Coffee consumption by type and risk of digestive cancer: a large prospective cohort study

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Title: Coffee consumption by type and risk of digestive cancer: A large prospective cohort study.

Running title: Coffee types and digestive cancer risk

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ABSTRACT

Background
Evidence of a protective effect of coffee consumption for liver cancer has been found but inconclusive for other digestive cancers. Few previous studies have investigated coffee type (specifically instant or ground coffee) and few investigated a range of digestive cancer types within the one cohort. We therefore investigated the association between coffee consumption by type with digestive cancers in a large UK population-based cohort.

Methods
We analysed data from the UK Biobank cohort study using self-reported coffee consumption and cancer-registry recorded incident digestive cancers. Hazard ratios (HRs) and 95% CIs were calculated using Cox regression. Risk of every type of digestive cancer was investigated in association with coffee consumption by dose-response and by coffee type (decaffeinated, instant, ground).

Results
Over 7.5 years of follow-up, 3,567 developed digestive cancer among 471,851 participants. A marked association was observed for hepatocellular carcinoma by any dose of coffee (HR 0.50, 95% CI 0.29, 0.87) and by instant coffee (HR 0.51, 95% CI 0.28, 0.93). We did not observe significant consistently reduced risks of other individual digestive cancer types amongst coffee drinkers.

Conclusion
We found some evidence that coffee consumption was inversely associated with hepatocellular carcinoma which was apparent for instant coffee consumption.
Keywords: coffee, cafféinated, decafféinated, instant coffee, hepatocellular carcinoma, digestive cancer.
Introduction

Coffee is one of the most commonly consumed beverages worldwide\(^1\). Coffee is mostly consumed as instant or ground with the type of coffee consumed varying between countries\(^2\). Instant and ground coffee have different chemical compounds reflecting the processes involved in their production. For instance, instant coffee, is reported to have higher concentrations of caffeine, polyphenols, and chlorogenic acid which contribute to antioxidant activity\(^3,4\). Instant coffee receipt has also been shown to reduce the size and number of neoplastic lesions, compared with conventional coffee or caffeine only, in an experimental study in rats\(^5\). However, instant coffee also contains twice as much acrylamide as ground coffee\(^6\), a substance which was classified in group 2A as a probable human carcinogen\(^7\) and about which there has been recent controversy regarding potential cancer risk in humans\(^8,9\).

Various meta-analyses have been conducted into the association between coffee consumption and risk of digestive cancers. A recent meta-analysis by the World Cancer Research Fund showed no association between coffee consumption and colorectal cancer risk\(^10\), but another recent review observed small reduced risks of colorectal cancer for high daily intakes of coffee (≥5 cups per day)\(^11\). Other meta-analyses have not found associations between coffee consumption and gastric\(^12\) or oesophageal cancer risk\(^13\). In contrast, there is evidence of an inverse association between coffee consumption and liver cancer, with two meta-analyses demonstrating every one cup per day increase is associated with a 14-15% reduced risk of liver cancer\(^14,15\).

Despite this accumulating research, few previous studies have investigated a range of digestive cancers within the same cohort. To our knowledge, most studies have investigated
consumption of any coffee type, caffeinated coffee or decaffeinated coffee\textsuperscript{15,16,17} and only one study investigated instant coffee\textsuperscript{18}, despite their biochemical compound differences, with respect to digestive cancer risk. Therefore, we aimed to investigate the association between coffee consumption and the risk of digestive cancers by type of coffee (decaffeinated, instant or ground) within a large prospective UK cohort.

**Methods**

Data source

The UK Biobank contains approximately 500,000 volunteer participants aged 40 to 69 from England, Scotland and Wales recruited from 2006 to 2010\textsuperscript{19}. A wide range of data was collected including lifestyle, environment, medical history and physical measures, along with biological samples. The UK Biobank is linked to cancer registry data from the Health and Social Care Information Centre (in England and Wales) and the National Health Service Central Register (in Scotland). The UK Biobank has ethical approval from the North West Multi-Centre Research Ethics Committee. All participants provided written informed consent.

Study design

A prospective cohort study was conducted among participants in the UK Biobank. Patients diagnosed with cancers of the digestive tract were identified using cancer registry records (based upon ICD 10 codes: oesophagus C15; stomach C16; small intestine C17; colon C18; rectal and anal cancer including rectosigmoid junction cancer C19, rectum cancer C20, and
anal cancer C21; liver C22, hepatocellular carcinoma C22.0, intrahepatic bile duct C22.1; gall bladder and extrahepatic bile duct C23-C24; pancreas C25) up to September 30, 2014. Participants with any cancer diagnosis prior to baseline or in the year after baseline were excluded (to avoid reverse causation). Consequently, cohort participants were followed from one year after baseline until the date of cancer diagnosis or censoring (on the earliest of the date of death, date of other cancer diagnosis, or September 30, 2014).

Exposure assessment

Coffee consumption was assessed at baseline. Participants were asked their average intake of coffee in the last year “how many cups of coffee do you drink each day”, and the most common type of coffee used (decaffeinated, instant, ground, or other type).

Covariates

Covariates were determined from patient interview or touch screen at baseline. These included age, sex, education (highest qualification achieved), Townsend deprivation scores (a socio-economic measure based on area of residence)\(^2\), and comorbidities (high cholesterol, diabetes, hypertension, angina, myocardial infarction, stroke, peptic ulcer disease, hepatitis, and cirrhosis). Lifestyle factors including physical activity (metabolic equivalents (METs) score was calculated based on the number of days per week with more than 10 minutes of walking, moderate or vigorous physical activity)\(^2\), fruit and vegetable intake (portions per day), tea intake (number of cups per day), smoking status (never smoker, previous smoker or
current smoker) and alcohol consumption (never, <1 day per week, 1-2 days per week, 3-4 days per week or >4 days per week) were also ascertained. Body mass index (BMI) in kg/m² (categorized as under or normal weight [<25], overweight [25 to <30], or obese [30 or higher]) was calculated from height and weight measurements recorded at baseline by trained research staff.

Statistical analysis

The UK Biobank cohort was analysed using Cox regression with age as the underlying time scale (individuals were considered at risk from birth and under observation from age at baseline, left truncated) to calculate hazard ratios (HR) and 95% confidence intervals (CI) for coffee use and risk of all digestive cancers, as well as by cancer type. Dose-response analyses were conducted by increasing cups of coffee intake. In adjusted analyses the model contained age at baseline, sex, deprivation, education, BMI, alcohol, smoking, fruit and vegetable intake, tea intake, physical activity and comorbidities at baseline (including high cholesterol, hypertension, diabetes, angina, myocardial infarction, stroke, peptic ulcer disease, hepatitis, and cirrhosis). Estimates of coffee intake by number of cups per day and by type in association with digestive cancer are presented in Tables 2 and 3, respectively.

Sensitivity analyses were performed for every site of digestive cancer and all digestive cancer by repeating the analyses starting follow-up at 2 years after baseline (to remove cancers within 2 years which could have influenced coffee consumption at baseline) (Supplementary Table 1 and 2).

Supplementary Figure 1 and 2 were added to visualize the dose response pattern of coffee and coffee by type in association with digestive cancer.
**Results**

A total of 471,779 participants were included in the study, following the exclusion of 30,839 participants with a previous history of cancer prior to baseline or in the year after baseline. Within the cohort, 104,465 participants (22.5%) were non-consumers of coffee. Among coffee drinkers, the type of coffee most frequently consumed was instant coffee (43.4%), followed by ground coffee (17.8%), decaffeinated coffee (14.9%), and other types reported by 1.4%.

