https://dx.doi.org/10.1016/j.tjnut.2025.01.009

Association of Sugar sweetened, Artificially Sweetened, and Unsweetened Coffee Consumption with Chronic Liver Disease and Liver Related Events: A Large Prospective Cohort Study

Yifei Li[1†], Peiting Zhang[1†], Yuqing Deng[2], Chao Yu[3], Xuechen Chen[4], Xinyu Liu[1], Qiaoqiao Yang[1], Jingcheng Jiang[5], Xu Chen[6,7]*, Hongliang Xue[1,8]*

[1] Department of Nutrition, School of Public Health, Guangzhou Medical University, Guangzhou, China;

[2] State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Centre, Sun Yat-sen University, Guangzhou, China;

[3] Medical Examination Center, Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, China;

[4] College of Pharmacy, Jinan University, Guangzhou, China;

[5] Department of Intergrative Physiology, University of Colorado, Boulder, USA;

[6] Department of Food Science and Nutrition, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong Special Administrative Regions;

[7] Research Institute for Future Food, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong Special Administrative Regions;

[8] The Key Laboratory of Advanced Interdisciplinary Studies, The First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China.

† Yifei Li and Peiting Zhang contributed equally to this article.

***Corresponding authors:**

Hongliang Xue, MD, PhD,

School of Public Health/The First Affiliated Hospital, Guangzhou Medical University

No.1, Xinzhao Road, Guangzhou, 510060 China

Tel: +86-15622265853

Email: 2022991056@gzhmu.edu.cn

Xu Chen, MD, PhD,

Department of Food Science and Nutrition/Research Institute for Future Food, The Hong Kong Polytechnic University

11 Yucai Road, Hung Hom, Kowloon, Hong Kong Special Administrative Regions

Tel: +86-18120557291

Email: cxu1024@gmail.com

Abbreviations:

CIs: Confidence intervals

CLD: Chronic liver disease

HR: Hazard ratios

LREs: Liver-related events

NAFLD: Nonalcoholic fatty liver disease

RERI: Relative excess risk due to interaction

TDI: Townsend deprivation index

Abstract

Background

Previous observational studies haven't reached an agreement on the association between coffee consumption and risk of liver diseases. Also, none of these studies took sweetener added in coffee into consideration.

Objective

We aim to explore the associations of consumption of sweetened and unsweetened coffee with chronic liver disease (CLD) and liver-related events (LREs), and evaluate the degree to which sweetener added counteracted the effect of coffee.

Methods

We performed a longitudinal cohort study of 170 044 participants without liver diseases or cancer at baseline investigation (2006-2010) and followed until 2022. Consumption of coffee and sweetener was assessed by 24-hour dietary recall questionnaire. Cox proportional hazards models and restricted cubic splines were used to estimate hazard ratios (HR) and 95% confidence intervals (CIs).

Results

During a median follow-up of 12.4 years, we identified 4152 incident CLD and 853 LREs . Compared with nonconsumers, unsweetened coffee consumers of various amount had lower risk of CLD (HR, 0.75 [95% CI, 0.67-0.83] for 1.5~2.5 drinks per day) and LREs (HR, 0.60 [95% CI, 0.46-0.80] for 2.5~3.5 drinks per day) in the multivariable Cox models. U-shaped associations of unsweetened coffee with CLD and LREs were observed. The results for sweetened coffee were less consistent and conclusive in both CLD and LREs. We detected positive associations between sweetener and CLD and LREs. Compared with unsweetened coffee consumers, consumers of different amount of sugar added

to coffee had higher risk of CLD in the multivariable cox model. For artificial sweetener, a significant higher risk of CLD (HR, 1.61 [95% CI, 1.25-2.05]) and LREs (HR, 1.82 [95% CI, 1.11-2.98]) was only found in those who added ≥2 teaspoons/drink. We detected significant interaction between artificial sweetener and coffee intake on the risk of CLD [HR for product term: 0.76 (95% CI 0.60 to 0.96), P=0.018; RERI: -0.32 (95% CI -0.58 to -0.06)].

Conclusions

Moderate consumption of unsweetened coffee was associated with lower risk of CLD and LREs. Adding sweetener into coffee could bring additional risk of liver diseases in coffee consumers.

Key words

Coffee; Sugar; Artificial sweetener; Chronic liver disease; Liver-related events

Introduction

Chronic liver disease (CLD) is a gradual and progressive dysfunction of liver lasting more than six months, encompassing nonalcoholic fatty liver disease (NAFLD), inflammatory liver disease, chronic hepatitis and various liver disorders, can progress to severe liver-related events (LREs), such as cirrhosis and liver cancer (1,2). CLD and LREs cause significant mortality, morbidity, and economic burden which has the trend of increasing primarily owing to the increasing burden of obesity(3). Coffee, as one of the most popular drinks worldwide, has remained controversial on the topic of liver health. While many observational studies reported that coffee was protective against CLD (4-6), liver cirrhosis (7,8) and liver cancer (9-11), a few articles argued that no association was found between coffee and liver steatosis (7,12,13). Notably, few studies focus on health effect of sugar and artificial sweetener in coffee consumption, especially when sugar sweetened beverages and artificially sweetened beverages have been found positively associated with multiple liver diseases (14-17). Unsweetened coffee has already shown better health effect against all-cause mortality than sugar sweetened and artificially sweetened coffee (18). However, the association between unsweetened, sugar sweetened and artificially sweetened coffee with the incidence of liver diseases remained unknown.

In the light of statements above, the aim of our study was to examine the association of unsweetened, sugar sweetened and artificially sweetened coffee with chronic liver disease and liver-related events (cirrhosis and liver cancer). Furthermore, we evaluated the degree to which sugar or artificial sweetener added to coffee counteracted the effect of unsweetened coffee.

Methods

Study design

We used data from the UK Biobank which is a very large and detailed prospective study with over 500 000 participants aged 40-69 years recruited from 22 assessment centers in 2006-2010. Detailed information of assessment visit can be found else where (19,20). For this analysis, we only included 210 943 participants who completed at least one 24-hour dietary recall questionnaire. Further, participants who had an implausible energy intake (defined as those in the highest or lowest 1% of the distribution of the ratio of energy intake to estimated energy requirement, n = 4219), those with cancer at baseline (n = 19 441, **Supplemental Table 1**), those with viral hepatitis, cirrhosis and chronic liver disease at baseline (n = 2498, **Supplemental Table 1**), those who had overlapped across unsweetened, sugar-sweetened, and artificially sweetened coffee (n = 6903, **Supplemental Table 2**), and those with any missing covariates (n = 8778) were excluded. 170 044 participants were included for the final analysis (**Figure 1**). The characteristics of the excluded participants were similar to those of the included (**Supplemental Table 3**).

