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Coffee consumption is associated with a reduced risk of colorectal cancer recurrence and all-cause mortality

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Abstract

Coffee consumption has been associated with a reduced risk of developing colorectal cancer (CRC). However, it is not clear whether coffee consumption is related to CRC progression. Hence, we assessed the association of coffee consumption with CRC recurrence and all-cause mortality using data from a prospective cohort study of 1719 stage I–III CRC patients in the Netherlands. Coffee consumption and other lifestyle characteristics were self-reported using questionnaires at the time of diagnosis. We retrieved recurrence and all-cause mortality data from the Netherlands Cancer Registry and the Personal Records Database, respectively. Cox proportional hazard regression models with and without restricted cubic splines were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) adjusted for age, sex, education, smoking status, cancer stage and tumor location. We observed 257 recurrences during a 6.2-year median follow-up and 309 deaths during a 6.6-year median follow-up. Consuming more than 4 cups/d of coffee compared to an intake of <2 cups/d was associated with a 32% lower risk of CRC recurrence (95% CI: 0.49, 0.94,). The association between coffee consumption and all-cause mortality was U-shaped; coffee intake seemed optimal at 3–5 cups/d with the lowest risk at 4 cups/d (HR: 0.68, 95% CI: 0.53, 0.88). Our results suggest that coffee consumption may be associated with a lower risk of CRC recurrence and all-cause mortality. The association

between coffee consumption and all-cause mortality appeared nonlinear. More studies are needed to understand the mechanism by which coffee consumption might improve CRC prognosis.

KEYWORDS
all-cause mortality, coffee consumption, colorectal cancer, recurrence

What's new?

Although existing evidence suggests that coffee consumption may lower colorectal cancer risk, the association with colorectal cancer prognosis remains unclear. This large prospective study of stage I–III patients in a country with a relatively high coffee intake revealed a strong inverse association between coffee consumption and colorectal cancer recurrence. The association between coffee consumption and all-cause mortality in colorectal cancer patients was nonlinear, suggesting an optimal intake of three to five cups per day. The findings could potentially inform future intervention studies as well as dietary guidelines for colorectal cancer patients.

1 | INTRODUCTION

Coffee consumption may help to prevent the development of colorectal cancer (CRC)[1,2] or improve prognosis after CRC diagnosis.[3–6] Two umbrella reviews[7,8] reported that consuming more than 1 cup of coffee daily may lower the risk of CRC by 11%–17% compared with non-coffee drinkers while a meta-analysis found no association.[9] Likewise, a prospective study among patients with stage III CRC found that consuming more than 4 cups/d of coffee was associated with improved disease-free survival (HR: 0.58, 95% CI: 0.34, 0.99) compared with non-coffee drinkers.[3] Additionally, four observational studies observed an 11%–54% reduced risk of mortality with consuming more than 4 cups/d of coffee compared to non-drinkers in patients with stage I–III[4,5,10] or advanced CRC.[6] Daily coffee consumption was associated with an increased 5-year survival rate compared to non-coffee drinkers with stages I–IV CRC.[11] Nevertheless, only one observational study has examined the association between coffee consumption and CRC recurrence in which CRC recurrence was defined as the occurrence of both tumor recurrence and new primary tumors in stage III CRC patients.[3] Moreover, four out of the six previous studies on coffee consumption and CRC prognosis were conducted among Americans,[3,4,6,10] with the other two studies among Chinese[5,11] and none among Europeans. Therefore, these findings[3–6,10,11] may not be generalizable to other populations due to potential differences in metabolism,[12–14] coffee preparation and serving techniques.[15,16]

Plausible underlying mechanisms by which coffee consumption may influence colorectal carcinogenesis involve various chemopreventive properties of the heterogeneous components of coffee.[17,18] These chemopreventive properties include anti-inflammatory, antioxidant, antiproliferative, pro-apoptotic and insulin-sensitizing properties.[19] Additionally, the gut microbiome acts on coffee components during digestion to produce additional bioactive metabolites with chemopreventive properties.[16,20]

Since the survival rate of CRC is increasing[21,22] and approximately 20%–30% of CRC patients are expected to experience a cancer recurrence,[23,24] more studies are needed to inform dietary guidelines for CRC patients. In light of the plausible biological mechanism and promising results for mortality, we assessed the association of coffee consumption with CRC recurrence and all-cause mortality in a large CRC patient cohort in the Netherlands, a country in Western Europe with a relatively high coffee intake.[25]

