No Association of alcohol use and the risk of ulcerative colitis or Crohn's disease: data from a European Prospective cohort study (EPIC).

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Running head: Alcohol use and risk of IBD

Abstract

Background

The role of long-term alcohol consumption for the risk of developing ulcerative colitis (UC) and Crohn's disease (CD) is unclear.

Aims

For the first time, to prospectively assess the role of pre-disease alcohol consumption on the risk of developing UC or CD.

Methods

Nested within the European Prospective Investigation into Cancer and Nutrition (EPIC-IBD), incident UC and CD cases and matched controls where included. At recruitment, participants completed validated food frequency and lifestyle questionnaires. Alcohol consumption was classified as either: non-use, former, light (≤0.5 and 1 drink/week), below the recommended limits (BRL) (≤1 and 2 drinks/day), moderate (≤2.5 and 5 drinks/day), or heavy use (>2.5 and >5 drinks/ day) for women and men, respectively; and was expressed as consumption at enrolment and during lifetime. Conditional logistic regression was applied adjusting for smoking and education, taking light users as the reference.

Results

Out of 262,451 participants in 6 countries, 198 UC incident cases/792 controls and 84 CD cases/336 controls were included. At enrolment, 8%/27%/32%/23%/11% UC cases and 7%/29%/40%/19%/5% CD cases were: non-users, light, BRL, moderate and heavy users, respectively. The corresponding figures for lifetime non-use, former, light, BRL, moderate and heavy use were: 3%/5%/23%/44%/19%/6% and 5%/2%/25%/44%/23%/1% for UC

and CD cases, respectively. There were no associations between any categories of alcohol consumption and risk of UC or CD in the unadjusted and adjusted odds ratios.

Conclusion

There was no evidence of associations between alcohol use and the odds of developing either UC or CD.

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Abbreviations list: Inflammatory bowel disease (IBD), Ulcerative colitis (UC), Crohn's disease (CD), European Prospective Investigation into Cancer and Nutrition study (EPIC study), Food frequency questionnaires (FFQ), Below the recommended limits (BRL), OR (odds ratio)

Introduction

The aetiology of the inflammatory bowel diseases (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC), is largely unknown, but may involve a dysfunctional immune response to the gut microbiota in those with a genetic susceptibility[1]. The contribution of genetic risk loci in association with IBD was estimated at less than 25 percent[2], leading to the assumption that environmental factors play an important role in aetiology. Among investigated environmental factors showing associations so far are: dietary intakes of fatty acids, protein, meat, sugars, fibre and fruits, physical activity and cigarette smoking[3-5]. Alcohol consumption is a ubiquitous lifestyle factor in European societies closely related to these and other dietary and life style factors[6, 7]. Hypothetically alcohol consumption may be related to IBD via several biological paths. For instance, the consumption of alcoholic beverages could have opposing effects on the gut mucosa, as ethanol can cause intestinal mucosal injury and increase bacterial translocation[8]. Alternatively, some components of alcoholic beverages such isoflavones could potentially have antioxidant and probiotical proprieties and possibly modulate the intestinal inflammatory bowel response[9]. In patients with established IBD[10-13], clinical studies have reported that alcohol consumption provoked symptoms or increased biomarkers of relapse in inactive disease[14], and this could explain why patients with IBD avoid its use[15] and why alcohol-related causes of death are less frequent in IBD patients[16, 17]

Only a few case-control studies have investigated alcohol consumption, often in combination with smoking and diet, in the aetiology of IBD and have reported inconsistent results. For UC, no associations were documented in Chinese and Swedish populations [18, 19], but there was an inverse association in alcohol users compared to non-users or infrequent users, in US American and Japanese populations[20-23]. Epidemiological

studies investigating alcohol consumption and the development of CD are scarce; one showing consuming alcohol at least once per week lowered the risk[24] and another reporting no association for use of alcoholic beverages[25].

Limitations of all these retrospective studies, where that they relied on self-reports of recalled previous alcohol use, which in cases may have been after establishment of the IBD diagnosis rather than before the onset of symptoms ,hence introducing recall bias. In prospective cohort studies, where initially healthy people report their diet and alcohol consumption and are then followed up to identify those who develop IBD, recall and selection biases are reduced. To date, no prospective epidemiological study has investigated the lifetime use of alcohol on the development of UC or CD. We aimed to address this by assessing whether there is an association between alcohol consumption at several time points during a participant's lifetime prior to the recruitment into the multi-centre European Prospective Investigation into Cancer and Nutrition (EPIC-IBD) study and the subsequent development of UC or CD.