Assessment of coffee and coffee additives consumption

A web-based 24-h dietary assessment method was administered in the UK Biobank to obtain information on the quantities of all foods and beverages consumed over the previous day including coffee and coffee additives consumption, which was validated to be acceptable to the public and a feasible strategy for large population-based studies (21,22). Participants were invited to complete the questionnaire on 5 occasions over 1 year to account for seasonal variations in dietary intake (18).

If participants reported drinking coffee in the previous day, they would be asked about the amount of different types of coffee they drank (including instant coffee and ground coffee) with 7 mutually exclusive responses (0.5, 1, 2, 3, 4, 5, or 6 or more drinks) for each type. One drink was equal to

approximately 250 mL. Decaffeinated coffee consumption of any type was asked while participants can report specific amount from 7 responses above or average level of their consumption. We classified participants who reported coffee drinking at any 1 dietary recall as coffee consumers; all others as nonconsumers. Further, coffee consumers could report the addition of sugar or artificial sweetener (any brand) in coffee ranging from 0-3 teaspoons (at least half of a teaspoon if consumed). One teaspoon was equal to approximately 5 grams. Among coffee consumers, we classified those who stick to the same type of coffee (unsweetened, sugar sweetened or artificially sweetened) in every times of dietary recalls they participated in as sole consumers; others as overlapped consumers. The habitual consumption of coffee was calculated according to the total amount of different types of coffee consumed and the number of times participants completed 24-hour dietary recalls. As the pearson correlation coefficients were quite strong between different dietary recalls of total coffee consumption and of three types of coffee consumption (**Supplemental Table 4-7**), so we use average consumption of different dietary recalls to reflect habitual consumption of coffee and coffee types.

Assessment of outcomes

Outcomes were extracted from both hospital records and death certificates to ensure comprehensive ascertainment. CLD was defined according to the Global Burden of Disease ICD-10 codes categorisation: I85-I85.9, 198.2, K72.1-K75, K75.2, K75.4-K76.2, K76.4-K77.8, R16-R18.9, Z52.6, Z94.4. LREs (cirrhosis and liver cancer) were identified according to the International Classification of Diseases or Operations/Procedure Codes Version 4 codes (**Supplemental Table 8**). The algorithm of cirrhosis was developed by Ratib and colleagues (23). Liver cancer included hepatocellular carcinoma as well as cholangiocarcinoma. The date and cause of death were identified by linking to death

registries of the National Health Service (NHS) Information Centre for participants from England and Wales, and NHS Central Register Scotland for participants from Scotland. Each participant contributed follow-up time from the date of registration to the date of hospital admission or death, or the end of follow-up (December 31, 2021, for England and Wales; February 28, 2022, for Scotland), whichever came first.

Assessment of covariates

We used the baseline questionnaire to assess the following potential confounders: age, sex, ethnicity, Townsend deprivation index (TDI), education level, smoking status, physical activity per week, hypertension history, diabetes history, vitamin supplement use, alcohol drinking, healthy diet, obesity and dietary intake of total energy, total sugar, and sweetened beverages. The TDI was categorized into three groups: <-2.0; ≥-2.0, <2.0; ≥2.0 which indicated relatively high, median, and low socioeconomic status in the region respectively. Regular physical activity was defined as ≥150 min moderate activity per week, or ≥75 min vigorous activity per week, or an equivalent combination. Healthy diet was defined as fruits: ≥3 servings/day; vegetables: ≥3servings/day; fish: two or more times per week; processed meats: one or fewer times per week; unprocessed red meat: two or fewer times per week; whole grains: ≥3 servings/day; refined grains: ≤2 servings/day. The details of these assessments can be found on the UK Biobank website (www.ukbiobank.ac.uk).

Statistical analysis

Detailed information on the missing covariates is presented in **Supplemental Table 9**, and we did Chi-square tests of covariates between people with missing covariates and those included in our study

which indicated no significant differences (**Supplemental Table 3**). Baseline characteristics are presented as mean (SD) for continuous variables and number (percentage) for categorical variables. The relevance between potential key confounders and coffee sweetener use was examined using Kruskal-Wallis rank sum test (**Supplemental Table 10**). Pearson correlations were used to demonstrate consistency of coffee consumption across multiple dietary recalls for all coffee consumers (**Supplemental Table 4**) and each type of coffee consumers alone (**Supplemental Table 5-7**). Addition of sugar or artificial sweetener and multiple comparisons among different groups were presented in **Supplemental Table 11 and 12**.

Dose-response relationships were examined using restricted cubic spline regression between consumption of different types of coffee and outcomes. Coffee consumers were then categorized into 4 groups: >0 to 1.5, >1.5 to 2.5, >2.5 to 3.5 and >3.5 drinks/day. Hazard ratios (HRs) and 95% CIs were calculated for outcomes associated with coffee consumption, using Cox proportional hazards models with proportional hazards assumption tested by Schoenfeld residuals. The basic models adjusted for age and sex, and the multivariable models additionally adjusted for ethnicity (White or other), smoking status (current, former, or never), education level (college, university degree or other), vitamin supplement use (yes or no [vitamin A, B, C, D or E; folic acid; or multivitamins]), regular physical activity (yes or no), healthy diet (yes or no), diabetes mellitus history (yes or no), hypertension history (yes or no), obesity (yes or no), alcohol drinking (yes or no), Townsend deprivation index (<-2.0; ≥-2.0, <2.0; ≥2.0), total sugar (low, high), sweetened beverages (continuous), total energy (continuous). Dose-response associations of coffee additives with CLD and LREs were examined similarly after removing sugar or artificial sweetener added to coffee from total sugar and the energy sugar added to coffee produced from total energy and adjusting for coffee consumption. Coffee additive consumption

was then categorized into three groups: >0 to 1, ≥1 to 2 and ≥2 teaspoons/drink. Fully adjusted Cox models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of associations between coffee additives and outcomes. We further performed combined analysis for coffee and coffee sweetener. Additive and multiplicative interactions between coffee consumption and coffee additives on the risk of CLD and LREs were tested.

We did subgroup analyses by ethnicity, sex, Townsend deprivation index, age, education, smoking status, alcohol drinking, obesity, diabetes mellitus history, hypertension history and genetic predisposition for hepatic steatosis. We did the following sensitivity analyses to ensure the robustness of the results. We excluded participants who experienced an outcome event during the first two years of follow-up, used multiple imputation to impute any missing covariate values with 5 data sets, removed sugar or artificial sweetener added to coffee from total sugar and the energy sugar added to coffee produced from total energy, used competing risk model (all-cause mortality as the competing event), excluded participants who reported only one coffee consumption day.

