Risk thresholds for alcohol consumption

Wood, Angela M.; Nordestgaard, Børge; Dahm, Christina C.; Linneberg, Allan René; Overvad, Kim; Tjønneland, Anne; Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group

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Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies


Summary

Background Low-risk limits recommended for alcohol consumption vary substantially across different national guidelines. To define thresholds associated with lowest risk for all-cause mortality and cardiovascular disease, we studied individual-participant data from 599,912 current drinkers without previous cardiovascular disease.

Methods We did a combined analysis of individual-participant data from three large-scale data sources in 19 high-income countries (the Emerging Risk Factors Collaboration, EPIC-CVD, and the UK Biobank). We characterised dose–response associations and calculated hazard ratios (HRs) per 100 g per week of alcohol (12.5 units per week) across 83 prospective studies, adjusting at least for study or centre, age, sex, smoking status, at least 1 year of follow-up after baseline, and no baseline history of cardiovascular disease. The main analyses focused on current drinkers, whose baseline alcohol consumption was categorised into eight predefined groups according to the amount in grams consumed per week. We assessed alcohol consumption in relation to all-cause mortality, total cardiovascular disease, and several cardiovascular disease subtypes. We corrected HRs for estimated long-term variability in alcohol consumption using 152,640 serial alcohol assessments obtained some years apart (median interval 5.6 years [5th–95th percentile 1.04–13.5]) from 71,011 participants from 37 studies.

Findings In the 599,912 current drinkers included in the analysis, we recorded 40,310 deaths and 39,018 incident cardiovascular disease events during 5.4 million person-years of follow-up. For all-cause mortality, we recorded a positive and curvilinear association with the level of alcohol consumption, with the minimum mortality risk around or below 100 g per week. Alcohol consumption was roughly linearly associated with a higher risk of stroke (HR per 100 g per week higher consumption 1.14, 95% CI, 1.09–1.20), coronary disease excluding myocardial infarction (1.32, 1.15–1.50), heart failure (1.03, 1.00–1.06), and total cardiovascular disease (1.14, 95% CI, 1.10–1.17). In contrast, increased alcohol consumption was log-linearly associated with a lower risk of myocardial infarction (HR 0.94, 0.91–0.98) in comparison to those who reported drinking >0–≤100 g per week, those who reported drinking >100–≤200 g per week, >200–≤350 g per week, or >350 g per week had lower life expectancy at age 40 years of approximately 6 months, 1–2 years, or 4–5 years, respectively.

Interpretation In current drinkers of alcohol in high-income countries, the threshold for lowest risk of all-cause mortality was about 100 g/week. For cardiovascular disease subtypes other than myocardial infarction, there were no clear risk thresholds below which lower alcohol consumption stopped being associated with lower disease risk. These data support limits for alcohol consumption that are lower than those recommended in most current guidelines.
Introduction

Alcohol consumption guidelines vary substantially across the globe. In the USA, for example, an upper limit of 196 g per week (about 11 standard UK glasses of wine or pints of beer per week) is recommended for men, and an upper limit of 98 g per week is recommended for women. Similar recommendations apply in Canada and Sweden. By contrast, guidelines in Italy, Portugal, and Spain recommend low-risk limits almost 50% higher than these. At the other extreme, UK guidelines recommend low-risk limits for men almost half that recommended by US guidelines. Such variation in policy might reflect ambiguity about drinking risk thresholds associated with the lowest risk of mortality, as well as uncertainty about the specific consequences of alcohol consumption, including those related to cardiovascular disease subtypes. For example, recent studies have challenged the concept that moderate alcohol consumption is universally associated with lower cardiovascular disease risk, but the dose–response associations of alcohol consumption with cardiovascular disease subtypes remain poorly understood. Therefore, to help in the formulation of evidence-based alcohol policy, we analysed individual-participant data from 83 long-term prospective studies in 19 high-income countries. Our aim was to characterise risk thresholds for all-cause mortality and cardiovascular disease subtypes in current drinkers of alcohol.

