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Coffee, alcohol and other beverages in relation to cirrhosis mortality: the Singapore Chinese Health Study

George Boon-Bee Goh, MBBS, MRCP[1], **Wan-Cheng Chow, MBBS, FRCP**[1,4], **Renwei-Wang, MD**[2], **Jian-Min Yuan, MD, PhD**[2,3], and **Woon-Puay Koh, PhD**[4,5]

[1]Department of Gastroenterology & Hepatology, Singapore General Hospital, Singapore

[2]Division of Cancer Control and Population Sciences, University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania, USA

[3]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[4]Duke-NUS Graduate Medical School Singapore, Singapore

[5]Saw Swee Hock School of Public Health, National University of Singapore, Singapore

Abstract

Limited experimental and epidemiologic data suggest that coffee may reduce hepatic damage in chronic liver disease. The association between consumption of coffee and other beverages, and risk of cirrhosis mortality was evaluated in The Singapore Chinese Health Study. This is a prospective population-based cohort of 63,275 middle-aged and older Chinese subjects who provided data on diet, lifestyle and medical histories through in-person interviews using structured questionnaire at enrollment between 1993 and 1998. Mortality from cirrhosis in the cohort was ascertained through linkage analysis with nationwide death registry. After a mean follow-up of 14.7 years, 114 subjects died from cirrhosis; 33 of them from viral hepatitis B (29%), two from hepatitis C (2%), and 14 from alcohol-related cirrhosis (12%). Compared to non-drinkers, daily alcohol drinkers had a strong dose-dependent positive association between amount of alcohol and risk of cirrhosis mortality. Conversely, there was a strong dose-dependent inverse association between coffee intake and risk of non-viral hepatitis related cirrhosis mortality (*p* for trend=0.014). Compared to non-daily coffee drinkers, those who drank two or more cups per day had 66% reduction in mortality risk (HR=0.34, 95% CI=0.14–0.81). However, coffee intake was not associated with hepatitis B related cirrhosis mortality. The inverse relationship between caffeine intake and nonviral hepatitis-related cirrhosis mortality became null after adjustment for coffee drinking. The consumption of black tea, green tea, fruit juices or soft drinks was not associated with risk of cirrhosis death.

Conclusion—This study demonstrates the protective effect of coffee on non-viral hepatitis related cirrhosis mortality, and provides further impetus to evaluate coffee as a potential therapeutic agent in patients with cirrhosis.

Correspondence to: Woon-Puay Koh, Office of Clinical Sciences, Duke-NUS Graduate Medical School, Singapore, 8 College Road Level 4, Singapore 169857, Singapore, Phone: (65) 6601 3147; Fax: (65) 6222 7453; woonpuay.koh@duke-nus.edu.sg.

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Keywords

coffee; caffeine; tea; alcohol; cirrhosis

Liver cirrhosis is a major chronic disease and significant cause of death accounting for approximately 800,000 deaths or 1.3% total death annually worldwide (1). Approximately 29 million people within the European Union are afflicted by a chronic liver disease, with liver cirrhosis alone accounting for 170,000 deaths in Europe each year (2). In the USA, liver cirrhosis is the 11th leading cause of death, with an age standardised mortality rate of 7.3 per 100,000 population (1).

Liver cirrhosis can result from diverse causative factors injuring the liver via different etiological pathways and mechanisms. The major risk factors for liver cirrhosis vary with geographical distribution. In populations such as those in Asia and Africa with endemic hepatitis B virus infection, chronic hepatitis B (CHB) is the most important risk factor (3–6) while chronic hepatitis C virus (CHC) may be more prominent in Japan, Egypt and Eastern Mediterranean countries (6, 7). Conversely, in other countries with relatively high per capita alcohol consumption and where hepatitis virus infection is less prevalent, such as USA, UK and other European countries, chronic alcohol abuse emerges as an important contributor (8–10). Finally, non-alcoholic fatty liver disease (NAFLD), which is associated with diabetes and obesity, is now the most common cause of elevated liver enzymes, and also increasingly recognised as an emerging risk factor for cirrhosis (11, 12). There is no good treatment option for many common chronic liver diseases, especially if unrelated to chronic viral hepatitis or autoimmune etiology. Hence, there is a need to identify potential therapeutic agents that may retard the cirrhotic process.

