1. TITLE PAGE

TITLE: Does physical activity moderate the association between alcohol drinking and all-cause, cancer and cardiovascular diseases mortality? A pooled analysis of eight British population cohorts.

AUTHORS
Perreault, K.\textsuperscript{1,2}, MSc; Bauman, A.\textsuperscript{2,5}, PhD; Johnson, N.\textsuperscript{2,3}, PhD; Britton, A.\textsuperscript{4}, PhD; Rangul V.\textsuperscript{5}, PhD; Stamatakis, E.\textsuperscript{2,3,4}, PhD.

AUTHORS’ WORK POSITIONS
Karine Perreault: PhD student, Public Health, Université de Montréal
Adrian Bauman: Sesquicentenary Professor of Public Health, University of Sydney
Nathan Johnson: Senior Lecturer, Exercise and Sport Science, University of Sydney
Annie Britton: Senior Lecturer of Epidemiology, University College London
Vegar Rangul: Postdoctoral fellow, Public Health, Norwegian University of Science and Technology
Emmanuel Stamatakis: National Health and Medical Research Council Senior Research Fellow & Associate Professor, University of Sydney

AUTHOR’S AFFILIATIONS AND FULL ADDRESSES
1. Université de Montréal, Département de médecine sociale et préventive, Institut de recherche en santé publique, 7101 avenue du Parc, C.P. 6128, Succ. Centre-Ville Montréal, Québec, H3C 3J7, Canada
2. University of Sydney, Charles Perkins Centre, School of Public Health, Johns Hopkins Drive, Camperdown NSW, 2006, Australia

3. University of Sydney, Faculty of Health Sciences, Discipline of Exercise and Sport Sciences, Cumberland Campus, 75 East St, Lidcombe NSW, 2141, Australia

4. University College London, Department of Epidemiology and Public Health, Gower Street Campus, 1 - 19 Torrington Place, London, United Kingdom, WC1E 6BT

5. HUNT Research Centre, Faculty of Medicine, Department of Public health and General practice, Norwegian University of Science and Technology, Postboks 8905, MTFS, 7491 Trondheim, Norway

ADDRESS FOR CORRESPONDENCE:
Emmanuel Stamatakis, Charles Perkins Centre, University of Sydney, Johns Hopkins Drive, NSW 2006, Sydney Australia.
e-mail: emmanuel.stamatakis@sydney.edu.au; Tel: (61)286271867.

AUTHORS’ CONTRIBUTIONS:
K. Perreault: contribution to study concept and design, data analysis and interpretation of data, manuscript drafting, manuscript revisions
A. Bauman: critical revision of the manuscript for important intellectual content; results interpretation
N. Johnson: critical revision of the manuscript for important intellectual content; results interpretation
A. Britton: critical revision of the manuscript for important intellectual content; results interpretation
R. Vegar: critical revision of the manuscript for important intellectual content; results interpretation

E. Stamatakis: conception of study idea and study design, dataset acquisition and harmonisation, study supervision, re-drafting of the manuscript, critical revision of the manuscript for important intellectual content, results interpretation.

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TRANSPARENCY DECLARATION

The first author (KP) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that no discrepancies from the study as planned have occurred.

EXCLUSIVE LICENCE STATEMENT
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2. ABSTRACT

Objective. To examine whether physical activity (PA) moderates the association between alcohol intake and all-cause mortality, cancer mortality and cardiovascular diseases (CVD) mortality.


Participants. 36,370 men and women aged forty years and over were included with a corresponding 5735 deaths and a mean of 353,049 person-years of follow-up.

Exposures. Six sex-specific categories of alcohol intake (UK units/week) were defined 1) Never drunk; 2) Ex-drinkers; 3) Occasional drinkers; 4) Within guidelines [<14 (women); <21 (men)]; 5) Hazardous [14-35 (women); 21-49 (men)]; 6) Harmful [>35 (women) >49 (men)]. PA was categorised as inactive (≤7MET-hour/week), active at the lower (>7.5MET-hour/week) and upper (>15MET-hour/week) of recommended levels.

Main Outcomes and Measures. Cox proportional-hazard models were used to examine associations between alcohol consumption and all-cause, cancer and CVD mortality risk after adjusting for several confounders. Stratified analyses were performed to evaluate mortality risks within each physical activity strata.

Results. We found a direct association between alcohol consumption and cancer mortality risk starting from drinking within guidelines [HR (95%CI) hazardous drinking: 1.40 (1.11-1.78)]. Stratified analyses showed that the association between alcohol intake and mortality risk was
attenuated (all-cause) or nearly nullified (cancer) among individuals who met the PA recommendations [HR (95%CI)].

Conclusion: Meeting the current physical activity public health recommendations offsets some of the cancer and all-cause mortality risk associated with alcohol drinking

Abstract: 247 words
3. NEW FINDINGS AND IMPACT ON CLINICAL PRACTICE

What are the new findings?