2 | METHODS

2.1 | Study design and population

We used data from a prospective cohort of CRC patients, the 'COlorectal cancer: Longitudinal, Observational study on Nutritional and lifestyle factors that influence colorectal tumor recurrence, survival and quality of life' (COLON) study. A detailed description of the COLON study has been provided elsewhere.[26] Briefly, 2113 CRC patients were recruited at diagnosis in 11 hospitals in the Netherlands between August 2010 and February 2020 and followed up during and after treatment. Men and women of all ages were eligible for the study. Patients were excluded if they did not speak Dutch, had a history of CRC or (partial) bowel resection, chronic inflammatory bowel disease, hereditary CRC syndromes (e.g., Lynch syndrome and Familial Adenomatous Polyposis), dementia or another mental condition that made it impossible to fill out a questionnaire correctly.

For this current analysis, we further excluded participants with incomplete information on coffee consumption (N = 189; Figure 1) or stage IV CRC (N = 205). Stage IV CRC patients were excluded for two reasons: (1) one could argue that stage IV CRC patients cannot experience recurrence but rather develop a progressive disease as the cancer was never cured and (2) the study research nurse could have selectively recruited stage IV CRC patients with relatively good prognosis and they might therefore not be representative of stage IV CRC patients in the Netherlands. In addition to these exclusion criteria, we excluded participants who had no surgery (N = 8) or had progressive disease

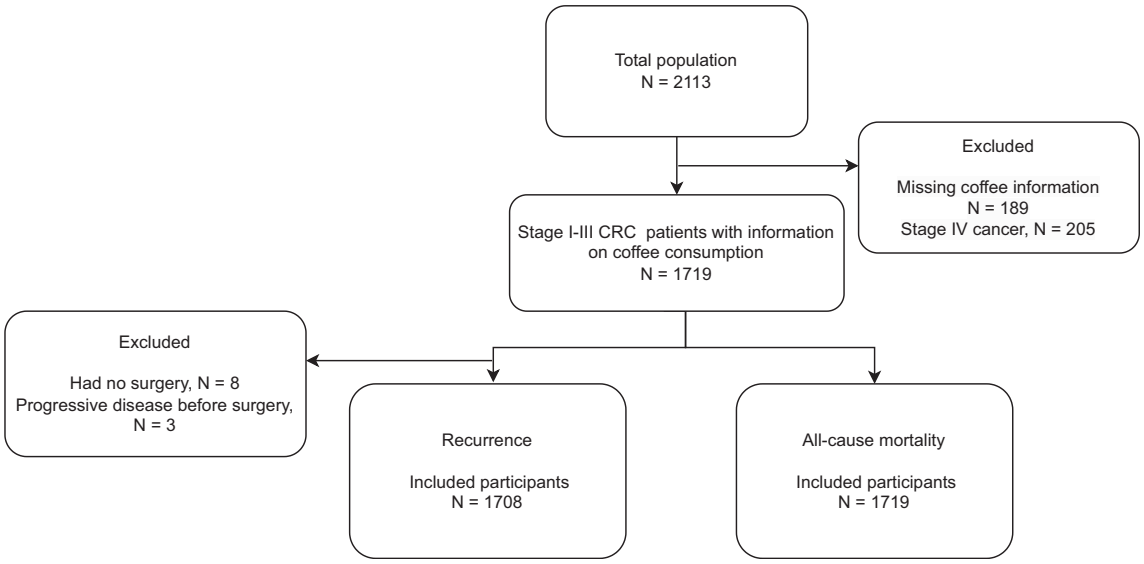

FIGURE 1 Flowchart showing the included participants in these analyses of the COLON study.

before surgery (N = 3) for the analysis of CRC recurrence. Consequently, we had a sample size of 1708 participants and 1719 participants for the analysis of CRC recurrence and all-cause mortality, respectively.

