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CANCER

A longitudinal evaluation of alcohol intake throughout adulthood and colorectal cancer risk

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Abstract

Background Alcohol intake is an established risk factor for colorectal cancer (CRC); however, there is limited knowledge on whether changing alcohol drinking habits during adulthood modifies CRC risk.

Objective Leveraging longitudinal exposure assessments on alcohol intake at different ages, we examined the relationship between change in alcohol intake and subsequent CRC risk.

Methods Within the European Prospective Investigation into Cancer and Nutrition, changes in alcohol intake comparing follow-up with baseline assessments were investigated in relation to CRC risk. The analysis included 191,180, participants and 1530 incident CRC cases, with exclusion of the first three years of follow-up to minimize reverse causation. Trajectory profiles of alcohol intake, assessed at ages 20, 30, 40, 50 years, at baseline and during follow-up, were estimated using latent class mixed models and related to CRC risk, including 407,605 participants and 5,008 incident CRC cases.

Results Mean age at baseline was 50.2 years and the follow-up assessment occurred on average 7.1 years later. Compared to stable intake, a 12 g/day increase in alcohol intake during follow-up was positively associated with CRC risk (HR = 1.15, 95%CI 1.04, 1.25), while a 12 g/day reduction was inversely associated with CRC risk (HR = 0.86, 95%CI 0.78, 0.95). Trajectory analysis showed that compared to low alcohol intake, men who increased their alcohol intake from early- to mid- and late-adulthood by up to 30 g/day on average had significantly increased CRC risk (HR = 1.24; 95%CI 1.08, 1.42), while no associations were observed in women. Results were consistent by anatomical subsite.

Conclusions Increasing alcohol intake during mid-to-late adulthood raised CRC risk, while reduction lowered risk.

Keywords Colorectal cancer · Alcohol change · Alcohol intake · Longitudinal exposure · Trajectory profile analysis · Latent class mixed models

Background

Lifestyle factors are associated with the risk of cancer at several sites [1–4]. These exposures change during the life course of an individual [5], either as the natural evolution of specific characteristics such as age-related increases in body weight [6], those due to personal decisions such as quitting smoking, or as a consequence of adverse health events for example developing a chronic disease. Most epidemiological evidence accumulated to date has relied on a single assessment of lifestyle exposure, typically at baseline [7], de facto disregarding changes in levels of exposure during adulthood [8].

Growing interest has recently emerged on the evaluation of lifestyle factors on cancer risk using trajectory profiles of exposure during study participants' adulthood, using

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retrospective and prospective exposure measurements to capture the variability of the exposure of interest [9, 10]. For example, in an evaluation of the progression of obesity during adulthood, individual trajectories of body fatness were used to determine the cumulative time spent overweight (BMI > 25 kg/m^2). These trajectories were subsequently associated with several obesity-related cancers including endometrial [11], colorectal, breast, liver and pancreatic cancers [12, 13].

Alcohol is an established risk factor for colorectal cancer (CRC) [1] with most evidence based on prospective studies that assessed exposures at study baseline [14, 15]. To complement this evidence, some studies averaged estimates of alcohol intake at different ages during early- and mid-adulthood, typically available for intakes at 20, 30, 40 and 50 years, into a variable referred to as 'lifetime alcohol' intake [16–21]. This approach however still ignores potential within-person changes in alcohol intake during adulthood [22]. Several studies focusing on alcohol drinking estimated alcohol intake trajectories over time using longitudinal data to account for intra-individual variation in exposure [23–28]. Although informative, these studies disregarded variation of alcohol across subgroups of participants with distinct patterns of alcohol intake from adolescence to later in life, and associations between trajectory profiles of alcohol intake and health outcomes were not investigated. To date, no study has evaluated the effect of changing alcohol intake during adulthood with respect to CRC risk using retrospective and/or prospective assessments.

By leveraging longitudinal exposure assessments within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, the relationship between alcohol intake and CRC risk was examined using two different metrics: first, alcohol changes were computed comparing (prospective) follow-up to baseline assessments. Second, trajectory profiles of alcohol use during adulthood were derived with latent class mixed models (LCMM) [29] based on retrospective assessments of alcohol intake at baseline, at ages 20, 30, 40, 50 years, and on prospective assessments collected during follow-up. The study extends current evidence on the relationship between alcohol intake and CRC risk by employing novel methodology to model longitudinal assessments of alcohol drinking in relation to colorectal carcinogenesis.

Methods

Study population

EPIC is a prospective study aimed at investigating the relationship between diet, lifestyle factors and cancer risk. The study design has been previously described [30, 31]. Briefly, 521,323 participants aged 25–70 years were recruited from 1992–2000 in 10 European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, The Netherlands and the United Kingdom) from the general population except for France and Utrecht, Ragusa and Oxford [32]. In France, Norway and Utrecht, only women were recruited. Dietary and lifestyle information were collected from participants using validated country or center-specific questionnaires. An informed consent was obtained from all participants at baseline and the ethical review boards of participating institutions approved the study.

Dietary and lifestyle assessment

Retrospective assessments of alcohol intake at ages 20, 30, 40 and 50 years were obtained at baseline for 76% of EPIC participants using lifestyle questionnaires [19]. Prospective alcohol intake assessments were collected at baseline using dietary questionnaires, or at follow-up using either lifestyle or dietary questionnaires, on average 7.1 years after baseline, as displayed in Table 1. Information on alcohol intake was collected as the number of standard drinks per day or week of beer, wine, spirits and fortified wine during the past 12 months. These quantities were converted into grams of alcohol intake per day [33]. Dietary intakes were collected at baseline with country-specific dietary questionnaires [30], while smoking status, education level, body mass index (BMI), height and other lifestyle variables were collected using questionnaires at baseline and during follow-up. Dietary variables are currently available at baseline only.

