Alcohol consumption and risk of colorectal cancer: Results from the UK Dietary Cohort Consortium

Running title: Alcohol consumption and colorectal cancer risk

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**Professor Rodwell (professionally known as Bingham) read an initial draft of this manuscript, but sadly passed away in June.

ABSTRACT

Background: Epidemiological studies suggest that excessive alcohol consumption increases colorectal cancer (CRC) risk. However, findings regarding tumour subsites and sex differences have been inconsistent.

Methods: We investigated prospective associations between alcohol consumption on overall and site- and sex- specific CRC risk. Analyses were conducted on 579 CRC cases and 1,996 matched controls nested within the UK Dietary Cohort Consortium using standardised data from food diaries as a main nutritional method and repeated using data from food frequency questionnaire (FFQ).

Results: Compared with individuals in the lightest category of drinkers (>0 to <5 g/day), the multivariable odds ratios of CRC were 1.16 (95% CI: 0.88, 1.53) for non-drinkers, 0.91 (95% CI: 0.67, 1.24) for drinkers with 5 to <15 g/day, 0.90 (95% CI: 0.65, 1.25) for drinkers with 15 to <30 g/day, 1.02 (95% CI: 0.66, 1.58) for drinkers with 30 to <45 g/day, and 1.19 (95% CI: 0.75, 1.91) for drinkers with ≥45 g/day. No clear associations were observed between site-specific CRC risk and alcohol intake in either sex. Analyses using FFQ showed similar results.

Conclusion: We found no significantly increased risk of colorectal cancer up to 30 g/day of alcohol intake within the UK Dietary Cohort Consortium.

Keywords: colorectal cancer; alcohol intake; prospective cohort study; food diary; food frequency questionnaire

INTRODUCTION

The descriptive epidemiology of colorectal cancer (CRC) shows significant geographical variation in incidence rates worldwide and provides strong circumstantial evidence that lifestyle plays an important role in colorectal carcinogenesis (Stewart and Kleihues, 2003). Alcohol drinking is one such important lifestyle factor (Ferrari *et al.*, 2007): the International Agency for Research on Cancer (IARC) recently added CRC to the list of alcohol-related malignancies (Baan *et al.*, 2007) and the 2007 World Cancer Research Fund/ American Institute for Cancer Research Expert Report (WCRF/AICR Report) concluded that consumption of ethanol from alcoholic drinks of >30 g/day is a convincing cause of CRC in men and a probable cause in women (WCRF/AICR, 2007). In the UK, 30g of alcohol is equivalent to 3-4 units, one unit being approximately 8g of alcohol (The National Health Service, 2008). Associations between alcohol intake and CRC risk according to anatomical subsites of the colorectum remain unclear (Akhter *et al.*, 2007; Bongaerts *et al.*, 2008; Chen *et al.*, 2005; Ferrari *et al.*, 2007; Lim and Park, 2008), although it is believed that colon and rectal cancers have different aetiologies (Li and Lai, 2009), and that within the colon proximal and distal sites have biologically distinct functions (Bufill, 1990; Lindblom, 2001). Evidence has mostly been available for men with high alcohol consumption (Allen *et al.*, 2009) and risks of CRC with alcohol intake for men and women have not been consistent.

Many epidemiological studies which investigated an effect of alcohol on health have relied on self-reports of alcohol intakes. Due to its simplicity in use and convenience in administration, food frequency questionnaires (FFQs) have been mostly used in alcohol consumption assessment (Feunekes *et al.*, 1999). As a nutritional instrument, however, FFQs have been questioned for their ability to detect relatively moderate risks (Bingham *et al.*, 2003; Schatzkin *et al.*, 2003) and for a number of nutrients food diaries have been shown to provide measurements that are more strongly associated with biomarker data (Bingham *et al.*, 2008; Bingham *et al.*, 1997; Day *et al.*, 2001). Furthermore, it has been suggested that food diaries can capture a more complicated individual dietary intake more accurately (Bingham *et al.*, 2003). However, less is known about whether food diaries provide a superior measure of food intake for infrequently or episodically consumed items, such as alcoholic drinks, compared with the FFQs. It is therefore important to compare the effects of alcohol intake on CRC risk using food diaries and FFQs.

In the UK, government recommendations on alcohol intake are for men to consume no more than 3-4 units/day (<32 g/day) and for women no more than 2-3 units/day (<24 g/day) (The National Health Service, 2008), however average annual alcohol consumption in the UK now

exceeds the European Union average (Department of Health, 2009) and CRC is the second major cause of cancer death in the country (Westlake and Cooper, 2008). Worldwide, over one million incident cases were recorded in 2002 (WCRF/AICR, 2007). Hence, even a moderate association between alcohol intake and CRC risk may have important public health implications.

The aim of this study was to examine the relationship between alcohol consumption and overall and site-specific CRC risks, including differences in sex-specific risks, using a case-control study nested within the UK Dietary Cohort Consortium, from which nutritional data were ascertained by food diaries and FFQs at baseline.

MATERIALS AND METHODS

Study population

The UK Dietary Cohort Consortium comprises seven established UK cohorts (EPIC-Norfolk, EPIC-Oxford, Guernsey Study, Oxford Vegetarian Study, MRC National Survey of Health and Development (NSHD), the UK Women's Cohort Study (UKWCS) and Whitehall II; **Table 1**) with a total cohort size of 153,000 individuals. The methods of recruitment, study design and ethical approval have been described for each of these cohorts in detail elsewhere (Allen *et al.*, 2005; Appleby *et al.*, 1999; Cade *et al.*, 2004; Davey *et al.*, 2003; Day *et al.*, 1999; Marmot and Brunner, 2005; Wadsworth *et al.*, 2006).

Case ascertainment

Case patients were individuals who were free of cancer (except non-melanoma skin cancer) at the date of food diary commencement and who developed CRC at least 12 months after the date of diary commencement and before the end of the study period, defined for each study centre by the latest date of complete follow-up for both cancer incidence and vital status.

Last dates of follow-up varied between cohorts, from 31 December 2003 to 1 January 2007. Individuals with self-reported or registry-reported prevalent cancer (except non-melanoma skin cancer) were omitted from the study. Incident CRC cases (International Statistical Classification of Diseases and Related Health Problems (ICD) 10th Revision, C18-20) were ascertained by record linkage with local cancer registries and the United Kingdom Office for National Statistics, which provided notification of all cancer registrations and deaths by cause for the cohort. For the present study, CRC cases were classified according to anatomical subsite: colon cancers were defined as tumours in the caecum, appendix, ascending colon and hepatic flexure, transverse colon, splenic flexure (proximal, C18.0-18.5; ICD 10th Revision), and descending and sigmoid colon (distal, C18.6-C18.7), as well as tumours that were overlapping or unspecified (C18.8 and C18.9). Cancer of the rectum included tumours occurring at the rectosigmoid junction (C19) and rectum (C20). Overall CRC was defined as a combination of all colon and rectal cancer cases.

