Does adequate Physical Activity Attenuate the Associations of Alcohol and Alcohol-Related Cancer Mortality? A Pooled Study of 54,686 British Adults

Short title: Physical Activity Attenuates the Associations of Alcohol and Alcohol-Related Cancer Mortality

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A list of abbreviations

BMI	Body Mass Index
CI	Confidence Interval
CVD	Cardiovascular Disease
GHQ	General Health Questionnaire
HR	Hazard Ratio
HSE	Health Survey for England
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
IQR	Interquartile Range
LSI	long-standing illness
MET	Metabolic Equivalent Task
NHS	National Health Service
PA	Physical activity
SHS	Scottish Health Survey

1. Introduction

Alcohol drinking is a pervasive behaviour in many parts of the world. In the United Kingdom in 2016, the average amount of alcohol consumed among individuals aged 15 years or older was equivalent to 11.5 litres of pure ethanol per person, almost double the global average (6.4 litres) (1). Alcohol consumption can have adverse effects on health and is recognised as a major contributor to all-cause mortality (2, 3), as well as cancer incidence and mortality (4, 5). Evidence currently suggests that the safest level of alcohol consumption is total avoidance (6). Reducing alcohol consumption is now widely recommended as a public health strategy to minimise compromised health, including cancer risk (7).

Contrary to alcohol drinking, adequate physical activity (PA) has been associated with a decreased risk of all-cause mortality (8, 9) and risk of certain cancers, such as esophageal adenocarcinoma, lung, kidney, myeloid leukaemia, myeloma, colon, head and neck, bladder and breast cancers (10, 11). A previous analysis of eight British cohorts (2) showed that PA attenuated the effects of alcohol consumption on all-cause mortality risk and nearly nullified the adverse effects of alcohol on overall cancer mortality risk. However, not all cancers have been related to alcohol consumption (4), and to date no study has examined whether PA offsets the risk specifically of alcohol-related cancer mortality. The potential of PA as a public health strategy to reduce alcohol-related cancer risks needs further elucidation and quantification to support policy and practice interventions. Therefore the aim of this study was to investigate whether PA moderates the effects of alcohol consumption on alcohol-related cancer mortality risk.

2. Materials and Methods

We pooled data from ten independent British studies: the Health Survey for England (HSE) 1994, 1997, 1998, 1999, 2003, 2004, 2006 and 2008 and the Scottish Health Survey (SHS) 1998 and 2003 (12, 13). Surveys in these years were selected as they included detailed PA data. The data were linked to mortality records, including date, age and cause of death, from the National Health Service (NHS) Central Register through a data linkage process. Participants were followed up for mortality until 31 March 2011 in HSE and 31 December 2009 in SHS. We censored competing cause at the date of death.

Harmonising and pooling individual participant data from population cohorts is a standard approach used in the epidemiological literature of PA and alcohol (e.g. (2, 11, 14-16)). We have also compared the demographics and health behaviours between participants of the HSE and SES and found they were broadly similar in terms of age (median = 50 for HSE and 55 for SES), Body Mass Index (BMI,

around 27 kg/m^2 for both HSE and SES), PA levels (5.1 Met-hour/week for HSE and 6.5 for SES) and alcohol consumption.

Outcome variables

The main outcome was alcohol-related cancer mortality, coded as a binary variable. Site specific cancers were classified as alcohol-related using two definitions (conservative and broad), depending on the strength of evidence for their relationship with alcohol based on existing literature and International Agency for Research on Cancer (IARC) (4, 17-20). The conservative definition included cancer sites with good evidence of a causal association with alcohol, while the broader definition included sites with any previous, including conflicting, evidence of an association with alcohol. We included oral cavity, throat, larynx, oesophagus, liver, colorectal, stomach and female breast as alcohol-related cancers based on the conservative definition, and additionally included pancreas and lung cancers in the broad definition. These categorisations aligned with the recommendations from the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (21).

Site specific cancers were identified according to the International Classification of Diseases 9th (ICD9) (22) and 10th Revision (ICD10) (23) diagnosis code (listed in the Appendix). An event of alcohol-related cancer death was defined as any record which contained at least one of the diagnosis codes for the cancers above as the underlying or contributory death cause.

Alcohol consumption

Participants in the HSE and SHS were asked whether they drink alcohol currently (24, 25). Those who reported 'no' were then asked whether they have always been a non-drinker to determine their status as never-drinkers (never having consumed alcohol) or ex-drinkers (not drinking nowadays but having drunk alcohol previously). Those who reported some level of alcohol consumption were asked further questions, including 'How often had you consumed alcohol in the past 12 months?', 'Have you consumed alcohol in the last 7 days?' and 'How many and what size have you drunk in any one day?' (24). Based on the daily alcohol volume and weekly drinking frequency, we derived the average weekly consumption among current drinkers using the same method as in (24), measured in UK units. One UK unit of alcohol contains 8 grams of pure alcohol, equivalent approximately to 0.57 US standard drink.