Methods

The EPIC study recruited approximately 520 000 participants during the years 1992 until 2000 namely women and men mainly ages 35 to 65 and 40 to 65 years in 23 collaborating centres in 10 European countries to investigate the role of diet and other lifestyle factors in the aetiology of cancer and other chronic diseases in a general population with a prospective study design[26]. At recruitment, participants completed questionnaires on diet and lifestyle factors, medical history and underwent anthropometric examinations in each centre. The study was approved in each centre by the relevant local ethics committee and each participant gave written consent.

The EPIC-IBD study was embedded in a sub-cohort of EPIC involving 401,326 initially healthy women and men without UC or CD, in the age range 20 to 80 years, recruited from 12 centres in 8 European countries. Information on lifetime use of alcohol was not collected in all these centres hence the study population was 262,451 participants in 7 centres in 6 European countries (table 1). The sub-cohorts were followed up until at least May 2004 and in some centres until December 2010 where incident cases of UC and CD were identified by several methods including national and regional IBD registries, follow-up questionnaires and hospital databases (table 1). All the medical records of potential cases were reviewed to obtain information from radiological, endoscopic, and histological reports to confirm the diagnoses and to document the extent of the disease in the gastrointestinal tract. Prevalent cases at recruitment and all cases of microscopic colitis were excluded. A nested case-control study design within the EPIC-IBD cohort was performed. Each case was matched with four randomly selected controls free of IBD and alive at the date of diagnosis of the case. The matching criteria were: age at enrolment (± 6 months), gender, centre and enrolment date (± 3 months). There were 2 UC controls and 2 CD controls where the FFQ-data on alcohol consumption at baseline was missing which is why they were excluded from this study (table 1).

Alcohol use was assessed as previously described[27]. At enrolment, alcohol consumption during the previous 12 months was recorded using validated country-specific food frequency questionnaires (FFQs), and in a standardized lifestyle questionnaire, participants reported on their habitual consumption of alcoholic beverages per week when they were 20, 30, 40, or 50 years old. Glasses of alcoholic beverages reported in both questionnaires were converted into grams of alcohol per day (g/day) by applying empirically derived definitions of standard drinks for each beverage and country

of EPIC[28]. According to the amount of alcohol intake at enrolment, the participants (women and men, respectively) were classified into either: non-users, light user (>0-1 and >0-2 g/day; corresponding to 0.5 and 1 drink per week), below the recommended limits (BRL) user (>1-12 and >2-24 g/d; corresponding to 1 and 2 drinks per day), moderate user (>12-30 and >24-60 g/d; corresponding to 1-2 and 2-5 drinks per day) and heavy users (>30 and >60 g/d; corresponding to >2.5 and >5 drinks per day)[29-31]. According to the recall of consumption in the years previous to enrolment, average lifetime alcohol consumption was determined as a weighted average of intake at different ages, with weights equal to the time of individual exposure to alcohol at different ages; categories of alcohol use were then defined as described above. Never drinkers were those participants who did not report any consumption of alcoholic beverages at all points during their lifetime, while those who reported alcohol consumption at ages 20, 30, 40 or 50 years, but not during the 12 month prior to the recruitment were categorized as former users[32]. Finally, the lifetime pattern of alcohol use was assessed taking variation over time into account; alcohol consumers at enrolment were classified according to the highest level ever reached into 'lifetime light' (always being a light user), 'lifetime BRL' (all points in time using alcohol maximally BRL), 'lifetime light to moderate' (all points in time using alcohol maximally moderately), and 'lifetime occasionally or always heavy'[29-31].

The self-completed questionnaires recorded: educational level and smoking status including the number of cigarettes. Information on dietary intake was derived from the FFQ, namely nine categories of consumption frequencies which varied from never to several times per day for approximately 200 food items. Using national databases of food composition from the EPIC-nutrient database, the 24-hours intake of total energy, food groups and individual nutrients were calculated[33].