- These are the first population set of cohorts to study the influence of PA as a moderator of all-cause, cancer, and cardiovascular risks death risk across a detailed categorisation of weekly alcohol intake, using those who never drunk as the reference group.

- Physical activity moderated the association between alcohol consumption and all-cause and cancer mortality risk. This effect is evident from the lower physical activity recommendations (7.5 MET-h/week).

- This study brings novel information about the potential of physical activity to promote health and reduce alcohol consumption-related risk of all-cause and cancer mortality.

How might it impact on clinical practice in the near future?

- Our results suggest that being physically active at the lower limit of public health recommendations (7.5 MET-h/week) mitigates some mortality risks associated with alcohol drinking.

- From a public health angle, our conclusions are oriented toward a behavioural strategy to reduce mortality risk associated with alcohol consumption.
INTRODUCTION

Alcohol consumption is an integral part of western culture. In 2013, 88% of American adults reported having drunk alcohol at some point in their lifetime; 56% in the past month. Similarly, in England, 63% of the population aged 16+ years old have reported drinking at least once a month [1], with 24% of men and 18% of women drinking more than the recommended amount [2]. High alcohol consumption is linked to an increased risk of all-cause mortality [3], cancer mortality [4-6] and cardiovascular diseases (CVD) mortality [7 8]. Public health strategies to reduce alcohol consumption have involved alcohol risk reducing campaigns and measures aimed at regulating sales, demand, and supply [9 10]. Despite these measures alcohol consumption remains high and thus, there is a need for strategies aimed at minimising the health risks associated with alcohol consumption.

There is compelling evidence showing that regular physical activity (PA) is associated with cardiovascular health [11 12], reduced all-cause mortality [13-17], cancer mortality [18 19] and CVD mortality [13 15 20] risk. However, the prevalence of physical inactivity is high worldwide[21], with estimates ranging from 34% in England [22] to 50% in the US [23]. Mechanistic research suggests that alcohol consumption and physical activity may be linked to chronic disease through shared pathways but acting in the opposing direction. For example, the biological pathways through which alcohol is thought to induce carcinogenesis [4 6 24] are similar to those by which physical activity may prevent cancer [25-27].
Limited epidemiological evidence has suggested that high level of PA, or high cardiorespiratory fitness, moderates the association between alcohol intake and all-cause and CVD mortality [28-29]. These studies were limited in that they pooled non-drinkers and ex-drinkers, an approach that has recently been shown to distort the associations between alcohol and mortality by over-estimating the protective effect of moderate drinking [30]. No study has explicitly examined the hypothesis that regular PA may offset mortality risks associated with alcohol consumption across a detailed categorization of weekly alcohol intake, a hypothesis that is difficult to subject to experimental testing due to ethical considerations.

The aim of this study was to examine if health-enhancing PA moderates the association between alcohol intake and all-cause, cancer and CVD mortality risk in a large analysis of eight pooled British population-based cohorts.

**METHODS**

**Participants**

The Health Survey for England (HSE) [31] and the Scottish Health Survey (SHS) [32] are continuous and annually repeated general population surveillance studies among independent samples of individuals living in private households in the two countries. Each sample is selected from a multistage, stratified probability design to give a socio-demographic nationally representative target population. Data collection was household-based and was carried out by interviewers. During the original survey interview, participants were asked to consent to their name, address and date of birth being sent to the Information Services Division (ISD) of National
Health Service (NHS) for confidential linkage to their health records and mortality data. Ethical approval was obtained from the North Thames Multicentre Research Ethics Committee for England, the Local Research Ethics Council in England, the Research Ethics Committee for all Area Health Boards in Scotland, and the Multicentre Research Ethics Committee for Scotland.

In this study we used HSE years 1994, 1998, 1999, 2003, 2004 & 2006 and SHS years 1998 & 2003 that included information on both alcohol consumption and physical activity among individuals aged 40 years or older (n=50,198). Were excluded those who did not consent to data linkage (n=5397) or had incomplete covariates profile (n=8,431), leaving 36,370 adults participants with a corresponding 5735 deaths and a mean of 353,049 person-years of follow up (mean follow-up period of 9.7 years (SD 4.3)).

**Outcomes**

HSE and SHS were linked to National Health Service (NHS) Central Register mortality data and participants were followed up for mortality until 31/12/2009 (SHS) or 31/03/2011 (HSE). Mortality was coded as a binary variable representing death or censoring. Diagnoses for primary causes of death were recorded according to the International Classification of Diseases, Ninth Revision (ICD9) and Tenth Revision (ICD10). Cancer and cardiovascular deaths were identified using the following codes. Cancer: ICD9 140.0-239.9, ICD10 C00.0-D48.9; Cardiovascular: ICD9 390.0-459.9, ICD10 I01.0-I99. These did not include injury, poisoning and other external causes.