Weekly alcohol consumption was then classified into six categories as previously described (2), according to the English Government's Alcohol Harm Reduction Strategy in place when most of the

baseline data were collected (29): (a) never-drinkers; (b) ex-drinkers; (c) occasional drinkers (having not drunk in the past 7 days); (d) within guidelines (<14 (women); <21 (men)); (e) hazardous (14–35 (women); 21–49 (men)) and (f) harmful drinking (>35 (women); >49 (men)).

Physical activity (PA)

PA was assessed based on the respondent's PA over the preceding 4 weeks of the interview using an established questionnaire described in detail elsewhere (26). It included the frequency and duration of domestic PA (light and heavy housework, gardening, do-it-yourself and building work); frequency, duration and pace of walking (slow, average, brisk, or fast); and frequency, duration, and perceived intensity of a range of sports and exercise activities (10 main groupings including running/jogging, cycling, swimming, gym workouts, aerobics, dance, football/rugby, badminton/tennis, squash and exercises (e.g. sit-ups)), followed by six open entries which could be added by the respondents (27). Light, moderate and vigorous intensities of PA were included in data collection, and intensity of activity for the sports and exercise domains was determined by nature of the activity and asking if the activity made them "out of breath or sweaty" (28). All assessment methods, including the physical activity questionnaire, in the HSE and SHS were developed by the same organisation and are consistent ((29, 30)). The PA questionnaire used in HSE and SHS has been validated in a previous study (31).

Covariates

We included age (age groups: 30-39, 40-49, 50-59, 60-69 and >=70 years old), sex (male/female), BMI (groups: <18.5 kg/m^2 (underweight), 18.5-24.99 (normal range), 25.0–29.99 (overweight), >=30 (obese)), smoking status (never regular smoker; ex-smoker; current smoker), education (age group when finishing full-time education: none, not yet finished, 14 year-old or under; 15-year old; 16-year old; 17-year old; 18-year old; 19-year or over), psychological distress (12-Item General Health Questionnaire (GHQ) score , continuous), social class (professional & managerial technical; skilled non-manual; skilled manual; semi- or un-skilled & other) and presence of long-standing illness (LSI, Yes/No) as covariates in the main multivariate analyses. LSI included neoplasms (defined as cancer including lumps, masses, tumours and growths and benign (non-malignant) lumps and cysts), diabetes, endocrine disorders, mental health, stroke/cerebral haemorrhage/cerebral thrombosis, heart attack/angina or other heart problem, hypertension/ high blood pressure, any respiratory problem etc. In a sensitivity analysis, we also added fruit and vegetable consumption (measured as portions of fruit and vegetables consumed on the day before the interview) as a proxy for

confounding by diet quality, given the established links between diet and cancer mortality. Questions on fruit and vegetable consumption focused on portion consumed on the day before the interview, which was assumed to be a 'typical' day and a 'portion' is equivalent to 80 grams of vegetables and fruits (32). The questions on fruit and vegetable consumption were asked in HSE 2003, 2004, 2006 and 2008 and SHS 2003.

Inclusion & exclusion criteria

We included all adults aged 30 years or older who consented to record linkage (N=67,128). We then excluded participants with missing data on cancer death (n=1,215), alcohol consumption and PA (n=225), the covariates (n=10,991) and those with incorrect information (e.g. interview date later than death date, n=11), leaving 54,686 participants in the core analytic dataset (Figure 1).

Statistical analyses

We used Cox proportional hazard models (33) to analyse the data. We constructed three models in the main analyses by pooling all participants using the broad definition of alcohol-related cancers. The exposure was alcohol-consumption, with never-drinkers as the reference group. In Model 1, we adjusted for age and sex. In Model 2, we additionally adjusted for BMI, smoking status, education, psychological distress, social class and presence of LSI. In Model 3, we further adjusted for PA. We also tested the interaction between PA and alcohol consumption using a likelihood ratio test (34). We then performed stratified analyses by PA stratum using two PA dichotomous classifications based on the lower (7.5 Metabolic Equivalent Task (MET)-hour/week) and upper (15 MET-hour/week) recommended limits.