Analyses were done using R software, version 4.3.3 for Windows. Statistical tests were 2-sided, and P values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

Among 170 044 participants, 40 440 (23.8%) did not drink coffee at all. About 56% of participants only drank unsweetened coffee and had an average consumption of 2.3 (SD, 1.3) drinks/day . Only 14.2% of the participants were sugar-sweetened coffee consumers who drank 2.0 (SD, 1.3) drinks/day on average and added an average of 1.1 (SD, 0.6) teaspoons/d of sugar. With an average consumption

of 2.4 (SD, 1.5) drinks/day, the remaining 6.1% of the participants were artificially sweetened coffee consumers who added an average of 1.4 (SD, 0.6) teaspoons/day of sweetener. Notably, for both sugar sweetened and artificially sweetened coffee consumers, the more coffee they drank, the less sweeteners they might add to coffee per drink (**Supplemental Table 12**). Unsweetened coffee consumers were more educated, of higher socioeconomic level and had healthier lifestyle compared with other coffee consumers or nonconsumers (**Table 1**). Compared to coffee consumers without sweetener, those use more coffee sweetener have less healthy diet. There was inverse association of coffee sugar intake with obese and diabetes, coffee artificial sweetener intake was positively correlated to obese and diabetes (**Supplemental Table 10**).

Association of coffee consumption with CLD

During an average of 12.4 years of follow up (total person-years, 2 102 864), we identified 4152 incidences of CLD. Using cox models with restricted cubic spline, we detected a statistically significant U-shaped dose-response relationship between unsweetened coffee and CLD ($P<0.05$). On the other hand, artificially sweetened coffee intake showed a negative relationship with CLD which also reached the overall significant level. Whereas the relationship between sugar sweetened coffee intake and CLD was not statistically significant (**Figure 2**).

We further categorized coffee consumption into four groups (>0 to 1.5, >1.5 to 2.5, >2.5 to 3.5 and >3.5 drinks/d). Compared with nonconsumers, unsweetened coffee consumers had lower risk of CLD with respective hazard ratios of 0.74 (95% CI, 0.67 to 0.82), 0.75 (CI, 0.67 to 0.83), 0.77 (CI, 0.68 to 0.87) and 0.76 (CI, 0.68 to 0.86) in the multivariable Cox models which adjusted for lifestyle, sociodemographic and metabolic comorbidities (**Table 2**). Different types of unsweetened coffee

including instant, ground and decaffeinated coffee were inversely associated with CLD (**Supplemental Table 13**). The association between sugar-sweetened coffee and CLD was not statistically significant with wide 95% CIs that included 1.0 in all four groups (**Table 2**). As for artificially sweetened coffee, the inverse association was only observed in the fourth group (>3.5 drinks/d) with hazard ratios of 0.71 (95% CI, 0.56 to 0.91) (**Table 2**). Interestingly, the risk reduction of artificially sweetened coffee was only found in the fourth group of instant coffee instead of ground or decaffeinated coffee (**Supplemental Table 13**).

Association of coffee consumption with liver-related events

We identified 853 incidences of LREs. The association of different types of coffee with LREs was largely consistent with that with CLD. U-shaped dose-response relationships of unsweetened coffee with LREs was statistically significant ($P<0.05$). Whereas, the dose-response relationships for sugar-sweetened coffee and artificially sweetened coffee did not reach the overall significant level (**Figure 2**). All groups of unsweetened coffee consumers showed significant lower risk of LREs when compared with nonconsumers. We found that all four groups of sugar-sweetened coffee or artificially sweetened coffee consumers showed no statistically significant reduction of LREs risk (**Table 2**).

Association of coffee additives with CLD and LREs

To unveil the health effects of coffee additives (sugar and artificial sweetener), we used consumption of coffee additive (teaspoons/per drink) as exposure factor. Positive dose-response relationships of artificial sweetener added to coffee with CLD and LREs were found (**Figure 3**). Non-linear positive dose-response relationship was found between sugar added to coffee and CLD (**Figure 3**). The

relationship between sugar added to coffee and LREs was not statistically significant (**Figure 3**). We then categorized coffee additive consumption into three groups (>0 to 1, ≥1 to 2 and ≥2 teaspoons/drink). Compared with unsweetened coffee consumers, consumers of different amount of sugar added to coffee had higher risk of CLD in the multivariable cox model after removing the sugar added to coffee from total sugar and the energy it produced from total energy, with respective hazard ratios of 1.18 (95% CI, 1.06 to 1.37), 1.25 (CI, 1.05 to 1.49) and 1.45 (CI, 1.18 to 1.78); the respective estimates for consumption of artificial sweetener were 1.05 (CI, 0.91 to 1.22), 1.17 (CI, 0.94 to 1.47) and 1.62 (CI, 1.26 to 2.08) (**Table 3**). Findings for LREs were only statistically significant in the third group (≥2 teaspoons/drink) of artificial sweetener with hazard ratios of 1.69 (95% CI, 1.02 to 2.79) (**Table 3**).

In the combined analysis of coffee and coffee sweetener, we found that coffee consumers without sweetener added showed decreased risk of CLD and LRE, but coffee consumers with sweetener added showed no significant risk reduction in both CLD and LREs (**Table 2**). We detected significant interaction between artificial sweetener and coffee intake on the risk of CLD [HR for product term: 0.76 (95% CI 0.60 to 0.95), P=0.019; RERI (relative excess risk due to interaction): -0.32 (95% CI -0.58 to -0.06) (**Table 2 and Supplemental Table 14**)], suggesting that sweetener use could counteract the health effect of coffee.

Subgroup and sensitivity analyses

In subgroup analysis by ethnicity, sex, Townsend deprivation index, age, education, smoking status, alcohol drinking, obesity, diabetes mellitus history, hypertension history or genetic risk, we didn't find significant interaction between unsweetened coffee and subgroup factors for CLD (**Supplemental**

Figure 1) or LREs (**Supplemental Figure 2**). Interaction was found between sugar sweetened coffee and smoking status for CLD which did not suggest effect modification in subgroups (**Supplemental Figure 1**). Townsend deprivation index and age had interaction with artificially sweetened coffee for CLD which showed risk reduction in those of higher socioeconomic level or those older (**Supplemental Figure 1**).