Selection of matched controls

Cases were matched within their respective cohort to four controls each, with the exception of some cases from EPIC-Oxford, the Guernsey Study and the Oxford Vegetarian Study who were matched to two controls, and some from the UKWCS who were matched to five controls. Matched controls were selected at random from the appropriate stratum of the set of all cohort

members who were free of CRC at the end of follow-up (due to death or censoring) and free of all cancer (except non-melanoma skin cancer) at the date of diary commencement. Matching criteria were sex, age at enrolment (± 3 years) and month of diary completion (± 3 months). Follow-up time for matched controls was also required to be at least as long as that for the case, with follow-up time defined as the time from the date of diary commencement to the date of CRC diagnosis for cases and the time from date of diary commencement until the end of follow-up for the controls. A total of 579 CRC cases and 1,996 matched controls were available for analysis.

Diet and lifestyle assessment

Each cohort collected dietary information using 4-day (Guernsey, Oxford Vegetarian Study, UKWCS)(Appleby *et al.*, 1999; Cade *et al.*, 2004), or 7-day food diaries (EPIC-Norfolk, NSHD, EPIC-Oxford, Whitehall II) (Bingham *et al.*, 2001; Brunner *et al.*, 2001; Davey *et al.*, 2003; Wadsworth *et al.*, 2006) completed on consecutive days at recruitment to the study or during a subsequent monitoring phase. Participants were asked to record in detail all the foods and beverages they consumed, prompted by time slots such as "Mid-morning – between breakfast time and lunchtime" and also by photographs of standard plates with three different portion sizes of representative foods to help participants estimate the amounts they consumed (Bingham *et al.*, 2001). Information on age, sex, height, weight, smoking status, educational level, social class, physical activity, and family history of CRC, were collected either by trained researchers or in questionnaires administered prior to the completion of the food diary. In four of the seven studies (EPIC-Norfolk, EPIC-Oxford, UKWCS, Whitehall II), FFQs were also administered prior to this data collection, and were available for analysis from most participants in these cohorts. The FFQs were based on that used in the US Nurses' Health Study, listed from 127 to 217 items, and have been validated for use in the UK (Bingham *et al.*, 1997; Brunner *et al.*, 2001; Cade *et al.*, 2004)

The majority of data from the food diaries were coded to give nutrient intakes and food group information using data entry and processing programs DINER and DINERMO developed at the MRC Centre for Nutritional Epidemiology in Cancer prevention and Survival (Welch *et al.*, 2001). One hundred and seven UKWCS food diaries were coded and processed using the DANTE program (Cade *et al.*, 2006). We compared 100 food diaries coded under both systems and found good agreement between DANTE and DINER/DINERMO for most nutrients, although the geometric mean intake of alcohol from DINER was 7% higher (95% CI= 3% to 11%) than from DANTE.

Alcohol consumption assessment

For the food diaries completed by all centres, *beer* (stout, bitter, lager; keg, draught, bottled, canned; low alcohol, strong, home-made; number of pints, bottles, cans), *cider* (sweet, dry, vintage, low alcohol; number of pints, bottles, cans), *spirits* (what sort: e.g. whisky, gin, vodka, rum; at home or in pub; single measures as in pub), *wine, sherry, port* (white, red; sweet, medium, dry; low alcohol; glasses) were assessed for alcohol intake.

The FFQs from EPIC-Norfolk, EPIC-Oxford, UKWCS and Whitehall II were designed to measure a participant's usual food intake during the previous year. In the four centres, FFQs asked participants to estimate how often they drink the following the beverages, *"Beer, larger or cider (half pint)", "Port, sherry, vermouth, liqueurs (glass)", and "Spirits, e.g. gin, brandy, whisky, vodka (single)"*. For each item on the list, participants were asked to indicate their usual consumption, choosing from nine frequency categories, ranging from "*never or less than once per month*" to "*more than 6 times per day".*

Statistical analysis

Conditional logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for the CRC risk according to alcohol consumption, with adjustment for potential confounding variables.

The participants were categorised into six groups according to their baseline alcohol consumption, with the lightest category of drinkers (>0 to <5 g/day) as a reference group: 0 (non-drinkers), >0 to <5, 5 to <15, 15 to <30, 30 to <45, ≥45 g/day. An initial unadjusted model was first created to estimate ORs for CRC across categories of alcohol intake. Because the matching of cases and controls by age was not exact, the conditional logistic regression models were adjusted for age in years to control for any residual confounding. Multivariable model 1 also adjusted for intakes of energy (kcal/day); folate (μg/day); dietary fibre (g/day); red meat (g/day); and processed meat (g/day) in addition to height (m), weight (kg), smoking status (never, former, current) and social class (6 categories). There were some missing data within-studies, with approximately 1% of individuals missing weight, height and smoking status, and approximately 5% missing social class, all of which were recorded in all studies. The distribution of alcohol consumption among individuals with and without these missing data was similar. For these variables missing values were assumed to be missing at random and were imputed using multiple imputation. Ten imputed datasets were created and multivariable models were fitted using the 'ice' (Royston, 2005) and 'mim'(Carlin, 2008) packages in STATA. Multivariable model 2 adjusted for physical activity (inactive, moderately inactive, moderately active, and active) and educational level (none, GCSE (completed to age 15), A Level

(completed to age 17), and degree level) in addition to the adjustments in multivariable model 1. Data on physical activity level were not available for NSHD and the Guernsey Study, and information on educational level was not available for Oxford Vegetarian Study. The effects of adjustment for these variables was assessed by fitting multivariable models 1 and 2 using the subset of participants (458 cases, 1,734 controls) with complete information on physical activity and educational level. Sex-specific models and anatomical subsite-specific models were also fitted using multivariable models 1 (579 cases, 1,996 controls) and 2 (458 cases, 1,734 controls). Tumours that were overlapping or unspecified were not included in site-specific analyses of the proximal and the distal colon cancer (n=60).

To investigate whether different nutritional instruments might alter our results, we repeated the analyses using FFQ data. Dietary data from FFQs were available for participants in EPIC-Norfolk, EPIC-Oxford, the UKWCS and Whitehall II (496 cases, 1,809 controls). These analyses were restricted to those 2,305 participants who completed both the FFQ and the food diary, and ORs were estimated using multivariable models 1 and 2.

Tests for trend were performed by modelling alcohol intake as a continuous variable in a conditional logistic regression analysis. To assess the possibility of a non-linear association between alcohol intake and CRC risk, the multivariable models were fitted with the inclusion of a quadratic term for continuous alcohol intake. Simple associations between categorical covariates and alcohol intake were assessed using Pearson's χ^2 tests for two independent proportions. For the continuous variables, means across categories of alcohol intake were compared by *t* tests or analysis of variance. All statistical tests were two-sided, and all statistical analyses were performed with the statistical software package STATA (version 10, Stata Corporation, College Station, Texas).

RESULTS

A total of 579 incident CRC cases and 1,996 matched controls were available for analysis from the 7 participating UK cohorts. Of these cancer cases, 380 were located in the colon and 199 in the rectum. There were no statistically significant differences in the means of alcohol intake between cases and controls in each cohort (Table 1).