In addition, we conducted five sets of sensitivity analyses to test the robustness of the results: (a) excluding participants who had been diagnosed with cancer, cardiovascular disease (CVD) or long-standing illness of neoplasms at baseline, given the links between cancer and CVD in the existing literature; (b) using the conservative definition of alcohol-related cancer; (c) adjusting for fruit and vegetable consumption in Model 2 and 3 in a sub-sample of participants with valid data ; (d) stratifying participants by smoking status at baseline (ex- or current smokers versus never regular smokers) to minimise the residual confounding due to smoking (35); and finally (e) excluding participants who died within first 12 months of follow-up. The broad definition of alcohol-related cancer was used in all sensitivity analyses except in (b).

All statistical analyses were carried out using STATA 15 software (36).

3. Results

Among the 54,686 participants in the core dataset, there were 1,339 alcohol-related site-specific cancer deaths based on the broad definition and 700 based on the conservative definition. The total analysis time at risk was 543,156 person-years, with a mean follow-up period of 9.9 years (Standard Deviation =4.6).

Cohort characteristics

Baseline characteristics of the study participants by alcohol consumption categories are presented in Table 1. The median age was 51 years (interquartile range (IQR) 40–64, range 30–102). 7.9% of participants were never-drinkers, while 14.7% exceeded the recommended guidelines at the time of the baseline data collection (women: 14 UK units & men: 21 UK Unit (37)). For physical activity, 23.3% reported no PA. Among those who reported any PA, the median was 9 MET-hours/week (IQR 3.5–19.6, range 0.1–150.8). 55.0% of participants engaged in PA for over 7.5 MET-hours/week and 33.4% for over 15 MET-hours/week.

Associations between alcohol consumption and alcohol-related cancer mortality

The Hazard Ratios (HRs) of alcohol-related cancer mortality for the main analysis are displayed in Table 2. In all three models, we found a significant association between alcohol consumption and alcohol-related cancer mortality: ex-drinkers and drinkers beyond the guidelines (at hazardous and harmful levels) displayed significantly higher risks of alcohol-related cancer mortality than never-drinkers. We also found a dose-response relationship between alcohol consumption and mortality risk of alcohol-related cancers in the fully adjusted model (Model 3): drinkers at the hazardous level presented a higher mortality risk (HR =1.39, 95% Confidence Interval (CI) = (1.06, 1.83)), whilst drinkers at the harmful level presented the highest mortality risk (HR =1.62, 95% CI = (1.13, 2.31)). Ex-drinkers also exhibited an increased mortality risk compared with never-drinkers (HR =1.46, 95% CI = (1.09, 1.94). In contrast, occasional drinkers (HR =1.21, 95% CI = (0.91, 1.61)) and drinkers within guidelines (HR =1.19, 95% CI = (0.94, 1.51) did not demonstrate statistically significantly higher risks in alcohol-related mortality.

Moderation effect of PA

The interaction terms of alcohol consumption* PA were not statistically significant when all participants were pooled together (P = 0.7093 when using the lower limit; P = 0.0595 when using the upper limit for PA recommendations). In the stratified analyses by PA stratum, we found that PA moderated the association between alcohol consumption and risk of alcohol-related cancer mortality, using either the lower or upper PA recommendation limit (Figure 2). Among the PA ≤ 7.5 MET-hour/week group (Figure 2A), there was a significant association between alcohol consumption and risk of alcohol-related cancer mortality: ex-drinkers (HR =1.53, 95% CI= (1.11, 2.12)), drinkers at hazardous (HR=1.47, 95% CI= (1.07, 2.02)) and harmful levels (HR=1.64, 95% CI= (1.07, 2.52)) had significantly higher mortality risks than never-drinkers. The increased risks were eliminated among the PA > 7.5 MET-hour/week individuals (Figure 2B). The broad patterns of effect modification by PA persisted when the upper PA limit was used (Figure 2C versus 2D).

Sensitivity analyses

The findings in the sensitivity analyses were broadly similar to the main analyses. In sensitivity analysis (a) where participants with neoplasms or CVD at baseline (n=15,300) were excluded, the significantly higher risk of alcohol-related cancer mortality among inactive ex-drinkers was attenuated among the active counterparts, based on either the lower or upper PA recommended level (Supplementary Figure S1). When the lower PA recommended level was used to classify PA, inactive drinkers at a hazardous level also presented a higher mortality risk, which was eliminated in the active participants.

The results broadly persisted when we used the conservative definition of alcohol-related cancer (sensitivity analysis (b)): PA attenuated the association between alcohol consumption and mortality risk of ex-drinkers (regardless how PA was stratified), drinkers at hazardous level (based on the lower recommended level), and drinkers at harmful levels (based on the upper recommended level) (Supplementary Figure S2). We also found higher HRs of alcohol-related cancer mortality among both physically inactive and active groups than the main analysis using the broad definition.