**Alcohol consumption**
Adults were asked about whether or not they drink alcohol nowadays. Of those who reported no current alcohol consumption, a clarification was made of their status as never drinkers or ex-drinkers. Supplementary questions were posed as “How often you consumed alcohol in the last 12 months?”; “Have you consumed alcohol in the last 7 days?” and “How many and what size have you drunk in any one day?” [30]. Total weekly UK units were calculated by summing the units of each type of beverage and multiplying by the reported frequency. In the UK, one unit is 8 grams (g) of alcohol, corresponding roughly with 25 ml measure of spirit, half a pint of beer, whereas a 175 ml glass of wine contains two units [33]. A US standard drink (StdDrk) is any drink that contains about 14 g of pure alcohol [34]. On that basis, one UK unit is equivalent to 0.57 US StdDrks.

Six sex-specific alcohol categories (UK units/week) were derived on the basis of the English Department of Health’s suggested weekly limits [35] and in accordance to recent findings emphasizing the importance of carefully choosing the alcohol referent group [30]: 1) Never drunk; 2) Ex-drinkers; 3) Occasional drinkers (who declared not having drunk in the last 7 days); 4) Within guidelines [<14 (women) (8 US StdDrks) and < 21 (men) (12 US StdDrks)]; 5) Hazardous drinking [14-35 (women) (8-20 US StdDrks) and 21-49 (men) (12-28 US StdDrks)]; 6) Harmful drinking [>35 (women) (20 US StdDrks) and >49 (men) (28 US StdDrks)]. ‘Never drunk’ is synonymous to lifetime abstainers, i.e. those who reported never having consumed alcohol. ‘Occasional drinkers’ declared being drinkers, but not having drunk in the last 7 days. We hypothesized their alcohol consumption to be less at risk than ‘Within guidelines’.

**Physical activity**
The PA measures used here have validity against accelerometry in a large population-based validation study[36]. Frequency and duration of leisure time physical activities in the 4 weeks prior to the interview were assessed across 3 domains: 1) light/heavy manual work/gardening/do-it-yourself activity; 2) walking for any purpose; and 3) light, moderate, and vigorous sports/exercise. The questionnaire also include items on domestic activity but these were not included as part of the exposure variable in our analyses on the grounds of previous evidence highlighting the absence of links with all-cause mortality [14] and CVD mortality [14 17].

Metabolic equivalent task (MET)-hour/week were computed as MET for each specific activity [36] multiplied by the number of hours the activity was performed per week. Extreme values of PA (on the basis of ≥ 5SDs from the mean) were excluded. In line with the most recent PA public health guidance [37] and recent evidence on the dose response association between PA and mortality [38], we defined adherence to the lower PA recommendation as >7.5 MET-h/week and adherence to the higher PA recommendation as >15 MET-h/week.

**Statistical analyses**

Cox proportional-hazard models were used to examine the associations between alcohol consumption (reference category: never drunk) and all-cause, cancer and CVD mortality risks. Statistical interaction between Alcohol *PA was tested by adding an interaction term in the both the unadjusted and the fully adjusted models. When interactions were significant, analyses by PA strata were performed.
Basic Cox models included adjustments for age (as a continuous variable) and gender. Further models were also adjusted for BMI (continuous), cigarette smoking status (never regular smoker, ex-smoker, current smoker), psychological distress/depression (12-point General Health Questionnaire score), registrar general’s social class (professional/managerial technical, skilled non manual, skilled manual, semiskilled/unskilled manual, or other) and presence of longstanding illness. In all-cause and CVD mortality analyses, the middle models were also adjusted for doctor-diagnosed cardiovascular diseases (CVD) (stroke or IHD, including angina) at baseline. Final models were additionally adjusted for PA (none, 0.1-≤7.5, 7.5-15, >15 MET-h/week). All statistical analyses were carried out using SPSS version 21.0 for mac (SPSS, Inc., Chicago, Illinois).

In a sensitivity analysis, we performed stratified analyses excluding specific pre-existing conditions. For all-cause mortality, we excluded individuals with longstanding cancers or CVD at baseline. For cancer mortality, we excluded people with longstanding cancers and for CVD mortality, we excluded those with CVD.

RESULTS

Sample characteristics

Characteristics of the population by groups of alcohol consumption (units per week) at baseline are presented in Table 1. Age ranged from 40 to 102 years with a median of 56 years (IQR 47-67). In the final sample of 36,370 adults, 5307 adults (14.6%) reported no alcohol intake (never
drinkers and ex-drinkers together). In total, 4845 adults (13.3%) exceeded the recommended weekly limits for alcohol (women: 14 UK units (8 US StdDrks); men: 21 (12 US StdDrks) [39]). Those who reported alcohol consumption in the last 7 days consumed a median of 6.3 units/week (IQR 1.3-15.3). With regard to PA, 27.5% (9996/36,370) reported no non-domestic PA. The lower limit of the recommended level of PA (7.5 MET-h/week) was met by 39.1% of the participants and the higher limit (15 MET-h/week) by 23.3%. A median of 8.8 MET-h/week (IQR 3.3-19.0) was found among those who reported any PA.