2.2 | Assessment of coffee consumption

Coffee consumption was assessed at diagnosis, during, and after treatment with a 204-item semi-quantitative food frequency questionnaire (FFQ) developed by Wageningen University.[27–29] We used data on coffee consumption at diagnosis for these analyses. The FFQ includes questions on the frequency, amount (1–12 cups), and cup size (cup or mug) of coffee consumption in the past month. For frequency, participants could select one option from the following seven responses: none this month, 1 day/month, 2–3 days/month, 1 day/week, 2–3 days/week, 4–5 days/week and 6–7 days/week. The frequency of consumption was converted into frequency per day as follows: 0, 0.036, 0.089, 0.143, 0.357, 0.643 and 0.929, respectively. Coffee consumption in cups/d was then calculated by multiplying the frequency of consumption per day by the number of cups that were consumed. We further accounted for the differences in the sizes of cups by multiplying coffee in cups/d by 1 (for cup) or 1.5 (for mug). No distinction was made between caffeinated and decaffeinated coffee. However, decaffeinated coffee is rarely consumed in the Netherlands.[30]

2.3 | Assessment of CRC recurrence and all-cause mortality

Data on CRC recurrence were obtained from the Netherlands Cancer Registry via the Netherlands Comprehensive Cancer Organization (in Dutch: Integraal kankercentrum Nederland, IKNL) in January/February 2022. CRC recurrence was defined as locoregional recurrence—recurrence in the same segment as the primary tumor, in the lymph nodes of the same segment or in the draining lymph nodes—or distant metastasis. Follow-up time was calculated from the date of surgery to the date of CRC recurrence. If the date of surgery was unavailable (N = 5), the date of filling out the FFQ was used. The follow-up time was censored at the date that CRC recurrence data was last updated, the date of death or migration out of the study area, whichever occurred first.

Information on vital status and date of mortality was obtained from the Personal Records Database (in Dutch: BasisRegistratie Persoonsgegevens, BRP) in May 2022. All-cause mortality was defined as death from any condition. The follow-up time was calculated from the date of surgery to the date of mortality. If the date of the surgery was unavailable (N = 14), the date of filling out the FFQ was used. The follow-up time was censored at the date that mortality data was last updated or the date of migration out of the study area.

2.4 | Assessment of covariates

Information on sociodemographic and lifestyle characteristics such as height, weight, education and smoking habits was collected with self-reported questionnaires simultaneously with coffee consumption. Body mass index (BMI; kg/m^2) was derived by dividing body weight (in kilograms) by the square of height (in meters). Education was classified into low, medium and higher education. Low education was defined as primary school and lower general secondary education, medium as lower vocational training and higher general secondary education, and high as high vocational training and university. Smoking status was defined as current, former and never smoker. Cigarette pack/d was calculated as the number of cigarettes smoked daily divided by 20. Pack year was then calculated as cigarette pack/d

multiplied by smoking duration in years. Physical activity was measured with the validated Short Questionnaire to ASsess Health-enhancing physical activity (SQUASH).[31] Activities with a Metabolic Equivalent score ≥3 were defined as moderate-to-vigorous physical activity.[32] Sugar-sweetened beverage (SSB) was defined as any breakfast drink, chocolate milk, orange juice, other fruit juices, plain soda, flavored milk and yogurt drink. Data on disease stage and tumor location were obtained through linkage with the Dutch ColoRectal Audit (DCRA).[33]

2.5 | Data analysis

The frequency of coffee consumption was divided into three categories—<2 cups/d, 2–4 cups/d and >4 cups/d—to ensure that there were sufficient participants in each group. The first category (<2 cups/d) also included 79 participants that were non-coffee drinkers. The participants' characteristics were summarized with medians, quartiles 1 and 3, or frequencies and percentages in the total population and across the categories of coffee intake.

Cox proportional hazards regression models were used to calculate hazard ratios (HR) and confidence intervals (CI) for the association of coffee consumption with CRC recurrence and all-cause mortality. A reference of <2 cups/d of coffee was selected for the categorical analysis in all our models. Coffee consumption was also assessed continuously in cups/d to minimize loss of information due to categorization.[34] We used Schoenfeld residuals to check for the proportionality assumption. As the proportional hazards assumption did not hold for cancer stage, cancer stage was included as a stratifying variable in all models.