Experimental studies suggest coffee may reduce hepatic damage and fibrosis in chemical-induced cirrhosis models in animals (13–16). There is some epidemiologic evidence that coffee drinking may be protective against chronic liver disease. A few cross-sectional studies have shown that coffee was associated with lower prevalence of having elevated serum transaminases or lower severity of fatty liver disease (17–20), while other case-control studies have shown an inverse association between coffee consumption and odds of cirrhosis (21, 22). There is also limited evidence on the protective effect of tea on liver disease (23). In contrast, consumption of soft drinks that contain high fructose content, may be an emerging risk factor for NAFLD and progression to cirrhosis (24, 25).

In our study, we examined the association between consumption of alcohol and common beverages, including coffee, black tea, green tea and soft drinks, and cirrhosis mortality among Chinese Singaporeans in a population-based cohort, The Singapore Chinese Health Study.

Materials and Methods

Study population

The design of the Singapore Chinese Health Study has been previously described (26). Essentially, the study was a population based prospective cohort drawn from permanent

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residents or citizens of Singapore who resided in the government-built housing estates (this entailed 86% of the Singapore population who resided in such facilities during the recruitment period). Subjects were between the ages of 45 and 74 years and recruitment was restricted to the two major dialect groups of Chinese in Singapore, the Hokkiens and the Cantonese. Between April 1993 and December 1998, 63,257 subjects (about 85% of eligible subjects approached) were enrolled. Approval by the Institutional Review Boards of the National University of Singapore and the University of Pittsburgh was given for the study. All subjects gave written informed consent.

Assessment of beverages consumption

At recruitment, an in-person interview was conducted in the subject's home by a trained interviewer using a structured questionnaire, encompassing demographics, lifetime use of tobacco, current physical activity, menstrual/reproductive history (for women), occupational exposure, medical history and family history of cancer. Dietary information, including alcohol, coffee, and tea and soft drink consumption, was assessed via a 165-item food frequency questionnaire that has been validated against a series of 24-hour dietary recall interviews (26) and selected biomarker studies (27, 28) conducted on random subsets of cohort participants.

Participants were asked about to choose from eight frequency categories (never or hardly, once a month, 2–3 times a month, once a week, 2–3 times a week, 4–6 times a week, once a day, and two or more times a day) and four defined portion sizes for the consumption of each of the four types of alcoholic beverages (beer, wine, western hard liquor and Chinese hard liquor). The portion sizes for beer was classified accordingly as; one small bottle (375 mL) or less, two small bottles or one large bottle (750 mL), two large bottles, and three large bottles or more. For wine, the portion sizes were one glass (118 mL) or less, two, three and four glasses or more. For Chinese or western hard liquor, the portion sizes were one shot (30 mL) or less, two, three and four shots or more. One drink was defined as 375 mL of beer (13.6 g of ethanol), 118 mL of wine (11.7 g of ethanol), and 30 mL of western or Chinese hard liquor (10.9 g of ethanol).

Similarly, the intake frequency of a standard serving of coffee, green tea and black tea was ascertained from nine predefined categories (never or hardly ever, 1–3 times a month, once a week, 2–3 times a week, 4–6 times a week, once a day, 2–3 times a day, 4–5 times a day and 6 or more times a day). The standard serving size was assigned on the questionnaire as "one cup" for coffee or "one glass" for tea. Subjects were also asked to report the intake frequency of a standard serving of soft drinks, and fruit/vegetable juices from the same 9 predefined categories. The standard serving size was assigned on the questionnaire as "one glass" or "one packet".

Levels of caffeine intake were estimated from self-report of coffee and tea intake. Coffee and black tea are considered the two major sources of caffeine in this population accounting for 82% and 13% of the caffeine intake respectively. Green tea is a minor contributor to caffeine (<5%) in the study population.

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Ascertainment of mortality

Deaths were identified through record linkage with the Singapore Registry of Births and Deaths. For the current analysis, we updated mortality data through December 31, 2011. As of December 31, 2011, only 47 subjects were known to be lost to follow-up due to migration out of Singapore or for other reasons. This suggests that emigration among these subjects was negligible and that vital statistics at follow-up was virtually complete.