When additionally adjusting for fruit and vegetable consumption in a sub-sample (sensitivity analysis (c), n=20,171), we compared characteristics of this sub-sample (median age = 52 years, BMI =27.0 kg/m^2) against those of the main sample (median age = 51 years, BMI = 26.4 kg/m^2) to ensure that no bias was introduced, and found their characteristics were similar. Ex-drinkers and current

drinkers did not present statistically significantly higher risks of alcohol-related cancer mortality risks than never drinkers in the fully adjusted model (Supplement Table S1).

When stratifying the sample by participants' smoking status at baseline (never regular smokers versus ex-/current smokers) (sensitivity analysis (d)), we found inactive ex-drinkers or hazardous drinkers who were also ex-/current smokers presented significantly higher alcohol-related cancer mortality risks, but PA eliminated the risks. Among never smokers, we did not find significant associations between alcohol consumption and alcohol-related cancer mortality risks, however wide 95% CIs were observed (Supplement Figure 3).

The results from sensitivity analysis (e) excluding participants who died within first 12 months of follow-up (n=392) were very similar to those from the main analysis (Supplement Table S2): ex-drinkers (HR=1.38, CI: 1.03-1.86 in the sensitivity analysis versus HR=1.46, CI: 1.09-1.94 in the main analysis), drinkers at hazardous (HR=1.34, CI: 1.02-1.77 versus HR=1.39, CI: 1.06-1.83) and harmful levels (HR=1.61, CI: 1.12-2.31 versus HR=1.62, CI: 1.13-2.31) consistently exhibited increased mortality risks in the fully adjusted model.

4. Discussion

Summary of findings

In this large-scale population-based study we found a significant association between alcohol consumption and mortality risk of alcohol-related cancers: ex-drinkers and drinkers who consumed beyond the guideline amount generally displayed considerably higher mortality risk than never-drinkers. Engaging in a recommended level of PA attenuated the negative effects of alcohol consumption on alcohol-related cancer mortality. Although we observed higher effect estimates of alcohol consumption on mortality risks among hazardous or harmful drinkers who met the upper recommended PA levels in some circumstances, this was likely due to the smaller sample size and loss of precision and caution is required when interpreting these results with wide CIs.

Nevertheless, the overall results found in our study suggest that promoting PA as an adjunct risk minimisation public health strategy could be of substantial value for alcohol-related cancer prevention. This is particularly relevant for ex-drinkers and heavy drinkers. It should however be noted that being physically active and not drinking alcohol is optimal for preventing alcohol-related cancers and decreasing mortality risk.

Comparison with the current literature

Our current paper expanded on, and added details and depth, on the cancer mortality findings of a previous study (2). Perreault et al (2) pooled eight British cohorts and observed that the risk of overall cancer mortality was eliminated among those meeting the PA recommendations. We included two additional cohorts (HSE 1997 and 2008) with 190,107 more person-years of follow-up and excluded non-alcohol related cancer mortality as outcomes. Our summary results are in the same direction as with the Perreault et al's findings in terms of overall cancer mortality risk, but our data provide additional information on the attenuating effects of PA specifically on alcohol-related cancer mortality. This specificity adds biological plausibility and permits a more immediate translation of our findings into policy and practice.

In the pooled analysis, both papers found that ex-drinkers and drinkers beyond the guideline limits (at hazardous and harmful levels) presented significantly higher cancer mortality risks in both partially and fully adjusted models. The aligned results confirmed the relevance and special importance of alcohol consumption and alcohol-related cancer mortality specifically. In contrast, drinkers within guidelines also presented an increased cancer mortality risk in Perreault et al's study, but they did not have significantly higher cancer mortality risks in our study when covariates other than age and sex were also adjusted (Model 2 & 3). This may suggest that the effects of alcohol on alcohol-related cancer mortality are particularly pronounced for heavy drinkers.

In the stratified analysis on PA strata, both studies found that inactive drinkers beyond the guidelines had increased cancer mortality risks and the risks were eliminated when they met the minimum PA recommendation. But when the upper PA recommended level was used, we found the increased alcohol-related cancer mortality risk persisted among drinkers at a harmful level when they did not meet the upper PA recommended level (but possibly met the lower limit), while Perreault et al found the increased cancer mortality risk was eliminated among harmful drinkers who met the lower PA levels. This suggests that heavy drinkers may need to engage in a higher level of PA to offset the negative effects of alcohol consumption on alcohol-related cancer mortality specifically. Additionally, we found a significantly higher mortality risk of alcohol-related cancer, based on either the broad or conservative definition, among inactive ex-drinkers, and PA offered protective effects among active counterparts. Such results were not available from Perreault et al's stratified analysis on PA strata (2), which combined never-drunk and ex-drinkers into one group. When using the conservative definition of alcohol-related cancer, we generally found higher hazard ratios of alcohol-related cancer mortality, which accentuate the relevance of alcohol consumption to alcohol-related cancer mortality. Previously published data on overall cancer mortality did not

elucidate these further insights, while our study provided new evidence for PA's protective effects against alcohol-cancer mortality risk specifically, as opposed to overall cancer mortality.