Table 2 presents participant characteristics according to categories of alcohol consumption. Among drinkers, 82% consumed <30 g/day alcohol. Average alcohol intake was approximately 17 g/day (~2 units/day) for men and 8 g/day (1 unit/day) for women. Men less frequently reported being non-drinkers and more frequently reported drinking ≥30 g/day of alcohol than women. Men who consumed ≥30 g/day were significantly younger and had slightly higher BMI compared to those who consumed <30 g/day. These men with ≥30 g/day of alcohol consumption more frequently reported being former or current smokers, had higher energy intake, were physically less active, and had attained a higher educational level as well as being more likely to be non-manual workers. Similar patterns were seen among women although women with ≥30 g/day of alcohol consumption had a lower mean BMI compared to non-drinkers and there was no significant difference in physical activity levels across categories of alcohol intake.

Table 3 shows the ORs for CRC by categories of alcohol intake as assessed by food diary from age-adjusted and multivariable models. Non-drinkers had a moderate, non-significant increased risk compared with those who drank >0 to <5 g/day (<1 unit/day) in the main models. As we were not able to differentiate individuals who did not drink in the time period during which their food diaries were recorded from never drinkers (former drinkers or life-long never-drinkers), the category of non-drinkers might include temporary non-drinkers who are in fact drinkers. We therefore focused on analyses from individuals who reported non-zero alcohol intake. In general, alcohol intake was not significantly associated with risk of CRC (Table 3). Compared with individuals in the lowest category of alcohol intake among drinkers (>0 to <5 g/day), individuals in the highest category of intake who consumed ≥45 g/day (~6 units/day) did not have a significantly higher CRC risk before or after adjustment for age, weight, height, smoking status, social class, and intakes of energy, fibre, folate, red meat, and processed meat (OR: 1.19; 95% CI: 0.75, 1.91). None of the other categories showed a significant association with CRC risk compared with the group consuming >0 to <5 g/day of consumption. There were no significant sex-specific associations observed between alcohol intake and CRC risk. When we conducted further analyses adjusting for non-alcohol energy as well as the same covariates used in multivariable models, the results scarcely differed and they did not vary by sex.

In the sensitivity analysis where further adjustment for physical activity and educational level was made in a subset of the study population with complete covariate information, being a non-drinker was significantly associated with an increased CRC risk. However, this result was seen under both multivariable models 1 and 2 in the sensitivity analysis, indicating that the result is not due to adjustment for physical activity and educational level but rather to the omission of some cohorts from the analysis. The point estimates for the highest category of alcohol intake tended to be higher in this subset of studies (OR: 1.41; 95% CI: 0.85, 2.34 for ≥45 g/day). As in the main analyses, adjustment for physical activity and educational level did not alter the results in the subset.

Multivariable models 1 and 2 were suggestive of a J-shaped association between alcohol intake and CRC risk. However, a further analysis using continuous alcohol intake with a quadratic term provided no evidence for a non-linear association between alcohol intake and CRC risk (*P* for quadratic term=0.17 for drinkers). Additional adjustment for family history of CRC (343 cases and 1,370 controls) did not make substantial differences to ORs (data not shown).

When we investigated these associations further by tumour subsites (stratified by sex), there were no clear associations observed between risks of overall colorectum, proximal/distal colon, or rectum and alcohol consumption in both sexes (Table 4). The analysis using multivariable model 2 for the subset of individuals with information on physical activity and educational level showed increased distal colon cancer risk for alcohol intake of ≥30 g/day compared with intake of >0 to <5 g/day (OR: 2.36; 95% CI: 1.13, 4.91, *P* trend for drinkers =0.03). However, this may be a chance finding.

Using data from food diaries we were also able to examine the association between specific alcoholic beverage consumption and risk of CRC. When we calculated multivariable ORs per 1 standard deviation (SD) increase in intake of beer (280 g), wine (70 g), spirits (20 g), and fortified wine (24 g), there were no clear associations observed. The results did not vary by sex (data not shown).

Table 5 and Figure 1 show a comparison of the results from using FFQ and food diary to obtain measurements of alcohol intake. Analyses using FFQ resulted in a similar pattern of associations to those using food diaries. The association between alcohol intake and CRC risk remains statistically non-significant using FFQ, though suggests an increasing trend in the odds ratio estimates with increasing alcohol intake (*P* for trend=0.09 among drinkers in multivariable model 1). The distribution of participants across the categories of alcohol consumption differed in the FFQ and food diary data. Among the subset of participants with both measurements (n=2,305), out of 646 individuals who reported 0 intake on the food diary, 305 (47 %) reported

being a non-drinker on the FFQ. Almost 95% of individuals (n=613) reporting 0 alcohol intake on the food diary consumed less than 5 g/day of alcohol according to the FFQ. There were 67 individuals (18 %) who reported 0 alcohol intake on FFQ and >0 alcohol intake on the food diary.

Sex-specific analyses of the linear association between CRC risk and an increase in alcohol intake of 8 g/day (1 unit/day) showed no clear linear associations in either sex (OR: 0.99; 95% CI: 0.93, 1.05 for men, OR: 1.01; 95% CI: 0.92, 1.12 for women in multivariable model 1). The results scarcely differed from the analyses using drinkers only. When we examined interactions between alcohol intake and BMI (<25 kg/m^2, ≥25 kg/m^2), smoking status (never, former or current), the *P* values for the interaction were 0.26 for BMI and 0.53 for smoking status. The Reference Nutrient Intake (RNI) in the UK for folate is 200 µg/day (Department of Health, 1999). When folate intake was dichotomised below and above this level, the *P* value for interaction was 0.59. There was no evidence of heterogeneity between centres in the association between alcohol intake and CRC risk in the different centres (*P*=0.30). Centre specific ORs for CRC per 8 g/day of alcohol intake (1 unit/day) were computed. The summary OR estimate for 8 g/day increase in alcohol intake was derived by fixed effects meta-analysis and found to be 1.00 (95% CI: 0.95, 1.05) after adjusting for age, and intakes of energy, folate, fibre, and red and processed meat.

DISCUSSION

In this large nested case-control study of 579 CRC cases and 1,996 matched controls, alcohol intake within the observed range was not associated with a significantly increased CRC risk after multivariable adjustment when compared with alcohol consumption of >0 to <5 g/day. In subgroup analyses of cancer sites including proximal/distal colon and rectum there were no clear associations observed with total alcohol intake. There was also no evidence of a difference between men and women in the association between alcohol intake and CRC risk. Analyses using a subset of participants that had completed both FFQs and food diaries showed similar shaped associations using each of the two instruments, though risk estimates were higher but still statistically non-significant when using FFQ data.