Conditional logistic regression was applied using SAS Enterprise 6.1 to calculate odds ratios (OR) and 95 percent confidence intervals (95% CI) for alcohol consumption at enrolment, during lifetime in average and for the lifetime pattern of alcohol use and the development of UC or CD. Light alcohol users (≤1 g/d and ≤2 g/d) were chosen as the reference group, as non-users may have heterogeneous reasons for abstention including health problems related to the diseases of interest and thus feigning a potential beneficial effect of alcohol use[34, 35].

Models were either unadjusted or adjusted for smoking status (never smoker, former smoker and smoker at enrolment), smoking duration, and educational attainment. Since the intake of polyunsaturated fatty acids were associated with UC in an earlier analysis[36], sensitivity analyses were performed, additionally adjusting the models of UC and CD for decosahexaenoic (n-3 PUFA) and linoleic acid (n-6 PUFA) (g/d, continuously), as well as excluding cases diagnosed within 18 months after enrolment (to assess the possibility of reverse causation), and running the models separately for men and women. All analyses were performed using the statistical software SAS (Version 9.4, Enterprise Guide 6.1, SAS Institute Inc., Cary, NC, USA).

Epidemiological data analyses of EPIC, including EPIC-IBD, may be conducted upon application addressed to the Steering Committee of EPIC. Each application will have to pass a review process by a scientific board.

Results

One hundred and ninety-eight UC and 84 CD incident cases and 792 matched UC-controls and 336 matched CD-controls were included (Table 2). The median time from recruitment to IBD diagnosis was around 3.5 years (UC: 3.7, interquartile range 2.4-5.6;

CD 3.5, interquartile range 1.6-5.9 years). Participants who developed UC were on average 2 years older at the time of enrolment than those who developed CD. More women than men developed IBD (63% of UC cases and 81% of CD cases). The proportion of smokers at the time of enrolment, compared to their controls, was 32% and 24% (respectively) among CD cases, whilst for UC cases, the proportion of former smokers was 40% compared to 32% of controls. Alcohol consumption was common, with only about 7% of IBD cases and 9% of controls being non-users at recruitment. According to lifetime average use half of the IBD cases as well as the UC controls consumed less than about 7-8g/d alcohol. The median and the range of average alcohol consumption during lifetime were lowest among CD controls. About 3% of the UC cases and controls, and about 5% and 7% of the CD cases and controls never used alcohol during lifetime. Most of the IBD cases and controls (about 77-83%) used alcohol during lifetime, although never heavily.

Table 3 shows the ORs for UC and CD according to the three assessments of alcohol consumption used in this study. There were no associations for the development of UC or CD according to either: alcohol consumption at recruitment, lifetime average alcohol use or pattern of lifetime alcohol use compared to participants with light alcohol consumption. Odds ratios were similar when the models were either not adjusted or adjusted for smoking and education. Additional adjustment of the models for dietary fatty acids namely linoleic and decosahexaenoic acid, the exclusion of the cases diagnosed within the 18 months of follow-up and the separate calculation of the OR for women and men did not change the results.

Discussion

This prospective study found there were no associations between alcohol consumption and the development of either UC or CD neither at recruitment, nor during lifetime from 20 years of age onwards or for any lifetime patterns of alcohol use. The findings were similar for abstention from or cessation of alcohol use at some time point before recruitment.

The literature previously discussed a role of the microbiota, genetics, diet and life style, and other environmental factors in the aetiology of IBD[37-39]. Alcohol use is part of socio-cultural life and part of dietary patterns, and its consumption has been reported to be increasing over the last decades in many European populations[40]. Therefore, it was hypothesized that alcohol may influence inflammatory responses in the gastrointestinal tract as it can cause direct mucosal injury as well as increasing bacterial translocation[8] and therefore increase the risk for IBD. Epidemiological studies on the role of alcohol in the aetiology of IBD are scarce[18-20, 23-25], and consist of only retrospective case-control investigations, which studied 167 to 384 UC cases and 58 to 315 CD cases. These observational studies retrospectively collected information on alcohol consumption before the onset of symptoms for disease, and reported either: lower risk for regular alcohol users compared to little or non-users[20, 23], no associations[19, 24] or the associations disappeared when controlling for smoking, appendectomy or other confounders[18, 25]. Our study is the first to prospectively investigate alcohol consumption and the subsequent development of IBD, nested in EPIC, an European-wide cohort multi-centre study investigating diet and the development of cancer and other chronic diseases with over half a million participants in 10 countries.