Cancer endpoint

The ascertainment of CRC cases was achieved through record linkage with population cancer registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. In France, Germany and Greece CRC cases were identified via study participants or next of kin and confirmed by a combination of methods such as health insurance records and pathology registries. Primary tumours were coded in accordance with international Classification of Diseases for Oncology (ICD-O-3). Incident cases of colon (C18), the recto sigmoid junction (C19) and rectal cancer (C20) were included. Anal canal tumours were excluded.

Exclusion criteria

Out of the initial 521,323 participants at baseline, we excluded those with prevalent cancer (n = 25,184), without end-point information of death or cancer diagnosis (n = 4,148), and those with no questionnaire information available at baseline (n = 6,259). We also excluded those who were categorized in the top or bottom 1% of the ratio

Table 1 Distribution of participants, alcohol intake (geometric means, and 10th and 90th percentiles, g/day) during lifetime (ages 20, 30, 40, and 50 years), at baseline and during follow-up and average time difference (10th and 90th percentiles, in years) between baseline and follow-up in the European prospective investigation into cancer and nutrition

	Country	n[a]	Alcohol intake at age 20	Alcohol intake at age 30	Alcohol intake at age 40	Alcohol intake at age 50	n[b]	Alcohol intake at baseline	n[c]	Alcohol intake at follow-up	Time difference[d]
Men	Italy	13,197	10 (1, 48)	16 (3, 53)	16 (2, 54)	16 (2, 56)	14,032	15 (2, 55)	6,944	14 (1, 54)	12 (9, 16)
	Spain	14,804	26 (1, 123)	27 (3, 110)	20 (1, 91)	–	15,139	14 (1, 68)	14,583	13 (1, 66)	4 (4, 5)
	UK	18,366	8 (1, 36)	9 (1, 38)	–	–	22,850	8 (1, 35)	11,152	10 (1, 47)	7 (6, 9)
	The Netherlands	–	–	–	–	–	9,626	10 (1, 45)	3,500	12 (2, 47)	11 (9, 12)
	Germany	20,388	11 (1, 54)	18 (4, 62)	19 (4, 67)	–	21,178	15 (3, 54)	17,979	12 (2, 44)	6 (5, 7)
	Sweden	–	–	–	–	–	22,306	6 (1, 24)	6,758	12 (3, 40)	6 (6, 7)
	Denmark	26,115	10 (2, 32)	14 (4, 41)	14 (5, 48)	17 (5, 50)	26,294	19 (5, 63)	–	–	–
Women	France	54,677	2 (1, 8)	3 (1, 19)	4 (1, 21)	-	67,403	7 (1, 30)	46,704	7 (1, 31)	13 (12, 14)
	Italy	24,418	3 (0, 15)	4 (1, 20)	4 (1, 20)	4 (1, 19)	30,513	4 (1, 25)	14,865	4 (1, 19)	12 (9, 14)
	Spain	24,291	3 (1, 17)	3 (1, 17)	2 (0, 17)	–	24,850	2 (1, 15)	24,038	2 (1, 10)	4 (4, 5)
	UK	40,908	5 (1, 25)	5 (1, 25)	–	–	52,566	5 (1, 18)	26,691	6 (1, 29)	7 (6, 9)
	The Netherlands	15,450	2 (1, 8)	–	6 (1, 24)	–	26,912	5 (1, 25)	4,113	6 (1, 27)	10 (9, 12)
	Germany	26,471	3 (1, 11)	5 (2, 15)	5 (2, 18)	–	27,379	6 (1, 24)	24,066	5 (1, 20)	6 (5, 7)
	Sweden	–	–	–	–	–	26,368	4 (1, 14)	8,545	6 (2, 19)	6 (6, 7)
	Denmark	28,456	3 (1, 11)	5 (1, 16)	7 (1, 23)	8 (1, 27)	28,720	9 (2, 36)	–	–	–
	Norway	–	–	–	–	–	33,975	3 (1, 8)	20,872	5 (2, 15)	7 (7, 8)

[a]Number of participants with information on alcohol intake during lifetime, collected at baseline (n_{total} = 307,541)

[b]Number of participants with information on alcohol intake at baseline (n_{total} = 450,111)

[c]Number of participants with information on alcohol intake at follow-up (complete case data: n_{total} = 230,810)

[d]Time difference from baseline to follow-up assessment in years

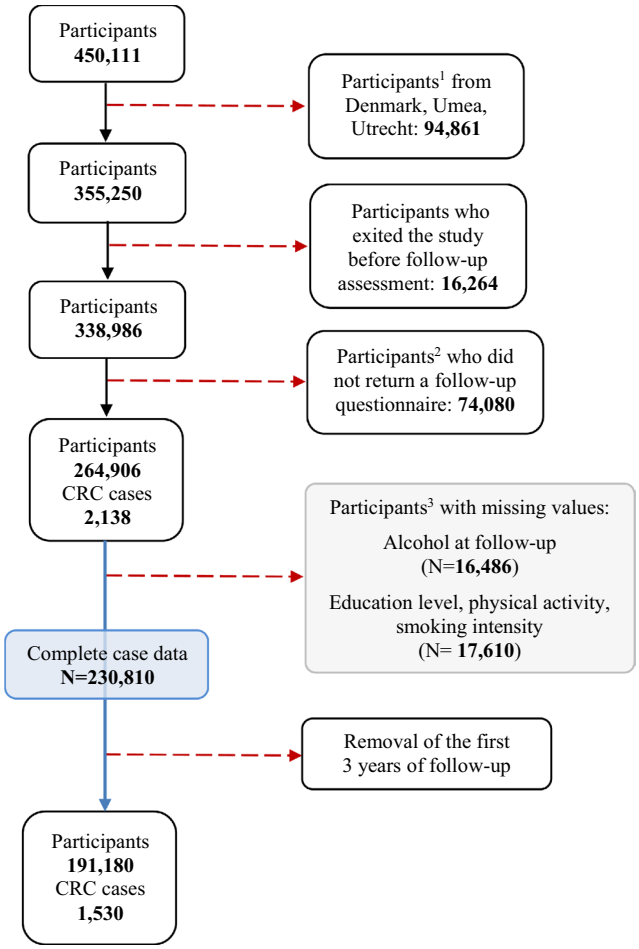


Fig. 1 Flowchart of exclusion criteria for the analysis of change of alcohol intake assessed at baseline and at follow-up