Table 1 shows the baseline characteristics of participants by coffee consumption. People who drank coffee, compared with those who did not, were more likely to be older, male, from less deprived areas and have higher education levels. They were also more likely to be previous or current smokers, consume higher levels of alcohol and have fewer comorbidities compared with non-coffee drinkers.

Over 7.5 years of follow-up, 3,567 digestive cancer cases were detected. The associations between any type of coffee consumption and risk of specific digestive cancers are presented in Table 2. Any coffee consumption was only associated with HCC (adjusted HR 0.50, 95% CI 0.29, 0.86) and was not significantly associated with other cancers. Results were largely similar in dose-response analyses of increasing number of coffee cups consumed per day compared to non-coffee drinkers. There was some evidence of more marked reductions in hepatocellular carcinoma (HCC) risk by increasing categories of coffee cups consumed (e.g. adjusted HR for ≥5 cups: 0.44, 95% CI 0.17, 1.12, p for trend=0.07), as well as per cup increase (adjusted HR 0.87, 95% CI 0.76, 1.01).
Associations between coffee consumption by type and risk of specific digestive cancers are presented in Table 3. The reduction of HCC risk ranged from 41-53% for different types of coffee but the most marked association was observed for instant coffee (adjusted HR 0.51, 95% CI 0.28, 0.93). Risk of pancreatic cancer was reduced by 34% in users of decaffeinated coffee compared to non-coffee drinkers, but this did not reach statistical significance (adjusted HR 0.66, 95% CI 0.43, 1.01). No significant associations were observed for any coffee type and risk of stomach, oesophagus, small intestine, colon, rectal and anal cancer, or intrahepatic bile duct carcinoma (Table 3). The risk of gall bladder and extra hepatic bile duct carcinoma was consistently increased with consumption of any type of coffee but the only significant increase in risk was observed for decaffeinated coffee (HR 2.44, 95% CI 1.10, 5.41).

After excluding the two-years following baseline, the association between increasing number of coffee cups consumed per day and digestive cancer risk showed similar results to the main analysis (Supplementary Table 1). In similar analysis by coffee type, associations were little altered for any digestive cancer site, except for gall bladder and extra hepatic bile duct carcinoma which attenuated and became non-significant (Supplementary Table 2).

**Discussion**

In a large prospective study, we found a reduced risk of HCC with coffee consumption, which was consistent in dose response analysis and by coffee type, was apparent for instant coffee.
Our study is consistent with the inverse association between coffee consumption and HCC risk that has been judged as ‘convincing’ evidence in the 2018 World Cancer Research Fund report\textsuperscript{15}, confirming previous individual studies\textsuperscript{22,17,16} and meta-analyses\textsuperscript{23,24}. Whilst we did not show marked differences in the inverse association between HCC and coffee consumption by type of coffee, an inverse association was apparent for instant coffee. Some previous studies have investigated caffeinated and decaffeinated coffee\textsuperscript{22,17,16}, but no previous studies, to date, have explored the association of instant coffee consumption and HCC.

The underlying biological mechanisms for a reduced risk of HCC with coffee consumption, especially with instant coffee, is not well known but some mechanisms have been proposed. Coffee has high levels of antioxidants\textsuperscript{25} including phenolic acids, diterpenes like cafestol and kahweol, and tocopherols\textsuperscript{26}. Compounds such as phenolic acids\textsuperscript{27,28} and caffeine\textsuperscript{29} have also been shown to have chemopreventive properties, including in liver carcinogenesis\textsuperscript{38}. These compounds have been shown to inhibit the proliferation of HCC cell lines \textit{in vitro} and suppress the progression of HCC \textit{in vivo}\textsuperscript{30}, while chlorogenic acid has been shown to prevent oxidative damage in hepatocytes\textsuperscript{31}. Instant coffee, in comparison with ground and decaffeinated coffee, has been demonstrated to have higher levels of those biochemical compounds\textsuperscript{3,4}, which therefore could partly explain the more marked reduced risk of HCC in our study. The underlying potential anti-cancer mechanism of instant coffee has also been observed in previous experimental studies. An animal study\textsuperscript{5} showed that mice receiving instant coffee had a reduction in the size and the number of hepatocellular neoplastic lesions compared with mice receiving ground coffee. Instant coffee administration in rats also resulted in a significantly higher expression of bax protein\textsuperscript{5}, which monitors cell apoptosis and is a known tumour suppressor\textsuperscript{32,33}. Another study in rats demonstrated that instant coffee
powder inhibited hepatoma cell proliferation, reduced metastasis, and positively altered lipoprotein profiles. Therefore it is plausible that instant coffee may have a stronger anti-cancer effects in comparison to other coffee types.

For other individual types of digestive cancer, we did not find any consistent association with coffee consumption. Our findings of no association between coffee and colorectal cancer confirm previous findings, although contrasts with suggestions that high-levels of coffee drinking reduced the risk of colon cancer. For small intestine and oesophageal cancer, our findings are similar to previous meta-analyses of no association with coffee consumption.

For gastric cancer, the results are inconclusive. Our findings of no association between coffee and risk of gastric cancer is in line with a recent meta-analysis, however contrasts two previous meta-analyses that showed a decrease and an increase in risk of gastric cancer with coffee use. In one meta-analysis, no association was observed following restriction to only cohort studies while in the other meta-analysis, the positive association between coffee consumption and gastric cancer risk attenuated and became non-significant after adjusting for risk factors such as smoking, alcohol intake and BMI.

Our study is similar to a more recent meta-analysis of four large cohort studies of female non-smokers which demonstrated no association between coffee intake and pancreatic cancer. Our study found no association between increasing number of coffee cups consumed and pancreatic cancer risk but there was suggestive evidence of an inverse association between decaffeinated coffee consumption and pancreatic cancer risk, which is in contrast to a previous US study showing no association for decaffeinated coffee. The difference in results might be explained by other underlying differences in population behaviours relevant
for pancreatic cancer aetiology, or differences in coffee consumption patterns, but is difficult to fully understand. Further investigations are warranted to explore the association between decaffeinated coffee and pancreatic cancer.

Our findings of an increased risk of gallbladder cancer with decaffeinated coffee consumption are not consistent with a previous meta-analysis of any coffee intake and biliary tract cancer risk although the previous study did not specifically investigate decaffeinated coffee\textsuperscript{14}. However, our result could be owing to chance since there was no clear dose-response relationship and the positive finding attenuated and became non-significant in sensitivity analysis.

The main strength of our study is that within UK Biobank, information on the type of coffee most commonly consumed was available, allowing for investigation of instant or ground or decaffeinated coffee and digestive cancer risk. Second, the UK Biobank contains over 500,000 participants who were prospectively followed for up to 7.5 years, allowing sufficient statistical power to detect even relatively weak associations. We were also able to investigate the impact of coffee consumption across a number of different digestive cancer sites, therefore minimising potential measurement error. Finally, we were able to control for various important confounders which are associated with coffee consumption and digestive cancer risk, such as BMI, alcohol and smoking habit, physical activity, fruit and vegetable intake, tea intake, and comorbidities. However, a number of weaknesses existed in our study. First, coffee consumption could have changed over time so misclassification of coffee consumption is possible. However, other cohorts have shown coffee consumption to remain relatively stable over time in adult populations\textsuperscript{41}. Second, we did not investigate the impact of milk, non-dairy creamer, and sweeteners on the association between coffee and digestive
cancer risk. Milk and non-dairy creamer have been found to alter biochemical activities of coffee by interacting with coffee components like polyphenol\textsuperscript{42}, however, the extent of its impact on the association of coffee and cancer risk has not yet been substantiated. Nevertheless, any measurement error of coffee intake and accompanying milk intake is unlikely to have affected our ability to identify associations with only cancers other than HCC. Further studies should investigate the underlying mechanisms of a protective effect of coffee against HCC. Additional large epidemiological studies are required to confirm the role of instant coffee among other types, as well the impact of milk, non-dairy creamer, and sweeteners in the association with digestive cancers.