We visualized the relationships between the potential confounders from the literature and the exposure and outcome variables with causal diagrams[35] in the Dagitty software.[36] The minimal set of confounders that were selected with the causal diagrams included age, sex, socioeconomic status, cancer stage and tumor location. However, the socioeconomic status of participants was not assessed and the available proxy variable was education. Adjusting for education in our models might not be sufficient to remove the total confounding effect of socioeconomic status. Therefore, we considered including other variables such as physical activity, BMI, alcohol consumption, SSB and energy intake in our model but these did not change the effect estimates. We did include the smoking status of participants in our multivariable models. Additionally, we attempted to adjust for the pack years of smoking of participants to prevent residual confounding by smoking. We chose not to include pack years in our models because adjusting for pack years did not change the effect estimates and 100 participants had missing information on pack years. Consequently, to preserve the power and parsimony of our models, the following variables were included in the multivariable model: age, sex, education, smoking status, cancer stage and tumor location. Current smokers were excluded in a sensitivity analysis to assess potential residual confounding by smoking status. **Participants who experienced CRC recurrence or died within 100 days after surgery were excluded to assess potential reverse causality in a sensitivity analysis.**

Restricted cubic splines (RCS) were used to explore the potential nonlinear relationship between coffee consumption, cancer recurrence and all-cause mortality. In the RCS analysis, we used a reference value of 1.86 cups/d—the median intake in the category of <2 cups/d of coffee. The appropriate number of knots was selected by using the Akaike information criterion while taking the sample size into account. The knots were placed at different percentiles of coffee intake for the analyses of recurrence (5th, 50th and 90th) and all-cause mortality (5th, 35th, 65th and 95th) according to the recommendation by Harrell.[37] Wald chi-square was used to test the nonlinearity of the associations.[38]

p values below .05 were considered statistically significant. All analyses were conducted in R version 4.1.0.

3 | RESULTS

3.1 | Characteristics of the study population

During a median follow-up of 6.2 years for CRC recurrence, 257 CRC recurrences occurred in 1708 participants. In 1719 participants with a median follow-up of 6.6 years for all-cause mortality, 309 participants died. Table 1 shows the distribution of the study population's characteristics in the total population and across the categories of coffee consumption. In the total population, the median (Interquartile range [IQR]) age of the participants at diagnosis was 66 [61–72 years], the majority were men (63%) and were diagnosed with stage III CRC (44%).

Participants who consumed >4 cups/d compared to those who consumed <2cups/d were more likely to be men (69% vs 54%), current smokers (15% vs 6%) with more pack years (10.1 pack years vs 3.2 pack years), were more physically active (720.0 min/wk vs 615.0 min/wk), and had higher intakes of energy (1978.7 Kcal/d vs 1670.8 Kcal/d) and alcohol (9.5 vs 3.7 g/d). On the contrary, participants who consumed >4 cups/d compared to those who consumed <2 cups/d were less likely to consume SSB (62.0 vs 72.1 g/d) and less likely to have their initial tumor in the proximal colon (25% vs 38%) (Table 1). No differences were observed for BMI, education and tea consumption across the categories of coffee consumption.

3.2 | Association between coffee consumption and CRC recurrence

In the multivariable-adjusted model, consuming >4 cups/d of coffee compared to an intake of <2 cups/d was associated with a 32% lower risk of CRC recurrence (HR: 0.68, 95% CI: 0.49, 0.94; Table 2). The test for nonlinearity was not statistically

TABLE 1 Characteristics of the study population in median (quartile 1 to quartile 3) or number (percentage).