[1]In Denmark, Umea and Utrecht alcohol intake at follow-up was not available; [2]The distribution of participants who did not return a questionnaire in EPIC centers that implemented a lifestyle assessment is detailed in Supplementary Table 1; [3]With these exclusions, the complete case data had n=230,810 (blue box). A multiple imputation chained equation model was carried out to impute missing values described in the light grey box.

of energy intake to estimated energy requirement (n = 9,573) and data from EPIC Greece (n = 26,048) which were not available for this analysis, leaving 450,111 participants.

Statistical analysis

Follow-up vs. baseline

From the 450,111 participants, as outlined in Fig. 1, we excluded participants recruited in centers where alcohol at follow-up was not available (n = 94,861), those who exited the study before the follow-up assessment (n = 16,264), those who did not return a follow-up questionnaire (n = 74,080). A multiple imputation chained equation (MICE) analysis was conducted to iteratively impute missing values for alcohol at follow-up (n = 16,486), and of education level, physical activity or smoking intensity (n = 17,610) assessed at baseline. Sex-specific MICE models were used, with a burn-in of 20 iterations. A total of 50 imputed datasets were created [34, 35].

Alcohol changes were evaluated using the difference between alcohol intake at follow-up and at baseline. The association between alcohol change and risk of CRC was modelled using restricted cubic splines with 4 knots [36]. Hazard ratios (HR) and associated 95% confidence intervals (CIs) were estimated using Cox proportional hazard regression models with attained age as the primary time variable and stratified by sex, age at follow-up (in 1-year categories) and center. To address potential reverse causation, analyses were carried out after exclusion of the first three after follow-up assessment. Therefore, entry time was participants' age at follow-up assessment plus three years, while exit time was defined as age at CRC diagnosis or censoring except non-melanoma skin cancer, death, emigration, loss or end

of follow-up, whichever came first. Models were adjusted for covariates measured at baseline, including physical activity (inactive, moderately inactive, moderately active, active), a composite variable summarizing smoking status and intensity (never, current [1–15, 16–25, 26 + cigarettes/day], former [quit ≤ 10, 11–20, 20 + years], current [pipe, cigar or occasionally]), education level (none, primary, technical/professional, secondary, university), BMI (continuous, kg/m^2) and height (continuous, cm). Models were consistently adjusted for alcohol intake at baseline and the log-transformed time difference between baseline and follow-up assessments. Additional adjustment for total energy intake, processed meat, red meat and dietary fibre did not alter the results and were not included as covariates. Overall and sex-specific models were run. Parameter estimates from each imputed dataset were averaged out via the Rubin's rule [34, 35] to account for uncertainty in the MICE models to impute missing values. Interaction terms by, in turn, sex and country, and the spline terms for alcohol change were tested with Wald-tests compared to a χ^2 distribution with degrees of freedom equal to the number of terms. Analyses with exclusion of the first two years after follow-up and without exclusion were also carried out as sensitivity analyses, and HR estimates were also computed for proximal colon, distal colon and rectal cancer.

Alcohol trajectories

All 450,111 participants were included in sex-specific LCMM [29, 37]. To account for exposure variation over time, log-transformed alcohol intakes at age 20, 30, 40, 50 years, at baseline, and at follow-up (if available) were modelled. Participants were attributed to latent classes and posterior probabilities were also estimated [38], which refer to the probability of each individual pertaining to the assigned class. Within each class, longitudinal measurements of alcohol intake were modelled as a function of assessment age with linear and quadratic terms, with models including random-effects intercepts and slopes. The number of trajectories to retain was decided by examination of the Akaike information criterion (AIC) and Bayesian information criterion (BIC) values of models involving a progressively larger number of latent classes, and by checking the interpretability of estimated trajectories [38]. HRs associated to each latent classes were estimated by Cox models, weighted by participant-specific posterior membership probabilities [29]. Entry time into the analysis was the latest assessment age, either participants' age at baseline or at follow-up, while exit time, adjustment for confounders and stratification was consistent with analyses for alcohol changes between baseline and follow-up.

Associations between, in turn, alcohol intake change and trajectory profiles were carried out by anatomical sub-site (proximal, distal colon, and rectum). The proportionality of hazards assumption was evaluated through the Schoenfeld's residuals [39]. Statistical tests were two-sided, and p values < 0.05 were considered statistically significant. Analyses were carried out with the 'lcmm' and 'coxph' packages in R [40], and the 'mi' package in STATA [41].

Results

Follow-up vs. baseline

During 1,717,542 person-years, 1,804 incident CRC cases (853 men and 951 women) were identified among 230,810 study participants. Mean age at baseline was 50.2 years and 74% of participants were women. The average time difference between baseline and follow-up assessments was 7.1 years (Table 1). Alcohol intake patterns were heterogenous across country and by sex, with Spanish men displaying large intake levels at age 20 and 30 years and Danish women showing the largest alcohol geometric means throughout adulthood.

BMI, education and physical activity were uniformly distributed across categories of alcohol intake change, as shown in Table 2. Overall, the percentage of current smokers was larger among participants who changed their alcohol intake, either decreasing or increasing it, than among participants with stable alcohol intake between the two assessments. The proportion of participants with hypertension or type-2 diabetes at baseline was largest among those who decreased their alcohol intake during follow-up.