Our sensitivity analyses largely showed consistent results when we excluded participants who experienced an outcome event during the first two years of follow-up (**Supplemental Table 15**), used multiple imputation to impute any missing covariate values with 5 data sets (**Supplemental Table 16**), removed coffee additives (sugar or artificial sweetener) from total sugar and total energy (**Supplemental Table 17**), used multivariable competing risk models (**Supplemental Table 18**). The results were slightly strengthened when we excluded coffee measurement if participants reported only one coffee consumption day on any of five occasions (**Supplemental Table 19**).

Discussion

In this prospective cohort of 170 044 participants, we found that the increasing unsweetened coffee consumption was associated with lower risk of incident CLD and LREs in a U shape dose-dependent manner. For instant, ground and decaffeinated coffee, the results were largely consistent. However, the results for sugar sweetened and artificially sweetened coffee were less consistent and conclusive in both CLD and LREs. The inverse association was only found in those who drank >3.5 drinks of artificially sweetened coffee per day. Moreover, we found that both sugar and artificial sweetener added to coffee were associated with higher risk of incident CLD when compared with unsweetened coffee. For LREs, significant positive association was only observed in those who consumed ≥2 teaspoons of

artificial sweetener.

Our findings can shed some light on why controversial results were found between coffee consumption and liver diseases. The results for unsweetened coffee in our study were largely consistent with most of the previous observational studies that moderate coffee consumption was inversely associated with CLD (4-6) and LREs (8-11) which was reasonable as unsweetened coffee consumers consisted of a large proportion of coffee consumers according to our study. The inverse association between liver diseases and coffee consumption were quite consistent considering the etiology of CLD and LREs including alcoholic and nonalcoholic fatty liver diseases and viral hepatitis (24). However, Mendelian randomization study did not support a causal relationship between coffee consumption and risk of non-alcoholic fatty liver disease (NAFLD) (25). Considering that CLD and LREs might have a larger size of genetic alleles than NAFLD and current genetic markers are relatively weak instruments as a proxy for coffee consumption, null findings from this Mendelian randomization study do not rule out true health effects of coffee (26). In our study, sugar sweetened and artificially sweetened coffee did not show significant risk reduction against CLD and LREs like unsweetened coffee. A few articles also reported that no association was found between coffee and liver steatosis (7, 12, 13). We believed that one of the reasons of null findings for these articles could be no evaluation of sugar or artificial sweetener added to coffee while a relatively large proportion of coffee consumers preferred to add some sweetener in these study populations.

Although few data have been available on the association between coffee additive consumption and liver diseases, we can pick up some evidence elsewhere. Obesity and diabetes are two important risk factors for CLD and LREs (2,27,28). Further, sugar added to coffee was positively correlated with the prevalence of obesity (29) or at least counteracted coffee's benefit for possible weight management

(30). Mendelian randomization studies of artificial sweetener showed a causal relationship between artificial sweetener intake in coffee and type 2 diabetes mellitus or some types of cancer (31,32). Besides, observational studies showed that sugar sweetened beverages and artificially sweetened beverages were associated with increased risk of multiple liver diseases (14-17). These statements above made us alert to the possible harmful effect of sugar or artificial sweetener added to coffee for CLD and LREs. Therefore, we calculated the average addition of sugar or artificial sweetener in coffee. We found that those who drank >3.5 drinks/d and those who drank instant coffee had relatively low consumption of sweetener which could be the reason why inverse association was only observed in those consumers of artificially sweetened coffee. In order to find out the counteraction effect of these two additives against the health benefits of unsweetened coffee, we further used coffee additive as exposure factor which showed that even small amount of sugar added to coffee could significantly weaken the health effect of unsweetened coffee for CLD and ≥2 teaspoons of artificial sweetener added to coffee could significantly weaken the health effect of unsweetened coffee for both CLD and LREs. It is worth noticing that why did one or two teaspoons of coffee sugar could lead to a clear increase in the risk of liver disease. First of all, for those who added two teaspoons or more sugar per drink, they added 8 grams of sugar into coffee per day on average which accounted for 40% of the total sugar increase compared with unsweetened coffee consumers. Second, sugar addition in coffee might be an indicator of other lifestyle factors which could contribute to the prevalence of liver diseases.

On one hand, coffee contains many biologically active compounds like caffeine and phenolic phytochemicals, that may have health benefits against liver diseases (33-36). This could back our study on why not only caffeinated coffee but also decaffeinated coffee was inversely associated with liver diseases. The potential mechanisms of health effect could be their antioxidant properties,

anti-inflammatory effect or regulation of some liver enzymes (37-39). On the other hand, biological mechanisms of dietary sugar have been studied to explain its harmful effects. Hepatic fructose metabolism precursors can be used for gluconeogenesis and de novo lipogenesis or act as nutritional regulators of the transcription factors which contribute to the onset of NAFLD (40,41). Although mechanism of artificial sweetener's effect on liver diseases remains largely unknown, artificial sweetener was found positively associated with some diseases potentially by affecting the hypothalamic-pituitary-gonadal axis or apoptosis and cell cycle arrest (42,43). Taken together, sugar or artificial sweetener might counteract the health benefits of other biologically active compounds in coffee like the results of our study.

We should take addition of sugar or artificial sweetener into account when evaluating the health effect of coffee. Coffee was considered one kind of healthy drink with possible protective effect against liver diseases on a population level (39,44), or an approach to mitigate some liver diseases (38,45). However, none of these studies give insight to the possible harmful effect of coffee additives. In 2023, International Agency for Research on Cancer (IARC) classified aspartame, an artificial sweetener widely used, as possibly carcinogenic to humans (46). Moreover, 8 ounces of cuppuccino at a popular coffee chain nowadays contains 6 grams of sugar (47) which would be a 21% increasement in risk of CLD when compared with unsweetened coffee, using the estimates in our study. Therefore, advice on the addition of coffee additives could be valuable. According to our study, moderate consumption of unsweetened coffee is recommended. If coffee additive is needed, sugar in any amount is not recommended and artificial sweetener should be controlled under 2 teaspoons/drink.

Our study has several strengths, including its prospective design, large sample size (>170000 participants), relatively long follow-up time (an average of 12.4 years) and substantial information on

confounders. Besides, detailed information on coffee additive consumption enabled us to explore the relationship between coffee additive and liver diseases. We also used a competing risk model to reduce the bias caused by competing events.