The strength of our study is the prospective design of the data collection and the coverage of a large part of the European population to which the results are generalizable. The information on how alcohol was used during lifetime was recalled, but was collected before participants developed the symptoms of IBD or were diagnosed with the illness. Self-reported use of alcohol is prone to recall bias and social desirability bias[41]; nevertheless, the assessment of lifetime consumption at the time of recruitment in prospective studies was reliable in studies on weight development[32] and mortality[27]. Due to the prospective recruitment, and the use of standardized FFQ and lifestyle questionnaires, we were able to adjust the models for variables that may be relevant for the development of IBD and also may be related to alcohol consumption (education, smoking, and polyunsaturated fatty acids). We used light alcohol users as reference because these participants in general tolerate alcohol; but its consumption is less likely to have any metabolic effect related to health. If the reference group were never-users, these may have several reasons for abstention including health problems related to the diseases of interest and thus feigning a potential beneficial effect of alcohol use[42-44]. A further strength of our study is that we included incident cases, which were medically verified, and that we performed a sensitivity analysis excluding those cases diagnosed early during the follow-up, to avoid including possible prevalent cases in the models. Our study has limitations. First is the relatively low number of cases of IBD compared to recently published numbers from a cohort in Europe[45]. The relatively small numbers of cases and the older age of our study population may limit our findings to IBD cases that occur later in life and are therefore not generalizable to the group of persons where the disease emerges at younger ages. However, the number of cases we identified was comparable to that of a previous cohort study (EC-IBD) which recruited new IBD cases in

1991-93, the same time the EPIC study recruited participants[46], suggesting that our procedures of identification of cases were equivalent. Secondly, due to the demographic nature of the EPIC study, the number of cases diagnosed in young is low (the median age at diagnosis of our cases is more than 15 years older than that reported for Europe[45]). Nevertheless, it can be supposed that in early-age and young-age the genetic factors may play a more relevant role than environmental factors in the aetiology of IBD, and IBD in adulthood may be more influenced by the latter[38]. Therefore, the potential influence of alcohol use in IBD pathogenesis would be greater in an adult cohort, such as ours. Thirdly, the assessment of alcohol consumption was only performed at the enrolment of participants, and not surveyed prospectively. Therefore, it is not possible to know if participants changed their alcohol habits during follow-up and if this might have any influence in the risk of IBD. However, as half of the cases were diagnosed during the first 3.5 years of follow-up, it is conceivable that factors reported at recruitment are still related to disease development. Alcohol consumption was reported to be increasing over the last decades in many European populations[40], together with an increase in the incidence of IBD[45], although our results would suggest the two are not associated.

In conclusion, our data does not support a role for alcohol consumption in the aetiology of either UC or CD.

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Specific author contributions: SSMC and ARH designed the study, recruited the centres, RL generated the master data set; WB calculated the alcohol variables, included them in the dataset and analysed the data and MMB and VH wrote the paper. The remaining co-authors HB, KTK, FvS, BO, BBdM, KO, DP, GM, FC, MB, AO, AT, RK, VK, ER and ARH are principal investigators in their respective centres who contributed to the local design, development and enrolment of participants into their cohorts. These authors generated the local IBD databases, and contributed to the analysis and writing of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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Table 1. Characteristics of the EPIC-cohorts and case ascertainment in the EPIC-IBD nested case-control study