Underlying causes of death were coded according to the International Classification of Diseases, Ninth Revision. We used code 070 for viral hepatitis-related mortality and code 571 for chronic liver disease and cirrhosis. For all deaths identified with these two codes, all causes of death for each case, direct and contributing, were reviewed and verified by two gastroenterologists (GBB Goh, WC Chow). There were 122 deaths due to cirrhosis. After excluding eight cases that had concomitant HCC via database linkage with the nationwide cancer registry, 114 cases of cirrhosis mortality were included as cases in this study, and the remaining 63,143 subjects were classified as “non-cases”.

Statistical analysis

For each study subject, person-years were counted from the date of baseline interview to the date of death, lost-to-follow-up or 31 December 2011, whichever occurred first. Cox proportional hazards regression methods were used to examine the association between beverage and liver cirrhosis mortality within the entire cohort. The magnitude of the associations was assessed by the hazard ratios (HRs) and their corresponding 95% confidence intervals (CI) and P values. All Cox regression models (model 1, 2) included the following covariates: age at recruitment (year), gender, dialect group (Hokkien, Cantonese), year of recruitment (1993–1995, 1996–1998), and level of education (no formal education, primary school, secondary school or higher). To assess the cofounding effect from other established factors of cirrhosis (model 2), we also included additional covariates such as body mass index (kg/m^2), history of diabetes (yes, no), alcohol intake (non, monthly, weekly, daily), smoking (never, former, current) and physical activity (hours of moderate activity per week, which included activities such as brisk walking, bowling, bicycling on level ground, tai chi or chi kung: 0, 0.5 to 4, 4+ hours). To examine linear trend, ordinal values of the categories of intakes for alcohol and beverages, or intake of caffeine (mg/day) in quartile were entered as a continuous variable in the Cox proportional hazards model.

Statistical computing was conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC) statistical software package. All P values quoted were two-sided. P values of <0.05 were considered statistically significant.

Results

After a mean follow-up of 14.7 years [standard deviation (SD) 4.1 years], there were 14,928 deaths (23.6%) within this cohort. Among these deaths, 114 deaths were from cirrhosis (0.76%); among them 33 were related to chronic hepatitis B (29%), two to chronic hepatitis C (2%), 14 to chronic alcohol consumption (12%), two cases to biliary cirrhosis, two cases to autoimmune cirrhosis and the rest were classified as cryptogenic cirrhosis or unspecified.

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Among cases, the mean age of death was 67.2 (SD 9.0) year. Compared to the rest of the cohort, cases of cirrhosis deaths were older at recruitment. Among cases, the non-viral hepatitis related ones had a mean age at recruitment of 59.7 years versus 56.8 years for the viral-hepatitis mortality cases. Compared to non-cases, cases who died from cirrhosis were more likely to be male, of Hokkien dialect group and more likely to ever smoke cigarettes, especially among the non-viral hepatitis cases. Compared to non-cases, subjects who died from non-viral hepatitis related cirrhosis had a higher prevalence of overweight (i.e. BMI≥25 kg/m^2) (*P*=0.06). The prevalence of self-reported history of diabetes was also higher among non-viral hepatitis related cirrhosis (26.6%) compared to non-cases (9.0%) (*P* <0.001) (Table 1).

Table 2 shows the association between coffee, black tea, green tea, fruit juice, soft drinks, alcohol and caffeine consumption in relation to liver cirrhosis mortality in the entire cohort. For coffee drinking, daily drinkers had a 38% reduction in cirrhosis mortality (HR=0.62, 95% CI=0.40–0.97) after adjustment for multiple risk factors. Additional adjustment for dietary factors including total fat and total cholesterol intake per day did not materially change the results (results not shown). On the other hand, there was no association between consumption of other beverages such as black tea, green tea, fruit juices and soft drinks, and cirrhosis mortality. Although the risk of liver cirrhosis mortality seemed to decrease with increasing caffeine intake, there was no significant trend in a dose-response association. Relative to non-drinkers, daily drinkers of alcoholic beverages had a strong dose-response relationship between increasing number of drinks per day and risk of cirrhosis mortality. HRs (95% CIs) were 2.72 (0.98–7.50) for one drink per day and 10.23 (4.89–21.38) for four or more drinks per day (p for trend<0.0001). Similarly, subjects who drank at least 20 g of ethanol daily had 7 times the risk of cirrhosis mortality (HR=7.07, 95% CI=4.01–12.47) relative to non-drinkers (Table 2).