There are several limitations in our study. First, as an observational study, there might be unmeasured confounding, especially when we evaluated the effect of coffee sweetener. For example, pre-diabetes could be a potential uncontrolled confounder which was associated with both artificial sweetener use and liver disease. This could lead to reverse causation as pre-diabetes participants might change their coffee and sweetener intake. Some other dietary habits like sweetened food preference could be associated with coffee sweetener use. Also, those who had healthier lifestyle may also engage in other behaviors that reduce liver disease risk. It is hard to disentangle all confouding factors from true causal effects of coffee sweeteners on liver disease. Therefore, caution should be applied to the interpretation. And more studies are needed to back our claims. Second, the UK Biobank is not representative of the sampling population which could cause some concern if the results would be used in the sampling population. Nonetheless, valid assessment of exposure-disease relationships may be widely generalizable and does not require participants to be representative of the population at large (48). Third, as the consumption of coffee and coffee additive were assessed in 1 year, there might be changes in the amount of coffee or additive added to coffee consumed later on which cannot be estimated in our study. Similar problems might occur when we used baseline characteristics of the confounders. Last, although we give some advice on the amount of coffee additive we can add to coffee, coffee consumers may have difficulties evaluating the amount of coffee additive they are consuming if we take a look at the complex ingredients of the ‘sugar free syrup’ at a popular coffee chain now (47).

In conclusion, Our study found that moderate consumption of unsweetened coffee significantly reduces the risk of CLD and LREs. Adding sugar or artificial sweetener into coffee could bring additional risk of CLD for coffee consumers. In the context of large and increasing morbidity and economic burden caused by CLD and LREs (3), our results can be thought-provoking for further studies.

Acknowledgments

Author contributions: Yifei Li (Li, Y): Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. Xu Chen (Chen, X.): Writing – review & editing, Supervision, Conceptualization. Peiting Zhang (Zhang, P.): Writing – review & editing, Supervision, Conceptualization. Yuqing Deng (Deng, Y.): Supervision, Conceptualization. Chao Yu (Yu, C.): Validation, Supervision, Software, Resources, Project administration. Xuechen Chen (Chen, X.): Software, Validation. Xinyu Liu (Liu, X.): Software, Validation. Qiaoqiao Yang (Yang, Q.): Software, Validation. Jingcheng Jiang (Jiang, J.): Software, Validation. Wenhua Ling (Ling, W.): Supervision, Resources, Funding acquisition. Hongliang Xue (Xue, H.): Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

We are grateful to the UK Biobank participants. This research has been conducted using the UK Biobank resource.

All authors read and approved the manuscript and the final version.

Data Sharing Statement

The UK Biobank data that support the findings of this study can be accessed by researchers on application (https://www.ukbiobank.ac.uk/register-apply/).

Ethical approval

UK Biobank was approved by the North-West Multi-Centre Research Ethics Committee (reference 11/NW/0382).

References

1. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. The lancet Gastroenterology & hepatology. 2020;5(3):245-66. doi: 10.1016/s2468-1253(19)30349-8.
2. Cheemerla S, Balakrishnan M. Global Epidemiology of Chronic Liver Disease. Clinical liver disease. 2021;17(5):365-70. doi: 10.1002/cld.1061.
3. Younossi ZM, Wong G, Anstee QM, Henry L. The Global Burden of Liver Disease. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2023;21(8):1978-91. doi: 10.1016/j.cgh.2023.04.015.
4. Hayat U, Siddiqui AA, Okut H, Afroz S, Tasleem S, Haris A. The effect of coffee consumption on the non-alcoholic fatty liver disease and liver fibrosis: A meta-analysis of 11 epidemiological studies. Annals of hepatology. 2021;20:100254. doi: 10.1016/j.aohep.2020.08.071.
5. Kennedy OJ, Fallowfield JA, Poole R, Hayes PC, Parkes J, Roderick PJ. All coffee types decrease the risk of adverse clinical outcomes in chronic liver disease: a UK Biobank study. BMC public health. 2021;21(1):970. doi: 10.1186/s12889-021-10991-7.
6. Ruhl CE, Everhart JE. Coffee and tea consumption are associated with a lower incidence of chronic liver disease in the United States. Gastroenterology. 2005;129(6):1928-36. doi: 10.1053/j.gastro.2005.08.056.
7. Alferink LJM, Fittipaldi J, Kiefte-de Jong JC, Taimr P, Hansen BE, Metselaar HJ, et al. Coffee and herbal tea consumption is associated with lower liver stiffness in the gen

eral population: The Rotterdam study. Journal of hepatology. 2017;67(2):339-48. doi: 10.1016/j.jhep.2017.03.013.
8. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Systematic review with meta-analysis: coffee consumption and the risk of cirrhosis. Alimentary pharmacology & therapeutics. 2016;43(5):562-74. doi: 10.1111/apt.13523.
9. Bai K, Cai Q, Jiang Y, Lv L. Coffee consumption and risk of hepatocellular carcinoma: a meta-analysis of eleven epidemiological studies. OncoTargets and therapy. 2016;9:4369-75. doi: 10.2147/ott.S109656.
10. Inoue M, Tsugane S. Coffee Drinking and Reduced Risk of Liver Cancer: Update on Epidemiological Findings and Potential Mechanisms. Current nutrition reports. 2019;8(3):182-6. doi: 10.1007/s13668-019-0274-1.
11. Zhao LG, Li ZY, Feng GS, Ji XW, Tan YT, Li HL, et al. Coffee drinking and cancer risk: an umbrella review of meta-analyses of observational studies. BMC cancer. 2020;20(1):101. doi: 10.1186/s12885-020-6561-9.
12. Niezen S, Mehta M, Jiang ZG, Tapper EB. Coffee Consumption Is Associated With Lower Liver Stiffness: A Nationally Representative Study. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2022;20(9):2032-40.e6. doi: 10.1016/j.cgh.2021.09.042.
13. Zelber-Sagi S, Salomone F, Webb M, Lotan R, Yeshua H, Halpern Z, et al. Coffee consumption and nonalcoholic fatty liver onset: a prospective study in the general population. Translational research : the journal of laboratory and clinical medicine. 2015;165(3):428-36. doi: 10.1016/j.trsl.2014.10.008.
14. Naomi ND, Ngo J, Brouwer-Brolsma EM, Buso MEC, Soedamah-Muthu SS, Pérez-Rodrigo C, et al. Sugar-sweetened beverages, low/no-calorie beverages, fruit juice and non-alcoholic fatty liver disease defined by fatty liver index: the SWEET project. Nutrition & diabetes. 2023;13(1):6. doi: 10.1038/s41387-023-00237-3.
15. Park WY, Yiannakou I, Petersen JM, Hoffmann U, Ma J, Long MT. Sugar-Sweetened Beverage, Diet Soda, and Nonalcoholic Fatty Liver Disease Over 6 Years: The Framingham Heart Study. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2022;20(11):2524-32.e2. doi: 10.1016/j.cgh.2021.11.001.
16. Tseng TS, Lin WT, Ting PS, Huang CK, Chen PH, Gonzalez GV, et al. Sugar-Sweetened Beverages and Artificially Sweetened Beverages Consumption and the Risk of Non alcoholic Fatty Liver (NAFLD) and Nonalcoholic Steatohepatitis (NASH). Nutrients. 2023;15(18). doi: 10.3390/nu15183997.
17. Zhao L, Zhang X, Coday M, Garcia DO, Li X, Mossavar-Rahmani Y, et al. Sugar-Sweetened and Artificially Sweetened Beverages and Risk of Liver Cancer and Chronic Liver Disease Mortality. Jama. 2023;330(6):537-46. doi: 10.1001/jama.2023.12618.
18. Liu D, Li ZH, Shen D, Zhang PD, Song WQ, Zhang WT, et al. Association of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Coffee Consumption With All-Cause and Cause-Specific Mortality : A Large Prospective Cohort Study. Annals of internal medicine. 2022;175(7):909-17. doi: 10.7326/m21-2977.
19. Palmer LJ. UK Biobank: bank on it. Lancet (London, England). 2007;369(9578):1980-2. doi: 10.1016/s0140-6736(07)60924-6.

20. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS medicine. 2015;12(3):e1001779. doi: 10.1371/journal.pmed.1001779.
21. Galante J, Adamska L, Young A, Young H, Littlejohns TJ, Gallacher J, et al. The acceptability of repeat Internet-based hybrid diet assessment of previous 24-h dietary intake: administration of the Oxford WebQ in UK Biobank. The British journal of nutrition. 2016;115(4):681-6. doi: 10.1017/s0007114515004821.
22. Liu B, Young H, Crowe FL, Benson VS, Spencer EA, Key TJ, et al. Development and evaluation of the Oxford WebQ, a low-cost, web-based method for assessment of previous 24 h dietary intakes in large-scale prospective studies. Public health nutrition. 2011;14(11):1998-2005. doi: 10.1017/s1368980011000942.
23. Ratib S, Fleming KM, Crooks CJ, Aithal GP, West J. 1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998-2009: a large population study. Journal of hepatology. 2014;60(2):282-9. doi: 10.1016/j.jhep.2013.09.027.
24. Setiawan VW, Porcel J, Wei P, Stram DO, Noureddin N, Lu SC, et al Coffee Drinking and Alcoholic and Nonalcoholic Fatty Liver Diseases and Viral Hepatitis in the Multiethnic Cohort. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2017;15(8):1305-7. doi: 10.1016/j.cgh.2017.02.038.
25. Zhang Y, Liu Z, Choudhury T, Cornelis MC, Liu W. Habitual coffee intake and risk for nonalcoholic fatty liver disease: a two-sample Mendelian randomization study. European journal of nutrition. 2021;60(4):1761-7. doi: 10.1007/s00394-020-02369-z.
26. Wee CC. The Potential Health Benefit of Coffee: Does a Spoonful of Sugar Make It All Go Away? Annals of internal medicine. 2022;175(7):1035-6. doi: 10.7326/m22-1465.
27. Maurice J, Manousou P. Non-alcoholic fatty liver disease. Clinical medicine (London, England). 2018;18(3):245-50. doi: 10.7861/clinmedicine.18-3-245.
28. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. Diabetes/metabolism research and reviews. 2012;28(2):109-22. doi: 10.1002/dmrr.1291.
29. Lee J, Kim HY, Kim J. Coffee Consumption and the Risk of Obesity in Korean Women. Nutrients. 2017;9(12). doi: 10.3390/nu9121340.
30. Henn M, Glenn AJ, Willett WC, Martínez-González MA, Sun Q, Hu FB. Changes in Coffee Intake, Added Sugar and Long-Term Weight Gain - Results from Three Large Prospective US Cohort Studies. The American journal of clinical nutrition. 2023;118(6):1164-71. doi: 10.1016/j.ajcnut.2023.09.023.
31. Pan H, Feng C, Zhou Z, Huang J, Deng J, Zhou Y, et al. The causal association between artificial sweeteners and the risk of cancer: a Mendelian randomization study. Food & function. 2024;15(8):4527-37. doi: 10.1039/d3fo05756a.
32. Zhang Y, Tang Z, Shi Y, Li L. Associations between artificial sweetener intake from cereals, coffee, and tea and the risk of type 2 diabetes mellitus: A genetic correlation, mediation, and mendelian randomization analysis. PloS one. 2024;19(2):e0287496. doi: 10.1371/journal.pone.0287496.

33. Kolb H, Kempf K, Martin S. Health Effects of Coffee: Mechanism Unraveled? Nutrients. 2020;12(6). doi: 10.3390/nu12061842.
34. Kennedy OJ, Roderick P, Buchanan R, Fallowfield JA, Hayes PC, Parkes J. Coffee, including caffeinated and decaffeinated coffee, and the risk of hepatocellular carcinoma: a systematic review and dose-response meta-analysis. BMJ open. 2017;7(5):e013739. doi: 10.1136/bmjopen-2016-013739.
35. Corrao G, Zambon A, Bagnardi V, D'Amicis A, Klatsky A. Coffee, caffeine, and the risk of liver cirrhosis. Annals of epidemiology. 2001;11(7):458-65. doi: 10.1016/s1047-2797(01)00223-x.
36. Yan Y, Liu N, Hou N, Dong L, Li J. Chlorogenic acid inhibits hepatocellular carcinoma in vitro and in vivo. The Journal of nutritional biochemistry. 2017;46:68-73. doi: 10.1016/j.jnutbio.2017.04.007.
37. Arauz J, Zarco N, Hernández-Aquino E, Galicia-Moreno M, Favari L, Segovia J, et al. Coffee consumption prevents fibrosis in a rat model that mimics secondary biliary cirrhosis in humans. Nutrition research (New York, NY). 2017;40:65-74. doi: 10.1016/j.nutres.2017.03.008.
38. Landerer S, Kalthoff S, Strassburg CP. UDP-glucuronosyltransferases mediate coffee-associated reduction of liver fibrosis in bile duct ligated humanized transgenic UGT1A mice. Hepatobiliary surgery and nutrition. 2021;10(6):766-81. doi: 10.21037/hbsn-20-9.
39. Li D, Li Z, Dong L, Zhang Y, Lu Y, Wang J, et al. Coffee prevents IQ-induced liver damage by regulating oxidative stress, inflammation, endoplasmic reticulum stress, autophagy, apoptosis, and the MAPK/NF-κB signaling pathway in zebrafish. Food research international (Ottawa, Ont). 2023;169:112946. doi: 10.1016/j.foodres.2023.112946.
40. Softic S, Cohen DE, Kahn CR. Role of Dietary Fructose and Hepatic De Novo Lipogenesis in Fatty Liver Disease. Digestive diseases and sciences. 2016;61(5):1282-93. doi: 10.1007/s10620-016-4054-0.
41. Ter Horst KW, Serlie MJ. Fructose Consumption, Lipogenesis, and Non-Alcoholic Fatty Liver Disease. Nutrients. 2017;9(9). doi: 10.3390/nu9090981.
42. Al-Ishaq RK, Kubatka P, Büsselberg D. Sweeteners and the Gut Microbiome: Effects on Gastrointestinal Cancers. Nutrients. 2023;15(17). doi: 10.3390/nu15173675.
43. Naik AQ, Zafar T, Shrivastava VK. The impact of non-caloric artificial sweetener aspartame on female reproductive system in mice model. Reproductive biology and endocrinology : RB&E. 2023;21(1):73. doi: 10.1186/s12958-023-01115-4.
44. Gow P, Spelman T, Gardner S, Hellard M, Howell J. Estimates of the global reduction in liver disease-related mortality with increased coffee consumption: an analysis of the Global Burden of Disease Dataset. Alimentary pharmacology & therapeutics. 2020;52(7):1195-203. doi: 10.1111/apt.16020.
45. Lee JH, Park J, Ahn SB. Different Associations of Coffee Consumption with the Risk of Incident Metabolic Dysfunction-Associated Steatotic Liver Disease and Advanced Liver Fibrosis. Nutrients. 2023;16(1). doi: 10.3390/nu16010140.
46. WHO. *Aspartame hazard and risk assessment results released* [Internet]. 2023; Available from: https://www.who.int/news/item/14-07-2023-aspartame-hazard-and-risk-assessment-results-released.

