RRs of alcoholic cirrhosis, calculated from two studies,[9, 12] and death from liver disease, calculated from four studies,[8, 12–14] for an increase in coffee consumption of two cups per day were 0.62 (95% CI 0.51–0.73; I^2 0.0%) and 0.55 (95% CI 0.35–0.74; I^2 90.3%) respectively.

DISCUSSION

Earlier meta-analyses have reported an inverse association between coffee consumption and liver cancer.[10, 30, 31] Studies have also reported protective effects of coffee in animals with liver disease and in humans where the outcomes were less severe CLD including abnormal LFTs.[9, 32, 33] However, this is the first meta-analysis to show a protective effect of coffee against cirrhosis. The analysis of five cohort and four case–control studies has shown that increasing daily coffee consumption by two cups is associated with a near halving of the risk of cirrhosis. While statistically significant heterogeneity existed across the studies, this was explained by the effect of one study, and the association was consistent through the sensitivity analysis. Sensitivity analyses showed that increasing daily coffee consumption by two cups is also associated with reduced RRs of alcoholic cirrhosis and death from cirrhosis.

One of the strengths of this meta-analysis was the inclusion of studies that reported a summary dose RR or RRs for three or more categories of coffee consumption only. This allowed the estimation of a clinically relevant dose–response between coffee and cirrhosis. We excluded four studies, including one conference abstract, which reported RRs for less than three categories of coffee consumption.[34–37] Those studies reported inverse associations between coffee and cirrhosis, which were statistically significant in three studies, and thus support the findings of this meta-analysis. There are also limitations. First, the studies included were observational which, by design, do not infer causation and are generally more susceptible to bias and confounding than randomised studies. In the risk of bias assessment, the case–control studies were at high risk of selection bias in choosing cases and controls and to recall bias in the estimation of coffee and alcohol consumption years previously. Despite the risk of bias, the case–control studies agreed broadly with the cohort studies. We found that overall adjustment (including for body mass index, diabetes, alcohol and viral hepatitis) increased the effect size away from null, which suggests that coffee drinkers had greater overall exposure to the known risk factors of cirrhosis compared to noncoffee drinkers. However, resid-

ual confounding may have existed in all studies due to confounding variables that were not measured accurately or not adjusted for. While all the studies adjusted for alcohol consumption (we were unclear as to what adjustments were made in the conference abstract[27]), which is the most critical confounder, only six studies adjusted for age, six for body mass index and gender, and four for diabetes. The cohort studies did not adjust for viral hepatitis status but prevalence was likely to be low in the populations studied. One particular concern is the potential for confounding from hidden nutritional and lifestyle factors not measured and adjusted for in the studies. If such factors were associated with coffee consumption and influenced the risk of cirrhosis, this would introduce bias into our findings. Another potential confounder is that people with pre-existing liver disease metabolise caffeine more slowly[38, 39] and, as a result, may drink less coffee. This may have been important in the case–control studies, in which participants estimated previous coffee consumption over a time when they probably already had reduced liver function. The corresponding effect would be diluted in the cohort studies due to the long follow-up (all were longer than 14 years) and the exclusion of pre-existing liver disease at baseline in two of the studies.[9, 13] Some of the cohort studies investigated confounding by pre-existing liver disease in sensitivity analyses. In one such analysis, Setiawan *et al.* found that the RR of CLD death for ≥ two cups of coffee daily compared to none remained comparable in magnitude and statistically significant (RR 0.54; 95% CI 0.42–0.69) when deaths in the first 2 years were excluded. Lai *et al.* found that the RR of CLD death for an extra cup of coffee per day was 0.53 (95% CI 0.44–0.64) in the first 10 years of the trial and 0.57 (95% CI 0.48–0.69) in the last 10 years. As such, drinking coffee appeared to protect against cirrhosis in participants who would have had varying levels of undiagnosed liver disease at baseline.

We investigated the overall effect of confounding by comparing the adjusted and unadjusted RRs across all trials. We found that adjustment for confounding increased the pooled RR away from null. In accordance with the GRADE system, this added to the overall quality of evidence for the protective effect of coffee against cirrhosis.

We found statistically significant heterogeneity between the studies, which may indicate important differences in the populations studied and in the study methods. The ages, countries and regions of origin, and proportions of men and women varied. In addition, and as noted above, participants with evidence of CLD at baseline were excluded from two cohort studies, while in the other cohort studies CLD was not looked for systematically at baseline and, thus, was not excluded. Between the cohort studies, the most significant difference in the populations was that in Lai *et al.* the participants were all Finnish male smokers recruited from an earlier study into lung cancer, while in the others participants were men and women recruited from databases more representative of the general population (see Table 1). When the study of Lai *et al.* was excluded during the sensitivity analysis, heterogeneity became statistically insignificant, whereas the pooled RR varied by 5% only.