Evidence before this study

We searched for prospective epidemiological studies of alcohol consumption investigating disease risk thresholds published in any language up until March 1, 2017 (with no specified earliest date), in PubMed, Scientific Citation Index Expanded, and Embase using relevant terms ("alcohol", "mortality", "survival", "cardiovascular disease", "cohort", and "prospective"). We found many primary reports and literature-based reviews. However, no study had combined the following key features required to achieve reliable estimates of dose–response associations: availability of individual-participant data; quantitative assessment of alcohol consumption levels using validated instruments; periodic re-surveys of alcohol consumption levels; recording of large numbers of deaths (eg, >20,000 deaths); and sufficient detail and power to disaggregate incident cardiovascular disease outcomes into subtypes (eg, >2,000 incident total cardiovascular disease outcomes).

Methods

Study design, data sources, and participants

We focused our study on current alcohol drinkers for three main reasons. First, alcohol guidelines provide recommendations about low-risk limits only for drinkers (we are unaware of any guidelines that encourage non-drinkers to consume alcohol). Second, a focus on current drinkers should limit potential biases that are difficult to control in observational studies (eg, reverse causality, residual confounding, and unmeasured effect modification) because ex-drinkers include people who might have abstained from alcohol owing to poor health itself, as well as those who have changed their habits to achieve a healthier lifestyle. Third, never-drinkers might differ systematically from drinkers in ways that are difficult to measure, but which might be relevant to disease causation.

We did a combined analysis of individual-participant data from three large-scale data sources available to our collaboration of prospective cohort studies with information about alcohol consumption (appendix p 21). First, the Emerging Risk Factors Collaboration (ERFC) is a collaboration of prospective cohort studies with information about a variety of risk factors, cardiovascular disease outcomes, and mortality. Of the 102 studies in the ERFC with information about alcohol status, 81 contained information about the quantity of consumption. Second,
EPIC-CVD, a ten-country case-cohort study nested in the European Prospective Investigation into Cancer and Nutrition (EPIC) prospective cohort study, had quantitative alcohol information from 22 of its 23 contributing centres.9 Third, UK Biobank—a single large prospective study—had cohort-wide data about quantitative alcohol consumption.4 Therefore, our combined analysis included information from a total of 83 prospective studies that each used broadly similar methods to quantify alcohol consumption, record risk factors, and ascertain cause-specific death and cardiovascular disease events. We harmonised records of alcohol consumption across the contributing studies using a conversion of 1 unit=8 g of pure alcohol to a standard scale of grams per week (appendix pp 1–2), enabling a common analytical approach despite variation in the methods used (eg, self-administered vs interview-led questionnaires; food frequency questionnaires vs dietary recall surveys), and in consumption scales over different periods of ascertainment. Details of contributing studies are in appendix pp 3–4, 10–11.

To be eligible for the analysis, participants had to have information recorded about their alcohol consumption amount and status (ie, non-drinker vs current drinker), plus age, sex, history of diabetes and smoking status, at least 1 year of follow-up after baseline, and no known baseline history of cardiovascular disease (defined as coronary heart disease, other heart disease, stroke, transient ischaemic attack, peripheral arterial disease, or cardiovascular surgery); appendix p 21. The main analyses focused on current drinkers, whose baseline alcohol consumption was categorised into eight predefined groups according to the amount in grams consumed per week: >0–<25, ≥25–<50, ≥50–<75, ≥75–<100, ≥100–<150, >150–<250, ≥250–<350, and ≥350 g per week. We assessed alcohol consumption in relation to all-cause mortality, total cardiovascular disease, and the following cardiovascular disease subtypes (defined in appendix p 5): fatal and non-fatal myocardial infarction; fatal and non-fatal coronary disease excluding myocardial infarction; fatal and non-fatal stroke (including ischaemic, haemorrhagic, subarachnoid, and unclassified subtypes of stroke); fatal and non-fatal heart failure; and mortality from other cardiovascular causes, including cardiac dysrhythmia, hypertensive disease, sudden death, and aortic aneurysm.9,20,21 In analyses of cardiovascular disease subtypes, participants contributed follow-up time until the first outcome recorded (ie, cardiovascular deaths subtypes, participants contributed follow-up time until stratified by centre.9 For the four case-control studies nested within prospective cohorts of the ERFC, odds ratios were calculated using, as appropriate, conditional or unconditional logistic regression models, taking into account relevant matching factors. Study-specific estimates were then pooled across studies by random-effects meta-analysis.9 We tested for violation of the proportional hazards assumption by including time interactions with alcohol consumption. To avoid model overfitting, studies with fewer than five incident cases of a particular outcome were excluded from analyses of that particular outcome.