Recent cohort studies where FFQs were the main nutritional instrument have shown no association (Chen *et al.*, 2005), or a significant adverse effect of alcohol when consumption is greater than about 16 g/day (Toriola *et al.*, 2008), 30 g/day (Bongaerts *et al.*, 2008; Ferrari *et al.*, 2007; Mizoue *et al.*, 2008), or about 45 g/day (Akhter *et al.*, 2007) compared with study-specific reference groups of lower intakes. These recent studies have not found consistent results in sex- and subsite- specific analyses, with several studies finding greater risk of rectal than colon cancer for alcohol consumption of ≥30 g/day (Bongaerts *et al.*, 2008; Ferrari *et al.*, 2007). The Million Women Study recently reported a positive association between moderate alcohol intake (>15 drinks/week) and rectal cancer risk but found no evidence of increased colon cancer risk among middle-aged women (Allen *et al.*, 2009). Previous studies have, however, failed to reach clear consensus on the association between moderate alcohol drinking (<30g/day) and colon or rectal cancer risk, and there are still few studies which have investigated proximal and distal colon cancer separately.

It has been suggested that the aetiology of CRC varies by subsite (Li and Lai, 2009; Stang and Kluttig, 2008). The proximal and distal colon have different embryonic origins and their physiology and functions may vary (Stang and Kluttig, 2008). Studies have also shown that microsatellite instability is often linked to proximal colon cancer while chromosomal instability is more common in distal colon cancer (Lindblom, 2001). Subsite-specific studies are therefore required for better understanding of the aetiology of CRC. Our study, exploring CRC subsites in men and women in detail, suggested elevated risk of distal colon cancer, for individuals with alcohol intake of ≥30 g/day compared with >0 to <5 g/day and a possible dose-response relationship among drinkers when analysed for the subset of cohorts with complete covariate information. Thus, future studies are warranted focusing on a possible role of alcohol use in risk of colon cancer, especially proximal or distal colon cancer.

The Panel of the WCRF/AICR Report judged that the evidence of alcohol consumption of >30 g/day as a cause of CRC is convincing in men and probable in women (WCRF/AICR, 2007), based on a sex-specific meta-analysis finding summary effect estimates of 1.09 (95% CI: 1.02, 1.15) per 10

g/day increase in alcohol intake for men, based on 7 cohort studies, and 1.00 (95% CI: 0.89, 1.40) for women, based on 3 cohort studies. There were no statistically significant differences in association by cancer site. The threshold of 30 g/day of alcohol intake is from the results of the pooled analysis of 8 cohort studies where no increased risk was observed below the threshold (Cho *et al.*, 2004).

Our results are consistent with the 2007 WCRF/AICR Report. We found no increased risk of CRC up to 30 g/day of alcohol intake, with no substantial differences detected in subsite specific analyses. Although men and women have been shown to have different physiological responses to alcohol (Ely *et al.*, 1999) and the effect of alcohol in our study seemed larger in men (OR:1.24, 95% CI:0.76-2.03 for drinkers with ≥ 30 g/day compared with the lightest category drinkers (>0 to <5 g/day)) than in women (OR:1.03, 95% CI:0.54-1.96 for drinkers with ≥ 30 g/day compared with the lightest category of drinkers (>0 to <5 g/day)), the associations were not statistically significant. We did not find differential associations with CRC risk by type of alcoholic beverage. This is consistent with the Report which judged that the causal factor is evidently alcohol itself, irrespective of the type of alcoholic drink. There were a limited number of studies included in the meta-analysis of alcohol intake and CRC risk in the WCRF/AICR Report. Our findings therefore contributes to update the current evidence for a future review, confirming no significantly increased risk of CRC with <30 g/day of alcohol consumption.

The mechanism by which alcohol may influence CRC risk is not well understood (Stewart and Kleihues, 2003). Hypotheses include a local solvent action which facilitates absorption of other carcinogens, e.g. a synergetic effect with tobacco smoking (Boffetta and Hashibe, 2006), and an indirect effect through associated deficiencies in nutrients, especially through changes in folate metabolism (Giovannucci *et al.*, 1995). However, in our study there were no significant interactions observed between alcohol consumption and folate intake or tobacco smoking with regard to CRC risk.

Our study has several strengths. Its prospective study design precluded bias attributable to differential recall of intake of alcohol by case status. We were able to examine the influence of alcohol consumption on site- and sex- specific CRC risk. Furthermore, different types of alcoholic beverages from food diaries were assessed in association with CRC risk.

This study provided the measure of alcohol intake by using both food diaries as well as FFQs whereas previous studies on alcohol and CRC risk have relied on FFQs only. Use of food diaries and FFQs for habitually consumed food items have been discussed (Bingham *et al.*, 2008; Bingham *et al.*, 1997; Bingham *et al.*, 2003). However, there have been few direct attempts to compare those two different nutritional instruments prospectively for episodically consumed food items, including alcohol. Previous studies have shown that FFQs were not inferior in measuring alcohol intake relative to prospective food diaries (Feunekes *et al.*, 1999), and FFQ showed a high level of reproducibility and validity compared to diet records as a reference method (Ferraroni *et al.*, 1996). Our study, which has information both from food diaries and FFQs from 7 different prospective cohort studies in the UK, found that although FFQs and food diaries cover different durations and measurements may differ

between the two instruments, using well constructed food diaries for measurement of infrequently consumed food items can provide results that do not differ substantially from those using FFQs.

This study used original data from seven UK mature cohorts with standardised diary data entry which enabled us to create identical categories for alcohol intake across studies that were in line with previous studies (Cho *et al.*, 2004), removing some potential sources of heterogeneity across studies. Furthermore, we were able to adjust for a range of known confounding factors.

An important limitation of this study is that we were not able to differentiate lifelong abstainers and former drinkers in the category of non-drinkers in either FFQs or diaries. As previously discussed, many non-drinkers may be former drinkers who had given up drinking due to incipient disease (Doll *et al.*, 1994), although a sensitivity analysis excluding a further 111 cases incident within 3 years of diary completion did not materially change our results. Moreover, in the 4-7 day diaries we were not able to differentiate non-drinkers and episodic drinkers who happened not to consume alcohol during the time period covered by the diary. Hence it is likely that the "non-drinker" category in our diary analyses contains participants who were actually drinkers at the time when diaries were administered. In light of this, we focused on analyses from non-zero alcohol drinkers and reported trend tests for drinkers separately. We found a moderate positive but non-significant CRC risk in those consuming ≥30 g/day of alcohol using data both from food diaries and FFQs. However, in our study, almost half of the participants reported drinking <5 g/day in both food diaries and FFQs and only 19% of men and 17% of women reported intake in excess of the recommended daily maxima of 3-4 units (<32 g) daily for men and 2-3 units (<24 g) daily for women. This compares with 34% of men and 22% of women of a similar age who reported exceeding the recommended daily maxima in a national sample (The National Health Service the Information Centre, 2008). Insufficient participants in the heavier categories prevented us from estimating any potential effect of high alcohol consumption with sufficient precision.

Another limitation was that alcohol intake was assessed only once by self-report. Since heavy alcohol drinking is considered to be unhealthy, it is likely that individuals under-report their alcohol intake, particularly in the case of heavy consumption (Rehm *et al.*, 1999), resulting in overestimation of the actual carcinogenic effect of the habit. In addition, drinking habits are liable to change throughout the lifetime. However, we conducted a sensitivity analysis using data from the EPIC-Norfolk cohort where information on alcohol consumption from participants recalling their habits at age 20 and 30 is available, and we again did not find any evidence of an association with CRC risk, although participants tended to report higher alcohol intake at the younger ages (data not shown). Nonetheless, more research with additional information on alcohol consumption over a longer period of time as well as on specific drinking behaviour such as binge drinking is needed to clarify any hazardous effect of excessive alcohol drinking on CRC risk.