Five-year changes in alcohol intake were related to CRC risk using cubic splines, as shown in Fig. 2. After excluding the first three years of follow-up, participants who increased their alcohol intake from baseline to follow-up by 12 g/day on average over five years displayed a HR of 1.15 (95% CI 1.04, 1.25), compared to stable intake over the two assessments. A statistically significant inverse association was observed for participants who decreased their alcohol intake, with a HR of 0.86 (95% CI 0.78, 0.95). Interaction terms by, in turn, sex and country were not statistically significant, with p-values equal to 0.46 and 0.48, respectively. Sex-specific analyses were displayed in Supplementary Fig. 1a and 1b. Weaker non-linear associations were observed in models that included the entire follow-up time and that excluded the first two years of follow-up (Supplementary Fig. 2a and 2b, respectively). Associations were of similar magnitude for proximal colon, distal colon and rectal cancers (Supplementary Fig. 3a, 3b and 3c, respectively). Last, HR estimates after multiple imputation were similar to findings using the complete case data (results not shown).

Table 2 Baseline and follow-up variable distributions, geometric means (10th, 90th percentiles) or percentages (%), of 230,810 participants (complete case data) in the European Prospective Investigation into Cancer and Nutrition

	Absolute change in alcohol intake				
	Decreased intake		Stable intake[a]	Increased intake	
	< − 15 g/day	− 15 to − 5 g/day	− 5 to 5 g/day	5 to 15 g/day	> 15 g/day
CRC cases	168	228	968	256	184
Participants[b]	16,937 (7%)	30,063 (13%)	135,033 (59%)	31,798 (14%)	16,979 (7%)n
Age at baseline, years	50.4 (40.6, 61.5)	50.7 (39.3, 62.4)	50.1 (38.9, 62.1)	49.8 (39.0, 61.8)	51.0 (40.8, 62.8)
Sex[b]					
% Men	14.7	16.7	40.6	15.0	13.0
% Women	4.7	11.7	64.9	13.4	5.3
Alcohol intake, g/day					
Baseline	41.0 (23.2, 76.1)	17.7 (8.9, 37.1)	3.6 (1.0, 15.7)	6.9 (1.7, 25.1)	11.1 (2.1, 41.1)
Follow-up	10.3 (1.0, 39.2)	6.9 (1.0, 26.9)	3.5 (1.0, 15.9)	17.2 (8.8, 35.1)	41.4 (23.2, 82.2)
% drinkers at baseline	100	100	61.6	86.2	90.4
% drinkers at follow-up	86.4	83.4	62.6	100	100
BMI, kg/m^2					
Baseline	26.8 (22.1, 32.4)	26.0 (21.6, 31.5)	25.9 (21.4, 32.0)	25.2 (21.3, 30.4)	25.9 (22.5, 31.2)
Follow-up	27.1 (22.5, 32.6)	26.3 (21.9, 31.8)	26.3 (21.7, 32.4)	25.2 (21.7, 31.1)	26.3 (21.9, 31.8)
Current smoking					
Baseline	28.7	20.5	16.4	18.7	24.5
Follow-up	24.5	17.3	14.1	15.7	21.6
Former smoking					
Baseline	32.6	28.3	23.3	30.6	34.1
Follow-up	39.5	34.9	28.9	38.3	42.1
Education[c]					
None	33.3	29.0	31.1	20.9	24.5
Secondary	37.2	39.6	43.0	47.2	44.7
University	29.5	31.4	25.9	31.9	30.8
Physical activity[d]					
(Moderately) Inactive	55.9	58.1	57.3	50.1	52.9
(Moderately) Active	44.1	41.9	42.7	49.9	47.1
Conditions[e]					
CVD	1.5	1.4	1.2	1.2	1.6
Type-2 diabetes	3.4	2.5	2.8	2.0	2.9
Hypertension[f]	23.0	19.3	17.9	15.0	17.4

[a]Stable intake refers to the absolute difference between follow-up and baseline

[b]Row percentages for participants, and by sex

[c]Education assessed at baseline and grouped as: None and primary; Technical, professional and secondary; University degree or higher

[d]Physical activity was assessed at baseline

[e]Morbid conditions were assessed at baseline: CVD, cardiovascular diseases including heart attack and stroke; type-2 diabetes and hypertension. Percentages were calculated excluding missing values (9%, 8%, and 12% of all values for heart attack or stroke, type-2 diabetes and hypertension, respectively)

[f]Hypertension was measured in mmHG and subjects were categorized as hypertensive if they displayed a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg

Alcohol trajectories

Sex-specific trajectory profiles of alcohol intake were computed in the range 20–60 years, and displayed in Fig. 3a and b, together with their associated 95% CI. In men, 5 trajectory profiles were retained, notably a profile displaying the lowest intake throughout adulthood (c1: "stable low", orange, 17% of male participants, used as reference), one with large intakes in early adulthood and later decrease (c2: "very high towards low", dark green, 1%), one with consistent moderate