To correct for measurement error and within-person variability in alcohol consumption over time, we estimated long-term average (henceforth, “usual”) alcohol consumption using multi-level regression calibration and information from 152 640 serial assessments in 71011 individuals from 37 studies. This calculation was achieved either by regressing re-survey measurements (for the repeat alcohol assessments available in the ERFC studies and UK Biobank) or lifetime alcohol consumption measurements (for calculated lifetime alcohol consumption measurements available in EPIC-CVD) on baseline alcohol consumption, adjusted for duration of follow-up and baseline age, sex, smoking status, history of diabetes, other relevant covariate(s), and with random effects for study and re-survey.29,30 The regression dilution ratio (ie, the calibration slope), which measures the extent of within-person variability,29 was extracted from the calibration model. HRs in this paper relate to usual alcohol consumption levels unless specified otherwise.

We assessed the shapes of associations for all-cause mortality and cardiovascular disease outcomes by calculating study-specific HRs within the predefined groups of baseline alcohol consumption, pooled them by multivariate random-effects meta-analysis, and plotted them against mean (and baseline) alcohol consumption within each group. We estimated 95% CIs for each group (including the reference group) that corresponded to the amount of information underlying each group.9,31 For each major outcome, we determined the best fitting first or second order fractional polynomial to describe the association with baseline alcohol consumption (using a 1% significance level as evidence for a second order fractional polynomial over a first order fractional polynomial) using Cox regression models stratified by sex, study, and centre. Further analyses assumed a linear association with alcohol consumption, expressing results per 100 g per week (12·5 units/week) in usual alcohol consumption. To assess the effect of excluding known current drinkers with missing alcohol consumption data, we did a sensitivity analysis using multiple imputation within studies, before combining.


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<tr>
<th>Study level characteristics</th>
<th>ERFC</th>
<th>EPIC-CVD</th>
<th>UK Biobank</th>
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<td>22 centres in 10 European countries</td>
<td>England, Scotland, and Wales</td>
<td>37 studies in 15 countries</td>
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<td>Known current drinkers at baseline</td>
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<td>Alcohol consumption (g/week), median (5th–95th percentiles)</td>
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<td>Systolic blood pressure, mm Hg</td>
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<th>Major outcomes restricted to current drinkers</th>
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<td>All-cause mortality events</td>
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<td>All cardiovascular disease</td>
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Data are n, n (%) or mean (SD), unless otherwise indicated. ERFC=Emerging Risk Factors Collaboration. EPIC-CVD=European Prospective Investigation into Cancer and Nutrition—Cardiovascular Disease. BMI=body-mass index. HDL-C=high-density-lipoprotein cholesterol. *At the time of analysis, measurements of HDL-C and total cholesterol were not available in the UK Biobank. †All-cause mortality events from EPIC derive only from the 13,670 participants in the random sub-cohort of EPIC-CVD, rather than from the entire EPIC prospective study. ‡Mean consumption (g/week) at baseline vs resurvey.