In summary, we found no increased risk of colorectal cancer up to 30 g/day of alcohol intake within the UK Dietary Cohort Consortium. However, due to an insufficient number of participants in

the heavier categories, a modest increased risk in those consuming ≥30 g/day cannot be excluded. Drinking-related morbidity and mortality constitute a large burden of diseases in Europe and worldwide (Ezzati *et al.*, 2004; Rehm *et al.*, 2006). Furthermore, IARC recently affirmed that alcoholic beverages as carcinogens (WHO/IARC, 2006), and excessive alcohol consumption has also been causally related to numerous disease categories in the 10th revision of the ICD (Rehm *et al.*, 2003). The risks of alcohol intake should therefore be carefully considered in any decisions about alcohol drinking.

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Table 1 Description of studies participating in the UK Dietary Cohort Consortium and summary of alcohol intake among colorectal cancer cases and matched controls[1]

Study	Age Range at Baseline	Size of the Cohort at Baseline	Assessment of alcohol intake	CRC cases		CRC controls		Mean alcohol intake for cases (SD)		Mean alcohol intake for controls (SD)	
				Men	Women	Men	Women	Men	Women	Men	Women
EPIC-Norfolk	40-77 yrs	25,000	7DD / FFQ	179	139	716	556	15.2 (18.6)	6.7 (11.9)	15.5 (21.1)	7.2 (10.8)
EPIC-Oxford	32-84 yrs	65,429	7DD / FFQ	39	82	87	193	17.0 (17.5)	8.4 (11.3)	21.0 (27.8)	8.1 (10.8)
Guernsey Study	39-78 yrs	6,127	4DD	N/A	28	N/A	55	N/A	7.6 (10.4)	N/A	6.0 (10.8)
Oxford Vegetarian Study	26-79 yrs	11,140	4DD	7	24	16	54	6.3 (7.3)	7.7 (15.9)	9.8 (12.5)	9.1 (13.3)
MRC National Survey of Health and Development (NSHD)	43 yrs	5,362	7DD	4	3	16	12	39.1 (66.1)	16.4 (14.3)	28.9 (23.7)	13.6 (11.6)
UK Women's Cohort Study (UKWCS)	44-78 yrs	35,792	4DD / FFQ	N/A	25	N/A	100	N/A	9.3 (13.9)	N/A	8.1 (11.3)
Whitehall II	41-62 yrs	10,308	7DD / FFQ	37	12	145	46	25.8 (26.3)	18.2 (17.2)	22.2 (20.4)	8.8 (10.4)

[1] A t-test indicated that there was no statistically significant difference in mean alcohol intake between the cases and controls.

Table 2 Distribution of participant characteristics by categories of alcohol intake as assessed by food diaries, shown separately for men and women

	Baseline alcohol intake						
	Non-drinkers	>0 to <5 g/d	5 to <15 g/d	15 to <30 g/d	30 to <45 g/d	≥ 45 g/d	*P* value[2]
All							
Cases/controls (*n*)	187/574	112/405	116/443	86/328	40/135	38/111	
Men							
Cases/controls (*n*)	68/200	39/175	55/224	45/188	28/96	31/97	
Alcohol at baseline (g/day)	0.0	2.7 (1.4)	9.5 (2.9)	21.8 (4.2)	36.6 (4.2)	66.1 (24.4)	<0.001
Age (years)	64.2 (8.4)	63.1 (8.3)	61.7 (9.8)	61.5 (9.1)	60.0 (8.5)	59.9 (9.2)	<0.001
Height (m)	1.73 (0.1)	1.73 (0.1)	1.75 (0.1)	1.75 (0.1)	1.75 (0.1)	1.75 (0.1)	<0.001
Weight (kg)	77.9 (11.7)	80.8 (13.2)	78.1 (11.2)	79.7 (10.3)	80.7 (11.1)	82.4 (11.6)	<0.001
BMI (kg/m^2)	26.1 (3.4)	26.9 (4.0)	25.6 (3.2)	26.1 (3.0)	26.2 (2.9)	26.8 (3.0)	<0.001
Cigarette smoking status (%)[3]							
Never	41.1	32.7	35.4	35.2	33.1	21.4	0.001
Former	49.1	60.7	57.4	55.4	53.2	60.3	
Current	9.8	6.6	7.2	9.4	13.7	18.3	
Total energy (Kcal)[4]	2077 (546)	2117 (470)	2218 (479)	2225 (486)	2345 (478)	2478 (545)	<0.001
Physical activity (%)[3,5]							
Low	67.3	56.9	60.9	47.6	61.7	63.1	0.001
High	32.7	43.1	39.1	52.4	38.3	36.9	
Educational level (%)[3,6]							
Low	58.0	43.1	41.3	42.3	37.9	33.9	<0.001
High	42.0	56.9	58.7	57.7	62.1	66.1	
Social class[3,7]							
Non-manual	50.2	59.6	64.3	76.3	80.0	77.0	<0.001
Manual	49.8	40.4	35.7	23.7	20.0	23.0	
Family history of colorectal cancer (%)[3]							
No	93.5	91.1	94.2	95.5	91.9	93.6	0.69
Yes	6.5	8.9	5.8	4.5	8.1	6.4	
Folate intake (µg/day)	282 (90)	274 (69)	293 (82)	294 (85)	308 (86)	314 (92)	<0.001
Fibre intake (g/day)	17 (7)	17 (6)	17 (6)	16 (6)	16 (5)	14 (6)	<0.001
Red meat intake (g/day)	33 (30)	34 (25)	39 (30)	40 (27)	40 (30)	46 (34)	<0.001
Processed meat intake (g/day)	24 (24)	27 (22)	25 (20)	29 (24)	27 (23)	30 (22)	0.02
Women							
Cases/controls (*n*)	119/374	73/230	61/219	41/140	12/39	7/14	
Alcohol at baseline (g/day)	0.0 (0.0)	2.5 (1.4)	9.4 (2.9)	21.5 (4.5)	35.3 (3.8)	56.9 (11.3)	<0.001
Age (years)	63.1 (9.7)	62.5 (9.0)	60.2 (9.5)	58.7 (10.6)	57.8 (10.9)	59.3 (11.5)	<0.001
Height (m)	1.60 (0.07)	1.61 (0.06)	1.62 (0.07)	1.62 (0.06)	1.64 (0.06)	1.60 (0.05)	<0.001
Weight (kg)	66.8 (13.1)	66.9 (11.7)	66.5 (11.0)	65.4 (10.9)	66.7 (10.1)	61.2 (9.4)	0.27
BMI (kg/m^2)	26.1 (4.8)	25.9 (4.3)	25.5 (4.0)	24.9 (4.1)	24.8 (3.3)	23.9 (3.7)	0.005
Cigarette smoking status (%)[3]							
Never	64.5	59.5	57.1	53.7	40.0	19.1	<0.001
Former	27.8	33.1	33.2	37.3	38.0	61.9	
Current	7.6	7.4	9.6	9.0	22.0	19.1	
Total energy (Kcal)[4]	1639 (418)	1653 (334)	1747 (369)	1803 (372)	1909 (354)	1916 (269)	<0.001
Physical activity (%)[3,5]							
Low	73.7	68.1	66.0	68.6	73.8	65.0	0.33
High	26.4	32.0	34.0	31.5	26.2	35.0	
Educational level (%)[3,6]							
Low	71.6	69.0	58.2	60.9	47.9	27.8	<0.001
High	28.4	31.0	41.8	39.1	52.1	72.2	
Social class[3,7]							
Non-manual	69.0	72.1	79.6	85.6	83.3	95.2	<0.001
Manual	31.0	27.9	20.4	14.4	16.7	4.8	
Family history of colorectal cancer (%)[3]							
No	91.4	93.9	87.4	93.9	93.3	100.0	0.20
Yes	8.6	6.1	12.7	6.1	6.7	0.0	
Folate intake (µg/day)	246 (78)	247 (70)	252 (70)	250 (73)	251 (65)	241 (72)	0.93
Fibre intake (g/day)	15 (6)	15 (5)	15 (5)	15 (5)	14 (4)	12 (5)	0.14
Red meat intake (g/day)	25 (26)	28 (26)	29 (26)	33 (32)	41 (36)	38 (25)	0.002
Processed meat intake (g/day)	16 (18)	15 (15)	15 (15)	17 (17)	17 (16)	16 (19)	0.96