In conclusion, our findings suggest an inverse association between coffee consumption and HCC which was apparent for instant coffee consumption. The underlying mechanism of a protective effect of coffee on hepatocellular carcinoma compared to other digestive cancers, particularly for instant coffee, are worthy of further investigation.
| Characteristics                          | Coffee use | p value |
|-----------------------------------------|------------|---------|
|                                          | No (104,465) | Yes (365,157) | |
| Age at baseline (years):                |            |         |
| 0-49                                    | 29,969 (28.7%) | 84,182 (23.1%) | <0.001 |
| 50-59                                   | 36,583 (35.0%) | 121,413 (33.2%) | |
| 60-69                                   | 37,513 (35.9%) | 157,846 (43.2%) | |
| 70+                                     | 400 (0.4%) | 1,716 (0.5%) | |
| Male                                    | 44,004 (42.1%) | 172,206 (47.2%) | <0.001 |
| Deprivation:                            |            |         |
| 1 (Least deprived)                      | 17,825 (17.1%) | 76,482 (20.9%) | |
| 2                                       | 18,848 (18.1%) | 75,006 (20.5%) | |
| 3                                       | 19,880 (19.0%) | 73,840 (20.2%) | <0.001 |
| 4                                       | 21,945 (21.0%) | 72,053 (19.7%) | |
| 5 (Most deprived)                       | 25,828 (24.7%) | 67,325 (18.4%) | |
| Missing                                  | 139 (0.1%) | 451 (0.1%) | |
| Education: College or university degree | 27,872 (26.7%) | 124,155 (34.0%) | |
| A level/AS level or equivalent          | 10,880 (10.4%) | 41,252 (11.3%) | |
| O level/GCSEs or equivalent             | 22,221 (21.3%) | 76,381 (20.9%) | |
| CSEs or equivalent                      | 6,963 (6.7%) | 18,690 (5.1%) | <0.001 |
| NVQ or HND or HNC equivalent            | 7,348 (7.0%) | 23,358 (6.4%) | |
| Other professional qualifications       | 5,113 (4.9%) | 18,800 (5.1%) | |
| None of the above                       | 21,679 (20.7%) | 56,480 (15.5%) | |
| Missing                                  | 2,389 (2.3%) | 6,041 (1.7%) | |
| BMI: Normal/under weight                |            |         |
| Overweight                              | 34,646 (33.2%) | 119,867 (32.8%) | <0.001 |
| Obese                                   | 42,406 (40.6%) | 156,214 (42.8%) | |
| Missing                                  | 777 (0.7%) | 1,727 (0.5%) | |
| Smoking status: Never                   |            |         |
| Never                                   | 61,572 (58.9%) | 195,888 (53.6%) | <0.001 |
| Previous                                | 32,229 (30.8%) | 128,414 (35.2%) | |
| Current                                 | 10,235 (9.8%) | 39,574 (10.8%) | |
| Missing                                  | 429 (0.4%) | 1,281 (0.4%) | |
| Alcohol consumption                     |            |         |
| Never                                   | 15,214 (14.6%) | 22,324 (6.1%) | |
| <1 day per week                         | 29,697 (28.4%) | 76,527 (20.9%) | |
| 1-2 days per week                       | 25,970 (24.9%) | 95,315 (26.1%) | <0.001 |
| 3-4 days per week                       | 18,424 (17.6%) | 90,390 (24.8%) | |
| >4 days per week                        | 15,045 (14.4%) | 80,321 (22.0%) | |
| Missing                                  | 115 (0.1%) | 280 (0.1%) | |
| Fruit & vegetable intake                |            |         |
| <2.5 portions per day                   | 22,939 (21.9%) | 68,417 (18.7%) | <0.001 |
| 2.5-5 portions per day                  | 39,898 (38.2%) | 149,040 (40.8%) | |
| >=5 portions per day                    | 38,251 (36.6%) | 138,186 (37.8%) | |
| Missing                                  | 3,377 (3.3%) | 9,514 (2.6%) | |
| Physical activity:                      |            |         |
| Low                                     | 14,539 (13.9%) | 47,718 (13.1%) | |
| Moderate                                | 31,313 (30.0%) | 119,318 (32.7%) | |
| High                                    | 32,617 (31.2%) | 116,169 (31.8%) | <0.001 |
| Missing                                  | 25,996 (24.9%) | 81,952 (22.4%) | |
| Comorbidities:                          |            |         |
| High cholesterol                        | 12,172 (11.7%) | 44,859 (12.3%) | <0.001 |
| Diabetes                                | 57,635 (5.5%) | 17,856 (4.9%) | <0.001 |
| Hepatitis                               | 520 (0.5%) | 1,856 (0.5%) | 0.45 |
| Condition        | Row 1 Value | Row 2 Value | P-value |
|------------------|-------------|-------------|---------|
| Cirrhosis        | 129 (0.12%) | 348 (0.10%) | 0.041   |
| Gallstones       | 1775 (1.70%)| 5700 (1.56%)| 0.002   |
| Peptic ulcer     | 1599 (1.5%) | 4090 (1.1%) | <0.001  |

Abbreviation: BMI, Body mass index; CSE, Certificate of Secondary Education; GCSE: General Certificate of Secondary Education; HNC: Higher National Certificate; HND: Higher National Diploma; NVQ: National Vocational Qualification
Table 2: The association between coffee intake by number of cups per day and digestive cancer within UK Biobank