Biological mechanisms

Literature is consistent on the effects of PA (11, 38) and alcohol on cancer risk (2, 18, 39) through shared pathways but in the opposite direction (2). A meta-analysis of 71 prospective cohort studies (40) showed that PA reduced cancer mortality through several potential mechanisms: lower BMI, decreased oxidative stress (41), sex hormones (42) and chronic inflammation (43), improved insulin sensitivity (44) and immune system (38, 43), and influence gene expression and DNA repair (45). For example, PA has been found to lower insulin levels and influence epigenetic variation in colorectal (46) and breast carcinogenesis (47), and up-regulate DNA repair and modulate canonical pathways for prostate cancer (45). In contrast, alcohol may affect carcinogenesis in the opposite direction through genotoxic effects of acetaldehyde, increase of oxidative stress, interaction with retinoid metabolism, increase in oestrogen concentration, epigenetic alterations, DNA methylation changes, and genetic polymorphisms (18, 39, 48-55). PA may protect against alcohol-related cancer mortality risk by blocking alcohol-related carcinogens through these shared mechanisms.

Strengths and limitations

To our knowledge, our study is the first to specifically study alcohol-related cancer in relation to PA and alcohol drinking behaviour. Since randomized controlled trials in this field are not possible for ethical reasons, large-scale population-based observational studies, such as our current study, provide unique insights to examining whether PA offsets alcohol drinking-related cancer mortality risk. The rigorous set of sensitivity analyses we performed also add to the robustness of our findings.

This study also has limitations. Alcohol-consumption and PA may be misclassified as they were self-reported, which may result in under-reporting of alcohol intake by heavy drinkers and over-reporting of PA by physically inactive participants due to social desirability biases (56). It is also possible that alcohol consumption and PA levels changed throughout the follow-up period due to the dynamic nature of PA and alcohol drinking behaviour. Additionally, the dietary quality variable used in the sensitivity analysis was limited as it only measures fresh fruit and vegetable intake. Other foods, such as consumption of processed meat has also been shown to be associated with an increased risk of cancer mortality (57). Despite a range of confounders already considered, our study is still subject to the possibility of unmeasured confounders. Another limitation is missing data, leading to exclusion of a relatively substantial proportion (18.5%) of the sample.

5. Conclusion

In this study, we pooled ten British population-based cohorts and found a strong direct association between alcohol consumption and alcohol-related cancer mortality risk, but the risks were substantially attenuated among physically active participants. This provides valuable evidence of the potential of promoting PA as an adjunct risk minimisation measure for alcohol-related cancer prevention. Being physically active and not drinking alcohol is optimal for preventing alcohol-related cancers and decreasing mortality risk.

6. Statements and disclosures

ES receives financial support from the National Health and Medical Research Council through a Senior Research Fellowship.

The authors declare there are no conflicts of interest.

Data Accessibility

Due to participant confidentiality and data custodian rules, the linked data are not publicly available. Data will be made available upon reasonable request.

Ethics

Ethical approval had been granted for all aspects of the studies by the Local Research Ethics Councils prior to each survey year data collection in HSE and SHS.

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Table 1 Characteristics of the study participants by groups of alcohol consumption (units per week) at baseline, Health Surveys for England (HSE) for the years of 1994, 1997, 1998, 1999, 2003, 2004, 2006 and 2008 and the Scottish Health Surveys (SHS) for the years of 1998 and 2003 (N=54,686)