*Insert Table 1 around here*

**Associations between alcohol consumption and mortality**

The hazard ratios of death by alcohol categories for all-cause, cancer and CVD are provided in Table 2, across three models with different levels of adjustments.

In both the partially adjusted and fully adjusted models, we found a direct association between alcohol drinking and all-cause mortality, with ex-drinkers and drinkers at harmful level showing clear higher risk of all-cause mortality, compared to never drinkers. We also observed a dose-response association between weekly alcohol consumption and cancer mortality, with increased risks from within guidelines consumption to harmful drinking. In contrast, we found weak evidence for an association between alcohol and CVD mortality, as only ex-drinkers were different to the referent group, and this also was persistent across all three models. Occasional drinkers appeared to have lower risk for all-caused and cancer mortality across all models.
Ex-drinkers presented an increased risk of mortality for the three mortality outcomes whereas occasional drinking was found to be protective against all-cause and CVD mortality. For example, the hazard ratio was 0.78 (0.63-0.97) for CVD mortality.

Insert Table 2 around here

Physical activity as a moderator of the association between alcohol and mortality

All interaction terms of alcohol consumption by PA were found significant in the fully adjusted Cox models for the three mortality outcomes (all P <0.001).

A direct association between alcohol consumption and all-cause mortality was found among those who did not meet the lower PA recommendation (≤7.5 MET-h/week) (Fig. 1A). HRs were attenuated up to hazardous level of drinking among those who did meet the lower and higher recommendations (>7.5 and >15 MET-h/week), but the pattern of the association remained the same across all PA strata (Fig. 1A, 1B and 1C). A protective effect of occasional drinking was observed among those who met the highest PA recommendation (HR (95%CI): 0.68 (0.46-0.99)).

In sensitivity analyses, these findings broadly persisted when we excluded participants with CVD at baseline (Suppl. Fig.1A, 1B and 1C). When excluding those with neoplasms at baseline, the associations were similar in the inactive group but were attenuated in the >7.5 and >15 MET-h/week PA groups (Suppl. Fig.1D, 1E and 1F).

Insert Figure 1 around here
The risk of cancer mortality was increased in a dose-response fashion among inactive participants (Fig. 2A). This association was attenuated in those who met the lower recommendation (Fig. 2B), and substantially attenuated in the higher recommendation group (Fig. 2C). Results were broadly similar in the sensitivity analyses when individuals with neoplasms at baseline were excluded (Suppl. Fig 2A, 2B and 2C).

*Insert Figure 2 around here*

No association between alcohol and CVD mortality risk was observed, although occasional drinking had a protective effect for CVD mortality in the lower and higher recommendations strata [HR (95%CI) for >7.5 MET-h/week: 0.56 (0.34-0.93) | >15 MET-h/week: 0.43 (0.19-0.97)] (Figure 3A, 3B and 3C). Results were consistent in the sensitivity analyses when individuals with CVD at baseline were excluded from the sample (Suppl. Fig. 3A, 3B and 3C).

*Insert Figure 3 around here*

**DISCUSSION**

In this large British general population cohort, we found the association between alcohol intake and mortality risk was moderated by physical activity.

In stratified analyses, alcohol-related mortality risk varied by PA levels. Participants who did not meet the lower recommendation of 7.5 MET-h/week showed a clear dose-response risk for
cancer mortality from drinking within guidelines and up to to harmful level. The risk of cancer mortality was attenuated or nullified in participants who met both the lower and higher PA recommendations (>7.5 and >15 MET-h/week), as none of the drinking categories were found to be substantially different to the referent group (never drinkers). The association between alcohol and all-cause mortality was similar across PA strata, although hazard ratios were slightly attenuated up to hazardous level of drinking among active participants (>7.5 and >15 MET-h/week). With regard to CVD mortality, no association was found except for a protective effect of occasional drinking in active participants only.

Regardless of PA levels, we found a nearly J-shaped association between alcohol consumption and all-cause and CVD mortality (with the beneficial associations being evident in the occasional drinkers only). Similarly to the conclusions of another recent analysis from a similar pool of British cohorts, our results confirmed that the inclusion of former drinkers in the referent group (forming a broad category of “non-drinkers”) has the potential to over-estimate the protective effect of drinking at the recommended level [30]. As for cancer mortality, we found no protective effect of occasional drinking, and an increased risk from within guidelines consumption. The public health relevance of our results is further emphasised by the recently updated alcohol consumption guidelines review of the UK Chief Medical Officers that found that cancer mortality risk starts from relatively low level of alcohol consumption [40].