| Coffee intake (cups/day) | HR per cup increase | p trend |
|--------------------------|---------------------|---------|
| HR per cup increase      |                     |         |
| n                        | 104,465             |         |
| Any                      | 365,157             |         |
| >0 to 2                  | 215,739             |         |
| 3 to 4                   | 97,022              |         |
| ≥5                       | 52,396              |         |
| Oesophageal cancer       |                     |         |
| Cases                    |                     |         |
| Cases                    |                     |         |
| Unadjusted HR            |                     |         |
| Adjusted HR              |                     |         |
| Unadjusted HR            |                     |         |
| Adjusted HR              |                     |         |
| Oesophageal squamous cell carcinoma |     |         |
| Cases                    | 15                  | 18      |
| Cases                    | 204                 | 52      | 42    |
| Unadjusted HR            | 0.72 (0.55, 0.96)   | 0.90 (0.61, 1.32) | 1.47 (0.98, 2.20) | 1.06 (1.01, 1.11) | 0.008 |
| Adjusted HR              | 0.98 (0.68, 1.41)   | 0.88 (0.59, 1.30) | 1.14 (0.73, 1.79) | 1.18 (0.70, 1.98) | 1.03 (0.97, 1.09) |
| Gastric cancer           |                     |         |
| Cases                    | 14                  | 12      |
| Cases                    | 65                  | 99      | 55    | 30    |
| Unadjusted HR            | 0.97 (0.51, 1.82)   | 1.40 (0.71, 2.78) | 1.68 (0.78, 3.64) | 1.05 (0.96, 1.14) | 0.27  |
| Adjusted HR              | 0.91 (0.78, 1.05)   | 0.89 (0.76, 1.05) | 0.97 (0.80, 1.18) | 0.87 (0.68, 1.11) | 0.97 (0.93, 1.01) |
| Small intestinal cancer  |                     |         |
| Cases                    | 14                  | 12      |
| Cases                    | 65                  | 99      | 55    | 30    |
| Unadjusted HR            | 1.18 (0.66, 2.11)   | 1.40 (0.71, 2.78) | 1.68 (0.78, 3.64) | 1.05 (0.96, 1.14) | 0.27  |
| Adjusted HR              | 1.39 (0.60, 2.87)   | 1.12 (0.49, 2.58) | 1.67 (0.67, 4.18) | 1.65 (0.56, 4.78) | 1.02 (0.90, 1.17) |
| Colon cancer             |                     |         |
| Cases                    | 14                  | 12      |
| Cases                    | 65                  | 99      | 55    | 30    |
| Unadjusted HR            | 0.93 (0.82, 1.05)   | 1.04 (0.89, 1.21) | 0.82 (0.67, 1.00) | 0.98 (0.95, 1.00) | 0.16  |
| Adjusted HR              | 0.91 (0.78, 1.05)   | 0.89 (0.76, 1.05) | 0.97 (0.80, 1.18) | 0.87 (0.68, 1.11) | 0.97 (0.93, 1.01) |
| Rectal and anal cancer   |                     |         |
| Cases                    | 176                 | 94      |
| Cases                    | 610                 | 361     | 155   | 94    |
| Unadjusted HR            | 0.91 (0.77, 1.08)   | 0.87 (0.70, 1.08) | 1.04 (0.81, 1.33) | 1.01 (0.98, 1.04) | 0.37  |
| Adjusted HR              | 0.88 (0.72, 1.08)   | 0.90 (0.72, 1.11) | 0.81 (0.62, 1.06) | 0.95 (0.70, 1.30) | 1.00 (0.96, 1.04) |
| Liver cancer             |                     |         |
| Cases                    | 48                  | 20      |
| Cases                    | 134                 | 82      | 32    | 20    |
| Unadjusted HR            | 0.72 (0.52, 1.00)   | 0.65 (0.41, 1.01) | 0.81 (0.48, 1.37) | 0.96 (0.89, 1.04) | 0.34  |
| Adjusted HR              | 0.87 (0.58, 1.30)   | 0.88 (0.57, 1.36) | 0.87 (0.51, 1.48) | 0.83 (0.45, 1.55) | 0.97 (0.89, 1.05) |
| Hepatocellular carcinoma |                     |         |
| Cases                    | 26                  | 14      |
| Cases                    | 62                  | 39      | 14    | 9     |
| Unadjusted HR            | 0.61 (0.39, 0.97)   | 0.52 (0.27, 1.00) | 0.68 (0.32, 1.45) | 0.93 (0.82, 1.04) | 0.22  |
| Adjusted HR              | 0.50 (0.29, 0.87)   | 0.55 (0.30, 1.00) | 0.44 (0.20, 0.96) | 0.44 (0.17, 1.12) | 0.87 (0.76, 1.01) |
| Intrahepatic bile duct carcinoma |     |         |
| Cases                    | 16                  | 14      |
| Cases                    | 56                  | 36      | 14    | 6     |
| Unadjusted HR            | 0.90 (0.52, 1.57)   | 0.84 (0.41, 1.73) | 0.72 (0.28, 1.85) | 0.95 (0.84, 1.07) | 0.43  |
| Adjusted HR              | 1.49 (0.71, 3.11)   | 1.47 (0.68, 3.18) | 1.80 (0.74, 4.34) | 1.06 (0.32, 3.48) | 1.00 (0.88, 1.14) |
|                                | Gall bladder and extrahepatic bile duct carcinoma | Pancreatic cancer | All digestive cancer |
|--------------------------------|-----------------------------------------------|-----------------|---------------------|
| Cases                          | 14  81  47  20  14                            | 81  303  171  83  49 | 784  2767  1,581  773  413 |
| Unadjusted HR                  | 1.00  1.48 (0.84, 2.61) 1.43 (0.78, 2.59) 1.37 (0.69, 2.71) 1.93 (0.92, 4.06) 1.05 (0.96, 1.13) | 1.00  0.95 (0.75, 1.22) 0.89 (0.68, 1.16) 0.98 (0.72, 1.33) 1.17 (0.82, 1.67) 1.03 (0.98, 1.07) | 1.00  0.91 (0.84, 0.99) 0.87 (0.80, 0.95) 0.96 (0.87, 1.06) 1.02 (0.91, 1.15) 1.01 (0.99, 1.02) |
| Adjusted HR                    | 1.00  1.63 (0.81, 3.27) 1.52 (0.74, 3.15) 1.56 (0.67, 3.64) 2.40 (0.98, 5.90) 1.06 (0.97, 1.15) | 1.00  0.89 (0.66, 1.20) 0.86 (0.63, 1.18) 0.88 (0.60, 1.28) 1.08 (0.71, 1.65) 1.02 (0.97, 1.06) | 1.00  0.95 (0.86, 1.05) 0.92 (0.83, 1.02) 0.98 (0.87, 1.11) 1.05 (0.90, 1.21) 1.00 (0.98, 1.02) |

Model contains age at baseline, sex, deprivation, education, BMI, alcohol, smoking, fruit and vegetable intake, tea intake, physical activity, comorbidities at baseline (including high cholesterol, hypertension, diabetes, angina, myocardial infarction, stroke, peptic ulcer disease, hepatitis, cirrhosis, and gallstones).
Table 3: The association between coffee type and digestive cancer within UK Biobank