We next analyzed the association between coffee or caffeine intake and risk of death from viral and non-viral hepatitis related cirrhosis. The risk of viral hepatitis-related cirrhosis mortality was not significantly associated with coffee or caffeine intake (Table 3). Excluding the two cases of CHC related cirrhosis mortality from the analysis on viral hepatitis related cirrhosis mortality did not materially change the results. On the other hand, there was a dose-dependent, inverse association between number of cups of coffee per day and risk of death from non-viral hepatitis related cirrhosis (p for trend=0.001). A similar inverse association between caffeine intake and risk of death from non-viral hepatitis related cirrhosis was observed (P for trend = 0.027).

In this cohort, coffee was the main source of caffeine exposure, accounting for 82 percent of total exposure. The inverse association between coffee intake and risk of nonviral hepatitis-related cirrhosis mortality remained the same following adjustment for total caffeine exposure, suggesting that the caffeine content of coffee was not responsible for the effect of coffee. Compared to non-daily drinkers, subjects who drank one or 2+ cups of coffee per day had a 38% and 66% reduction in risk of death from non-viral hepatitis related cirrhosis, respectively (P for trend=0.014) (Table 3). In contrast, the strong inverse association with caffeine became null after adjustment for coffee intake (Table 3).

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We further conducted sensitivity analysis for risk of death from non-viral hepatitis related cirrhosis after excluding cases with the underlying causes of chronic alcoholism (n = 14), biliary liver disease (n = 2), and autoimmune hepatitis (n=2), the dose-dependent association between coffee and risk of death from cryptogenic cirrhosis or unspecified cirrhosis remained essentially unchanged. Compared to non-daily drinkers, subjects who drank one cup or two or more cups of coffee per day had a 43% (HR=0.57, 95% CI=0.31–1.03) and 54% reduction in risk of cirrhosis death (HR=0.46, 95% CI=0.24–0.87), respectively.

We conducted some sensitivity analysis after excluding patients who died from liver cirrhosis within 4 years post enrolment or had follow-up for less than 4 years. The inverse association between coffee and risk of death from non-viral hepatitis related cirrhosis remained. Compared to non-daily drinkers, daily drinkers of one and 2+ cups of coffee had a 40% (HR=0.60, 95% CI=0.33–1.07) and 53% reduction in risk of cirrhosis death (HR=0.47, 95% CI=0.25–0.90), respectively (*P* for trend = 0.019). We also examined the potential modifying effect of sex and smoking on the coffee-liver cirrhosis death association, and found a statistically borderline significant interaction between sex and coffee consumption (*P* for interaction = 0.09), but no interaction effect between smoking and coffee consumption (*P* for interaction=0.80).

Discussion

The present study showed that coffee consumption was associated with significantly reduced risk of death from liver cirrhosis, in particular, non-viral hepatitis related cirrhosis. Ingredients of coffee other than caffeine appear to be responsible for this beverage's effect on risk reduction. Heavy alcohol consumption was found to be a strong risk factor for cirrhosis mortality in the present study population, which was consistent with previous studies in other populations (30). The present study did not find any association between the consumption of tea, fruit juices or soft drinks and risk of death from cirrhosis regardless the underlying causes.

Several cross-sectional studies in US and Japan have demonstrated the dose-dependent relationship between increasing coffee consumption and decreasing level of serum liver enzymes [serum gamma-glutamyltransferase (GGT), alanine and aspartate aminotransferase (ALT, AST)], both among healthy subjects and those with regular alcohol consumption (17, 19, 20, 31), suggesting that coffee intake could lead to attenuation of hepatic necro-inflammation. Two case-control studies from Italy also reported the existence of an inverse association between increasing coffee intake and risk of cirrhosis (21, 22), although the authors could not rule out temporal bias since the reduction of coffee drinking in subjects with cirrhosis could be due to impaired caffeine metabolism (22). Subsequently, prospective data from a population-based multi-ethnic cohort in US showed that the risk of cirrhosis decreased in a dose-dependent manner with increasing daily consumption of coffee among alcoholic subjects. Conversely, there was no significant association between coffee consumption and risk of cirrhosis among non-alcoholic subjects, more than half of whom were judged to have chronic viral disease (31). A population-based cohort study in Norway used mortality as the outcome, and showed that mortality rates from cirrhosis were

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noticeably lower in subjects drinking three or more cups of coffee daily compared to those drinking two or less cups of coffee daily (32).