		Frequency of coffee consumption		
	Total population	<2 cups/d	2–4 cups/d	>4 cups/d
Characteristic	(N = 1719)	(N = 508)	(N = 669)	(N = 542)
Age at diagnosis, years	66 (61–72)	67 (62–73)	67 (63–73)	64 (59–69)
Male, (%)	1085 (63)	275 (54)	436 (65)	374 (69)
Education,[a] (%)				
Low	418 (24)	127 (25)	161 (24)	130 (24)
Medium	739 (43)	223 (44)	293 (44)	223 (41)
High	558 (33)	157 (31)	213 (32)	188 (35)
Smoking status,[b] (%)				
Current	176 (10)	30 (6)	63 (9)	83 (15)
Former	1006 (59)	284 (56)	405 (61)	317 (59)
Never	533 (31)	193 (38)	199 (30)	141 (26)
Pack years[c]	7.0(0.0–21.0)	3.2(0.0–14.8)	7.8(0.0–21.0)	10.1(0.0–26.0)
BMI, kg/m^2	26.2 (24.0–28.7)	26.0 (23.9–28.7)	26.2 (23.9–28.9)	26.4 (24.2–29.0)
Physical activity,[d] min/wk	675.0 (333.8–1170.0)	615.0 (285.5–1137.5)	720.0 (360.0–1170.0)	720.0 (360.0–1200.0)
Energy intake,[e] Kcal/d	1810.9 (1505.5–2174.5)	1670.8 (1361.0–1953.7)	1811.5 (1543.3–2157.3)	1978.7 (1651.2–2341.0)
Alcohol intake,[e] g/d	8.1 (1.0–20.5)	3.7 (0.1–17.1)	9.2 (1.5–20.9)	9.5 (2.1–22.0)
Sugar-sweetened beverage,[e] (g/d)	64.8(13.2–158.7)	72.1(13.4–160.7)	64.0(10.7–167.1)	62(13.4–144.5)
Tea,[e] (cups/d)	2 (1–3)	2(1–4)	2(1–3)	2(1–2)
Tumor location,[f] (%)				
Proximal	530 (31)	191 (38)	205 (31)	134 (25)
Distal	641 (37)	182 (36)	248 (37)	211 (39)
Rectum	546 (32)	135 (27)	215 (32)	196 (36)
Stage (%)				
I	465 (27)	124 (24)	194 (29)	147 (27)
II	469 (27)	153 (30)	186 (28)	130 (24)
III	760 (44)	226 (44)	277 (41)	257 (47)
Unspecified[g]	25 (1)	5 (1)	12 (2)	8 (1)

Abbreviation: BMI, body mass index.

[a]Low education was defined as primary school and lower general secondary education; medium as lower vocational training and higher general secondary education; high as high vocational training and university. The data of four participants were missing.

[b]The data of four participants were missing.

[c]The data of 100 participants were missing.

[d]Physical activity is defined as moderate-to-vigorous intensity activity (a Metabolic Equivalent score ≥3). The data of seven participants were missing.

[e]The data of five participants were missing.

[f]Proximal colon includes the caecum, appendix, ascending colon, hepatic flexure and transverse colon. The distal colon includes the splenic flexure, descending and sigmoid colon. Rectum includes the rectosigmoid junction and rectum. The tumor location of two participants was unknown/missing.

[g]The stage of cancer was derived from the TNM scoring system, participants with unknown stages in this study are those who do not have metastasis (M = 0), so they were diagnosed at either stage I, II, or III but their T and N scores were missing.

significant (*p* value for nonlinearity: 0.56; Figure 2A), which supports a linear association between coffee consumption and CRC recurrence.

In the sensitivity analysis in which current smokers were excluded, the association between coffee consumption and CRC recurrence was not materially changed (Table S1). Excluding participants who experienced CRC recurrence within 100 days after surgery did not materially change the association between coffee consumption and CRC recurrence (Table S2).

3.3 | Association between coffee consumption and all-cause mortality

In the multivariable-adjusted model, consuming >4 cups/d of coffee compared with an intake of <2 cups/d was associated with a 29% lower risk of all-cause mortality (HR: 0.71, 95% CI: 0.53, 0.94; Table 2). The association was more pronounced with the intake of 2–4 cups/d of coffee (HR: 0.62, 95%CI: 0.48, 0.81). This was supported by the result from the RCS analysis that suggested a U-shaped

TABLE 2 Association of coffee consumption with CRC recurrence & all-cause mortality.

Recurrence					All-cause mortality			
Frequency of consumption					Frequency of consumption			
Variable	1 cup/d (increment)	<2 cups/d	2–4 cups/d	>4 cups/d	1 cup/d (increment)	<2 cups/d	2–4 cups/d	>4 cups/d
No. of events/no. of participants	257/1708	90/501	94/667	73/540	309/1719	117/508	106/669	86/542
Person-years	9946.79	2814.21	3986.52	3146.06	11043.84	3201.03	4398.66	3444.15
Age & sex-adjusted HR (95%CI)	0.93 (0.87, 0.99)	1.00 (ref.)	0.73 (0.55, 0.98)	0.69 (0.50, 0.94)	0.96 (0.91, 1.03)	1.00 (ref.)	0.63 (0.49, 0.83)	0.74 (0.56, 0.99)
No. of events/no. of participants	255/1702	89/499	93/664	73/539	307/1713	116/506	105/666	307/1713
Person-years	9919.40	2810.90	3968.20	3140.30	11013.50	3195.60	4379.70	3438.20
Multivariable adjusted HR (95%CI)[a]	0.93 (0.87, 0.99)	1.00 (ref.)	0.74 (0.55, 0.99)	0.68 (0.49, 0.94)	0.95 (0.89, 1.02)	1.00 (ref.)	0.62 (0.48, 0.81)	0.71 (0.53, 0.94)