[1] Mean (SD) or number (%), and ***P*** values for tests of association

[2] For continuous variables analysis of variance or a Kruskal-Wallis test (for red meat and processed meat intake) was used to test whether the variable differed significantly across categories of alcohol intake. For categorical variables X^2 tests were used to assess association with alcohol intake.

[3] Numbers do not sum to the total number of participants due to missing data

[4] Total energy includes energy from alcohol

[5] Low physical activity was defined as being inactive or moderately inactive and high physical activity was defined as being moderately active or active

[6] Educational levels were regrouped into low educational level (no qualification or GCSE level or equivalent) and high educational level (degree or equivalent, A-level or equivalent)

[7] Social class was classified according to the Registrar General's occupation based classification scheme and was dichotomised into non-manual (social class I, II, and IIInm) and manual (IIIm, IV, and V)

Table 3 Odds ratios (95% confidence intervals) from multivariable models for colorectal cancer risk in categories of total alcohol intake as assessed by food diaries

	Alcohol intake (g/day)							
	Non-drinkers	>0 to <5 g/d	5 to <15 g/d	15 to <30 g/d	30 to <45 g/d	≥ 45 g/d	*P* for trend	*P* trend for drinkers
Main models [1]								
No. of all participants	761	517	559	414	175	149		
Colorectal cancer cases	187	112	116	86	40	38		
Age- adjusted model[2]	1.15 (0.88 – 1.51)	1.00	0.93 (0.69 – 1.26)	0.93 (0.68 – 1.28)	1.13 (0.74 – 1.72)	1.29 (0.83 – 2.01)	0.79	0.31
Multivariable model 1[3]	1.16 (0.88 – 1.53)	1.00	0.91 (0.67 – 1.24)	0.90 (0.65 – 1.25)	1.02 (0.66 – 1.58)	1.19 (0.75 – 1.91)	0.82	0.44
Male	1.53 (0.98 – 2.41)	1.00	1.06 (0.66 – 1.69)	1.02 (0.63 – 1.66)	1.20 (0.68 – 2.12)	1.24 (0.69 – 2.22)	0.97	0.21
Female	1.00 (0.70 – 1.42)	1.00	0.84 (0.56 – 1.26)	0.87 (0.55 – 1.37)	0.90 (0.43 – 1.87)	1.52 (0.56 – 4.10)	0.72	0.97
Sensitivity analysis [4]								
Multivariable model 1[3]	1.48 (1.08 – 2.03)	1.00	0.94 (0.66 – 1.33)	1.00 (0.69 – 1.45)	1.21 (0.75 – 1.96)	1.41 (0.85 – 2.34)	0.79	0.22
Multivariable model 2[5]	1.49 (1.08 – 2.05)	1.00	0.93 (0.65 – 1.33)	0.98 (0.68 – 1.43)	1.23 (0.76 – 1.99)	1.39 (0.83 – 2.32)	0.82	0.17

[1] Main conditional logistic regression models: All participants (579 cases, 1,996 controls); *P* values for trend were drawn from tests for trend by modeling alcohol intake as a continuous variable in a conditional logistic regression analysis while *P* values trend for drinkers were drawn from tests for trend only from non-zero alcohol drinkers.
[2] Age adjusted
[3] Adjusted for age, weight, height, smoking status, social class, intakes of energy, fibre, folate, red meat, and processed meat.
[4] Sensitivity analyses: restricted to individuals with complete covariates information (458 cases, 1,734 controls)
[5] Adjusted for age, weight, height, physical activity, educational level, smoking status, social class, intakes of energy, fibre, folate, red meat, and processed meat,.

Table 4 Odds ratios (95% confidence intervals) by subsite of colorectal cancer according to alcohol intake