In differentiating among cirrhosis from different liver disease etiologies, the protective effect of coffee has been demonstrated mainly in relation to alcoholic liver disease and NAFLD, which are the two commonest etiologies for cirrhosis in Western populations (10, 11). Two hospital-based studies have shown that the degree of hepatic fibrosis based on either liver biopsy (18) or ultrasound examination (33) was reduced in a dose-response manner with increasing cups of coffee drinking among patients with NAFLD. Among patients with CHC, higher coffee consumption was related to less severe steatosis on liver biopsy (34) and less severe hepatic fibrosis (35). In contrast, in a study of 1,045 patients with CHB in Hong Kong, there was no difference in incidence of advanced fibrosis among subjects who drank one of more cups of coffee daily compared to those who drank less than one cup daily (36).

Our study is the first to demonstrate a differential effect of coffee consumption between non-viral and viral hepatitis related cirrhosis mortality, and thus harmonize the seemingly conflicting results on the effect of coffee in Western and Asian-based studies. In this cohort, however, vast majority of viral hepatitis were CHB cases (33 out of 35 cases) and CHC was uncommon, which coincided with the very low prevalence of hepatitis C infection reported in this cohort previously (37). Our finding between coffee and viral hepatitis related cirrhosis mortality in this study concurs with the null findings between coffee and cirrhosis in the Hong Kong study that included only CHB subjects (36). Our results do not support the hypothesis that the coffee may affect progression of disease to cirrhosis in liver disease related to CHB. Patients who died from non-viral related cirrhosis in the present study were older, and more likely to have diabetes or to be overweight than the rest of the cohort subjects, which are consistent with the characteristics seen in patients with NAFLD (11). Thus, our observation of a protective effect of coffee in reducing the risk of alcoholic or NAFLD cirrhosis corresponds with that in Western population-based studies where liver diseases of such etiologies predominate.

The disparate effect of coffee on non-viral hepatitis related cirrhosis and CHB cirrhosis is biologically plausible as they have distinct mechanistic pathways of pathogenesis. The molecular mechanisms underlying alcohol related liver injury and NAFLD are similarly characterised by steatosis, increased oxidative stress, generation of reactive oxygen species (ROS), mitochondrial and microsomal dysfunction, leading to hepatocyte apoptosis and inflammation (38–40). Conversely, in viral hepatitis (CHB/CHC), viral infection leads to ongoing immune-mediated responses involving both innate and adaptive immune systems, ultimately resulting in hepatocyte inflammation, apoptosis and substantial liver injury (41–43). In the case of CHC, one of its unique features is the tendency to accumulate more hepatocellular steatosis compared to CHB, the mechanism of which may differ amongst different genotypes of hepatitis C virus (44). In fact, CHC may affect lipid metabolism in the liver by impairing lipid secretion, augmenting lipogenesis and inhibiting fatty acid degradation (44, 45), and induce insulin resistance and increased oxidative stress to result in hepatic steatosis similar to the pathogenesis of NAFLD (46). Hence, the pathology of CHC shares overlapping features with NAFLD.