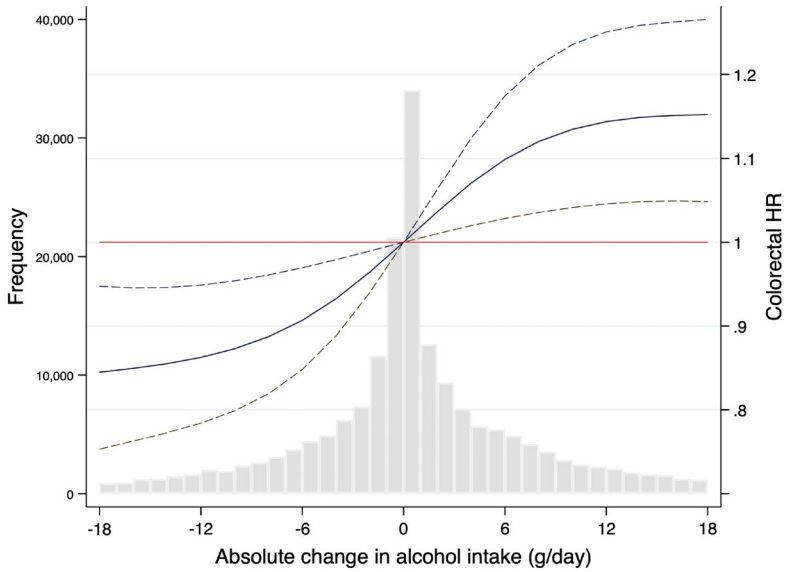


Fig. 2 CRC risk (HR 95%CI)[1] by change of alcohol intake change (g/day) between baseline and follow-up in the European Prospective Investigation into Cancer and Nutrition (1,530 CRC cases, 191,180 participants), after excluding the first three years of follow-up

[1]CRC HR estimates were adjusted for alcohol intake at baseline, the log-transformed time difference between baseline and follow-up assessments, physical activity (Cambridge Index), smoking status, education, BMI and height at baseline, and stratified by sex, age at follow-up and study center. The cubic splines were modelled using 4 knots. Analyses were carried out after excluding the first three years of follow-up, after the follow-up assessment. The blue solid curve expresses the CRC HR by change in alcohol intake with stable alcohol intake as reference. The dashed lines represent the 95% confidence intervals. Histograms represent frequency of study participants by alcohol intake change.

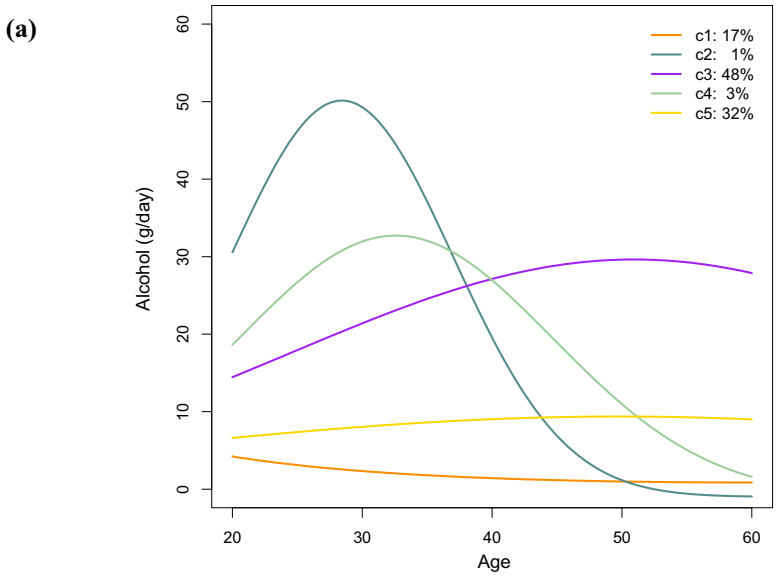
to elevated intake throughout adulthood (c3: "medium–high towards high", purple, 48%), one with large intakes in mid-adulthood and later decrease (c4: "medium–high towards low", light green: 3%), and one with consistent low intake throughout adulthood (c5: "stable moderate", yellow: 32%).

Compared to profile c1, men displaying consistent moderate to elevated alcohol intake during adulthood (c3: "medium high towards high") had a HR of 1.22 (95% CI 1.06, 1.39) for CRC risk (Tables 3, 4). Country-specific CRC HRs were homogeneous (p-value for interaction equal to 0.21) and were reported in Supplementary Table 2. Similar associations were observed for colon and rectal cancer HR of 1.19 (95% CI 1.00, 1.42) and 1.19 (95% CI 0.94, 1.49), respectively, and for proximal and distal colon cancer (results not shown). Trajectory profiles c2 ("very high towards low") and c4 ("medium high towards low"), characterized by large amounts of alcohol in early and mid-adulthood and a later decrease, had HR equal to 0.93 (0.52, 1.65) and 1.07 (0.80, 1.43) compared to profile c1 ("stable low"), respectively. Profiles c2 ("very high towards low") and particularly c4 ("medium–high towards low") displayed the highest prevalence of morbid conditions assessed at baseline, i.e. cardiovascular diseases, type-2 diabetes and hypertension. Profiles c2 and c4 had average lifetime intakes equal to 44.2 and 34.1 g/day, respectively, while average lifetime intake of c3 was 30.3 g/day.

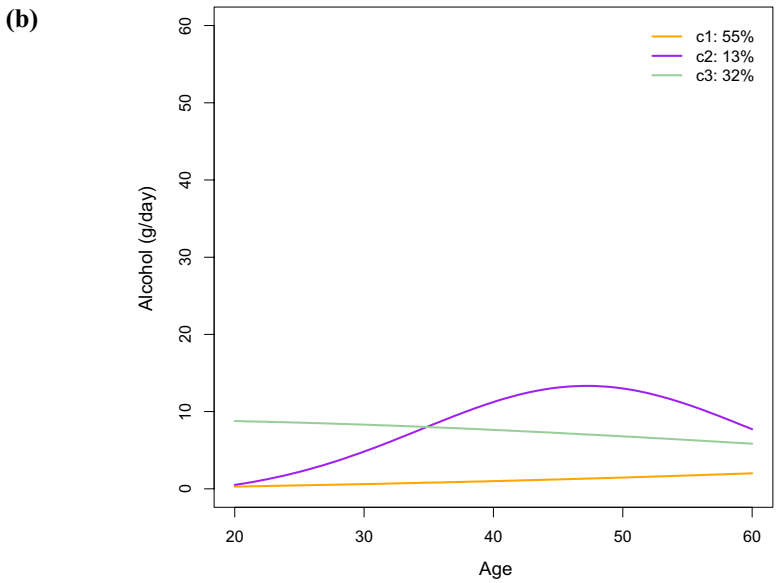
Three trajectory profiles were identified in women, notably a trajectory profile characterised by a stable low intake (c1: "stable low", orange, 55% of women, used as reference category), an trajectory with increasing intake throughout adulthood (c2: "moderately increasing", purple, 13%), and a profile with light constant intake (c3: "slightly decreasing", light green, 32%) as displayed in Fig. 3b. The risk of CRC, proximal, distal colon (results not shown) and rectal cancers did not significantly differ according to the three trajectory profiles. The proportion of never smokers and of participants with prevalent morbid conditions at baseline was evenly distributed among the three profiles.

