Research Article

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# Coffee and herbal tea consumption is associated with lower liver stiffness in the general population: The Rotterdam study

Louise J.M. Alferink[1], Juliana Fittipaldi[1,2], Jessica C. Kiefte-de Jong[2,3], Pavel Taimr[1], Bettina E. Hansen[1,4], Herold J. Metselaar[1], Josje D. Schoufour[2], M. Arfan Ikram[2,5,6], Harry L.A. Janssen[1,4], Oscar H. Franco[2], Sarwa Darwish Murad[1,*]

[1]*Department of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands;* [2]*Department of Epidemiology, Erasmus MC University Medical Centre, Rotterdam, The Netherlands;* [3]*Leiden University College, The Hague, The Netherlands;* [4]*Liver Centre, Toronto Western & General Hospital, University Health Network, Toronto, Canada;* [5]*Department of Radiology, Erasmus MC University Medical Medical Centre, Rotterdam, The Netherlands;* [6]*Department of Neurology, Erasmus MC University Medical Medical Centre, Rotterdam, The Netherlands*

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**Background & Aims**: Coffee and tea have been proposed to limit the progression of liver fibrosis in established liver disease, but it is unknown if this is also true for subclinical fibrosis. We therefore aimed to evaluate whether coffee and tea consumption are associated with liver stiffness in the general population.

**Methods**: The Rotterdam Study is an ongoing prospective population-based cohort. We included participants who underwent transient elastography, ultrasound and completed a food frequency questionnaire. Coffee and tea consumption were categorized into no, moderate (>0–3), or frequent (⩾3) intake (cups/day), and tea further into green, black and herbal tea (no/any). Significant fibrosis was defined as liver stiffness measurements (LSM) ⩾8.0 kPa. We performed regression analyses relating coffee and tea intake with fibrosis, steatosis and log-transformed LSM and adjusted for energy, sugar and creamer intake, age, gender, BMI, steatosis/LSM, HOMA-IR, ALT, alcohol, smoking, soda, healthy diet index and physical activity.

**Results**: We included 2,424 participants (age 66.5 ± 7.4; 43% male) of whom 5.2% had LSM ⩾8.0 kPa and 34.6% steatosis. Proportion of LSM ⩾8.0 kPa decreased with higher coffee consumption (7.8%, 6.9% and 4.1% for no, moderate and frequent respectively; $P_{trend} = 0.006$). This inverse association was confirmed in multivariable regression ($OR_{mod}$ 0.75, 95% CI 0.33–1.67; $OR_{freq}$ 0.39, 95% CI 0.18–0.86; $p = 0.005$). Amongst tea consumers, only herbal tea consumers (36.3%) had lower log-transformed LSM after adjustment (Beta-0.05, 95% CI-0.08;-0.02, $p = 0.001$). Subtypes of tea were associated with steatosis in univariate but not multivariable analysis.

**Conclusions**: In the general population, frequent coffee and herbal tea consumption were inversely related with liver stiffness but not steatosis. Longitudinal analyses, as well as studies validating and unravelling underlying mechanisms are needed.

**Lay summary**: The Rotterdam Study is a large ongoing population study of suburban inhabitants of Rotterdam in whom data on liver stiffness, as proxy for liver fibrosis, presence of fatty liver on ultrasound and detailed information on coffee and tea consumption were obtained in 2,424 participants. The consumption of herbal tea and daily consumption of three or more cups of coffee was related to the presence of lower liver stiffness, independent of a great number of other lifestyle and environmental factors. Previous studies have found a protective effect of coffee on established liver disease and we now show for the first time that this effect is already measurable in the general population.



## Introduction

Chronic liver diseases constitute a major public health problem. Liver cirrhosis was the 12th cause of death worldwide and the sixth cause of life-years lost in the adult population in developed countries in 2010.[1,2] Chronic liver diseases are often silent for over 20 years until cirrhosis develops. Indeed, several studies have suggested that liver fibrosis may be present within unselected individuals. Using transient elastography (TE) as a diagnostic tool for liver fibrosis, a prevalence of 6–7% was found in the general population[3,4] and even up to 17% in those high-risk populations with metabolic syndrome and type 2 diabetes.[5]

Lifestyle is an important factor in the pathogenesis of many liver diseases, examples of which include alcohol abuse in alcoholic liver disease and high caloric diet and inactivity in non-alcoholic fatty liver disease (NAFLD). At the same time, a healthy lifestyle, such as implementing a well-balanced diet or

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* Corresponding author. Address: Office Ha-211, Postbus 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 628021137; fax: +31 10 436 5916.