	Alcohol Consumption Categories*					
Characteristic	**Never drinkers (N=4,340)**	**Ex-drinkers (N=3,246)**	**Occasional drinkers (N=13,195)**	**Within guidelines (N=25,882)**	**Hazardous (N=6,483)**	**Harmful (N=1,540)**
Physical activity, median (IQR), MET-hours/week[#]	2.5 (0.0-11.2)	2.5 (0.0-11.4)	5.6 (0.6-15.8)	5.5 (0.7-15.4)	7.2 (1.4-18.8)	5.8 (0.7-18.8)
Age, median (IQR), years	52 (40-69)	58 (45-69)	51 (40-64)	50 (39-64)	47 (38-59)	47 (38-56)
Female (%)	64.1	58.3	82.2	56.7	41.2	23.2
Body Mass Index (BMI), median (IQR), kg/m^2	26.4 (23.6-29.8)	27.0 (23.9-30.6)	26.9 (23.9-30.9)	26.3 (23.6-29.3)	26.2 (23.8-28.9)	26.5 (24.0-29.3)
Psychological distress (12-Item General Health Questionnaire (GHQ) score[¶]), median (IQR)	0 (0-2)	0 (0-3)	0 (0-1)	0 (0-2)	0 (0-2)	0 (0-2)
Social class (%), professional or managerial**	25.9	23.4	32.0	31.7	40.1	34.2
Cigarette smoking status (%), Never regular smoker	70.3	36.0	53.7	47.6	34.8	43.8
Cigarette smoking status (%), Ex-smoker	12.7	33.1	24.2	29.0	34.5	24.3
Cigarette smoking status (%), <10 cigarettes a day	6.4	6.3	5.9	5.9	7.1	31.9
Cigarette smoking status (%), 10-19 cigarettes a day	6.6	12.7	9.8	9.7	11.1	6.4
Cigarette smoking status (%), 20+ cigarettes a day	4.0	11.9	6.5	7.8	12.6	11.8
Education (%), finish full-time education at 19 or over[¶¶]	23.5	11.2	17.8	15.4	19.7	15.1
Long-standing illness (%), Yes	50.6	66.5	50.4	45.8	41.1	45.3

*Alcohol consumption categories are based on the average weekly intake of standard drinks according to the English Department of Health guidelines. In the UK, one standard drink equals to 8 grams of pure alcohol: within guidelines (<14 (women); <21 (men)); hazardous level (14-35 (women); 21-49 (men)) and harmful level (>35 (women); >49 (men)).

[#]Physical activity (PA) patterns were based on the frequency and duration of PA in the 4 weeks prior to the survey. PA was quantified in Metabolic Equivalent Task (MET)-hour/week, computed by multiplying the activity by the MET value and then summing the number of MET-hours spent performing each activity per week.

[¶]GHQ is a common measure of psychological well-being, including depression, anxiety, somatic symptoms and social withdrawal.

**Categories used for social class: professional & managerial technical; skilled non-manual; skilled manual; semi- or un-skilled & other.

[¶¶] Categories used for age group when finishing full-time education: none, not finished school, 14-year-old or under; 15-year old; 16-year old; 17-year old; 18-year old; 19-year or over.

Table 2. Hazard ratios (95% CIs) for alcohol-related cancer mortality by alcohol consumption, Health Surveys for England (HSE) for the years of 1994, 1997, 1998, 1999, 2003, 2004, 2006 and 2008 and the Scottish Health Surveys (SHS) for the years of 1998 and 2003 (N=54,686)

Categories of alcohol consumption*	**Model 1**			**Model 2**			**Model 3**		
(number of deaths/number of participants)	**HR**	**[95% CI]**		**HR**	**[95% CI]**		**HR**	**[95% CI]**	
Never drinkers (79/4,340)	1.00			1.00			1.00		
Ex-drinkers (120/3,246)	1.99	1.50	2.64	1.45	1.09	1.94	1.46	1.09	1.94
Occasional drinkers (140/13,195)	1.29	0.98	1.71	1.20	0.90	1.59	1.21	0.91	1.61
Within guidelines (751/25,882)	1.33	1.05	1.68	1.18	0.93	1.50	1.19	0.94	1.51
Hazardous (194/6,483)	1.64	1.26	2.14	1.37	1.05	1.80	1.39	1.06	1.83
Harmful (55/1,540)	2.25	1.58	3.20	1.60	1.12	2.28	1.62	1.13	2.31

HR: Hazard Ratio; CI: Confidence Interval

*Alcohol consumption categories are based on the average weekly intake of standard drinks according to the the English Department of Health guidelines. In the UK, one standard drink equals to 8 grams of pure alcohol: within guidelines (<14 (women); <21 (men)); hazardous level (14-35 (women); 21-49 (men)) and harmful level (>35 (women); >49 (men)).

Model 1 is adjusted for sex and age only. **Model 2** is additionally adjusted for body mass index (BMI), smoking status, education, 12-point General Health Questionnaire score, social class, and presence of long-standing illness. **Model 3** is further adjusted for physical activity (PA). PA patterns were classified based on the frequency and duration of PA in the 4 weeks prior to the survey. PA was quantified in Metabolic Equivalent Task (MET)-hour/week, computed by summing the number of hours spent performing each specific activity per week. Participants were classified as physically inactive if their PA was ≤7.5 MET-hour/week.

