Supplementary Information: Coffee, Including Caffeinated and Decaffeinated Coffee, and the Risk of Hepatocellular Carcinoma: A Systematic Review and Dose-Response Meta-Analysis

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THE ASSOCIATION BETWEEN COFFEE AND HCC ACCORDING TO RISK FACTOR EXPOSURE

Viral hepatitis B and C

Individual studies reported statistically significant reductions in the RR of HCC with increasing coffee consumption in participants who were HBV positive,[1] HCV positive[2] and negative for both.[3] Three studies reported RRs stratified by HBV/HCV status in a manner suitable for dose response analysis.[2-4] One of those studies reported RRs in a subgroup with HCV,[2] one in a subgroup with HBV and/or HCV[3] and one in two subgroups with (i) HBV or (ii) HCV[4] (some participants were co-infected and in both subgroups). The pooled RR of HCC for an extra two cups of coffee per day with HBV/HCV was 0.59 (95% CI 0.34-1.00; three studies) and 0.56 (95% CI 0.42-0.74; three studies) when

we included the HBV and HCV estimates, respectively, from the study with separate subgroups. Both those were weaker than the corresponding RR without HBV/HCV of 0.42 (95% CI 0.26-0.70; three studies) and the p-values for the differences were 0.50 ($\tau^2 = 0$) and 0.64 ($\tau^2 = 0$).

Diabetes and BMI

Two studies reported RRs of HCC according to coffee consumption stratified by diabetes status.[5, 6] For both studies, the RRs for an extra two cups of coffee per day were statistically significant for participants without but not with diabetes, although this may have been due to small sample size for DM. The pooled RR of HCC for an extra two cups of coffee per day was 0.79 (95% CI 0.72-0.86; two studies) without diabetes, which was larger than the corresponding RR of 0.84 (95% CI 0.69-1.04; two studies) with diabetes. The p-value for the difference was 0.70 ($\tau^2 = 0.01$).

Four studies reported RRs of HCC according to coffee consumption stratified by BMI.[5-8] The RRs for an extra two cups of coffee per day were statistically significant in two of the four studies in both the highest (above 25 and 30 kg/m2) and lowest (below 25 and 30 kg/m2) BMI categories.[6, 8] For the other studies, the RRs were statistically significant in the highest BMI category only (above 25 kg/m2 for both).[5, 7] In all four studies, the associations were stronger in the highest BMI category than the lowest. The pooled RR for an extra two cups of coffee per day was 0.72 (CI 95% 0.63-0.81; four studies) in the highest BMI category, which was larger than the corresponding RR in the lowest of 0.78 (95% CI 0.71-0.86; four studies). The p-value for the difference was 0.13 ($\tau^2 = 0$).

Alcohol consumption

Five studies reported RRs of HCC according to coffee consumption stratified by alcohol intake in a manner suitable for dose-response analysis.[3-5, 8, 9] The RRs of HCC for an

extra two cups of coffee per day were statistically significant in three studies for the highest categories of alcohol consumption[3, 4, 8] and in three studies for the lowest.[5, 8, 9] The pooled RR of HCC for an extra two cups of coffee per day in the highest category of alcohol consumption was 0.63 (95% CI 0.51-0.77; five studies) compared to 0.71 (95% CI 0.63-0.79; five studies) in the lowest. The p-value for the difference was 0.53 ($\tau^2 = 0$).

Smoking

Five studies reported RRs of HCC for three or more categories of coffee consumption separately for smokers and non-smokers[4-6, 8, 9]. The non-smoker groups mostly contained never smoker and ex-smokers. The RRs of HCC for an extra two cups of coffee per day were statistically significant in four studies for smokers [4-6, 8] and in two studies for non-smokers [5, 8]. The pooled RRs were 0.68 (95% CI 0.55-0.83; five studies) for smokers and 0.78 (95% CI 0.70-0.87; five studies) for non-smokers. The p-value for the difference was 0.13 ($\tau^2 = 0$).

PRISMA-P PROTOCOL

Section and topic	Checklist item
ADMINISTRATIVE INFORMATION	
Identification	We will perform a systematic review with meta-analysis of the relationship between caffeinated and decaffeinated coffee and hepatocellular carcinoma (HCC). There are existing meta-analyses on coffee and HCC but none on decaffeinated coffee or the influence of HCC aetiology.
Registration	Our protocol is unregistered
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Support	There are no sponsors or financial interests to declare.
INTRODUCTION	
Rationale	Primary liver cancer is the sixth most commonly diagnosed cancer worldwide. Hepatocellular carcinoma (HCC) is the most common subtype of primary liver cancer. Of concern is the

	global increase of non-alcoholic steatohepatitis/metabolic syndrome which can progress to HCC in the absence of cirrhosis. A number of studies have shown drinking coffee is inversely associated with the risk of diseases affecting the liver, including HCC.
Objectives	To determine quantitatively the relationship between caffeinated and decaffeinated coffee and the risk of HCC. To investigate whether the relationship between coffee and HCC is influenced by pre-existing liver disease or specific risk factors (e.g. EtOH, HBV/HCV, metabolic factors)
METHODS	
Eligibility criteria	We will include studies in our meta-analysis that: • are cohort or case-control studies • report effect sizes (RRs, OR, HRs) for primary liver cancer/HCC according to coffee intake (adults only). We will exclude studies that: • report no dose-response or provide insufficient information for one to be computed. • are published in a language other than English.
Information sources	Searches will be performed for published studies using Web of Science, Pubmed and Embase, and no limitation of date of publication will be imposed. Manual searches of reference lists will be performed.
Study selection process	Duplicates will be removed before two authors screen studies, first by abstracts and titles followed by full text.
Data collection process	The following data will be extracted from the included studies: • first author, date of publication, country, the design of the study, the exclusion and inclusion criteria, the estimates and adjustments, the numbers of participants (or controls) and cases, the methods of measuring exposure and case identification, cohort follow-up (time, losses), whether baseline liver disease was excluded. • the most rigorously adjusted effect sizes and effect sizes stratified by pre-existing chronic liver disease, alcohol consumption, BMI, hepatitis B and C virus status, diabetes, and type of coffee. • RRs for total caffeinated and decaffeinated coffee consumption, including RRs stratified by pre-existing liver disease and aetiology.
Data items	We will assume that hazard ratios, odds ratios and relative risks are the same.
Outcomes and prioritization	HCC stratified by risk factors / aetiology / type of coffee
Risk of bias	Newcastle-Ottawa scale shall be used for risk of bias assessment
Data synthesis	We will calculate RRs for a two cups/day increase and for 1-5 cups per day, where possible stratified by risk factors. I2 and Cochrane Q will be used to assess heterogeneity. We will re-run the analysis while omitting each study.
Additional analyses	Eggers test and a trim-and-fill analysis will be used to

	investigate publication bias.
Confidence in cumulative evidence	GRADE will be used for assessment of evidence quality

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