Table 1: Study-level and participant-level characteristics of the contributing data sources

University of Athens, Athens, Greece (P Lagiou, A Karakatsani, Prof A Trichopoulou); Harvard TH Chan School of Public Health, Boston, MA, USA (P Lagiou); Office of Public Health Studies, University of Hawaii, Honolulu, HI, USA (Prof B Rodriguez MD); Instituto de Salud Pública de Navarra, IdiSNA - Navarra Institute for Health Research, Pamplona, Spain (C Moreno-Iribas PhD); Red de Investigación en the data in a meta-analysis. We investigated associations with alcohol type (wine, beer, and spirits), consumption frequency (dichotomised as drinkers who consumed alcohol on ≤2 days per week or those who consumed alcohol on >2 days per week) and episodic heavy drinking (dichotomised as binge drinkers who consumed ≥100 g per drinking occasion or non-binge drinkers who consumed <100 g per drinking occasion).

We used regression calibration methods similar to those described above to estimate and adjust for longitudinal levels of potential confounding factors or mediators in individuals with available information. HRs were adjusted for usual levels of available potential confounders or mediators, including body-mass index (BMI), systolic blood pressure, high-density-lipoprotein cholesterol (HDL-C), low-density-lipoprotein cholesterol (LDL-C), total cholesterol, fibrinogen, and baseline measures for smoking amount (in pack-years), level of education reached (no schooling or primary education only vs secondary education vs university), occupation (not working vs manual vs office vs other), self-reported physical activity level (inactive vs moderately inactive vs moderately active vs active), self-reported general health (scaled 0–1 where low scores indicate poorer health),...
self-reported red meat consumption, and self-reported use of anti-hypertensive drugs. We investigated effect modification with formal tests for interaction, using a 0.1% significance threshold to make some allowance for multiple testing. Heterogeneity was investigated by grouping studies according to recorded characteristics and through meta-regression, assessed by the $I^2$ statistic. Evidence of small study effects was assessed visually with funnel plots and by Begg and Mazumdar’s test and Egger’s test.

Methods we used to estimate reductions in life expectancy (years of life lost) are described in the appendix (pp 6–7). Briefly, estimates of cumulative survival from 40 years of age onwards in different categories of baseline alcohol consumption were calculated by applying estimated HRs (specific to age-at-risk) for cause-specific mortality to the detailed mortality component of the US Centers for Disease Control and Prevention’s WONDER database, which recorded 10 million deaths (from all causes) in more than 305 million individuals in the USA during 2007–10. Results were modelled from age 40 years and enabled estimation of years of life lost between light drinkers (defined as those consuming >0–≤100 g/week of alcohol) and pre-defined groups of >100–≤200, >200–≤350, and >350 g per week. This method does not make use of the survival estimates from the modelled data; instead, it makes inferences by estimating age-at-risk specific HRs, which are then combined with external population age-specific mortality rates.

Analyses used Stata (version 14.2 and 15.1). All p values presented are for 2-sided tests.

Role of the funding source
The funders of the study did not have any role in the study design, data analysis, or reporting of this manuscript. AMW and SK had full access to the combined dataset, and, together with EDA and JD, had responsibility for the decision to submit the manuscript for publication.

Results
Of the 786 787 participants with sufficient information for inclusion in this consortium, 186 875 (19%) reported not drinking at baseline, leaving 599 912 current drinkers without a history of cardiovascular disease at baseline who were eligible for the prespecified principal analysis. The current drinkers were derived from ERFC (247 504 participants), EPIC-CVD (26 036), and the UK Biobank (326 372; table 1). Baseline year of recruitment ranged from 1964 to 2010. The mean age of the participants was 57 years (SD 9). 265 910 (44%) of 599 912 participants were women, and 128 085 (21%) were current smokers (appendix p 12). About 50% reported drinking more than 100 g of alcohol per week, and 8.4% drank more than 350 g per week (table 1). During 5.4 million person-years (median 7.5 years of follow-up [5th–95th percentiles 5.0–18.4]), there were 40 310 deaths from all causes, (including 11 762 vascular and 15 150 neoplastic deaths), and 39 018 first incident cardiovascular disease outcomes, including 12 090 stroke events, 14 539 myocardial infarction events, 7 990 coronary disease events excluding myocardial infarction, 2 711 heart failure events, and 1 121 deaths from other cardiovascular diseases (appendix p 13).