*E-mail address:* s.darwishmurad@erasmusmc.nl (S. Darwish Murad).

consumption of nutraceuticals, *i.e.* foods or nutrients with a health benefit, can prevent and even attenuate liver disease.[6]

Coffee and tea are the most consumed beverages worldwide and emerging as promising nutraceuticals for liver health.[7] Both beverages are part of well-rooted cultural traditions and also represent the second most traded commodity on the world markets.[8] Consumption of these nutraceuticals has been associated with lower all-cause and cause-specific mortality, presumably through reducing the risk of features of the metabolic syndrome.[9,10]

Coffee consumption was for the first time associated to liver health, that is lower liver enzymes, almost two decades ago.[11] Evidence supporting this protective effect of coffee on liver enzymes rapidly emerged henceforth.[12] Coffee consumption seemed to attenuate alcoholic liver disease[13] and studies in hepatitis C showed less severe fibrosis in coffee consumers.[14] Also in NAFLD patients, coffee consumption was inversely associated with fibrosis grade, but inconclusive concerning the relation to steatosis.[15–17] To date, only one study examined the correlation between coffee and liver fibrosis in the general population, albeit using a surrogate serum biomarker test as a proxy for fibrosis, and found lower odds for fibrosis in frequent coffee consumers.[17]

The association between tea and liver health is less well established than that of coffee. All studies are either limited to Asian populations or include only serum transaminases as a primary endpoint. In addition, results of these studies are inconclusive regarding the presumed health benefit of tea.[18–22]

To our knowledge, there are no studies examining whether coffee and tea consumption are associated with a lower prevalence of steatosis and liver fibrosis, using reliable imaging techniques, in the general population. Hence, we conducted a cross-sectional analysis of individuals within a large prospective cohort study, who completed extensive dietary questionnaires, liver stiffness measurements (LSM), as proxy for fibrosis, and hepatic ultrasound (US) for the diagnosis of steatosis. Our aim was to determine whether coffee and tea consumption were associated with lower risk of liver fibrosis and steatosis in the general population.

## Participants and methods

### *Study population*

This is a cross-sectional analysis of The Rotterdam Study, a large ongoing population-based cohort of participants aged 45 years and older living in a suburb of Rotterdam, The Netherlands. The rationale and design of this study have been described previously and a more detailed description of the design is added as Supplementary methods.[23] For the purpose of our study, all participants visiting the research center between January 2011 and September 2013 were included and underwent anthropometric assessment, abdominal US, TE and blood sampling. For all cohorts, this was the first hepatic examination in The Rotterdam Study. The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus MC University Medical Center Rotterdam and by the review board of The Netherlands Ministry of Health, Welfare and Sports. Written informed consent was obtained from all participants.

### *Coffee and tea consumption*

All participants completed an externally validated 389-item food frequency questionnaire (FFQ) developed for Dutch adults.[24,25] The questionnaire addressed the type of food consumed over the last month, as well as frequency, portion size and preparation methods. Incomplete or unreliable FFQs, *i.e.* total energy intake less than 500 or more than 7,500 kilocalories per day, were excluded. Questions regarding coffee and tea consumption included: "How often did you drink coffee last month?" and "How often did you drink black/green/herbal tea (*e.g.* chamomile, red bush and nettle) last month?" to which the possible answers were: "1) not at all, 2) 1 or 2–3 times, or 3) 1; 2–3; 4–5 or 6–7 times a day", and in case of daily consumption "1–2; 3–4; 5–6; 7–8; 9–10 or 11 or more cups per day". Coffee and tea consumption was thereafter categorized into no (0), moderate (>0–3) and frequent (⩾3) consumption (in cups/day, one cup equals 150 g). Tea consumption was further specified into herbal, green and black tea and subsequently dichotomized into no (0) and any (>0) consumption. Additionally, data on consumption of soda, alcohol, sugar and cream use in coffee or tea were obtained and used as covariates (in g/day). Excessive alcohol consumption was defined as >14 units per week for women and >21 units per week for men (one unit equals 10 g). Furthermore, to account for confounding by overall dietary quality, the Dutch Healthy Diet Index (DHDI) was added to multivariable analyses.[26]