Country (centre)	Size of cohort No.	Years of recruitment	Month and year of last diagnosis in the data set	Nature of cohort	Number of participants with incident IBD a) Total b) Within the 1st 5 years	
					UC cases/controls	CD cases/controls
Denmark (Aarhus, Copenhagen)	57,053	1993-97	11/2001	Population-based cohort of men and women aged 50–64 years. Cases identified from national registry of inflammatory bowel disease.	a) 49 / 196 b) 40 / 160	16 / 64 13 / 52
United Kingdom (Norfolk)	25,639	1993-97	12/2002	Population-based cohort of men and women aged 45–74 years. Cases identified from follow-up questionnaires, in-patient admission data and histopathology records.	a) 51 / 206 b) 42 / 170	16 / 66 13 / 55
Germany (Heidelberg)	25,540	1994-98	11/2003	Population-based cohort of men aged 45–65 years and women aged 35–65 years. Cases identified from follow-up questionnaires and subsequently were medically verified.	a) 6 / 24 b) 6 / 24	11 / 44 5 / 20
Germany (Potsdam)	27,548	1994-98	09/2006	Population-based cohort of men and women, aged 35–64 years. Cases identified from follow-up questionnaires and subsequently were medically verified.	a) 37 / 148 b) 19 / 76	5 / 20 3 / 12
The Netherlands (Amsterdam, Doetinchem, Maastricht, Utrecht)	40,092	1993-97	01/2008	Population based cohort of men and women, aged 20-70 years in 3 cities (Amsterdam, Doetinchem & Maastricht) and women from the breast cancer screening programme in Utrecht. Cases were identified using a population-based pathology database with subsequent verification via hospital records	a) 13 / 52 b) 5 / 20	7 / 27 3 / 11
France	72,996	1993-97	06/2005	Women aged 40–65 years, enrolled in the Nation-wide health insurance programme (MGEN) for teachers and school workers. Cases identified via insurance records.	a) 33 / 130 b) 16 / 53	25 / 99 15 / 59
Italy (Florence)	13,583	1993-97	05/2002	Population-based cohort of men aged 45-64 and women aged 35.64 years. Cases identified from regional registry of inflammatory bowel disease	a) 9 / 36 b) 8 / 32	4 / 16 3 / 12

UC ulcerative colitis, CD Crohn's disease

Table 2. Characteristics of participants

	UC Cases (n=198)	UC Controls (n=792)	CD Cases (n=84)	CD Controls (n=336)
Age at recruitment (years, median (range)	52.7 (23.2, 77.1)	52.8 (23.2, 77.1)	50.9 (23.0, 75.8)	50.8 (22.8, 76.2)
Gender (women (n, %))	124 (62.6)	497 (62.8)	68 (81.0)	269 (80.1)
Age at diagnosis (years, median (range)	56.9 (28.0, 80.8)	–	55.8 (27.0, 78.7)	–
Time between recruitment and diagnosis				
(years, median (min, max))	3.7 (0.0, 12.5)		3.5 (0.1, 11.9)	
IQR	(2.4, 5.6)	–	(1.6, 5.9)	–
Current smoker (%)	23.4	21.9	32.1	23.8
Former smoker (%)	40.1	32.1	26.2	29.5
Intakes:				
Energy (kcal/d, mean (SD))	2198 (664)	2131 (653)	2105 (549)	2054 (594)
decosahexaenoic acid (g/d, mean (SD))	0.26 (0.20)	0.28 (0.24)	0.25 (0.22)	0.27 (0.27)
linoleic acid (g/d; mean (SD))	12.2 (5.1)	11.1 (5.2)	9.5 (3.7)	11.0 (5.4)
University degree (%)	28.3	29.2	29.8	30.1
Alcohol use at recruitment				
% non-user	7.6	8.8	7.1	8.9
Median g/d (min, max)	9.1 (0.0, 155.9)	8.9 (0.0, 184.1)	6.4 (0.0, 72.2)	7.1 (0.0, 114.9)
Lifetime average alcohol use				
Median g/d (min, max)	7.8 (0.0, 114.6)	7.9 (0.0, 228.0)	6.8 (0.0, 134.6)	5.5 (0.0, 65.6)
Lifetime pattern of alcohol use (%)				
Never	3.0	3.4	4.8	6.9
Former[1]	4.6	5.4	2.4	2.1
Lifetime light[2]	14.1	13.0	13.1	14.9
Lifetime BRL[3]	33.3	33.8	40.5	35.7
Lifetime light to moderate[4]	29.8	30.3	29.8	29.2
Lifetime occasionally or always heavy[5]	15.2	14.0	9.5	11.3

IQR: interquartile range; BRL: below the recommended limits.

[1]Those participants reported the use of alcohol at ages: 20, 30, 40, or 50 years of age but not for the time of enrolment.

[2]Always being a light user (>0 g/d–1 or 2 g/d for women or men).

[3]At least one point time being BRL user (>1 or 2 g/d–12 or 24 g/d for women or men).

[4]At least one point time being moderate user (>12 or 24 g/d–30 or 60 g/d for women or men).

[5]At least one point time being heavy user (>30 or 60 g/ for women or men).