Baseline alcohol consumption varied substantially across studies, was generally lower in more recent calendar periods of recruitment, and was positively skewed (median 96 g/week [5th–95th percentiles 6.4–48.8]; appendix p 22). It was weakly and positively correlated with male sex, smoking status and amount, systolic blood pressure, HDL-C level, fibrinogen, and lower socioeconomic status (appendix pp 23–24). 152 640 serial assessments of alcohol consumption were available for 71 011 participants from 37 studies (median interval between baseline and serial measurements 5–6 years [5th–95th percentiles 1–0.04–13.5]). Participants with serial measurements were younger, had slightly higher baseline alcohol consumption, and were more likely to be men than those without serial measurements (table 1, appendix p 14). The regression dilution ratio for alcohol consumption was 0.50 (95% CI 0.47–0.52), similar to that for systolic blood pressure (0.52, 0.50–0.55) but lower than that for HDL-C concentration (0.74, 0.72–0.76) in a common set of participants.

For all-cause mortality, there was a positive and curvilinear association with alcohol consumption, with the lowest risk for those consuming below 100 g per week (figure 1, appendix p 25). Associations were similar for men and women (appendix p 26), but weaker at older ages (appendix p 27). There was a J-shaped association for the aggregate of cardiovascular disease outcomes (figure 1, appendix p 25). However, disaggregation showed two opposing sets of associations (figure 2).
After adjustment for age, sex, smoking, and history of diabetes, the amount of alcohol consumed had positive and roughly linear associations with stroke (HR per 100 g/week higher consumption 1.00–1.10–1.17), coronary disease excluding myocardial infarction (1.06–1.00–1.11), heart failure (1.09–1.03–1.15), fatal hypertensive disease (1.24–1.15–1.33), and fatal aortic aneurysm (1.15–1.03–1.28; figures 2, 3). By contrast, there was an inverse and approximately log-linear association with myocardial infarction (0.94–0.91–0.97; figures 2, 3). Stroke associations were similar for fatal and non-fatal outcomes (appendix p 28) and across subtypes (appendix p 29). However, for coronary disease excluding myocardial infarction, associations were stronger for fatal than non-fatal outcomes (appendix p 28). For myocardial infarction, inverse associations were possibly more pronounced with non-fatal than fatal outcomes (figure 3, appendix p 28).

With the following notable exceptions, further adjustment for additional covariates did not substantially change HRs (table 2, appendix pp 15, 30). First, adjustment for HDL-C level weakened the inverse association between alcohol consumption and myocardial infarction, but strengthened the positive association between alcohol consumption and both coronary disease and heart failure. Second, adjustment for systolic blood pressure strengthened the inverse association between alcohol consumption and myocardial infarction, but weakened the positive associations between alcohol consumption and all other cardiovascular disease outcomes. Our analysis confirmed the established association of alcohol consumption with cancers of the digestive system, which did not change after additional adjustment for the factors listed above (appendix p 16). Furthermore, additional adjustment for smoking amount abolished the apparent association of alcohol consumption with lung cancer (appendix pp 16), in line with the accepted view that alcohol consumption does not cause lung cancer. When including never-drinkers and ex-drinkers, we reproduced previously reported U-shaped associations of
alcohol consumption with total cardiovascular disease and all-cause mortality (appendix p 31). However, we observed notable differences in baseline characteristics between never drinkers and current drinkers (eg, in relation to sex, ethnicity, smoking, and diabetes status; appendix p 12), supporting the validity of focusing on current drinkers in our main analysis. We recorded similar findings to those reported above in sensitivity analyses that involved the following approaches: used multiple imputation rather than complete-case analysis (appendix p 32); used fractional polynomials (appendix p 34); used a fixed-effect meta-analysis (appendix p 35); included studies that of Sydney and Royal Prince Alfred Hospital, Sydney, NSW, Australia (Prof H Arima MD); Department of Preventive Medicine and Public Health, Kyushu University, Fukuoka, Japan (Prof H Arima); School of Health Science and Education, Harokopio University, Athens, Greece (Prof D B Panagiotakos PhD); Department of Family Medicine and Public Health, University of California, San Diego, CA, USA (E Barrett-Connor MD); EMDGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, Netherlands (N van Schoor MD); Aalborg University Hospital, Aalborg, Denmark (Prof K Overvad); Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland (Prof H Arima MD); Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, UK (Prof N Wareham MD), C Langenberg MD, Prof N Forouhi PhD); Department of Kinesiology, Laval University, Quebec City, QC, Canada (Prof J P Despres DPhil); Department of Medicine, University of Vermont, Burlington, VT, USA (Prof M Cushen MD); Wake Forest University School of Medicine, Winston-Salem, NC, USA (Prof C Rodriguez); Wake Forest Baptist Medical Center, Winston-Salem, NC, USA (Prof C Rodriguez); Department of Social and Environmental Medicine, Kanazawa Medical University, Ishikawa, Japan (M Sakurai MD); Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia (J E Shaw PhD); Busselton Population Medical Research Institute, Busselton, WA, Australia (Prof H Brenner); School of Population and Global Health, The University of Western Australia, Perth, WA, Australia (Prof M Ensminger MD); Helmholtz Zentrum München German Research Center for Environmental Health, Germany (Prof C Meisinger MD); Danish Cancer Society Research Center, Copenhagen, Denmark (A Tjønneland MD); Division of Clinical Epidemiology and Aging Research, University of Heidelberg, Heidelberg, Germany (Prof H Brenner); Istituto Superiore di Sanità,
Figure 4: Estimated future years of life lost by extent of reported baseline alcohol consumption compared with those who reported consuming >0–≤100 g per week.