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We postulate that the observation of the benefit of coffee on the progression of liver disease may be due to its effects on the oxidative stress/lipotoxicity pathway, which underlie the pathogenesis of cirrhosis related to alcohol, NAFLD and possibly, in part, CHC. However, since oxidative stress is not the predominant mechanism of injury seen in CHB, coffee has no beneficial effect. Polyphenols and melanoidins, which are major components of coffee, have been shown to mediate multiple protective mechanisms in a rat model of steatohepatitis, ranging from increased fatty acid β oxidation, mitigating oxidative stress and curtailing liver inflammation (47). The other components of coffee, cafestol and kahwoel, can induce phase II detoxifying enzymes, including sulfotransferase, UDP-glucuronosyl transferase, glutathione transferase and peroxidase, and thus contribute to the anti-oxidant properties of coffee (14, 48). In addition, chemicals in coffee such as polyphenols and the diterpenes have been shown to down-regulate proinflammatory, fibrogenic cytokines such as transforming growth factor beta (TGF-β) and its downstream modulator, connective tissue growth factor (CTGF), collagen and stellate cell activation (13–16).

Epidemiologic studies on caffeine have been inconsistent in demonstrating a protective effect in liver disease since other caffeine-containing beverages such as tea have not shown to be protective (19–21). Similarly, in our study, the inverse association with caffeine became null after adjustment for coffee, suggesting that ingredients of coffee other than caffeine appear to be responsible for this beverage's effect on risk reduction. Furthermore, other caffeine-containing beverages like green tea and black tea had no significant effects with cirrhosis mortality in this study. Fructose has been linked to steatohepatitis, and beverages with high content of fructose, such as soft drinks, have been associated with NAFLD (24, 25). In our cohort, among the few subjects who drank soft drinks daily, there was a suggestion an increased risk for cirrhosis mortality although the increased risk estimate of 1.59 was not statistically significant due to small sample size.

Alcohol is well established as an important risk factor for liver disease. Yet, as to the risk threshold, in terms of daily alcohol intake that can induce alcohol liver damage, there is no uniformed conclusion with a wide range between 30 g/d and 80 g/day (30). While an Italian study has defined the risk threshold for developing alcoholic liver disease as 30 g ethanol per day (49), our findings concur with a study in China which showed that the risk threshold was 20 g alcohol per day (50), suggesting that the risk limit could indeed be lower in Chinese. Nevertheless, since only 19% of this cohort drank alcohol at least once a month and the number of death from cirrhosis was also relatively small, we recognize our limitation in defining the threshold value with precision.

The strengths of this study include the prospective study design in a population-based cohort with a long-term follow-up among cohort participants. Singapore is a small city-state with a system for easy access to specialized medical care. Causes of death were ascertained from the nationwide registry, where mortality assessment can be considered complete and reliable. A comprehensive questionnaire for collection of data on other known factors of cirrhosis, such as body mass index and history of diabetes, were included in the statistical models to reducing confounding. However, there are a number of potential limitations in our study. First, we only used the baseline intake of alcohol and beverages in our analysis. Any subsequent change in the consumption of coffee post recruitment could lead to

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nondifferential misclassification and potentially underestimate the coffee-cirrhosis mortality risk association. However, results from the responses obtained during our Follow-up II Survey, which was conducted, on average, about 12 years post enrollment, revealed that among the 39,528 cohort subjects re-interviewed about their coffee drinking habit, 72.3% retained their coffee-drinking status as 20.9% remained non-daily drinkers and 51.4% remained daily drinkers. Second, viral hepatitis diagnosis were only ascertained from death records and may be under-reported, leading to an inadvertent inclusion of such cases in the non-viral hepatitis related group. This could again cause an underestimation the coffee-mortality association reported for non-viral hepatitis related cirrhosis.

In conclusion, our study demonstrates the protective effect of coffee on non-viral hepatitis related cirrhosis mortality, and concurs with experimental evidence that the effect could be mediated via antioxidant and anti-inflammatory mechanisms. Our finding suggests that while the benefit of coffee may be less apparent in the Asian population where CHB predominates currently, this is expected to change with the changing epidemiology in these regions, accompanying the increasing affluence and changing dietary patterns amongst their younger populations. Since coffee is widely consumed globally, it has significant clinical and public-health implications and provides further impetus to evaluate coffee as a potential therapeutic agent in patients with chronic liver diseases in randomized interventional trials.