**Previous studies in the field**

Very few studies to date have specifically examined the effects of alcohol use jointly with PA on mortality. In a prospective study including 29,402 men, Shuval et al. (2012) found that moderate and high cardiorespiratory (CR) fitness (a direct indicator of habitual PA [41]) was protective
against all-cause mortality at all levels of drinking. For example, the heavy drinkers in the highest category of CR fitness presented an all-cause mortality risk reduction of 38% compared to the heavy drinkers in the lowest CR fitness category. This study did not observe such associations with CVD mortality and the only protective effect found for CVD mortality was in the high-fitness/moderate drinking category (3-14 US StdDrinks/week or 5-25 UK units/week). Our results indicate similar findings, as lower and higher PA recommendations slightly attenuated the risk of all-cause mortality up to hazardous level of drinking; and occasional drinkers presented a reduced risk of all-cause and CVD mortality among active participants.

**Potential biological mechanisms**

Alcohol has been recognized as a major contributor to cancer mortality [5 42]. The study of the links between PA and cancer is a recent field and current evidence shows that there is a robust decreased risk with increased PA for breast and colon cancers and perhaps several other cancer sites (e.g. ovarian, lung and prostate cancers) [25 43 44]. In a very large recent study from 12 US and European cohorts, high levels of leisure-time physical activity were associated with lower risks for 13 of 26 site-specific cancers [45], including several types of cancer that are specifically associated with increased alcohol consumption (e.g. esophageal, gastric cardia, liver, colon, rectum, breast) [40]. Our results on the presence of a nearly-linear association between alcohol and cancer mortality in the inactive group strengthen further current knowledge on the links between alcohol and health risks. The associations we observed were substantially attenuated among participants who met both the lower (>7.5 MET-h/week) and higher (>15 MET-h/week) physical activity guidelines. There are several biological mechanisms by which alcohol is believed to contribute to carcinogenesis [4 6 24] which appear to be similar to those by which physical activity may prevent cancer [25-27], but acting in opposite direction. These pathways
include (alcohol vs PA): increase [46-49] vs decrease [50-53] of oxidative stress and inflammatory markers, elevation [54-55] vs diminution [56-58] of sex steroid hormones levels, and reduced [59-60] vs enhanced [61-63] immune function. A recent study based on an animal model demonstrated that exercise decreases tumour incidence and growth by over 60% through enhanced immune function [64]. These results suggest that PA may not only be a powerful preventive strategy against cancer onset but also mediate cancer regression. Such exercise-activated anti-tumour immunity pathways are yet to be demonstrated in humans but they are receiving increased attention [65].

**Dose-response effects of physical activity**

Notably, we did not observe appreciable differences in mortality across alcohol intake categories between the upper and lower PA cut-offs (>7.5 and >15 MET-h/week). We hypothesized that higher level of PA would confer an extra reduction in mortality risk, based on the recent large pooled study that found a dose response risk reduction in all-cause mortality and cancer mortality with several multiples of the minimal dose of PA recommendations [38]. This might be due to the reduced statistical power in our most active category (the >15 MET-h/week strata included n=8123 corresponding to 713 all-cause mortality events and 288 cancer mortality events), or a ceiling effect often observed in smaller epidemiological studies studying the dose-response of PA and mortality risk [66].

**Strengths and limitations**

This study has some strength and some limitations. To our knowledge, this is the first set of population cohorts to examine the influence of PA as a moderator of all-cause, cancer and CVD mortality risks across a detailed categorisation of weekly alcohol intake. Moreover, all previous studies in the area pooled all non-drinkers as the reference group (combining lifelong abstainers
and former drinkers that may have quit due to health issues increasing the chance for bias [30 67]). On the other hand, the alcohol measure used in this study assessed the quantity of alcohol intake (UK units/week), but not the drinking pattern (e.g. binge drinking), which have important health implications [67 68]. Also, the possibility of unmeasured confounding (including dietary [69 70]) factors remains. Misclassification because of underreporting of heavy drinkers [71 72] may explain the limited number of participants in the harmful drinking group, which requires cautious interpretation. Because alcohol drinking [73] and PA [74] had been shown to be dynamic behaviours, the baseline measurements we used may not reflect the actual alcohol intake / PA level over the follow up period.

CONCLUSION

We found evidence of a dose-response association between alcohol intake and cancer mortality in inactive but not in physically active participants. PA slightly attenuates the risk of all-cause mortality up to hazardous level of drinking. The protective effects of PA were evident from a level of meeting the minimal public health recommendations of physical activity. Our results provide an additional argument for the role of PA as a means to promote the health of the population even in the presence of other less healthy behaviours.
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FIGURES TITLES AND LEGENDS

**Figure 1.** Hazard ratios (HRs) of all-cause mortality according to alcohol consumption categories and physical activity strata (MET-h/week).