[a]Adjusted for age, sex, education, smoking status, cancer stage and tumor location.

association between coffee consumption and all-cause mortality (P-value for nonlinearity <0.001; Figure 2B). Coffee consumption seemed optimal at 3–5 cups/d and with the lowest risk at 4 cups/d (HR: 0.68, 95% CI: 0.53, 0.88). We observed a similar U-shaped association in the 533 never smokers in our study (Figure S1).

In the sensitivity analysis in which current smokers were excluded, the association between coffee consumption and all-cause mortality was not materially changed (Table S1). Excluding participants who died within 100 days after surgery did not materially change the association between coffee consumption and all-cause mortality (Table S2).

4 | DISCUSSION

In this prospective study using data from 1719 patients with stage I–III CRC, coffee consumption was associated with a lower risk of CRC recurrence and of all-cause mortality. The observed association between coffee consumption and all-cause mortality was nonlinear and U-shaped.

We observed an inverse association between coffee consumption and CRC recurrence, which is in the same direction as the findings of the only study that previously investigated coffee consumption and cancer recurrence.[3] However, the association between coffee consumption and cancer recurrence in the previous study was non-significant (consuming ≥4 cups/d vs none HR: 0.71, 95% CI: 0.41, 1.23). In the previous study, the precision of the observed association as measured by the CI may be attenuated by a large number of categories of coffee consumption (n = 5) relative to the number of events (n = 329) and the sample size (n = 953).[3] Moreover, the inverse association observed in the previous study became stronger and statistically significant when the outcome variable was extended to include death from any cause (disease-free survival [DFS], ≥4 cups/d vs none, HR: 0.58, 95% CI: 0.34, 0.99).[3] Nevertheless, our study may not be totally comparable with the previous study on coffee consumption and cancer recurrence because the previous study: (1) assessed coffee consumption during and after chemotherapy, (2) defined recurrence as both cancer recurrence and the risk of another primary tumor in the colon and (3) restricted the study population to 953 patients with stage III colon cancer, whereas we included stages I–III patients with colorectal cancer.[3]

The mechanisms that underlie the potential benefits of coffee consumption on CRC recurrence are yet to be fully elucidated. However, coffee consumption has been proposed to be protective against the hallmarks of cancer[16] by activating pathways such as nuclear factor erythroid 2(Nrf2)-regulated pathways that reduce oxidative stress.[39] Coffee consumption could also modulate microbiota composition which in turn may promote the chemopreventive or chemotherapeutic actions against CRC.[20,40–42] Coffee consumption may also prevent metastatic growth of CRC by improving the function of the liver in CRC patients[43] and by protecting against non-alcoholic fatty liver disease,[44] which is considered a risk factor for liver metastasis.[45]

The inverse association we observed for all-cause mortality complements the findings of the five previous studies that examined