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Abbreviations

CHB	chronic hepatitis B
CHC	chronic hepatitis C virus
NAFLD	non-alcoholic fatty liver disease
SD	standard deviation
HR	hazard ratios
CI	confidence interval

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Table 1

Description of selected demographic and lifestyle characteristics among non-cases and cases of death from cirrhosis, the Singapore Chinese Health Study, 1993–2011

	Non-cases*	Death of liver cirrhosis	Death of viral- hepatitis related cirrhosis	Death of non- viral hepatitis related cirrhosis
N	63,143	114	35	79
Age (year), mean (SD)	56.5 (8.0)	58.8 (8.2)	56.8 (7.6)	59.7 (8.4)
Body mass index (kg/m^2), mean (SD)	23.1 (3.3)	23.6 (3.1)	23.5 (2.5)	23.7 (3.4)
Overweight†, n (%)	13,750 (21.8)	34 (29.8)	10 (28.6)	24 (30.4)
Gender, n (%)				
Males	27,886 (44.2)	68 (59.7)	23(65.7)	45 (57.0)
Females	35,257 (55.8)	46 (40.3)	12 (34.3)	34 (43.0)
Dialect, n (%)				
Cantonese	29,240 (46.3)	44 (38.6)	11 (31.4)	33 (41.8)
Hokkien	33,903 (53.7)	70 (61.4)	24 (68.6)	46 (58.2)
Level of education, n (%)				
No formal education	17,303 (27.4)	30 (26.3)	5 (14.3)	25 (31.7)
Primary school	27,997 (44.3)	53 (46.5)	18 (51.4)	35 (44.3)
Secondary school or above	17,843 (28.3)	31 (27.2)	12 (34.3)	19 (24.0)
Had history of diabetes, n (%)	5,670 (9.0)	26 (22.8)	5 (14.3)	21 (26.6)
Smoking status, n (%)				
Never	43,861 (69.5)	69 (60.5)	22(62.9)	47 (59.5)
Former	6,975 (11.0)	18(15.8)	8 (22.9)	10 (12.7)
Current	12,307 (19.5)	27 (23.7)	5 (14.2)	22 (27.8)
Moderate physical activity‡, n (%)				
None	49,185 (77.9)	87 (76.3)	28 (80.0)	59 (74.7)
0.5–4 hours/week	8,776 (13.9)	12 (10.5)	3 (8.6)	9 (11.4)
4+ hours/week	5,182 (8.2)	15 (13.2)	4 (11.4)	11 (13.9)

*Non-cases = entire cohort – deaths of liver cirrhosis.

†Body mass index ≥ 25.0 kg/m^2.

‡Included activities such as brisk walking, bowling, bicycling on level ground, tai chi or chi kung.

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Table 2

Consumption of coffee, tea, fruit juice, soft drinks and alcohol in relation to cirrhosis mortality, The Singapore Chinese Health Study, 1993–2011

Characteristics	Total subjects	Death of liver cirrhosis	Model 1* HR (95% CI)	Model 2† HR (95% CI)
Coffee				
None/less than daily	18816	45	1.00	1.00
1 cup/day	22803	34	0.62 (0.40–0.97)	0.62 (0.40–0.97)
2+ cups/day	21638	35	0.62 (0.40–0.97)	0.63 (0.40–1.00)
P for trend			0.033	0.047
Black tea				
None/Monthly	45485	83	1.00)	1.00
Weekly	10762	20	0.99 (0.60–1.61)	0.99 (0.61–1.62)
Daily	7010	11	0.77 (0.41–1.45)	0.77 (0.40–1.44)
P for trend			0.47	0.47
Green tea				
None/Monthly	44563	76	1.00	1.00
Weekly	10861	16	0.88 (0.51–1.51)	0.80 (0.46–1.37)
Daily	7833	22	1.56 (0.96–2.53)	1.36 (0.84–2.21)
P for trend			0.15	0.40
Fruit juices				
None/less than Monthly	42831	77	1.00	1.00
Monthly	11185	23	1.29 (0.81–2.07)	1.29 (0.80–2.07)
Weekly	8079	12	0.94 (0.51–1.74)	0.92 (0.49–1.70)
Daily	1162	2	0.99 (0.24–4.04)	0.93 (0.23–3.81)
P for trend			0.86	0.94
Soft drinks				
None/less than monthly	48093	89	1.00	1.00
Monthly	5985	9	0.92 (0.46–1.83)	0.99 (0.50–1.98)
Weekly	7215	11	0.97 (0.52–1.84)	0.99 (0.52–1.88)
Daily	1964	5	1.59 (0.64–3.95)	1.59 (0.64–3.98)
P for trend			0.65	0.58
Alcohol (ethanol per day)				
None	51384	84	1.00	1.00
<20 g	10278	12	0.67 (0.36–1.24)	0.72 (0.39–1.35)
20 g or more	1595	18	6.38 (3.68–11.05)	7.07 (4.01–12.47)
P for trend			<0.0001	<0.0001
Daily caffeine intake (mg)				
Quartile 1 (<45.8 mg)	15815	33	1.00	1.00
Quartile 2 (45.8–<83.7 mg)	15829	26	0.77 (0.46–1.29)	0.75 (0.45–1.26)
Quartile 3 (83.7–<141.1 mg)	16116	28	0.75 (0.45–1.25)	0.73 (0.44–1.22)
Quartile 4 (141.1+ mg)	15497	27	0.71 (0.42–1.20)	0.70 (0.41–1.18)