**Legend Fig.1:** Stratified analysis were performed on three physical activity strata: Fig.1A ≤7.5 MET-h/wk; Fig.1B >7.5 MET-h/wk and Fig.1C >15MET-h/wk. Five groups of alcohol consumption were defined [UK units/week (equivalent in US standard drinks)]: Never drunk and Ex-drinkers: no drinking; Occasional drinkers (drinkers, but have not drunk in the last 7 days); Within guidelines: <14 (8) (women) and <21 (12) (men); Hazardous: 14-35 (8-20) (women) and 21-49 (12-28) (men); Harmful: >35 (20) (women) and > 49 (28) (men). Vertical bars represent the 95% confidence intervals for the HRs. The reference group included subjects who never drunk. HRs of all-cause mortality were adjusted for age, gender, body mass index, social class, cigarette smoking status, psychological distress/depression score (12-point General Health Questionnaire score), long standing illness, doctor diagnosed CVD (stroke or ischemic heart diseases, including angina) and physical activity level.

**Figure 2.** Hazard ratios (HRs) of cancer mortality according to alcohol consumption categories and physical activity strata (MET-h/week).

**Legend Fig.2:** Stratified analysis were performed on three physical activity strata: Fig.2A ≤7.5 MET-h/wk; Fig.2B >7.5 MET-h/wk and Fig.2C >15MET-h/wk. Five groups of alcohol consumption were defined [UK units/week (equivalent in US standard drinks)]: Never drunk and Ex-drinkers: no drinking; Occasional drinkers (drinkers, but have not drunk in the last 7 days); Within guidelines: <14 (8) (women) and <21 (12) (men); Hazardous: 14-35 (8-20) (women) and 21-49 (12-28) (men); Harmful: >35 (20) (women) and > 49 (28) (men). Vertical bars represent the 95% confidence intervals for the HRs. The reference group included subjects who never drunk. HRs of cancer mortality were
adjusted for age, gender, body mass index, social class, cigarette smoking status, psychological distress/depression score (12-point General Health Questionnaire score), long standing illness and physical activity level.

**Figure 3.** Hazard ratios (HRs) of cardiovascular diseases (CVD) mortality according to alcohol consumption categories and physical activity strata (MET-h/week).

**Legend Fig.3:** Stratified analysis were performed on three physical activity strata: Fig.3A ≤7.5 MET-h/wk; Fig.3B >7.5 MET-h/wk and Fig.3C >15MET-h/wk. Five groups of alcohol consumption were defined [UK units/week (equivalent in US standard drinks)]: Never drunk and Ex-drinkers: no drinking; Occasional drinkers (drinkers, but have not drunk in the last 7 days); Within guidelines: <14 (8) (women) and <21 (12) (men); Hazardous: 14-35 (8-20) (women) and 21-49 (12-28) (men); Harmful: >35 (20) (women) and > 49 (28) (men). Vertical bars represent the 95% confidence intervals for the HRs. The reference group included subjects who never drunk. HRs of CVD mortality were adjusted for age, gender, body mass index, social class, cigarette smoking status, psychological distress/depression score (12-point General Health Questionnaire score), long standing illness, doctor diagnosed CVD (stroke or ischemic heart diseases, including angina) and physical activity level.
### Table 1. Characteristics by groups of alcohol consumption (units per week) at baseline, Health Survey for England (1994; 1998; 1999; 2003; 2004; 2006) and Scottish Health Survey (1998; 2003) (n=36,370).