|                      | Most common type of coffee used |       |
|----------------------|---------------------------------|-------|
|                      | Non-use | Decaffeinated | Instant | Ground | Other types | Heterogeneity |
|                      | n       |              |         |         |             | p*             |
| Oesophageal cancer   |         |              |         |         |             |                |
| Cases                | 104,465 | 69,363       | 201,912 | 82,865  | 6,674       |                |
| Unadjusted HR        | 74      | 53           | 166     | 46      | 7           | 0.18           |
|                      | 1.00    | 0.91 (0.64, 1.30) | 1.03 (0.78, 1.36) | 0.76 (0.52, 1.09) | 1.43 (0.66, 3.11) |                |
| Adjusted HR          | 1.00    | 1.27 (0.82, 1.98) | 1.12 (0.78, 1.59) | 1.08 (0.78, 1.59) | 1.58 (0.56, 4.41) | 0.63           |
| Oesophageal squamous cell carcinoma
| Cases                | 15      | 14           | 36      | 8       | <5          |                |
| Unadjusted HR        | 1.00    | 1.21 (0.58, 2.52) | 1.12 (0.61, 2.05) | 0.65 (0.27, 1.54) | 2.04 (0.46, 8.92) | 0.54           |
| Adjusted HR          | 1.00    | 1.33 (0.79, 2.24) | 1.16 (0.52, 2.58) | 1.03 (0.38, 2.83) | 4.17 (0.89, 19.46) | 0.87           |
| Oesophageal adenocarcinoma
| Cases                | 55      | 36           | 122     | 35      | 6           |                |
| Unadjusted HR        | 1.00    | 0.83 (0.54, 1.26) | 1.01 (0.73, 1.39) | 0.77 (0.50, 1.18) | 1.64 (0.71, 3.83) | 0.60           |
| Adjusted HR          | 1.00    | 1.33 (0.79, 2.24) | 1.18 (0.78, 1.80) | 1.17 (0.69, 1.97) | 1.65 (0.50, 5.41) | 0.63           |
| Gastric cancer       |         |              |         |         |             |                |
| Cases                | 65      | 29           | 117     | 31      | <5          |                |
| Unadjusted HR        | 1.00    | 0.57 (0.37, 0.88) | 0.83 (0.61, 1.12) | 0.59 (0.38, 0.90) | 0.93 (0.34, 2.56) | 0.13           |
| Adjusted HR          | 1.00    | 1.70 (0.65, 4.41) | 1.07 (0.46, 2.51) | 1.16 (0.42, 3.15) | 4.39 (0.93, 20.8) | 0.34           |
| Small intestinal cancer
| Cases                | 14      | 11           | 35      | 12      | <5          |                |
| Unadjusted HR        | 1.00    | 1.04 (0.47, 2.30) | 1.18 (0.63, 2.20) | 1.06 (0.49, 2.29) | 2.20 (0.50, 9.70) | 0.82           |
| Adjusted HR          | 1.00    | 1.70 (0.65, 4.41) | 1.07 (0.46, 2.51) | 1.16 (0.42, 3.15) | 4.39 (0.93, 20.8) | 0.34           |
| Colon cancer         |         |              |         |         |             |                |
| Cases                | 320     | 220          | 650     | 223     | 22          |                |
| Unadjusted HR        | 1.00    | 0.90 (0.76, 1.07) | 0.95 (0.83, 1.09) | 0.86 (0.72, 1.02) | 1.05 (0.68, 1.62) | 0.51           |
| Adjusted HR          | 1.00    | 0.95 (0.78, 1.17) | 0.91 (0.77, 1.07) | 0.84 (0.68, 1.04) | 1.21 (0.73, 2.02) | 0.50           |
| Rectal and anal cancer
| Cases                | 176     | 103          | 371     | 119     | 8           |                |
| Unadjusted HR        | 1.00    | 0.77 (0.61, 0.99) | 0.99 (0.83, 1.19) | 0.83 (0.66, 1.05) | 0.69 (0.34, 1.42) | 0.06           |
| Adjusted HR          | 1.00    | 0.83 (0.62, 1.11) | 0.95 (0.76, 1.18) | 0.80 (0.60, 1.05) | 0.56 (0.20, 1.53) | 0.39           |
| Liver cancer         |         |              |         |         |             |                |
| Cases                | 48      | 23           | 80      | 26      | <5          |                |
| Unadjusted HR        | 1.00    | 0.62 (0.37, 1.02) | 0.77 (0.54, 1.11) | 0.67 (0.41, 1.07) | 0.95 (0.29, 3.06) | 0.72           |
| Adjusted HR          | 1.00    | 0.82 (0.45, 1.49) | 0.91 (0.59, 1.41) | 0.84 (0.47, 1.50) | 0.58 (0.07, 4.24) | 0.92           |
| Hepatocellular carcinoma
| Cases                | 26      | 11           | 37      | 11      | <5          |                |
| Unadjusted HR        | 1.00    | 0.54 (0.27, 1.10) | 0.66 (0.40, 1.09) | 0.52 (0.25, 1.05) | 1.17 (0.28, 4.95) | 0.71           |
| Adjusted HR          | 1.00    | 0.59 (0.25, 1.37) | 0.51 (0.28, 0.93) | 0.47 (0.20, 1.08) | Too small       | 0.53           |
| Intrahepatic bile duct carcinoma
| Cases                | 16      | 9            | 33      | 12      | <5          |                |
| Unadjusted HR        | 1.00    | 0.72 (0.32, 1.64) | 0.95 (0.52, 1.73) | 0.92 (0.43, 1.94) | 0.95 (0.12, 7.17) | 0.91           |
| Adjusted HR          | 1.00    | 0.97 (0.38, 2.43) | 1.27 (0.63, 2.55) | 1.46 (0.63, 3.35) | 1.48 (0.19, 11.54) | 0.91          |
| Gall bladder and extrahepatic bile duct carcinoma | Cases | 14 | 25 | 34 | 18 | <5 |
|------------------------------------------------|-------|----|----|----|----|----|
| Unadjusted HR                                  | 1.00  | 2.28 (1.18, 4.39) | 1.11 (0.60, 2.08) | 1.57 (0.78, 3.16) | 2.17 (0.78, 3.16) | 0.06 |
| Adjusted HR                                    | 1.00  | 2.44 (1.10, 5.38) | 1.33 (0.63, 2.82) | 1.84 (0.77, 4.44) | Too small         | 0.11 |

| Pancreatic cancer                              | Cases | 81 | 46 | 178 | 69 | <5 |
|------------------------------------------------|-------|----|----|-----|----|----|
| Unadjusted HR                                  | 1.00  | 0.72 (0.50, 1.03) | 1.00 (0.77, 1.31) | 1.04 (0.75, 1.43) | 0.93 (0.37, 2.30) | 0.17 |
| Adjusted HR                                    | 1.00  | 0.66 (0.43, 1.03) | 0.95 (0.69, 1.29) | 0.99 (0.68, 1.45) | 0.81 (0.25, 2.60) | 0.31 |

| All digestive cancer                           | Cases | 784 | 507 | 1614 | 536 | 53 |
|------------------------------------------------|-------|-----|-----|------|-----|----|
| Unadjusted HR                                  | 1.00  | 0.84 (0.75, 0.94) | 0.96 (0.88, 1.04) | 0.84 (0.75, 0.93) | 1.03 (0.78, 1.36) | 0.007 |
| Adjusted HR                                    | 1.00  | 0.95 (0.83, 1.09) | 0.97 (0.87, 1.07) | 0.89 (0.78, 1.02) | 1.03 (0.72, 1.47) | 0.61 |

Model contains age at baseline, sex, deprivation, education, BMI, alcohol, smoking, fruit and vegetable intake, tea intake, physical activity, comorbidities at baseline (including high cholesterol, hypertension, diabetes, angina, myocardial infarction, stroke, peptic ulcer disease, hepatitis, cirrhosis, and gallstones).

*P value for Likelihood ratio test comparing cancer risk by coffee type (decaffeinated, instant, ground, other coffee)
Supplementary Table 1: Sensitivity analysis by excluding two years after baseline for association between coffee intake by number of cups per day and digestive cancer within UK Biobank

| Coffee intake (cups/day) | HR per cup increase | p trend |
|--------------------------|---------------------|---------|
| 0            | Any                | >0 to 2 | 3 to 4 | ≥5 |
| n            | 103 560            | 361 910 | 213 775 | 96 175 | 51 960 |

**Oesophageal cancer**
- Cases: 58 228 118 59 51
- Adjusted HR: 1.00 1.29 (0.88, 1.89) 1.21 (0.80, 1.81) 1.24 (0.78, 1.98) 1.76 (1.08, 2.87) 1.04 (0.98, 1.10) 0.14

**Oesophageal squamous cell carcinoma**
- Cases: 11 51
- Adjusted HR: 1.00 1.72 (0.70, 4.20) 1.26 (0.48, 3.29) 1.68 (0.57, 4.89) 3.77 (1.36, 10.41) 1.09 (1.02, 1.16) 0.006

**Oesophageal adenocarcinoma**
- Cases: 44 166
- Adjusted HR: 1.00 1.28 (0.82, 2.00) 1.29 (0.81, 2.06) 1.14 (0.65, 1.99) 1.45 (0.80, 2.62) 1.01 (0.94, 1.08) 0.70

**Gastric cancer**
- Cases: 52 147
- Adjusted HR: 1.00 1.04 (0.70, 1.56) 0.91 (0.59, 1.41) 1.23 (0.75, 2.03) 1.33 (0.75, 2.34) 1.04 (0.98, 1.10) 0.11