47. Starbucks. *Hot Coffees: Starbucks Coffee Company* [Internet]. 2024; Available from: https://www.starbucks.com/menu/drinks/hot-coffees.
48. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. American journal of epidemiology. 2017;186(9): 1026-34. doi: 10.1093/aje/kwx246.

Figure Legends

Figure 1. Study flow diagram.

CLD = chronic liver disease; LREs = liver related events; HR = hazard ratio; y = years

Figure 2. Dose-response associations of coffee consumption with CLD (A) and LREs (B).

Multivariable Cox regression model with restricted cubic splines adjusted for age, sex, ethnicity, smoking status , education level, vitamin supplement use, regular physical activity, healthy diet, diabetes mellitus history, hypertension history, obesity, alcohol drinking, Townsend deprivation index, total sugar, sweetened beverages, total energy.

CLD = chronic liver disease; LREs = liver related events; HR = hazard ratio.

Figure 3. Dose-response associations of coffee additives with CLD (A) and LREs (B).

Multivariable Cox regression model with restricted cubic splines adjusted for age, sex, ethnicity, smoking status , education level, vitamin supplement use, regular physical activity, healthy diet, diabetes mellitus history, hypertension history, obesity, alcohol drinking, Townsend deprivation index, total sugar, sweetened beverages, total energy, coffee consumption.

CLD = chronic liver disease; LREs = liver related events; HR = hazard ratio

Table 1. Baseline Characteristics of Participants

Characteristic	Total	Nonconsumers	Coffee consumers		
			Unsweetened	Sugar-sweetened	Artificially sweetened
Participants, n(%)	170044(100.0)	40440(23.8)	94937(55.8)	24157(14.2)	10510(6.1)
Mean age(SD),y	55.8(7.9)	54.4(8.0)	56.1(7.7)	56.0(8.3)	57.3(7.7)
Male sex, n(%)	76751(45.1)	17061(42.2)	40279(42.4)	14660(60.7)	4751(45.2)
Ethnicity, n(%)					
White	163270(96.0)	37373(92.4)	92904(97.9)	22832(94.5)	10161(96.7)
Other	6774(4.0)	3067(7.6)	2033(2.1)	1325(5.5)	349(3.3)
Education level, n(%)					
College or university degree	74147(43.6)	15370(38.0)	46954(49.5)	8570(35.5)	3253(31.0)
Other	95897(56.4)	25070(62.0)	47983(50.5)	15587(64.5)	7257(69.0)
Smoking status,n(%)					
Never	97695(57.5)	24892(61.6)	55981(59.0)	12233(50.6)	4589(43.7)
Former	59689(35.1)	12894(31.9)	33345(35.1)	8629(35.7)	4821(45.9)
Current	12660(7.4)	2654(6.6)	5611(5.9)	3295(13.6)	1100(10.5)
Townsend deprivation index					
≥2.0	21561(12.7)	6087(15.0)	10523(11.1)	3527(14.6)	1424(13.5)
≥-2.0, <2.0	54414(32.0)	13584(33.6)	29750(31.3)	7830(32.4)	3250(30.9)
<-2.0	94069(55.3)	20769(51.4)	54664(57.6)	12800(53.0)	5836(55.5)
Vitamin supplement use, n(%)	54820(32.2)	13453(33.3)	30319(31.9)	7251(30.0)	3797(36.1)
Regular physical activity, n(%)	98434(57.9)	22822(56.4)	55906(58.9)	14035(58.1)	5671(54.0)
Healthy diet	70405(41.4)	15800(39.1)	44030(46.4)	6731(27.9)	3844(36.6)
Diabetes mellitus history, n(%)	6990(4.1)	1743(4.3)	3761(4.0)	350(1.4)	1136(10.8)
Hypertension history, n(%)	43365(25.5)	10506(26.0)	23000(24.2)	6150(25.5)	3709(35.3)
Obesity, n(%)	34892(20.5)	8864(21.9)	18538(19.5)	4009(16.6)	3481(33.1)
Alcohol drinking, n(%)	139646(82.1)	30062(74.3)	81456(85.8)	19934(82.5)	8194(78.0)
Mean intake(SD)					
Total energy, kj/d	8790(2354.7)	8608(2455.5)	8735(2258.2)	9366(2447.0)	8657(2398.2)
Total sugar, g/d	119.9(46.9)	119.6(49.9)	116.2(43.7)	136.9(49.7)	115.2(47.3)
Sweetened beverages, drinks/d[1]	1.1(1.1)	1.1(1.2)	1.0(1.0)	1.1(1.1)	1.2(1.2)
Coffee, drinks/d[1]	1.7(1.5)	-	2.3(1.3)	2.0(1.3)	2.4(1.5)
Instant	1.2(1.5)	-	1.6(1.5)	1.6(1.5)	2.0(1.5)
Ground	0.7(1.0)	-	1.0(1.0)	0.7(1.0)	0.6(1.0)
Decaffeinated	0.3(0.8)	-	0.4(0.8)	0.3(0.8)	0.5(0.8)
Mean completed 24-h dietary recalls(SD),n	2.2(1.2)	1.9(1.1)	2.3(1.2)	2.1(1.2)	2.1(1.1)