Table 3. Odds ratios for use of alcohol and the development of IBD

Alcohol use	Cases n	Controls n	OR[1] (95% CI)[1]	OR[2] (95% CI)[2]
Ulcerative Colitis				
Alcohol use at recruitment				
Non-use	15	70	0.77 (0.40-1.49)	0.80 (0. 41-1. 59)
Light[3]	54	200	REF	REF
BRL[4]	63	278	0.84 (0.56-1.28)	0.82 (0.54-1.25)
Moderate[5]	45	169	0.99 (0.62-1.58)	0.95 (0.58-1.54)
Heavy[6]	21	75	1.04 (0.57-1.89)	0.95 (0.52-1.76)
Lifetime average alcohol use				
Never user	6	27	0.88 (0.36-2.19)	1.10 (0.43-2.80)
Former user[7]	9	43	0.78 (0.35-1.74)	0.79 (0.34-1.81)
Light[3]	45	174	REF	REF
BLR[4]	88	351	1.03 (0.68-1.56)	1.14 (0.74-1.74)
Moderate[5]	38	168	0.91 (0.60-1.39)	0.85 (0.55-1.32)
Heavy[6]	12	29	1.67 (0.81-3.45)	1.70 (0.80-3.58)
Pattern of lifetime alcohol use				
Never	6	27	0.80 (0.30-2.12)	0.92 (0.34-2.48)
Former	9	43	0.72 (0.30-1.73)	0.67 (0.27-1.66)
Lifetime light[8]	28	103	REF	REF
Lifetime BLR[9]	66	268	0.90 (0.54-1.51)	0.86 (0.51-1.47)
Lifetime light to moderate[10]	59	240	0.90 (0.53-1.53)	0.82 (0.48-1.42)
Lifetime occasionally or always heavy[11]	30	111	0.99 (0.54-1.82)	0.86 (0.46-1.64)

Table continuing

Table continuing Alcohol use	Cases n	Controls n	OR[1] (95% CI)[1]	OR[2] (95% CI)[2]
Crohn's Disease				
Alcohol use at recruitment				
Non-use	6	30	0.70 (0.26-1.93)	0.71 (0.25-2.08)
Light[3]	24	86	REF	REF
BLR[4]	34	115	1.05 (0.57-1.92)	1.00 (0.52-1.95)
Moderate[5]	16	78	0.73 (0.36-1.46)	0.67 (0.30-1.49)
Heavy[6]	4	27	0.52 (0.17-1.64)	0.43 (0.13-1.47)
Lifetime average alcohol use				
Never user	4	23	0.64 (0.20-2.06)	0.64 (0.19-2.19)
Former user[7]	2	7	1.33 (0.25-7.08)	1.28 (0.21-7.79)
Light[3]	21	86	REF	REF
BLR[4]	37	146	0.97 (0.53-1.80)	0.97 (0.50-1.89)
Moderate[5]	19	67	1.16 (0.61-2.21)	0.88 (0.43-1.81)
Heavy[6]	1	7	0.58 (0.07-4.71)	0.57 (0.06-5.20)
Pattern of lifetime alcohol use				
Never	4	23	0.73 (0.21-2.56)	0.71 (0.19-2.67)
Former[7]	2	7	1.52 (0.26-8.93)	1.48 (0.22-9.99)
Lifetime light[8]	11	50	REF	REF
Lifetime BLR[9]	34	120	1.30 (0.62-2.70)	1.26 (0.58-2.74)
Lifetime light to moderate[10]	25	98	1.15 (0.52-2.50)	1.00 (0.42-2.39)
Lifetime occasionally or always heavy[11]	8	38	0.98 (0.36-2.68)	0.82 (0.28-2.42)

BRL: Below the recommended limits.

[1]Not adjusted.

[2]Adjusted for educational attainment and smoking status.

[3]>0 g/d–1 or 2 g/d for women or men.

[4]>1 or 2 g/d–12 or 24 g/d for women or men.

[5]>12 or 24 g/d–30 or 60 g/d for women or men.

[6]>30 or 60 g/ for women or men.

[7]Those participants reported the use of alcohol at ages: 20, 30, 40, or 50 years of age but not for the time of enrolment.

[8]Always being a light user.

[9]At least one point time being BRL user.

[10]At least one point time being moderate user.

[11]At least one point time being heavy user.