**Small intestinal cancer**
- Cases: 12 48
- Adjusted HR: 1.00 1.34 (0.54, 3.31) 1.01 (0.38, 2.68) 2.16 (0.78, 5.97) 1.65 (0.48, 5.66) 1.04 (0.91, 1.19) 0.51

**Colon cancer**
- Cases: 271 903
- Adjusted HR: 1.00 0.86 (0.72, 1.02) 0.82 (0.68, 0.98) 0.94 (0.75, 1.16) 0.91 (0.70, 1.18) 0.98 (0.94, 1.02) 0.33

**Rectal and anal cancer**
- Cases: 141 470
- Adjusted HR: 1.00 0.86 (0.68, 1.08) 0.86 (0.68, 1.10) 0.81 (0.60, 1.09) 0.93 (0.66, 1.32) 1.00 (0.96, 1.05) 0.71

**Liver cancer**
- Cases: 41 110
- Adjusted HR: 1.00 0.89 (0.56, 1.40) 0.90 (0.55, 1.48) 0.97 (0.54, 1.74) 0.72 (0.34, 1.50) 0.95 (0.87, 1.05) 0.31

**Hepatocellular carcinoma**
- Cases: 23 54
- Adjusted HR: 1.00 0.52 (0.29, 0.94) 0.56 (0.29, 1.07) 0.48 (0.21, 1.11) 0.44 (0.16, 1.20) 0.88 (0.75, 1.02) 0.09

**Intrahepatic bile duct carcinoma**
- Cases: 13 42
- Adjusted HR: 1.00 1.62 (0.65, 4.01) 1.65 (0.64, 4.26) 2.25 (0.83, 6.50) 0.44 (0.05, 3.72) 0.99 (0.83, 1.15) 0.86

**Gall bladder and extrahepatic bile duct carcinoma**
- Cases: 13 66
- Adjusted HR: 1.00 1.51 (0.72, 3.15) 1.44 (0.66, 3.11) 1.37 (0.55, 3.43) 2.18 (0.82, 5.75) 1.05 (0.96, 1.17) 0.25

**Pancreatic cancer**
- Cases: 69 251
- Adjusted HR: 1.00 0.91 (0.66, 1.25) 0.89 (0.63, 1.24) 0.87 (0.58, 1.30) 1.11 (0.70, 1.75) 1.02 (0.96, 1.08) 0.42
| All digestive cancer | Cases | Adjusted HR  |
|---------------------|-------|-------------|
|                     | 650   | 1.00        |
|                     | 2,206 | 0.95 (0.85, 1.05) |
|                     | 1,244 | 0.90 (0.80, 1.01) |
|                     | 620   | 0.99 (0.87, 1.14) |
|                     | 342   | 1.09 (0.93, 1.27) |
|                     |       | 1.01 (0.99, 1.03) |

Model contains age at baseline, gender, deprivation, education, BMI, alcohol, smoking, fruit and vegetable intake, tea intake, physical activity, comorbidities at baseline (including high cholesterol, hypertension, diabetes, angina, myocardial infarction, stroke, peptic ulcer disease, hepatitis, cirrhosis, and gallstones).
Supplementary Table 2: Sensitivity analysis by excluding two years after baseline for association between coffee type and digestive cancer within UK Biobank

| Most common type of coffee used | n | Non-use | Decaffeinated | Instant | Ground | Other types |
|--------------------------------|---|---------|---------------|---------|--------|-------------|
| Oesophageal cancer             |   | 103 560 | 68 756        | 200 045 | 82 196 | 6606        |
| Cases                          |   | 58      | 42            | 135     | 39     | 6           |
| Adjusted HR                    |   | 1.00    | 1.38 (0.84, 2.27) | 1.27 (0.85, 1.90) | 1.21 (0.73, 1.99) | 1.58 (0.48, 5.16) |
| Oesophageal squamous cell carcinoma | | 11     | 10            | 30      | 8      | <5          |
| Cases                          |   | 1.00    | 1.59 (0.50, 5.08) | 1.52 (0.59, 3.89) | 1.61 (0.52, 4.90) | 6.35 (1.27, 31.75) |
| Oesophageal adenocarcinoma      | | 44     | 31            | 97      | 28     | 5           |
| Cases                          |   | 1.00    | 1.46 (0.82, 2.59) | 1.27 (0.79, 2.03) | 1.15 (0.63, 2.08) | 1.42 (0.33, 6.02) |
| Gastric cancer                 |   | 52      | 20            | 97      | 25     | <5          |
| Cases                          |   | 1.00    | 0.87 (0.48, 1.56) | 1.12 (0.73, 1.72) | 0.92 (0.52, 1.61) | 1.16 (0.28, 4.88) |
| Small intestinal cancer        |   | 12      | 8             | 26      | 9      | <5          |
| Cases                          |   | 1.00    | 1.61 (0.52, 4.92) | 1.03 (0.38, 2.76) | 1.33 (0.43, 4.06) | 6.05 (1.21, 30.24) |
| Colon cancer                   | | 271    | 171           | 518     | 173    | 17          |
| Cases                          |   | 1.00    | 0.88 (0.70, 1.11) | 0.86 (0.71, 1.03) | 0.82 (0.65, 1.03) | 1.01 (0.55, 1.86) |
| Rectal and anal cancer         | | 141    | 78            | 286     | 92     | 6           |
| Cases                          |   | 1.00    | 0.78 (0.56, 1.09) | 0.91 (0.71, 1.17) | 0.81 (0.60, 1.11) | 0.70 (0.26, 1.92) |
| Liver cancer                   | | 41     | 18            | 67      | 21     | <5          |
| Cases                          |   | 1.00    | 0.74 (0.37, 1.49) | 0.93 (0.57, 1.52) | 0.94 (0.50, 1.77) | 0.75 (0.10, 5.56) |
| Hepatocellular carcinoma       | | 23     | 9             | 33      | 10     | <5          |
| Cases                          |   | 1.00    | 0.50 (0.19, 1.31) | 0.51 (0.27, 0.98) | 0.62 (0.26, 1.47) | Too small |
| Intrahepatic bile duct carcinoma | | 13     | 7             | 25      | 8      | <5          |
| Cases                          |   | 1.00    | 1.33 (0.40, 4.47) | 1.71 (0.66, 4.44) | 1.51 (0.46, 4.93) | 3.35 (0.40, 28.02) |
| Gall bladder and extrahepatic bile duct carcinoma | | 13     | 19            | 27      | 17     | <5          |
| Cases                          |   | 1.00    | 1.96 (0.82, 4.67) | 1.22 (0.54, 2.72) | 2.18 (0.88, 5.41) | Too small |
| Pancreatic cancer              | | 69     | 36            | 150     | 58     | <5          |
| Cases                          |   | 1.00    | 0.59 (0.36, 0.96) | 0.97 (0.69, 1.35) | 1.11 (0.74, 1.67) | 0.64 (0.15, 2.62) |
| All digestive cancer           | | 1146  | 6606         | 200 045 | 82 196 | 6606        |
| Cases | Adjusted HR |
|-------|-------------|
| 650   | 1.00        |
| 392   | 0.90 (0.78, 1.05) |
| 1,295 | 0.96 (0.85, 1.08) |
| 429   | 0.94 (0.81, 1.08) |
| 41    | 0.99 (0.66, 1.49) |