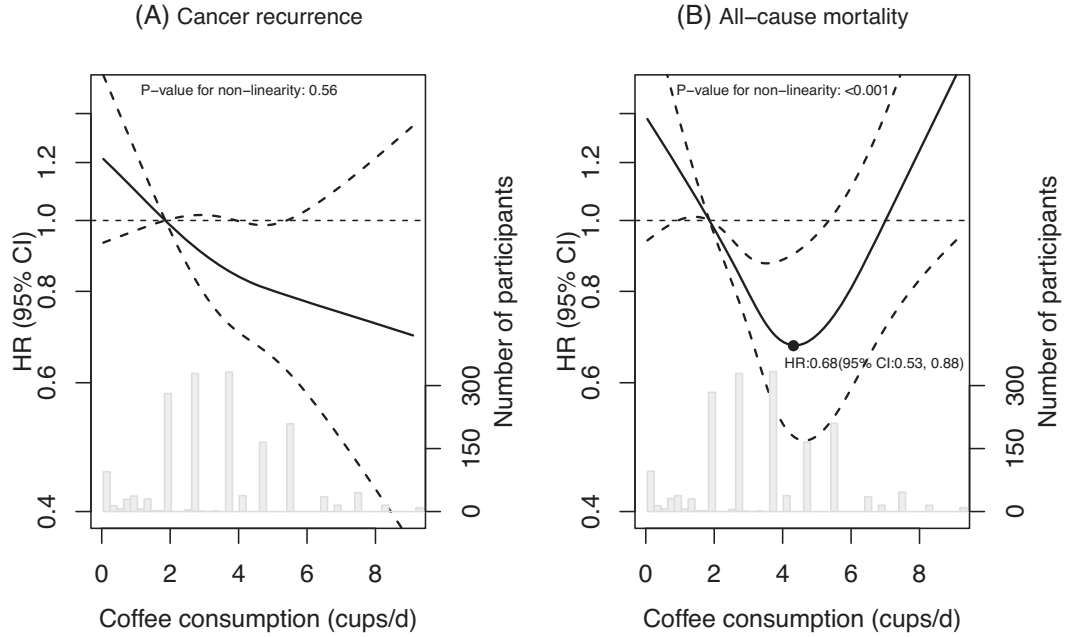

FIGURE 2 The restricted cubic spline shows the relationship between coffee consumption and (A) CRC recurrence, where the fitting included three knots: at the 5th, 50th and 90th percentile of coffee intake. (B) all-cause mortality, where the fitting included four knots: at the 5th, 35th, 65th and 95th percentile of coffee intake. HRs and corresponding 95% CI were estimated with multivariable Cox proportional hazards regression with adjustment for age, sex, education, smoking status, cancer stage and tumor location. The solid and grey dashed lines represent the HR and 95% CIs, respectively. The dashed line at HR = 1 represents a null association.

coffee consumption and mortality or survival in CRC patients in the US[4,6,10] and China.[5,11] However, three of the previous studies may not be directly comparable with our study because they examined all-cancer and CRC-related death in non-smokers[10] or performed only univariable analysis without adjusting for confounders,[11] or included only advanced or metastatic cancer patients.[6] Our study is comparable with two of the studies in the US[4] and in China.[5] The previous study in the US found a 30% lower risk of all-cause mortality among CRC patients who consumed ≥4 cups/d of coffee compared with non-coffee drinkers (HR: 0.70, 95% CI: 0.54, 0.91).[4] Likewise, the study in China reported that having a coffee consumption habitus was associated with a 54% lowered risk of all-cause mortality compared to having no coffee consumption habitus in CRC patients (HR: 0.46, 95% CI: 0.24, 0.87).[5] Our finding on all-cause mortality was similar to that of the previous studies[4,5] regardless of the potential differences in the coffee preparation and serving techniques (e.g., a standard cup of coffee in the Netherlands is 125 vs 250 ml in the US[15]).

To our knowledge, the current study is the first to assess the potential nonlinear association between coffee consumption and all-cause mortality in CRC patients. Our findings suggest that the inverse association between coffee consumption and all-cause mortality is optimal with the intake of 3–5 cups/d of coffee. Although the exact mechanism that underlies the association we observed between coffee consumption and all-cause mortality is unclear, the finding is unlikely to be due to residual confounding by smoking status. The number of current smokers in our study is relatively small (N = 176, 10% of the study population). Moreover, we observed a similar U-shaped association between coffee consumption and all-cause mortality in never smokers, and adjusting for pack years of smoking did not change the observed U-shaped association between coffee consumption and all-cause mortality. A previous study in a general population also reported a nonlinear association between coffee consumption and all-cancer-related mortality in former smokers.[10] A meta-analysis on coffee consumption and all-cause and cardiovascular disease (CVD) mortality in a general population observed a nonlinear inverse association with the largest reduction in risk at 4 cups/d.[46] We could not assess the specific cause of death in our study because the data was unavailable within our cohort due to legal restrictions in the Netherlands. Notwithstanding, CVD is the leading cause of non-cancer-related death in CRC patients.[47] Perhaps, the association between coffee consumption and all-cause mortality is indeed nonlinear, which may be explained, at least in part, by the potential nonlinear association between coffee consumption and CVD mortality.[46] Components of coffee, especially chlorogenic acids are potent antioxidants that could improve endothelial and vascular function by increasing the availability of nitric oxides,[48] which are important for maintaining cardiovascular health.[49] Additionally, the inverse association between coffee consumption and all-cause mortality may be partly explained by the potential reduced risk of CRC recurrence with increased coffee consumption. Approximately 20%–30% of CRC patients experience recurrence[23,24] which is an independent risk factor for mortality.[50] Notwithstanding, more research is needed to fully understand the specific underlying mechanism by which coffee consumption could improve CRC prognosis.