Discussion

Complementing existing evidence on alcohol intake assessed at baseline and during lifetime, our study on alcohol trajectory profiles showed that consistent moderate-to-elevated exposure to alcohol intake throughout adulthood could increase CRC risk. Two strategies were used in this analysis: first, alcohol change was computed by comparing intake levels at follow-up with those reported at baseline; second, retrospective and prospective assessments of alcohol intake were used to identify trajectory profiles of alcohol intake during adulthood. This study indicated that irrespective of level of intake at baseline, increasing alcohol intake during mid-to-late adulthood was positively associated with CRC risk compared to having a stable intake between follow-up and baseline. Conversely, the analysis showed that reducing



[1] Classes in men: c1=Stable low; c2=very high towards low; c3=medium-high towards high; c4=medium high towards low; c5=stable moderate.



[2] Classes in women: c1=stable low; c2=moderately increasing; c3=slightly decreasing.

Fig. 3 Sex-specific trajectory profiles of alcohol intake during adulthood in the European Prospective Investigation into Cancer and Nutrition in **a** men: 5 classes[1] (n = 122,395) and **b** women: 3 classes[2] (n = 285,210). Classes refer to subgroups of study participants who have similar trajectory profiles of alcohol intake throughout adulthood

alcohol intake was inversely associated to CRC risk. Trajectory profiles in men displaying alcohol increases from early throughout late adulthood were positively associated with CRC risk compared to patterns of alcohol intake characterised by consistently low intake. No associations between trajectory profiles and CRC risk were observed in women.

Previous evaluations of the relationship between alcohol intake and CRC risk pointed towards an absence of heterogeneity by sex, consistently in EPIC [19], in a recent meta-analysis of 16 studies [42] and in a pooled study [43]. Trajectory profiles in women were different from those of men, who consumed larger amounts of alcohol than women, and were not associated with CRC risk.

Current evidence on the relationship between alcohol intake and CRC is based on observational studies that generally relied on one alcohol assessment at baseline, reflecting the intake of the year preceding the inclusion in the study, or using lifetime alcohol intake by averaging out retrospective estimates at different ages prior to baseline [19, 28]. Within a study in the Danish Diet, Cancer and Health cohort, comparing baseline with follow-up alcohol intake, women who increased their intake by one drink per day over five years had higher breast cancer risk than those with stable intake. A recent study from Thailand examined the association between alcohol intake trajectories and cancer mortality using repeated assessments to show that consistent-regular

Table 3 Associations between alcohol intake trajectory profiles (class[a]) estimated using alcohol intake (at ages 20, 30, 40, 50 years, at baseline and at follow-up) and colorectal (CRC), colon and rectal cancer risk[b] in men (n = 121,960), together with class-specific baseline characteristics of the study populations: geometric mean (10th, 90th) and percentages (%) for continuous and categorical variables, respectively

Men	Class 1 Stable low	Class 2 Very high towards low	Class 3 Medium–high towards high	Class 4 Medium–high towards low	Class 5 Stable moderate
n	20,600	1,442	58,238	3255	38,425
CRC cases	340	16	1,281	73	750
HR_{CRC} (95% CI)	1 (ref)	0.97 (0.57, 1.63)	1.23 (1.08, 1.40)	1.18 (0.90, 1.53)	1.10 (0.96, 1.26)
p-value[c]	–	0.896	0.002	0.225	0.153
Colon cancers	215	7	738	42	415
HR_{colon} (95% CI)	1 (ref)	0.71 (0.33, 1.54)	1.19 (1.01, 1.39)	1.08 (0.77, 1.53)	1.03 (0.87, 1.22)
p-value[c]	–	0.386	0.037	0.653	0.740
Rectal cancers	118	9	480	30	300
HR_{rectum} (95% CI)	1 (ref)	1.45 (0.71, 2.99)	1.26 (1.01, 1.27)	1.39 (0.92, 2.11)	1.19 (0.95, 1.49)
p-value[c]	–	0.310	0.038	0.119	0.128
Lifetime alcohol intake	4.1 (1.0, 16.6)	44.1 (17.0, 125.0)	30.4 (14.7, 66.3)	34.1 (13.4, 89.4)	9.8 (4.6, 20.8)
BMI	26.9 (22.6, 32.0)	28.0 (23.5, 33.6)	27.3 (23.5, 32.1)	28.4 (24.1, 33.8)	26.9 (23.0, 31.5)
Smoking (%)					
Never	46.8	19.8	27.2	24.3	41.3
Former	29.4	34.2	39.1	39.7	35.2
Current	23.8	46.0	33.7	36.0	23.5
Education (%)[d]					
None	36.8	45.4	32.7	51.5	30.3
Secondary	40.5	35.4	37.3	29.9	40.9
University	22.7	19.2	30.0	18.6	28.8
Country (%)[e]					
Italy	16.4	1.1	57.3	3.7	21.4
Spain	16.4	4.0	56.5	7.1	16.0
UK	24.4	0.8	38.0	1.5	35.3
The Netherlands	20.7	0.3	48.6	0.8	29.6
Germany	9.7	1.6	53.4	4.1	31.2
Sweden	30.1	0	23.1	0.4	46.4
Denmark	5.6	0.7	60.6	1.6	31.5
Conditions (%)[f]					
CVD	4.1	3.2	3.4	6.4	4.2
Type-2 diabetes	4.3	5.0	3.3	10.1	3.4
Hypertension[h]	23.5	25.4	24.7	34.0	23.4