	Overall Colorectum				Colon				Proximal Colon				Distal Colon				Rectum			
	Cases	OR (95%CI)	*P* for trend	*P* trend for drinkers	Cases	OR (95%CI)	*P* for trend	*P* trend for drinkers	Cases	OR (95%CI)	*P* for trend	*P* trend for drinkers	Cases	OR (95%CI)	*P* for trend	*P* trend for drinkers	Cases	OR (95%CI)	*P* for trend	*P* trend for drinkers
Multivariable model 1 [1]																				
All participants																				
Non-drinkers	187	1.16 (0.88 −1.53)	0.72	0.69	122	1.18 (0.83 −1.66)	0.85	0.63	60	1.26 (0.81 −1.97)	0.54	0.59	46	0.97 (0.60 −1.56)	0.46	0.17	65	1.10 (0.68 −1.78)	0.76	0.86
>0 to <5 g/d	112	1.00 (Reference)			74	1.00 (Reference)			33	1.00 (Reference)			29	1.00 (Reference)			38	1.00 (Reference)		
5 to <30 g/d	202	0.91 (0.69 −1.19)			132	0.88 (0.63 −1.22)			58	0.88 (0.57 −1.34)			48	0.91 (0.58 −1.45)			70	0.97 (0.60 −1.58)		
≥30 g/d	78	1.09 (0.76 −1.58)			52	1.21 (0.77 −1.90)			23	1.03 (0.57 −1.86)			23	1.60 (0.85 −3.01)			26	0.93 (0.48 −1.78)		
Male participants																				
Non-drinkers	68	1.52 0.97 −2.39)	0.90	0.23	46	1.82 (1.02 −3.22)	0.69	0.21	23	2.46 (1.10 −5.51)	0.40	0.28	20	1.22 (0.56 −2.65)	0.86	0.42	22	1.14 (0.53 −2.43)	0.93	0.90
>0 to <5 g/d	39	1.00 (Reference)			26	1.00 (Reference)			20	1.00 (Reference)			19	1.00 (Reference)			13	1.00 (Reference)		
5 to <30 g/d	100	1.04 (0.68 −1.58)			61	1.05 (0.62 −1.77)			28	1.41 (0.67 −2.97)			22	0.83 (0.42 −1.66)			39	1.10 (0.53 −2.26)		
≥30 g/d	59	1.24 (0.76 −2.03)			39	1.49 (0.81 −2.74)			20	1.93 (0.83 −4.50)			16	1.16 (0.50 −2.66)			20	1.04 (0.43 −2.51)		
Female participants																				
Non-drinkers	119	1.00 (0.70 −1.43)	0.54	0.63	76	0.93 (0.60 −1.46)	0.55	0.73	37	0.93 (0.53 −1.63)	0.16	0.14	26	0.88 (0.46 −1.67)	0.19	0.27	43	1.15 (0.60 −2.19)	0.84	0.97
>0 to <5 g/d	73	1.00 (Reference)			48	1.00 (Reference)			23	1.00 (Reference)			16	1.00 (Reference)			25	1.00 (Reference)		
5 to <30 g/d	102	0.85 (0.59 −1.23)			71	0.81 (0.51 −1.27)			30	0.73 (0.42 −1.28)			26	1.05 (0.55 −2.00)			31	0.94 (0.48 −1.86)		
≥30 g/d	19	1.03 (0.54 −1.96)			13	1.09 (0.49 −2.42)			3	0.52 (0.17 −1.61)			7	3.34 (1.11 −10.02)			6	0.95 (0.30 −2.95)		
Multivariable model 2 [2]																				
All participants																				
Non-drinkers	147	1.49 (1.08 −2.05)	0.93	0.32	99	1.63 (1.09 −2.43)	0.67	0.20	57	1.99 (1.18 −3.34)	0.76	0.77	34	1.31 (0.73 −2.34)	0.08	0.03	48	1.23 (0.70 −2.17)	0.67	0.73
>0 to <5 g/d	84	1.00 (Reference)			55	1.00 (Reference)			28	1.00 (Reference)			23	1.00 (Reference)			29	1.00 (Reference)		
5 to <30 g/d	156	0.95 (0.70 −1.30)			107	1.00 (0.68 −1.47)			49	0.97 (0.59 −1.61)			39	1.23 (0.71 −2.12)			49	0.86 (0.49 −1.53)		
≥30 g/d	71	1.30 (0.86 −1.95)			47	1.47 (0.89 −2.43)			20	1.25 (0.63 −2.47)			23	2.36 (1.13 −4.91)			24	1.01 (0.48 −2.11)		
Male participants																				
Non-drinkers	61	1.64 (1.01 −2.66)	0.76	0.16	42	2.08 (1.14 −3.82)	0.53	0.14	23	2.80 (1.17 −6.67)	0.57	0.41	17	1.44 (0.63 −3.29)	0.63	0.21	19	1.04 (0.43 −2.51)	0.96	0.73
>0 to <5 g/d	34	1.00 (Reference)			23	1.00 (Reference)			9	1.00 (Reference)			12	1.00 (Reference)			11	1.00 (Reference)		
5 to <30 g/d	90	1.05 (0.67 −1.64)			58	1.13 (0.65 −1.95)			27	1.43 (0.64 −3.18)			20	0.98 (0.47 −2.06)			32	0.99 (0.43 −2.28)		
≥30 g/d	56	1.36 (0.80 −2.30)			37	1.65 (0.86 −3.14)			19	1.78 (0.71 −4.46)			16	1.64 (0.64 −4.16)			19	1.06 (0.39 −2.92)		
Female participants																				
Non-drinkers	86	1.34 (0.87 −2.08)	0.59	0.82	57	1.31 (0.76 −2.28)	0.75	0.92	34	1.65 (0.81 −3.35)	0.19	0.10	17	1.05 (0.43 −2.57)	0.09	0.26	29	1.44 (0.64 −3.25)	0.77	0.83
>0 to <5 g/d	50	1.00 (Reference)			32	1.00 (Reference)			19	1.00 (Reference)			11	1.00 (Reference)			18	1.00 (Reference)		
5 to <30 g/d	66	0.82 (0.52 −1.30)			49	0.88 (0.50 −1.54)			22	0.71 (0.34 −1.49)			19	1.56 (0.63 −3.84)			17	0.65 (0.27 −1.59)		
≥30 g/d	15	1.19 (0.56 −2.53)			10	1.20 (0.46 −3.13)			1	0.50 (0.11 −2.37)			7	3.76 (0.92 −15.37)			5	1.53 (0.40 −5.91)		

[1]Age, weight, height, smoking status, social class, intakes of energy, fibre, folate, red meat, and processed meat, adjusted (579 cases, 1,996 controls)

[2]Age, weight, height, physical activity, educational level, smoking status, social class, intakes of energy, fibre, folate, red meat, and processed meat, adjusted (458 cases, 1,734 controls)

Table 5 Odds ratios (95% confidence intervals) from multivariable models for colorectal cancer risk in categories of alcohol intake as assessed by food diaries and FFQs among participants with both measures[1]

	Alcohol intake (g/day)							
	Non-drinkers	>0 to <5 g/d	5 to <15 g/d	15 to <30 g/d	30 to <45 g/d	≥45 g/d	*P* for trend	*P* trend for drinkers
Food diaries								
No. of all participants	646	477	510	371	165	136		
Colorectal cancer cases	149	100	100	75	38	34		
Multivariable model 1[2]	1.18 (0.88 – 1.60)	1.00	0.91 (0.66 – 1.26)	0.92 (0.65 – 1.30)	1.08 (0.68 – 1.70)	1.24 (0.76 – 2.04)	0.97	0.60
Multivariable model 2[3]	1.38 (1.00 – 1.91)	1.00	0.90 (0.63 – 1.29)	0.98 (0.67 – 1.42)	1.20 (0.74 – 1.95)	1.32 (0.79 – 2.22)	0.84	0.25
FFQs								
No. of all participants	372	867	662	226	100	78		
Colorectal cancer cases	84	171	150	46	26	19		
Multivariable model 1[2]	1.43 (1.04 – 1.97)	1.00	1.22 (0.94 – 1.58)	1.16 (0.79 – 1.72)	1.36 (0.81 – 2.28)	1.40 (0.79 – 2.49)	0.12	0.09
Multivariable model 2[3]	1.33 (0.96 – 1.86)	1.00	1.16 (0.87 – 1.53)	1.07 (0.71 – 1.61)	1.18 (0.68 – 2.03)	1.30 (0.72 – 2.38)	0.36	0.07

[1] Conditional logistic regression analyses were restricted to participants who completed both the FFQ and the food diary (496 cases, 1,809 controls). Because of missing information in FFQ data, models were not adjusted for intakes of energy, red meat, and processed meat. Adjusting for these variables in models using diary information did not alter the results. *P* values for trend were drawn from tests for trend by modeling alcohol intake as a continuous variable in a conditional logistic regression analysis while *P* values trend for drinkers were drawn from tests for trend only from non-zero alcohol drinkers.