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Characteristics	Total subjects	Death of liver cirrhosis	Model 1* HR (95% CI)	Model 2† HR (95% CI)
P for trend			0.21	0.19

*Adjusted for age at recruitment (years), year of recruitment (1993–1995, 1995–1998), gender, dialect group (Hokkien, Cantonese), education categories (no formal education, primary school, secondary school or higher); CI, confidence interval.

†Additionally adjusted for diabetes (yes, no), body mass index (continuous), alcohol intake (non, monthly, weekly, daily), smoking (never, former, current) and moderate physical activity (no, 0.5–4 hours/week, 4+ hours/week).

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Table 3

Coffee and caffeine intake in relation to viral-hepatitis or non-viral hepatitis related cirrhosis mortality, The Singapore Chinese Health Study, 1993–2011

	N	Model 1* HR (95% CI)	Model 2† HR (95% CI)
Viral-hepatitis related cirrhosis	35		
Coffee			
None/less than daily	11	1.00	1.00
1 cup per day	6	0.49 (0.18–1.33)	0.56 (0.18–1.71)
2+ cup per day	18	1.49 (0.69–3.21)	2.07 (0.48–8.86)
P for trend		0.23	0.39
Caffeine (mg/day)			
Quartile 1 (<45.8 mg)	9	1.00	1.00
Quartile 2 (45.8–<83.7 mg)	5	0.57 (0.19–1.71)	0.42 (0.12–1.46)
Quartile 3 (83.7–<141.1 mg)	8	0.81 (0.31–2.11)	0.48 (0.12–1.99)
Quartile 4 (141.1+ mg)	13	1.33 (0.55–3.31)	0.64 (0.12–3.40)
P for trend		0.40	0.84
Non-viral hepatitis related cirrhosis	79		
Coffee			
None/less than daily	34	1.00	1.00
1 cup/day	28	0.65 (0.39–1.07)	0.62 (0.35–1.08)
2+ cups/day	17	0.39 (0.21–0.70)	0.34 (0.14–0.81)
P for trend		0.001	0.014
Daily caffeine (mg)			
Quartile 1 (<45.8 mg)	24	1.00	1.00
Quartile 2 (45.8–<83.7 mg)	21	0.81 (0.45–1.45)	1.21 (0.62–2.36)
Quartile 3 (83.7–<141.1 mg)	20	0.69 (0.38–1.26)	1.26 (0.60–2.63)
Quartile 4 (141.1+ mg)	14	0.47 (0.24–0.93)	1.17 (0.44–3.08)
P for trend		0.027	0.71

*Adjusted for age at recruitment (years), year of recruitment (1993–1995, 1995–1998), gender, dialect group (Hokkien, Cantonese), education categories (no formal education, primary school, secondary school or higher), diabetes (yes, no), body mass index (continuous), alcohol intake (non, monthly, weekly, daily), smoking (never, former, current), moderate physical activity (no, 0.5–4 hours/week, 4+ hours/week) and soft drink consumption (none, monthly, weekly, daily); CI, confidence interval.

†Additionally adjusted for coffee (none/less than daily, 1 cup/day, 2+ cups/day) or caffeine intake (mg/day, quartile)