<table>
<thead>
<tr>
<th>Alcohol categories in units/week$^a$</th>
<th>Never drunk (N=3090)</th>
<th>Ex-drinkers (N=2217)</th>
<th>Occasional drinkers$^b$ (N=9756)</th>
<th>Within guidelines$^c$ (N=16,462)</th>
<th>Hazardous$^d$ (N=3905)</th>
<th>Harmful$^e$ (N=940)</th>
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</thead>
<tbody>
<tr>
<td>Exposure variables</td>
<td></td>
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<tr>
<td>Alcohol consumption, median (IQR)$^f$, units/week$^a$</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>3.5 (0.8-8.3)</td>
<td>25.3 (21.0-31.6)</td>
<td>57.9 (52.0-74.5)</td>
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<tr>
<td>Physical activity – sports and walking, median (IQR), MET-h$^g$/week</td>
<td>1.6 (0.0-9.8)</td>
<td>1.5 (0.0-9.3)</td>
<td>5.0 (0.0-15.2)</td>
<td>4.5 (0.0-14.0)</td>
<td>6.3 (1.0-17.7)</td>
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<td>Covariates</td>
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<tr>
<td>Age, median (IQR), years</td>
<td>60 (48-71)</td>
<td>61 (51-70)</td>
<td>56 (47-75)</td>
<td>57 (48-68)</td>
<td>53 (46-64)</td>
<td>51 (45-61)</td>
</tr>
<tr>
<td>Body mass index, median (IQR), kg/m$^2$</td>
<td>26.7 (23.9-30.2)</td>
<td>27.0 (24.0-30.3)</td>
<td>26.8 (23.9-30.4)</td>
<td>26.6 (24.1-29.7)</td>
<td>26.5 (24.1-29.1)</td>
<td>26.8 (24.3-29.6)</td>
</tr>
<tr>
<td>GHQ$^h$, median (IQR), score /12</td>
<td>0 (0-2)</td>
<td>1 (0-3)</td>
<td>0 (0-1)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Social class$^i$, % (frequency), professional or managerial</td>
<td>27.2 (841/3090)</td>
<td>24.1 (534/2217)</td>
<td>20.4 (1997/9756)</td>
<td>34.2 (5641/16,462)</td>
<td>44.8 (1749/3905)</td>
<td>35.4 (333/940)</td>
</tr>
<tr>
<td>Cigarette smoking status$^j$, % (frequency), current smoker</td>
<td>15.1 (467/3090)</td>
<td>30.7 (683/2217)</td>
<td>53.1 (5176/9756)</td>
<td>21.4 (3519/16,462)</td>
<td>27.1 (1059/3905)</td>
<td>41.6 (392/940)</td>
</tr>
<tr>
<td>Long standing illness$^k$, % (frequency), yes</td>
<td>57.3 (1771/3090)</td>
<td>69.6 (1544/2217)</td>
<td>42.0 (4093/9756)</td>
<td>51.2 (8424/16,462)</td>
<td>46.0 (1797/3905)</td>
<td>48.8 (459/940)</td>
</tr>
<tr>
<td>Doctor diagnosed CVD$^l$, % (frequency), yes</td>
<td>12.1 (374/3090)</td>
<td>17.1 (378/2217)</td>
<td>5.5 (541/9756)</td>
<td>8.8 (1453/16,462)</td>
<td>6.9 (271/3905)</td>
<td>5.3 (50/940)</td>
</tr>
</tbody>
</table>

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$a$. In the UK, one unit is 8 grams (g) of alcohol or 10 millilitres (ml) of pure ethanol (alcohol); in the US, a standard drink is any drink that contains about 14 g of pure alcohol (17.5 ml). On that basis, one UK unit is equivalent (eq.) to 0.57 US standard drink.

$b$. Occasional drinkers: Drinkers who declared not having drunk in the last 7 days.

$c$. Within guidelines: Women: <14 units/wk (eq. 8 US standard drinks); Men: <21 units/wk (eq.12 US standard drinks).


$e$. Harmful: Women: >35 units/wk (eq. 20 US standard drinks); Men: >49 units/wk (eq. 28 US standard drinks).

$f$. Interquartile range

$g$. MET-h/wk: metabolic equivalent per hour per week (energy expenditure from sports and walking during a week).

$h$. GHQ: the General Health Questionnaire is a measure of the common mental health problems/domains of depression, anxiety, somatic symptoms and social withdrawal. Any score exceeding the threshold value of 3 is classed as achieving 'psychiatric caseness'.

$i$. Categories used for social class: Professional or managerial technical, skilled non-manual, skilled manual, unskilled, others.

$j$. Categories used for cigarette smoking status: never regular smoker, ex-smoker, current smoker.

$k$. Categories used for long standing illness: yes, no.

$l$. Categories used for cardiovascular diseases (stroke or IHD, including angina), diagnosed by a doctor: yes, no.