Heterogeneity may also exist in the measurement of coffee consumption. In all studies, participants estimated the usual daily intake of coffee or the daily average over a specified preceding period (e.g. 1 year). Participants' responses may have been influenced if they knew they were in a study investigating nutrition, leading to overestimation or underestimation of consumption. This may be more significant for the case–control studies because participants recalled coffee consumption over longer periods and because cases may recall their diet differently to controls leading to differential misclassification of exposure. CLD in cases may have reduced consumption and hence overestimated the apparent protective effect. Differences in cup sizes, the methods of preparation (e.g. filtered vs. boiled) and the types of coffee (e.g. decaffeinated vs. caffeinated) might also be important. For example, one study[13] found that the RR of cirrhosis for an additional cup per day was 0.50 (95% CI 0.40–0.63) for filtered coffee and 0.62 (95% 0.43–0.88) for boiled coffee. Another study[8] found that the RR of CLD death for ≥ two daily cups of decaffeinated coffee was 0.54 (95% CI 0.35–0.85), although this was broadly similar to that for caffeinated coffee.

Heterogeneity might have arisen due to the different outcome measures. First, four studies identified outcomes using death records only, four studies used hospital records only, and one study used both. The importance of these differences is unclear as the pooled RR of death, calculated from studies using death records only, was similar to the RR pooled from the case–control studies, which used hospital records only. Secondly, studies identified cases differently, for example, by histology, a compelling clinical picture or by searching death and hospital records for Classification of Diseases (ICD) codes, for example, 9th edition code 571: '*Chronic liver disease and cirrhosis*'. Histology is the reference standard, and ideally would have been used to confirm all cases, but the clinical picture of cirrhosis is specific (e.g. oesophageal varices or spontaneous bacterial peritonitis) and patients who die from

CLD (i.e. ICD 571) but do not have HCC are highly likely to have cirrhosis. However, there was one study[8] which appeared to include ICD codes relating to acute liver disease in the total count of CLD deaths. We were uncertain how differences in outcome measurements affected our pooled RR, which did not vary substantially during the sensitivity analysis and remained statistically significant.

The use of biopsy in some studies [9, 27, 29] may have introduced ascertainment bias if there were differential biopsy use according to baseline coffee consumption or to other correlated risk factors. Bias may also have been introduced if there were undetected cases of compensated cirrhosis on account of the included studies using hospital and/or death records only to identify cases. Some compensated cases might have been detected if biopsies were performed on asymptomatic participants in hospital (e.g. for a reason other than cirrhosis), but undiagnosed compensated cases in the community would have been missed. The risk of bias from these undetected cases is uncertain because the pathological pro-fibrotic mechanism which causes the initial establishment of cirrhosis is the same irrespective of aetiology or subsequent clinical sequelae (i.e. whether the individual remains asymptomatic, is hospitalised or dies). Thus, it is logical to expect that the alleged protective effect of coffee, which likely begins long before cirrhosis is established, would apply equally to cases detected by the included studies and those that were not. However, the uncertainty highlights the need for randomised trials.

We could only partially examine the influence of aetiology on the inverse association between coffee consumption and cirrhosis. We found that the pooled RR for alcoholic cirrhosis was similar to the overall estimate. However, there was insufficient data to calculate estimates for other important aetiologies of cirrhosis, such as viral hepatitis and NAFLD. While the potential influence of aetiology is unclear since the underlying pathological process leading to cirrhosis is the same, this issue should be considered further in new studies.

There also exists the possibility of language bias since we included English language studies only. However, most studies are published in English, and studies investigating the effect of language bias in meta-analyses generally report limited evidence of an effect.[40] There is also some evidence that non-English language trials tend to be of lower quality and report larger effect sizes,[41] and so the inclusion of English language studies only is unlikely to lead to significant bias in our findings. Finally, there also exists the potential of publication bias. While Egger's regression test detected no statistically significant publication bias, we were unable to rule out publication bias completely. First, the relatively small number of studies provided limited statistical power and, secondly, studies with statistically significant results are more likely to be published compared to those with null results.[42] As such, the pooled RR reported in this study may be exaggerated compared to the true value.

It is biologically plausible that coffee protects the liver against the inflammatory and fibrotic process leading to cirrhosis. Caffeine is thought to be important, and animal studies show that caffeine not from coffee protects against toxin-induced liver fibrosis.[33, 43] Caffeine's protective mechanism of action may be through antagonism of the adenosine receptor A2aAR.[44] Hepatic stellate cells (HSCs) are the primary effector cells mediating fibrogenesis in the liver and express A2aAR. Activation of A2aAR markedly up-regulates collagen synthesis in HSCs,[45, 46] whereas mice lacking expression of A2aAR are protected from toxin-induced fibrosis.[47] Caffeine might also attenuate fibrosis by suppression of inflammation and oxidative stress. Caffeine inhibits tumour necrosis factor-α, a pro-inflammatory cytokine and reactive oxygen species production by Kupffer cells.[48] While caffeine might be important, there is evidence that other noncaffeine-mediated mechanisms also contribute to the protective effect seen. First, adjusting for coffee consumption pushes the association between caffeine and cirrhosis towards null, and some studies report no association between cirrhosis and noncoffee sources of caffeine.[7, 8] Secondly, and as is mentioned above, there is some epidemiological evidence that decaffeinated coffee protects against cirrhosis and abnormal liver function tests.[8, 49] Decaffeinated coffee also protects against toxin-induced fibrosis in animal studies.[43] The evidence for decaffeinated coffee protecting against cirrhosis is weaker overall than for regular coffee, but there is still biological plausibility. Coffee contains a range of biologically active ingredients beyond caffeine, including anti-oxidative and anti-inflammatory agents, such as chlorogenic acid, kahweol and cafestol, and there is evidence that these may confer protection against liver fibrosis.[43]