[1] 1 drink is equal to approximately 250 mL

Table 2. Associations of Coffee Consumption With CLD and LREs

Outcomes	Non-consumers	Coffee consumers(drinks/d)[1]				P-int [2]
		0~1.5	1.5~2.5	2.5~3.5	>3.5	
CLD						
Unsweetened coffee (n=135377)						
Events, n(%)	1139 (2.8)	688 (2.0)	569 (2.1)	385 (2.2)	363 (2.3)	
Basic model [3]	1 (Reference)	0.66 (0.60-0.72)	0.66 (0.60-0.73)	0.71 (0.63-0.80)	0.77 (0.68-0.86)	
Multivariable model [4]	1 (Reference)	0.74 (0.67-0.82)	0.75 (0.67-0.83)	0.77 (0.68-0.87)	0.76 (0.68-0.86)	
Sugar sweetened coffee (n=64597)						0.96
Events, n(%)	1139 (2.8)	282 (2.6)	185 (2.8)	91 (2.6)	98 (3.1)	
Basic model [3]	1 (Reference)	0.83 (0.73-0.94)	0.89 (0.76-1.04)	0.82 (0.66-1.02)	1.01 (0.82-1.24)	
Multivariable model [4]	1 (Reference)	0.90 (0.79-1.03)	0.98 (0.83-1.15)	0.87 (0.70-1.08)	1.01 (0.82-1.25)	
Artificially sweetened coffee (n=50950)						0.019
Events, n(%)	1139 (2.8)	132 (3.7)	92 (3.4)	59 (3.1)	69 (2.9)	
Basic model [3]	1 (Reference)	1.19 (0.99-1.43)	1.04 (0.84-1.29)	0.96 (0.74-1.25)	0.92 (0.72-1.18)	
Multivariable model [4]	1 (Reference)	0.99 (0.82-1.18)	0.87 (0.70-1.07)	0.80 (0.61-1.04)	0.71 (0.56-0.91)	
LREs						
Unsweetened coffee (n=135377)						
Events, n(%)	231 (0.6)	150 (0.4)	109 (0.4)	65 (0.4)	71 (0.5)	
Basic model [3]	1 (Reference)	0.70 (0.57-0.86)	0.61 (0.49-0.77)	0.57 (0.43-0.75)	0.72 (0.55-0.94)	
Multivariable model [4]	1 (Reference)	0.78 (0.64-0.97)	0.68 (0.54-0.86)	0.60 (0.46-0.80)	0.70 (0.53-0.92)	
Sugar sweetened coffee (n=64597)						0.92
Events, n(%)	231 (0.6)	60 (0.6)	36 (0.5)	25 (0.7)	17 (0.5)	
Basic model [3]	1 (Reference)	0.78 (0.58-1.03)	0.74 (0.52-1.06)	0.96 (0.64-1.46)	0.75 (0.46-1.24)	
Multivariable model [4]	1 (Reference)	0.91 (0.68-1.22)	0.87 (0.61-1.25)	1.08 (0.71-1.65)	0.81 (0.49-1.34)	
Artificially sweetened coffee (n=50950)						0.11
Events, n(%)	231 (0.6)	34 (1.0)	26 (1.0)	13 (0.7)	16 (0.7)	
Basic model [3]	1 (Reference)	1.42 (0.99-2.03)	1.32 (0.88-1.99)	0.95 (0.54-1.66)	0.96 (0.58-1.60)	
Multivariable model [4]	1 (Reference)	1.12 (0.78-1.61)	1.02 (0.68-1.54)	0.72 (0.41-1.26)	0.69 (0.41-1.15)	

CLD = chronic liver disease

LREs = liver-related events

[1] 1 drink is equal to approximately 250 mL.

[2] Multiplicative interaction was evaluated using hazard ratios for the product term between coffee consumption (low, high; using median to categorize) and coffee sweetener consumption (yes, no).

[3] Estimates are hazard ratios (95% CIs) from Cox regression models adjusted for age (continuous) and sex

[4] Estimates are hazard ratios (95% CIs) from multivariable Cox regression models additionally adjusted for ethnicity (White or other), smoking status (current, former, or never), education level (college, university degree or other), vitamin supplement use (yes or no [vitamin A, B, C, D or E; folic acid; or multivitamins]), regular physical activity (yes or no), healthy diet (yes or no), diabetes mellitus history (yes or no), hypertension history (yes or no), obesity (yes or no), alcohol drinking (yes or no), Townsend deprivation index (<-2.0; ≥-2.0, <2.0; ≥2.0), total sugar (low, high), sweetened beverages (continuous), total energy (continuous).

Table 3. Associations of Coffee additives With CLD and LREs.

Outcome	Coffee additive(teaspoons/drink)[1]			
	0	**0~1**	**1~2**	**≥2**
Sugar sweetened coffee (n=119094)[2]				
CLD	1(Reference)	1.18 (1.06-1.32)	1.25 (1.05-1.49)	1.45 (1.18-1.78)
LREs	1(Reference)	1.19 (0.93-1.52)	1.28 (0.87-1.87)	1.33 (0.84-2.11)
Artificially sweetened coffee(n=105447)[2]				
CLD	1(Reference)	1.05 (0.91-1.22)	1.17 (0.94-1.47)	1.62 (1.26-2.08)
LREs	1(Reference)	1.23 (0.91-1.67)	1.33 (0.85-2.09)	1.69 (1.02-2.79)

CLD = chronic liver disease

LREs = liver-related events

[1] 1 teaspoon is equal to approximately 5g.

[2] Estimates are hazard ratios (95% CIs) from multivariable Cox regression models adjusted for age (continuous), sex, ethnicity (White or other), smoking status (current, former, or never), education level (college, university degree or other), vitamin supplement use (yes or no [vitamin A, B, C, D or E; folic acid; or multivitamins]), regular physical activity (yes or no), healthy diet (yes or no), diabetes mellitus history (yes or no), hypertension history (yes or no), obesity (yes or no), alcohol drinking (yes or no), Townsend deprivation index (<-2.0; ≥-2.0, <2.0; ≥2.0), total sugar (low, high; excluding sugar or artificial sweetener added to coffee), sweetened beverages (continuous), total energy (continuous; excluding energy produced by sugar added to coffee), coffee consumption (continuous).