### *Liver stiffness measurements and hepatic steatosis*

LSM were performed using TE (FibroScan®, EchoSens, Paris, France) by a single operator who had performed more than 1,000 examinations before the start of the study. Practical implementation of TE has been described previously.[3] The operator obtained 10 serial measurements of stiffness, using the M- or the XL-probe according to the manufacturer's instructions. Participants were excluded from our analyses if: 1) LSM did not meet the reliability criteria of Boursier *et al.*, *i.e.* interquartile range (IQR)/median LSM >0.30 with median LSM ⩾7.1 kPa;[27] 2) no LSM was obtained after at least 10 shots (defined as failure) and; 3) intra-cardiac devices or physical disabilities prohibited the use of TE.

Clinically relevant fibrosis was defined as LSM ⩾8.0 kPa and clinically relevant cirrhosis as LSM ⩾13.0 kPa. At these cut-off levels, previous studies showed high positive predictive values for the presence of liver fibrosis and cirrhosis, respectively.[4,28,29]

Abdominal US was carried out by a certified and experienced technician on Hitachi HI VISION 900. Images were stored digitally and re-evaluated by a single hepatologist with more than 10 years of experience in US (P.T.). Diagnosis of steatosis was determined dichotomously according to the protocol of Hamaguchi *et al.*,[30] as presence or absence of a hyper-echogenic liver parenchyma.

### *Biochemistry*

Fasting blood samples were collected just before US and TE imaging. Blood lipids, platelet count, glucose, alanine aminotransferase (ALT), aspartate aminotransferase, gamma-glutamyltransferase (GGT), alkaline phosphatase and total bilirubin were measured using automatic enzyme procedures (Roche Diagnostic GmbH, Mannheim, DE). Insulin, hepatitis B surface antigen and anti-hepatitis C virus were measured by an automatic immunoassay (Roche Diagnostic GmbH). Patients with viral hepatitis were excluded from the analyses.

### *Additional covariates*

Data concerning demographics, education level, medical history, physical activity, comorbid conditions, smoking behavior and drug use were obtained during an extensive home interview by trained interviewers. Detailed information on medication use was obtained from automated linkage to pharmacies with which 98% of the participants were registered. Anthropometric measurements were performed by well-trained research assistants. Body mass index (BMI) was calculated as weight (kg)/height ($m^2$) and waist circumference (WC) in centimeters. Blood pressure measurements were taken as the average of two subsequent measurements on the same day in upright position. According to the Adult Treatment Panel III criteria,[31] metabolic syndrome was diagnosed if at least three of the following five traits were present: 1) abdominal obesity, defined as WC >102 cm (40 inch) in men and >88 cm (35 inch) in women; 2) serum triglycerides ⩾150 mg/dl (1.0 mmol/L) or drug treatment for elevated triglycerides; 3) serum high-density lipoprotein cholesterol (HDL-C) <40 mg/dl (1.0 mmol/L) in men and <50 mg/dl (1.3 mmol/L) in women or drug treatment for low HDL-C; 4) blood pressure ⩾130/85 mmHg or drug treatment for elevated blood pressure; 5) fasting plasma glucose (FPG) ⩾100 mg/dl (5.6 mmol/L) or drug treatment for elevated blood glucose. Homeostasis model assessment of insulin resistance (HOMA-IR) was used as proxy for insulin resistance and calculated by multiplying fasting glucose (mmol/dl) by fasting insulin (mU/L) divided by 22.5.[32]

### *Statistical analyses*

Population characteristics were described using descriptive statistics. Continuous data were presented as mean ± standard deviation or median with interquartile range (IQR) according to the distribution of the variable. Chi-square test,