[a]Class refers to subgroups of study participants with similar alcohol intake patterns during adulthood

[b]Cox models were adjusted by a composite variable reflecting smoking status and intensity, education, BMI, and stratified by center

[c]p-values corresponding to a z-score for the parameter expressing log(HR) comparing each class with the reference category

[d]Education assessed at baseline and grouped as: None and primary; Technical, professional and secondary; University degree or higher

[e]Row percentages per country

[f]Morbid conditions were assessed at baseline: CVD, cardiovascular diseases including heart attack and stroke; type-2 diabetes and hypertension. Percentages were calculated excluding missing values (8%, 8%, and 13% of all values for heart attack or stroke, type-2 diabetes and hypertension, respectively)

[h]Hypertension was measured in mmHG and participants were categorized as hypertensive if their systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg

drinkers had a greater risk of death compared to consistent-occasional drinkers [44].

Emerging evidence from the analysis of longitudinal data on lifetime exposures, particularly BMI, has emphasized the importance of comprehensively characterizing exposure

Table 4 Associations between alcohol intake trajectory profiles (class[a]) estimated using alcohol intake (at ages 20, 30, 40, 50 years, at baseline and at follow-up) and colorectal (CRC), colon and rectal cancer in women (n = 292,348), together with class-specific baseline characteristics of the study populations: geometric mean (10th, 90th) and percentages for continuous and categorical variables, respectively

Women	Class 1 Stable low	Class 2 Moderately increasing	Class 3 Slightly decreasing
N	157,589	39,833	94,926
CRC cases	1,757	420	1,002
HR_{CRC} (95% CI)	1 (ref)	1.04 (0.93, 1.16)	1.02 (0.93, 1.11)
p-value[c]	–	0.521	0.713
Colon cancers	1,178	271	653
HR_{colon} (95% CI)	1 (ref)	1.01 (0.88–1.16)	0.99 (0.89–1.10)
p-value[c]	–	0.915	0.840
Rectal cancers	513	133	303
HR_{rectum} (95% CI)	1 (ref)	1.13 (0.91, 1.39)	1.08 (0.92, 1.26)
p-value[c]	–	0.265	0.371
Lifetime alcohol intake	2.1 (1.0, 5.0)	10.5 (5.5, 21.4)	11.1 (4.9, 25.5)
BMI	25.7 (21.2, 32.1)	24.8 (21.0, 30.2)	25.3 (21.2, 31.1)
Smoking (%)[d]			
Never	62.6	55.1	49.6
Former	19.3	25.6	27.9
Current	18.1	19.3	22.5
Education (%)[e]			
None and primary	32.9	19.3	23.3
Secondary	47.5	48.7	48.5
University	19.6	32.0	28.2
Country (%)[f]			
France	56.2	27.0	16.8
Italy	55.3	12.3	32.4
Spain	62.2	5.0	32.8
UK	34.7	10.3	55.0
The Netherlands	48.8	15.8	35.4
Germany	46.7	17.8	35.5
Sweden	74.5	2.6	22.9
Denmark	37.2	16.9	45.9
Norway	77.3	0.1	22.6
Conditions (%)[g]			
CVD	1.4	1.3	1.0
Type-2 diabetes	2.5	2.0	1.8
Hypertension[h]	21.2	19.1	18.1

[a]Class refers to subgroups of study participants with similar alcohol intake patterns during adulthood

[b]Cox models were adjusted by a composite variable reflecting smoking status and intensity, education, BMI, and stratified by center

[c]p-values corresponding to a z-score for the parameter expressing log(HR) comparing each class with the reference category

[d]Education assessed at baseline and grouped as None and primary; Technical, professional and secondary; University degree or higher

[e]Row percentages per country

[f]Morbid conditions assessed at baseline: CVD, cardiovascular diseases including heart attack and stroke; type-2 diabetes and hypertension. Percentages were calculated excluding missing values (7%, 7%, and 13% of all values for heart attack or stroke, type-2 diabetes and hypertension, respectively)

[g]Hypertension was measured in mmHG and participants were categorized as hypertensive if their systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg

throughout the life-course for etiological investigations of cancer and other chronic conditions. Studies evaluating participants' body fat via repeated assessments at different ages were instrumental to exploit exposure variations over time. A pooled analysis of eight cohorts on trajectories of BMI across ages showed that a longer duration of overweight was significantly associated with a higher risk of postmenopausal breast and CRC [12]. Following this rationale, for the first time we assessed trajectory profiles of alcohol intake during adulthood in relation to CRC risk.

This analysis has several strengths. First, this is the first study that evaluated the relationship between alcohol intake and CRC risk using six alcohol intake assessments during adulthood at different time points, notably retrospective assessments collected at baseline (at age 20, 30, 40, 50 years and at baseline) and one prospective assessment during follow-up. Our study emphasizes the need for repeated (longitudinal) measurements of alcohol exposure in cancer epidemiology to accurately characterize individual variation of alcohol intake at different ages during adulthood. The variable lifetime alcohol intake summarizes retrospective assessments of alcohol intake at different ages [19] but de facto disregards within-person variability and the longitudinal nature of exposure data [38, 45].