It is important to consider the potential limitations of this study. Although we cannot completely rule out potential reverse causality, coffee consumption did not seem to vary across the stages of CRC in our study. In addition, HR and 95% CI did not materially change after excluding participants who experienced recurrence or died within 100 days after surgery. Potential information errors in the assessment of coffee consumption might have biased the observed associations. However, coffee consumption was measured before the onset of CRC recurrence or all-cause mortality. Any information error that could arise from the measurement of coffee is unlikely to differ between participants who eventually developed CRC recurrence or died and those who did not. Due to the observational nature of our study, we cannot infer a cause-effect relationship between coffee consumption and CRC prognosis. As mentioned earlier, our questionnaire did not distinguish between the various types of coffee but decaffeinated coffee is rarely consumed in the Netherlands.[30] Moreover, a previous study in the US showed a similar association between all-cause mortality and the consumption of decaffeinated and caffeinated coffee.[4] The reference group in our study was not defined as non-coffee drinkers because the sample size of non-coffee drinkers (n = 79) was relatively small compared to coffee drinkers. However, our finding is similar to the results of other studies where the reference group was defined as non-coffee drinkers.[4,5] Although we adjusted for different sets of confounding variables in our analysis and conducted a sensitivity analysis, we cannot completely rule out the possibility of residual confounding. Residual confounding could have been introduced due to possible misclassification of education or smoking status. We recognize that CRC patients may change their coffee consumption after diagnosis. Nevertheless, coffee consumption at diagnosis was strongly correlated with coffee consumption at 6 months and 2 years after treatment in the CRC patients (Spearman correlation coefficient: 0.67 and 0.71, respectively). This was in line with the previous study that reported a correlation coefficient of 0.63 between pre and post-diagnostic coffee consumption in CRC patients.[4]

The strengths of our study include its prospective cohort design, large sample size, detailed lifestyle and dietary data and the potential to explore possible nonlinear associations. Additionally, the extensive follow-up and the comprehensive data from the Netherlands Cancer Registry allowed us to examine CRC recurrence separately from new primary tumors.[3]

In conclusion, our results suggest that coffee consumption may be associated with a lower risk of CRC recurrence in patients with stages I–III CRC. We also observed a nonlinear, U-shaped association between coffee consumption and all-cause mortality with the lowest risk observed for the intake of 3–5 cups/d of coffee. Although we cannot infer a cause-and-effect relationship in our observational study, our findings could inform future intervention studies and provide evidence to develop guidelines for CRC patients. More studies are needed to fully understand the mechanisms by which coffee might improve CRC prognosis.

AUTHOR CONTRIBUTIONS

Conceptualization, Abisola M. Oyelere, Dieuwertje E. Kok, Fränzel J. B. van Duijnhoven, Ellen Kampman; methodology, Abisola M. Oyelere, Dieuwertje E. Kok, Fränzel J. B. van Duijnhoven, Ellen Kampman; validation, Abisola M. Oyelere, Dieuwertje E. Kok, Fränzel J. B. van Duijnhoven, Ellen Kampman; formal analysis, Abisola M. Oyelere; investigation Abisola M. Oyelere; resources, Johannes H. W.de Wilt, Henk K. van Halteren, Ewout A. Kouwenhoven; data curation, Abisola M. Oyelere; writing-original draft preparation, Abisola M. Oyelere; writing-review and editing, all authors; visualization, Abisola M. Oyelere; supervision; Dieuwertje E. Kok, Fränzel J. B. van Duijnhoven, Ellen Kampman; project administration, Abisola M. Oyelere; funding acquisition, Dieuwertje E. Kok, Daniel Bos, Marc J. Gunter, Pietro Ferrari, Pekka Keski Rahkonen, Fränzel J. B. van Duijnhoven, Ellen Kampman. The work reported in this article has been performed by the authors, unless clearly specified in the text. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings are available on request from the corresponding author.

ETHICS STATEMENT

The COLON study (NCT0319110; ClinicalTrials.gov) was approved by an institutional review board (region Arnhem-Nijmegen, 2009–349) and all participants provided written informed consents.

DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policies, or views of the International Agency for Research on Cancer/World Health Organization.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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