Appendix:

Alcohol-related cancers diagnosis code and number of death: based on the International Classification of Diseases (ICD), 9th Revision (ICD9) and 10th Revision (ICD10) diagnosis code

	ICD9	ICD10	Number of death*
Conservative definition			
Oral cavity	141-145	C00-C08	15
Throat	146-149	C09-C14	11
Larynx	161	C32	15
Esophagus	150	C15	102
Liver	155	C22	34
Colorectal	152-154	C18-C20	237
Stomach	151	C16	94
Female breast	174	C50	201
Additional cancer sites according to conservative definition			
Pancreas	157	C25	128
Lung	162	C34	517

*Note: the numbers of death for each cancer type do not add up to the total number of alcohol-related cancer deaths due to multiple cancer death indicators.

Figure 1 Flow Diagram for Study Inclusion & Exclusion

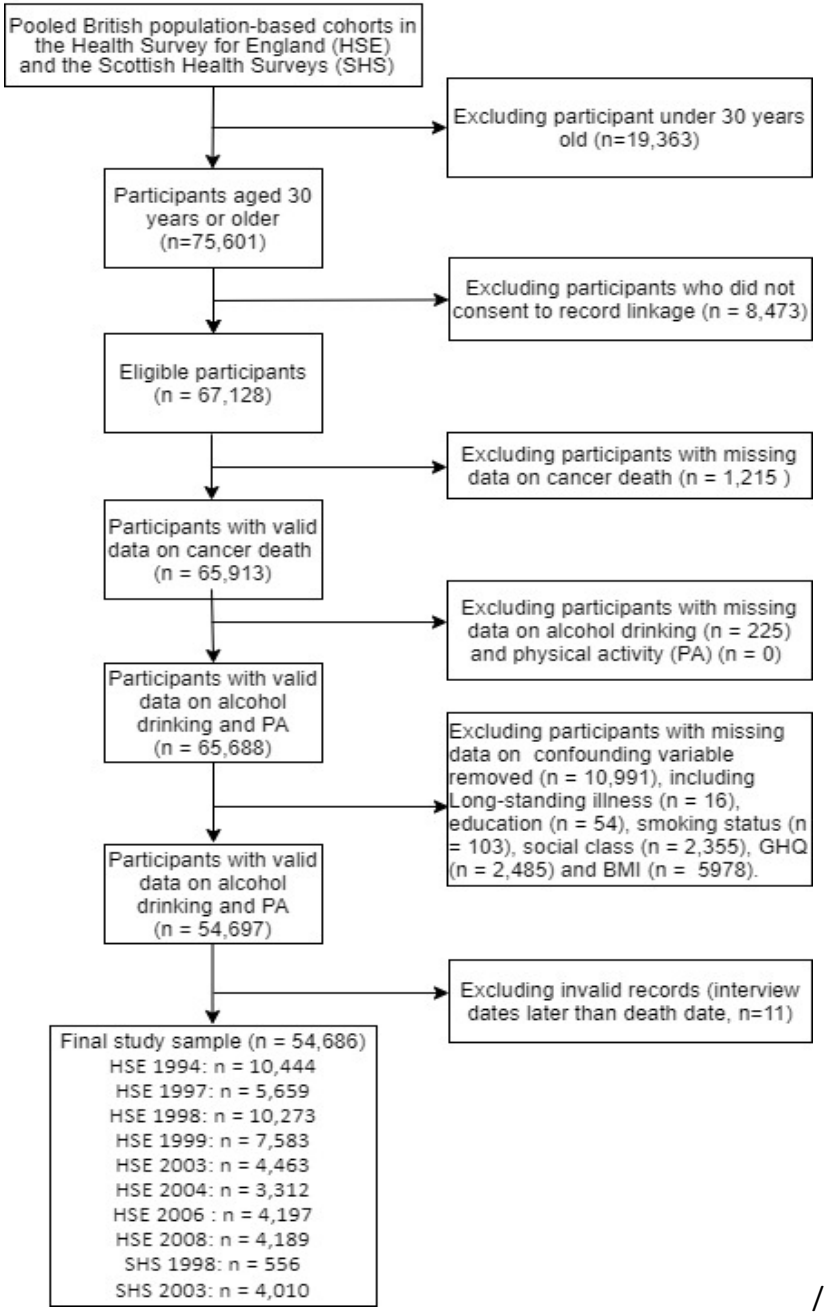

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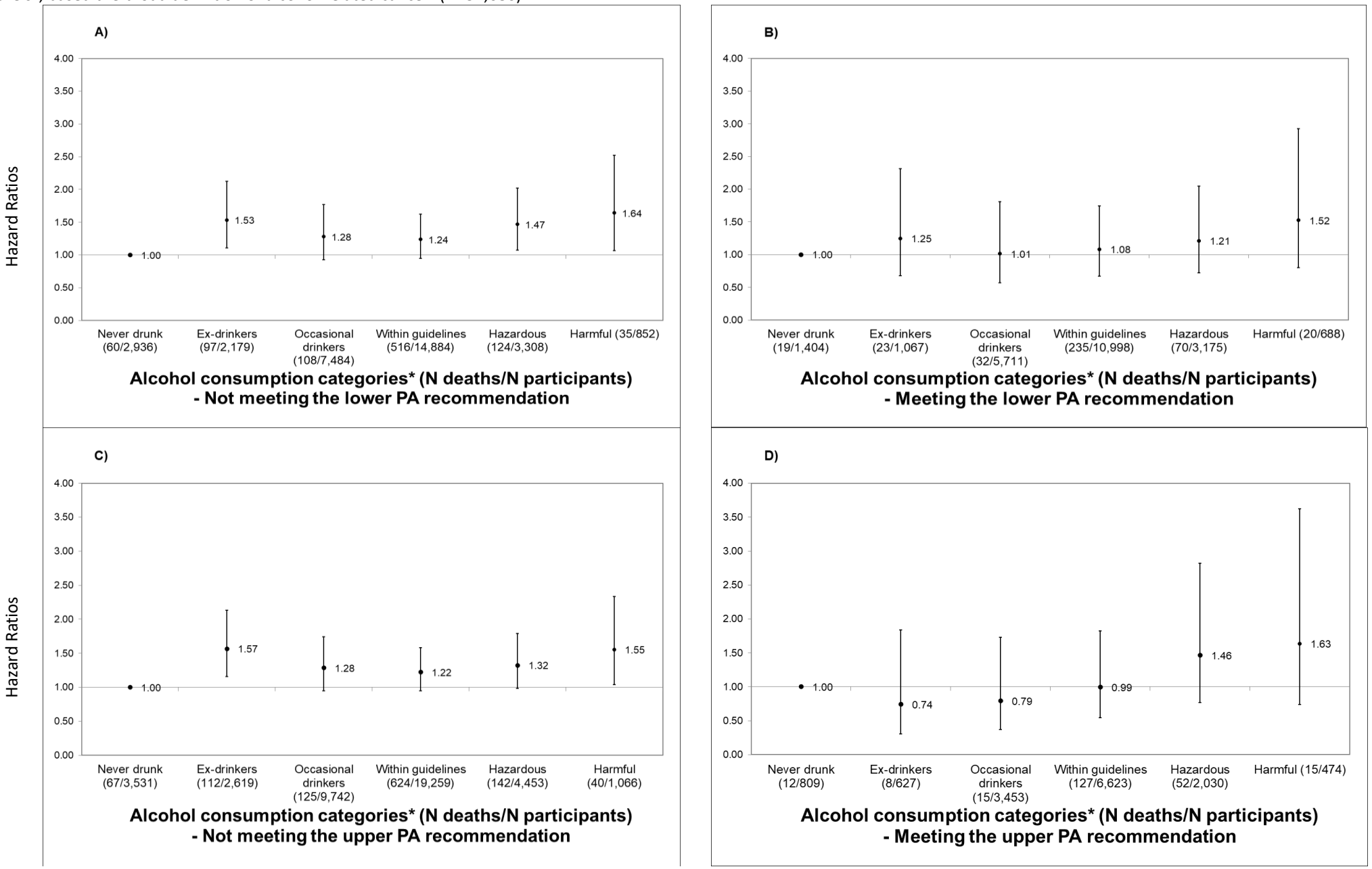
Figure 2 Hazard ratios of cancer mortality according to alcohol consumption categories* and physical activity strata according to the lower and upper physical activity (PA) recommended levels¶, based the broad definition of alcohol-related cancer# (N=54,686)



* Weekly alcohol consumption was classified into six categories according to the English Government's Alcohol Harm Reduction Strategy (29), measured in UK units (One UK unit of alcohol contains 8 grams of pure alcohol): (a) never-drinkers; (b) ex-drinkers; (c) occasional drinkers (having not drunk in the past 7 days); (d) within guidelines (<14 (women); <21 (men)); (e) hazardous (14–35 (women); 21–49 (men)) and (f) harmful drinking (>35 (women); >49 (men)).

¶ The lower physical activity (PA) recommendation level used for classifying PA strata was 7.5 MET-hour/week and upper PA level was 15 MET-hour/week (2).
# Alcohol-related cancer according to the broad definition included oral cavity, throat, larynx, esophagus, liver, colorectal, stomach, female breast, pancreas and lung cancer.