Model contains age at baseline, gender, deprivation, education, BMI, alcohol, smoking, fruit and vegetable intake, tea intake, physical activities, comorbidities at baseline (including high cholesterol, hypertension, diabetes, angina, myocardial infarction, stroke, peptic ulcer disease, hepatitis, cirrhosis, and gallstones).
Supplementary Table 3: The association between any coffee intake and risk of digestive cancer adjusting for additional smoking variable.

|                        | Coffee intake |
|------------------------|---------------|
|                        | No            | Yes           |
|                        | 104,465       | 365,157       |
| Oesophageal cancer     |               |               |
| Cases                  | 74            | 279           |
| Unadjusted HR          | 1.00          | 0.97 (0.75, 1.25) |
| Adjusted HR            | 1.00          | 1.27 (0.87, 1.86) |
| Oesophageal squamous cell carcinoma |        |               |
| Cases                  | 15            | 61            |
| Unadjusted HR          | 1.00          | 1.05 (0.60, 1.86) |
| Adjusted HR            | 1.00          | 1.12 (0.49, 2.54) |
| Oesophageal adenocarcinoma |           |               |
| Cases                  | 55            | 204           |
| Unadjusted HR          | 1.00          | 0.94 (0.70, 1.27) |
| Adjusted HR            | 1.00          | 1.49 (0.94, 2.36) |
| Gastric cancer         |               |               |
| Cases                  | 65            | 184           |
| Unadjusted HR          | 1.00          | 0.72 (0.55, 0.96) |
| Adjusted HR            | 1.00          | 0.93 (0.64, 1.35) |
| Small intestinal cancer|               |               |
| Cases                  | 14            | 63            |
| Unadjusted HR          | 1.00          | 1.18 (0.66, 2.11) |
| Adjusted HR            | 1.00          | 1.85 (0.70, 4.88) |
| Colon cancer           |               |               |
| Cases                  | 320           | 1,141         |
| Unadjusted HR          | 1.00          | 0.93 (0.82, 1.05) |
| Adjusted HR            | 1.00          | 0.91 (0.77, 1.07) |
| Rectal and anal cancer |               |               |
| Cases                  | 176           | 610           |
| Unadjusted HR          | 1.00          | 0.91 (0.77, 1.08) |
| Adjusted HR            | 1.00          | 0.85 (0.68, 1.05) |
| Liver cancer           |               |               |
| Cases                  | 48            | 134           |
| Unadjusted HR          | 1.00          | 0.72 (0.52, 1.00) |
| Adjusted HR            | 1.00          | 0.79 (0.50, 1.23) |
| Hepatocellular carcinoma |           |               |
| Cases                  | 26            | 62            |
| Unadjusted HR          | 1.00          | 0.61 (0.39, 0.97) |
| Adjusted HR            | 1.00          | 0.49 (0.27, 0.90) |
| Intrahepatic bile duct carcinoma |         |               |
| Cases                  | 16            | 56            |
| Unadjusted HR          | 1.00          | 0.90 (0.52, 1.57) |
| Adjusted HR            | 1.00          | 1.26 (0.56, 2.78) |
| Cancer Type                        | Cases | HR Unadjusted | 95% CI Unadjusted | HR Adjusted | 95% CI Adjusted |
|-----------------------------------|-------|---------------|-------------------|-------------|-----------------|
| Gall bladder and extrahepatic bile duct carcinoma | 14    | 1.00          | 1.48 (0.84, 2.61) | 11.49       | 0.74 (3.00)     |
| Pancreatic cancer                 | 81    | 1.00          | 0.95 (0.75, 1.22) | 0.86        | 0.63 (1.18)     |
| All digestive cancer              | 784   | 1.00          | 0.91 (0.84, 0.99) | 0.94        | 0.63 (1.18)     |

Model contains age at baseline, sex, deprivation, education, BMI, alcohol, smoking (never, ex stop>=20yrs, >=10-20yrs, ex stop<10yrs, current <=10 cigarettes per day, 10-20per day, >20per day), fruit and vegetable intake, tea intake, physical activity, comorbidities at baseline (including high cholesterol, hypertension, diabetes, angina, myocardial infarction, stroke, peptic ulcer disease, hepatitis, cirrhosis, and gallstones).
Supplementary Table 4: The association between coffee intake and hepatocellular carcinoma by sex, BMI, alcohol, and smoking status

|                          | Unadjusted HR (95% CI) | Adjusted HR (95% CI) | P for interaction |
|--------------------------|------------------------|----------------------|------------------|
| **Main analysis**        |                        |                      |                  |
|                          | 88                     | 64                   |                  |
|                          | 0.61 (0.39, 0.97)      | 0.50 (0.29, 0.87)    |                  |
| **Sex**                  |                        |                      |                  |
| Male                     | 71                     | 53                   | 0.21             |
|                          | 0.54 (0.32, 0.89)      | 0.48 (0.26, 0.86)    |                  |
| Female                   | 17                     | 11                   |                  |
|                          | 0.91 (0.29, 2.80)      | 1.10 (0.21, 5.55)    |                  |
| **BMI**                  |                        |                      |                  |
| Normal/under weight      | 15                     | 9                    |                  |
|                          | 0.30 (0.10, 0.82)      | 0.12 (0.02, 0.57)    |                  |
| Overweight               | 36                     | 28                   | 0.056            |
|                          | 0.49 (0.24, 0.99)      | 0.46 (0.20, 1.04)    |                  |
| Obese                    | 37                     | 27                   |                  |
|                          | 1.2 (0.52, 2.73)       | 0.86 (0.30, 2.41)    |                  |
| **Alcohol consumption**  |                        |                      |                  |
| Never                    | 17                     | 12                   |                  |
|                          | 1.20 (0.44, 3.27)      | 0.24 (0.06, 0.95)    |                  |
| < 1 day per week         | 20                     | 13                   |                  |
|                          | 0.96 (0.34, 2.65)      | 0.73 (0.20, 2.62)    |                  |
| 1-2 days per week        | 14                     | 11                   | 0.76             |
|                          | 0.65 (0.20, 2.09)      | 0.44 (0.11, 1.77)    |                  |
| 3-4 days per week        | 17                     | 12                   |                  |
|                          | 0.82 (0.23, 2.87)      | 0.88 (0.16, 4.59)    |                  |
| >4 days per week         | 20                     | 16                   |                  |
|                          | 0.25 (0.10, 0.62)      | 0.49 (0.15, 1.60)    |                  |
| **Smoking status**       |                        |                      |                  |
| Never                    | 30                     | 19                   |                  |
|                          | 0.56 (0.26, 1.19)      | 0.66 (0.24, 1.81)    |                  |
| Previous                 | 40                     | 31                   |                  |
|                          | 0.54 (0.27, 1.08)      | 0.44 (0.20, 0.99)    | 0.83             |
| Current                  | 18                     | 14                   |                  |
|                          | 0.85 (0.28, 2.59)      | 0.40 (0.11, 1.48)    |                  |