<table>
<thead>
<tr>
<th>Categories of alcohol consumption(^a) (N of deaths / N of subjects)</th>
<th>Multivariate HR(^b) (95% CF) Model 1(^d)</th>
<th>p value</th>
<th>Multivariate HR(^b) (95% CF) Model 2(^e)</th>
<th>p value</th>
<th>Multivariate HR(^b) (95% CF) Model 3(^f)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never drunk (519/3090)</td>
<td>1.00 (reference)</td>
<td>&lt;0.001</td>
<td>1.00 (reference)</td>
<td>&lt;0.001</td>
<td>1.00 (reference)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ex-drinkers (557/2217)</td>
<td>1.64 (1.45-1.84)</td>
<td></td>
<td>1.35 (1.19-1.52)</td>
<td></td>
<td>1.37 (1.21-1.55)</td>
<td></td>
</tr>
<tr>
<td>Occasional drinkers (543/9756)</td>
<td>0.81 (0.72-0.92)</td>
<td></td>
<td>0.81 (0.72-0.92)</td>
<td></td>
<td>0.83 (0.74-0.94)</td>
<td></td>
</tr>
<tr>
<td>Within guidelines (3283/16462)</td>
<td>1.10 (1.00-1.20)</td>
<td></td>
<td>1.08 (0.98-1.19)</td>
<td></td>
<td>1.13 (1.02-1.24)</td>
<td></td>
</tr>
<tr>
<td>Hazardous (644/3905)</td>
<td>1.15 (1.02-1.30)</td>
<td></td>
<td>1.13 (1.00-1.27)</td>
<td></td>
<td>1.19 (1.06-1.35)</td>
<td></td>
</tr>
<tr>
<td>Harmful (189/940)</td>
<td>1.79 (1.51-2.12)</td>
<td></td>
<td>1.59 (1.34-1.89)</td>
<td></td>
<td>1.64 (1.38-1.95)</td>
<td></td>
</tr>
<tr>
<td>Cancer mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never drunk (114/3090)</td>
<td>1.00 (reference)</td>
<td>&lt;0.001</td>
<td>1.00 (reference)</td>
<td>&lt;0.001</td>
<td>1.00 (reference)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ex-drinkers (140/2217)</td>
<td>1.80 (1.40-2.30)</td>
<td></td>
<td>1.47 (1.15-1.89)</td>
<td></td>
<td>1.49 (1.16-1.91)</td>
<td></td>
</tr>
<tr>
<td>Occasional drinkers (189/9756)</td>
<td>1.08 (0.85-1.36)</td>
<td></td>
<td>1.02 (0.81-1.30)</td>
<td></td>
<td>1.04 (0.82-1.32)</td>
<td></td>
</tr>
<tr>
<td>Within guidelines (975/16,462)</td>
<td>1.41 (1.16-1.72)</td>
<td></td>
<td>1.32 (1.08-1.61)</td>
<td></td>
<td>1.36 (1.11-1.65)</td>
<td></td>
</tr>
<tr>
<td>Hazardous (212/3905)</td>
<td>1.50 (1.19-1.90)</td>
<td></td>
<td>1.36 (1.07-1.72)</td>
<td></td>
<td>1.40 (1.11-1.78)</td>
<td></td>
</tr>
<tr>
<td>Harmful (50/968)</td>
<td>2.13 (1.56-2.92)</td>
<td></td>
<td>1.70 (1.24-2.34)</td>
<td></td>
<td>1.74 (1.27-2.39)</td>
<td></td>
</tr>
<tr>
<td>CVD mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never drunk (182/3090)</td>
<td>1.00 (reference)</td>
<td>&lt;0.001</td>
<td>1.00 (reference)</td>
<td>&lt;0.001</td>
<td>1.00 (reference)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ex-drinkers (192/2217)</td>
<td>1.60 (1.31-1.96)</td>
<td></td>
<td>1.37 (1.11-1.68)</td>
<td></td>
<td>1.39 (1.13-1.70)</td>
<td></td>
</tr>
<tr>
<td>Occasional drinkers (162/9756)</td>
<td>0.74 (0.60-0.92)</td>
<td></td>
<td>0.77 (0.62-0.96)</td>
<td></td>
<td>0.78 (0.63-0.97)</td>
<td></td>
</tr>
<tr>
<td>Within guidelines (1009/16,462)</td>
<td>0.96 (0.81-1.12)</td>
<td></td>
<td>0.99 (0.84-1.16)</td>
<td></td>
<td>1.03 (0.87-1.21)</td>
<td></td>
</tr>
<tr>
<td>Hazardous (191/3905)</td>
<td>0.98 (0.80-1.21)</td>
<td></td>
<td>1.04 (0.84-1.29)</td>
<td></td>
<td>1.10 (0.89-1.37)</td>
<td></td>
</tr>
<tr>
<td>Harmful (48/940)</td>
<td>1.33 (0.96-1.84)</td>
<td></td>
<td>1.30 (0.94-1.81)</td>
<td></td>
<td>1.35 (0.97-1.87)</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{a. In UK units/week (equivalent in US standard drinks). Never drunk and Ex-drinkers: Stopped drinking; Occasional drinkers: Drinkers but no drinking in the last 7 days; Within guideline: }<14 (8) \text{ (women) and }<21 (12) \text{ (men); Hazardous: 14-35 (8-20) (women) and 21-49 (12-28) (men); Harmful: }>35 (20) \text{ (women) and }>49 (28) \text{ (men).}

\(\text{b. Hazard ratios;}

\(\text{c. Confidence interval.}

\(\text{d. Model 1: Adjusted for age and gender.}

\(\text{e. Model 2: Adjusted as model 1, and body mass index, cigarette smoking status, social class status, psychological distress/depression score (12-point GHQ score) and longstanding illness. All-cause and CVD mortality were also adjusted for doctor diagnosed cardiovascular diseases (stroke or IHD, including angina).}

\(\text{f. Model 3: Adjusted as model 2, and physical activity.}\)