The protective effect of coffee against cirrhosis may also involve indirect mechanisms that modify risk factors. Laboratory studies have shown that various constituents of coffee inhibit the activities of hepatitis B and C viruses.[50–52] In addition, and of even greater significance to public health, is the inverse association between coffee (both caffeinated and decaffeinated) and type 2 diabetes mellitus (T2DM). A recent meta-analysis calculated that the RR of

T2DM for an increase in consumption of one cup per day was 0.91 (95% CI 0.89–0.94) for regular coffee and 0.94 (95% CI 0.91–0.98) for decaffeinated coffee.[53] The mechanism of action of coffee on T2DM is unclear, but caffeine is unlikely to be the sole mediator. Caffeine causes a short-term reduction in insulin sensitivity[54] and generally studies do not show a protective effect of caffeine against T2DM after adjustment for coffee and tea intake.[55, 56] Chlorogenic acid in coffee is likely important; it has been shown to inhibit glucose absorption in the gut. It also inhibits hydrolysis of glucose-6-phosphate, which is the final step of glucose production by gluconeogenesis and glycogenolysis.[57] Other constituents in coffee that may improve glucose metabolism and partly explain the relationship between coffee and T2DM include magnesium, trigonelle, lignans and quindes.[58–61] The favourable metabolic effects of coffee would be expected to protect against NAFLD and the related inflammation (NASH) which can lead to fibrosis and cirrhosis.

Cirrhosis is by far the most important risk factor for HCC. Accordingly, the findings of this meta-analysis may in part explain observational studies showing an inverse association between coffee and HCC. However, while it is logical to suggest that preventing cirrhosis would reduce HCC, other mechanisms involving a direct anti-carcinogenic effect of coffee may exist. Caffeine is thought to directly inhibit the proliferation of HCC cells.[62] In addition, cafestol and kahweol upregulate phase II enzymes in the liver, which may increase clearance of potentially carcinogenic toxic insults,[63, 64] and the anti-oxidative effects of coffee may reduce DNA damage from reactive oxygen species. Observational studies do not show a consistent association between HCC and decaffeinated coffee,[8, 65] which indicates that caffeine may be the primary agent. This is supported by a recent meta-analysis which showed an inverse association between HCC and green tea, a noncoffee source of caffeine.[66]

Before recommending an increase in coffee consumption to those at risk of cirrhosis, consideration is required of the wider effects of coffee. There is evidence of an association of coffee with lung and bladder cancer and with bone fractures.[19, 67, 68] However, there are also benefits of coffee beyond those on the liver. Coffee has been inversely associated with all-cause mortality,[69] neurological diseases [70] and a number of different cancers.[71] Coffee may also protect against stroke,[72] although there is a need for further work to understand fully the effects of coffee on the cardiovascular system. This is especially important at higher levels of consumption, where there is less evidence concerning the beneficial effects of coffee as well as the potential harms.

In conclusion, this meta-analysis shows that an increase in daily coffee consumption of two cups is associated with a near halving of the risk of cirrhosis. This is a large effect compared to many medications used for the prevention of disease. For example, statin therapy reduces the risk of cardiovascular disease by 25%.[73] Furthermore, unlike many medications, coffee is generally well tolerated and has an excellent safety profile. The findings of this meta-analysis are important given the high incidence of severe liver disease, the positive interaction between alcohol and obesity for liver disease risk and the lack of specific treatments to prevent liver disease due to these factors. The next steps should be to develop interventions that support patients at risk of or with mild–moderate CLD, to increase their coffee consumption, even in existing coffee drinkers given the dose–response relationship, and then to evaluate the effect of increasing consumption on robust markers of CLD in well-designed randomised studies. However, such studies would be challenging (e.g. blinding would not be possible) and would require careful consideration of patient selection/stratification, trial methodology and the availability of suitable surrogate endpoints, given that hard clinical endpoints would take years to occur.

SUPPORTING INFORMATION

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

Figure S1. Risk of bias graph and summary: review authors' judgements about each risk of bias item separately and as percentages across all included studies. *The assessment of the risk of bias from the measurement of exposure included changes in exposure over time. **The assessment of the risk of bias from missing data included loss to follow-up for cohort studies.

Table S1. PRISMA-P protocol.

Table S2. Summary of Findings table according to the GRADE assessment.

AUTHORSHIP

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Author contributions: JP, PJR and OJK conceived the study. OJK performed the search. OJK and RB reviewed and selected the studies. OJK and PJR did the risk of bias and overall quality of evidence assessment. OJK extracted the data which were checked by RB. OJK performed the statistical analysis. OJK drafted the manuscript. All authors critically reviewed the manuscript and provided comments or made amendments.

All authors approved the final version of the article, including the authorship list.

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