Model contains age at baseline, gender, deprivation, education, BMI, alcohol, smoking, fruit and vegetable intake, tea intake, physical activities, comorbidities at baseline (including high cholesterol, hypertension, diabetes, angina, myocardial infarction, stroke, peptic ulcer disease, hepatitis, cirrhosis, and gallstones).
Supplementary Figure 1: The dose response pattern of coffee consumption and digestive cancer

| Digestive cancer sites | Adjusted HR, 95% CI | Adjusted HR, 95% CI |
|------------------------|---------------------|---------------------|
| Oesophageal cancer      |                     |                     |
| 0                      | Ref                 |                     |
| Any                    | 1.15 [0.83, 1.59]   |                     |
| >0 to 2                | 1.11 [0.77, 1.60]   |                     |
| 3 to 4                 | 1.08 [0.71, 1.64]   |                     |
| ≥ 5                    | 1.47 [0.94, 2.30]   |                     |
| Gastric cancer         |                     |                     |
| 0                      | Ref                 |                     |
| Any                    | 0.98 [0.68, 1.41]   |                     |
| >0 to 2                | 0.88 [0.59, 1.31]   |                     |
| 3 to 4                 | 1.14 [0.73, 1.78]   |                     |
| ≥ 5                    | 1.18 [0.70, 1.99]   |                     |
| Small intestinal cancer|                     |                     |
| 0                      | Ref                 |                     |
| Any                    | 1.39 [0.60, 3.22]   |                     |
| >0 to 2                | 1.12 [0.49, 2.56]   |                     |
| 3 to 4                 | 1.67 [0.67, 4.16]   |                     |
| ≥ 5                    | 1.65 [0.56, 4.86]   |                     |
| Colon cancer           |                     |                     |
| 0                      | Ref                 |                     |
| Any                    | 0.91 [0.78, 1.06]   |                     |
| >0 to 2                | 0.89 [0.76, 1.04]   |                     |
| 3 to 4                 | 0.97 [0.80, 1.18]   |                     |
| ≥ 5                    | 0.87 [0.68, 1.11]   |                     |
| Rectal and anal cancer |                     |                     |
| 0                      | Ref                 |                     |
| Any                    | 0.88 [0.72, 1.08]   |                     |
| >0 to 2                | 0.90 [0.72, 1.13]   |                     |
| 3 to 4                 | 0.81 [0.62, 1.06]   |                     |
| ≥ 5                    | 0.95 [0.70, 1.29]   |                     |
| Liver cancer           |                     |                     |
| 0                      | Ref                 |                     |
| Any                    | 0.87 [0.58, 1.31]   |                     |
| >0 to 2                | 0.88 [0.57, 1.36]   |                     |
| 3 to 4                 | 0.87 [0.51, 1.48]   |                     |
| ≥ 5                    | 0.83 [0.45, 1.53]   |                     |
| Hepatocellular carcinoma|                   |                     |
| 0                      | Ref                 |                     |
| Any                    | 0.50 [0.29, 0.86]   |                     |
| >0 to 2                | 0.55 [0.30, 1.01]   |                     |
| 3 to 4                 | 0.44 [0.20, 0.97]   |                     |
| ≥ 5                    | 0.44 [0.17, 1.14]   |                     |
| Intrahepatic bile duct carcinoma| | | |
| 0                      | Ref                 |                     |
| Any                    | 1.49 [0.71, 3.13]   |                     |
| >0 to 2                | 1.47 [0.68, 3.18]   |                     |
| 3 to 4                 | 1.80 [0.74, 4.38]   |                     |
| ≥ 5                    | 1.06 [0.32, 3.51]   |                     |
| Gall bladder and extra hepatic bile duct carcinoma| | | |
| 0                      | Ref                 |                     |
| Any                    | 1.63 [0.81, 3.28]   |                     |
| >0 to 2                | 1.52 [0.74, 3.12]   |                     |
| 3 to 4                 | 1.56 [0.67, 3.63]   |                     |
| ≥ 5                    | 2.40 [0.98, 5.88]   |                     |
| Pancreatic cancer      |                     |                     |
| 0                      | Ref                 |                     |
| Any                    | 0.89 [0.66, 1.20]   |                     |
| >0 to 2                | 0.86 [0.63, 1.17]   |                     |
| 3 to 4                 | 0.88 [0.60, 1.29]   |                     |
| ≥ 5                    | 1.08 [0.71, 1.64]   |                     |
| All digestive cancer   |                     |                     |
| 0                      | Ref                 |                     |
| Any                    | 0.95 [0.86, 1.05]   |                     |
| >0 to 2                | 0.92 [0.83, 1.02]   |                     |
| 3 to 4                 | 0.98 [0.87, 1.10]   |                     |
| ≥ 5                    | 1.05 [0.90, 1.22]   |                     |
Supplementary Figure 2: Coffee consumption by type and risk of digestive cancer

| Digestive cancer sites                           | Adjusted HR, 95% CI      | Adjusted HR, 95% CI      |
|--------------------------------------------------|--------------------------|--------------------------|
| Decaffeinated vs. None                           |                          |                          |
| Oesophageal cancer                               | 1.27 [0.82, 1.97]        |                          |
| Gastric cancer                                   | 0.88 [0.52, 1.49]        |                          |
| Small intestinal cancer                          | 1.70 [0.65, 4.45]        |                          |
| Colon cancer                                     | 0.95 [0.78, 1.16]        |                          |
| Rectal and anal cancer                           | 0.83 [0.62, 1.11]        |                          |
| Liver cancer                                     | 0.82 [0.45, 1.49]        |                          |
| Hepatocellular carcinoma                        | 0.59 [0.25, 1.39]        |                          |
| Intrahepatic bile duct carcinoma                 | 0.97 [0.38, 2.48]        |                          |
| Gall bladder and extra hepatic bile duct carcinoma| 2.44 [1.10, 5.41]        |                          |
| Pancreatic cancer                                | 0.66 [0.43, 1.01]        |                          |
| Instant vs. None                                 |                          |                          |
| Oesophageal cancer                               | 1.12 [0.78, 1.61]        |                          |
| Gastric cancer                                   | 1.04 [0.70, 1.55]        |                          |
| Small intestinal cancer                          | 1.07 [0.46, 2.49]        |                          |
| Colon cancer                                     | 0.91 [0.77, 1.08]        |                          |
| Rectal and anal cancer                           | 0.95 [0.76, 1.19]        |                          |
| Liver cancer                                     | 0.91 [0.59, 1.40]        |                          |
| Hepatocellular carcinoma                        | 0.51 [0.28, 0.93]        |                          |
| Intrahepatic bile duct carcinoma                 | 1.27 [0.63, 2.56]        |                          |
| Gall bladder and extra hepatic bile duct carcinoma| 1.33 [0.63, 2.81]        |                          |
| Pancreatic cancer                                | 0.95 [0.69, 1.31]        |                          |
| Ground vs. None                                  |                          |                          |
| Oesophageal cancer                               | 1.08 [0.78, 1.50]        |                          |
| Gastric cancer                                   | 0.87 [0.52, 1.46]        |                          |
| Small intestinal cancer                          | 1.16 [0.42, 3.20]        |                          |
| Colon cancer                                     | 0.84 [0.68, 1.04]        |                          |
| Rectal and anal cancer                           | 0.80 [0.60, 1.07]        |                          |
| Liver cancer                                     | 0.84 [0.47, 1.50]        |                          |
| Hepatocellular carcinoma                        | 0.47 [0.20, 1.10]        |                          |
| Intrahepatic bile duct carcinoma                 | 1.46 [0.63, 3.38]        |                          |
| Gall bladder and extra hepatic bile duct carcinoma| 1.84 [0.77, 4.40]        |                          |
| Pancreatic cancer                                | 0.99 [0.68, 1.44]        |                          |

0.2 0.5 1 2 5 10
Decreased risk Increased risk
Additional information

Ethics approval and consent to participate: The UK Biobank has ethical approval from the North West Multi-Centre Research Ethics Committee. All participants provided written informed consent.

Availability of data and materials: The UK Biobank resource is available to all bona fide researchers for all types of health-related research which is in the public interest.

Conflict of interest statement: All authors have no conflict of interest to declare.

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