[2] Adjusted for age, weight, height, smoking status, social class, intakes of fibre, and folate adjusted in the main model (496 cases, 1,809 controls)

[3] Adjusted for age, weight, height, physical activity, educational level, smoking status, social class, intakes of fibre, and folate in the sensitivity analyses restricted to individuals with complete covariate information (442 cases, 1,701 controls)

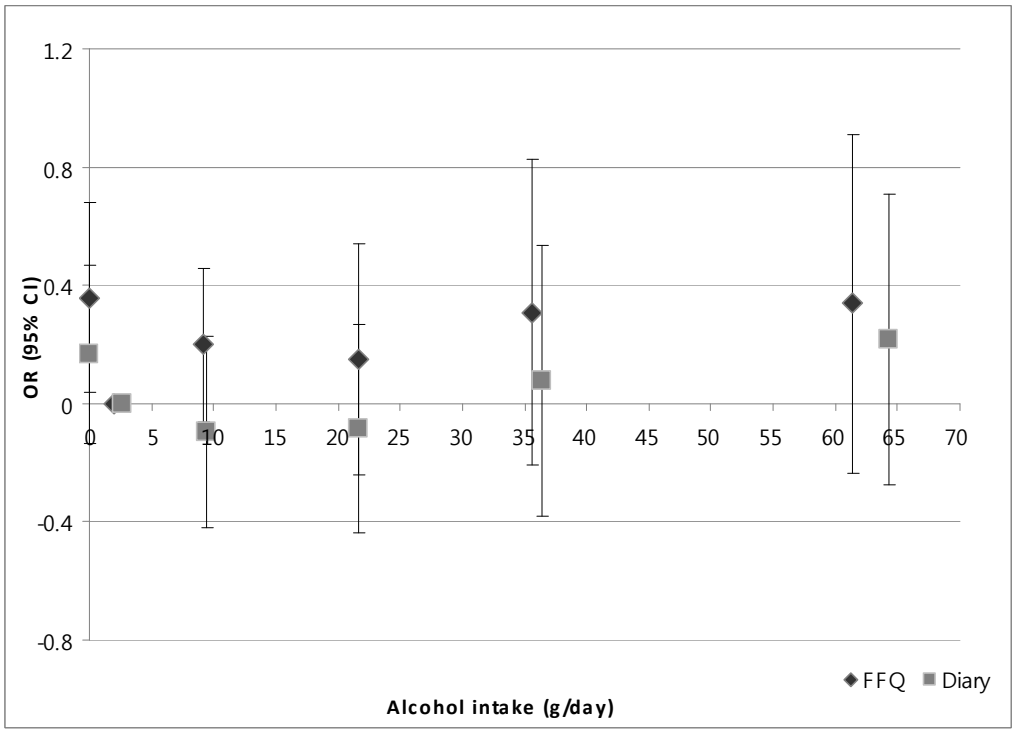
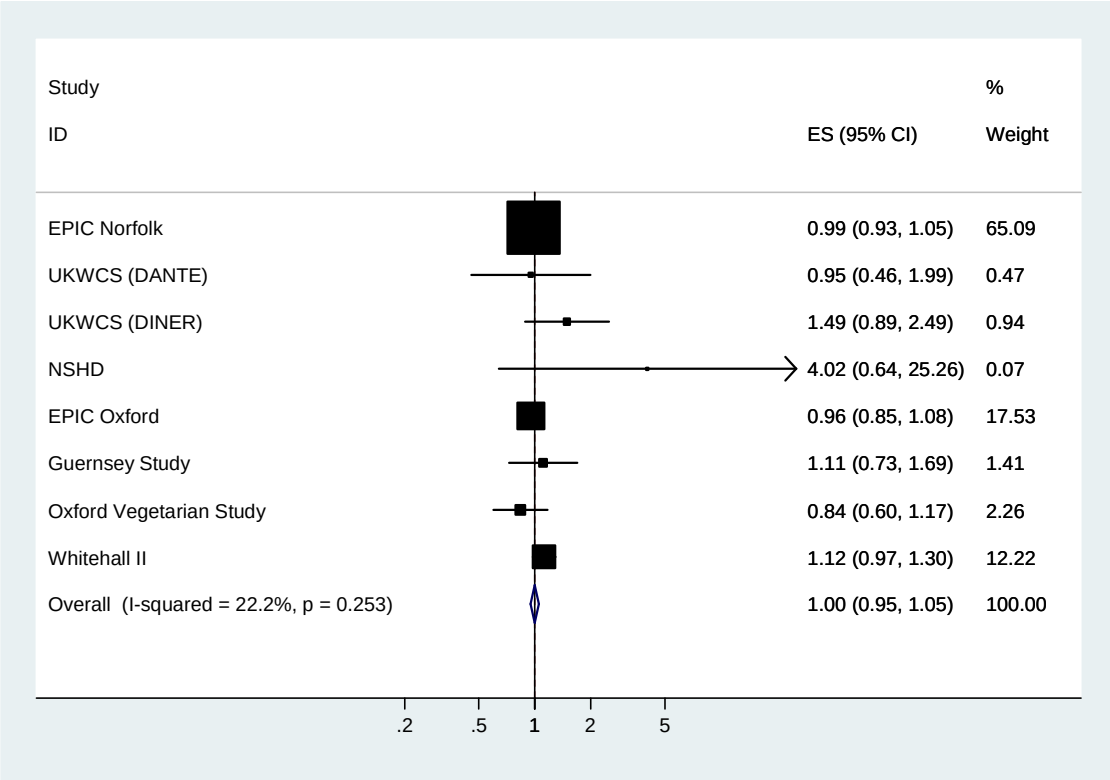


Figure 1 Comparison of odds ratios in a log scale for categories for alcohol intake data (0, >0 to <5 (reference), 5 to <15, 15 to <30, 30 to <45, and ≥45 g/day) obtained by food diaries or by FFQ. A total of 2,305 study participants had complete alcohol intake information from both diaries and FFQ (n=496 cases, 1,809 controls). Odds ratios for each category were plotted against the mean alcohol intake (g/day) for each category (0, 2.6, 9.4, 21.7, 36.4, and 64 g/day for food diaries and 0, 1.9, 9.1, 21.7, 35.6, and 61.3 g/day for FFQ, respectively) and were adjusted for age, weight, height, smoking status, social class, intakes of fibre, and folate.



Supplemental Data for Reviewers Only. Centre specific odds ratios (95% confidence intervals) for colorectal cancer per 8 g/day (1 unit/day) of alcohol intake. All participants (579 cases, 1,996 controls) were included and odds ratios were adjusted for age, intakes of energy, folate, fibre, and red and processed meat. The summary estimate was derived by fixed effects meta-analysis.