Second, trajectory profile analysis was conducted using a methodology specifically designed for the analysis of longitudinal data, the LCMM [29], a statistical method for longitudinal data that classifies study participants into groups (classes) based on their initial intake and patterns of change over time [46]. Within each class, mixed models with random-effect intercept and slopes were estimated to account for participant-specific effects, as well as quadratic terms to capture potential deviation from linearity [47]. Although the uncertainty of each profile was small due to the large sample size of the study, the variability of participants' patterns of intake around each trajectory profile was not as small as the Figure indicated. In this respect, a particularly appealing feature of LCMM is the computation of posterior probabilities for participants for each latent class, whereby low values of posterior probabilities reflected limited adherence to a specific profile. This method has not been frequently used in cancer epidemiology studies possibly due to its complexity and the need for repeated exposure assessments.

Third, other than evaluating trajectory profiles throughout adulthood, short-term changes of alcohol intake during mid-to-late adulthood were evaluated comparing prospective assessments of alcohol intake at baseline and during follow-up. To the best of our knowledge, this is the first study investigating the extent of changing alcohol intake during adulthood with respect to CRC risk, using retrospective or prospective exposure assessments.

The first three years of follow-up were systematically excluded in analyses on alcohol change and CRC risk to account for potential reverse causation. Compared to models that excluded the first two years or did not exclude follow-up time, associations were stronger, and indicated that increasing or reducing alcohol intake were, respectively, positively and inversely associated with CRC risk. No exclusion of follow-up time was carried in out in analyses relating trajectory profiles and CRC risk as long-term associations were evaluated.

The study also had limitations: first, despite the relatively large size of the EPIC cohort, the number of participants with missing assessments of alcohol intake during adulthood (retrospective and not collected in Naples, Bilthoven, Umeå, Malmö and Norway) or during follow-up was quite substantial. Nonetheless, this is the largest study to date investigating changes in alcohol intake during early- through mid- and late-adulthood in relation to CRC risk. Second, individual within-person variation during adulthood of potential confounding factors was not taken into account in our models. Unlike for alcohol intake, retrospective information on lifetime exposure for smoking, obesity and physical activity was lacking in EPIC to properly account for variation in these factors in trajectory profile analyses. No covariates were added in the LCMM models, as global heterogeneity of alcohol intake over time was modelled across study participants, without conditioning to any specific factors.

Third, although the comparison of follow-up with baseline intakes provided valuable information, the average time differences between the two assessments in EPIC was slightly over seven years, a timeframe possibly too limited to capture exposure changes that could be relevant for health outcomes [48]. The loss of study participants after accounting for missing values in assessments collected during follow-up and after moving cohort entry forward was sizeable. Fourth, participants that underwent CRC screening might have decreased their alcohol intake, yet this information was not available in EPIC. Changes in alcohol intake over time may also be linked to changes in BMI and smoking status, making it challenging to disentangle the factors responsible for the observed CRC risk association. Lastly, despite the evaluation of the validity of alcohol measurements at baseline in EPIC [49], the accuracy of retrospective assessments of intake during early adulthood, i.e. at age 20 and 30 years, was not evaluated due to the lack of a suitable gold standard. Alcohol assessments at young ages might have been characterised by exposure misclassification, thus introducing bias in the definition of trajectory profiles and their relationships with CRC risk.

While the CRC risk for participants who increased their intake over time was significantly increased, the trajectory analyses indicated that reducing alcohol intake after high level of intakes during early adulthood had limited CRC benefit. Alcohol reductions over time might, among many reasons, also be the consequence of health issues (reverse

causation), including pre-cancerous colorectal lesions, which we could not control for in this study. Interestingly, the occurrence of morbid conditions at baseline, i.e. cardiovascular diseases, type-2 diabetes and hypertension, was highest for trajectory profiles c2 and particularly c4 in men displaying large intakes during early- and mid-adulthood followed by a decrease. These findings possibly suggest that alcohol reductions were at least partially the results of participants experiencing chronic conditions. On the other hand, our findings also suggest that participants with heavy alcohol drinking during early- and mid-adulthood who reduced their alcohol intake afterwards had similar CRC risk to participants with low intake throughout their adulthood.

Our findings are in line with previous studies describing the relationship between alcohol intake and CRC risk [50] with alcohol intake assessed at one point in time. The mechanisms by which alcohol exerts its carcinogenic potential on the colorectum are complex and not fully elucidated [51]. Potential mechanisms by which alcohol could impact CRC development include B-vitamin deficiencies and oxidative stress, which could lead to genetic, epigenetic, biochemical, and immunological abnormalities [51, 52]. However, how alcohol may contribute to colorectal carcinogenesis remains unclear, including whether the timing of exposure is etiologically relevant, and what the relative role of duration and intensity of alcohol drinking is. Our findings suggest that continuous long-term alcohol exposure could be necessary to impact colorectal carcinogenesis, in line with other studies indicating a time-dependent relationship between alcohol exposure and CRC [48, 53].

In this work, while similar associations were observed for alcohol changes comparing assessments at follow-up and baseline, no trajectory profiles were related to CRC risk in women, possibly reflecting the lower range of intakes throughout reported in women than in men.

The evidence generated in this study requires replication in larger collaborative initiatives, particularly on trajectory profiles that were under-powered in the current analysis. Our study on longitudinal measurements sets the basis for a new generation of studies examining changing patterns of alcohol intake and other lifestyle exposures (i.e. dietary factors, physical activity) during adulthood and their impact on cancer development. It further emphasizes that comprehensive evaluations of study participants' exposure variation over time may inform the aetiology of chronic conditions and cancer in particular.

In conclusion, we provide novel evidence on the alcohol-CRC relationship by evaluating alcohol intake patterns using longitudinal measurements of retrospective and prospective exposure assessments. Overall, consistent moderate to elevated intake during early-to-mid adulthood and increasing alcohol intake during late adulthood were positively associated with CRC risk, compared to low intake throughout adulthood. These results may have strong public health potential and corroborate existing evidence that reducing alcohol intake throughout adulthood could prevent CRC development.

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Declarations

IARC 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, policy or views of the International Agency for Research on Cancer /World Health Organization.

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