The estimates of cumulative survival from 40 years of age onwards in the alcohol-drinking groups were calculated by applying hazard ratios (specific to age at risk) for all-cause mortality associated with categorised baseline alcohol consumption to US death rates at the age of 40 years or older. Mean usual levels of alcohol consumption within each baseline alcohol consumption category were 56, 123, 208 and 367 g per week, respectively, for the groups >0–≤100 g per week, >100–≤200 g per week, >200–≤350 g per week, and >350 g per week.

Rome, Italy (L Palmieri PhD); Institut Pasteur de Lille, Lille, France (J-P Dallongeville MD); Assmann-Stifftung for Prevention, Munster, Germany (Prof G Assmann MD); The City College of New York, New York, NY, USA (M Trevisan MD); Howard University Hospital, Washington DC, USA (R F Gillum MD); Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK (Prof I Ford PhD); Prof N Sattar FMedSci; Emerging Risk Factors Collaboration and EPIC-CVD Coordinating Centres, Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge, CB1 8RN; amw79@medschl.cam.ac.uk or Professor John Danesh, Emerging Risk Factors Collaboration and EPIC-CVD Coordinating Centres, Department of Public Health and Primary Care, Strangeways Research Laboratory, University of Cambridge, Cambridge, CB1 8RN; amw79@medschl.cam.ac.uk

Discussion

The main finding of this analysis was that the threshold for lowest risk for all-cause mortality was about 100 g per week. For men, we estimated that long-term reduction of alcohol consumption from 196 g per week (the upper limit recommended in US guidelines) to 100 g per week or below was associated with about 1–2 years of longer life expectancy at age 40 years. Exploratory analyses suggested that drinkers of beer or spirits, as well as binge drinkers, had the highest risk for all-cause mortality.

Our study has highlighted the complex and diverse potential mechanisms by which alcohol consumption may exert cardiovascular effects. It has shown that the association between alcohol consumption and total cardiovascular disease risk comprises several distinct and opposite dose–response curves, rather than a single J-shaped association. In particular, whereas higher alcohol consumption was roughly linearly associated with a higher risk of all stroke subtypes, coronary disease excluding myocardial infarction, heart failure, and several less common cardiovascular disease subtypes, it was approximately log-linearly associated with a lower risk of myocardial infarction. Our results are concordant with recent observational data and Mendelian randomisation studies.
Our results contribute toward understanding of the basis for these directionally divergent cardiovascular disease associations. For example, our data have suggested that elevated systolic blood pressure could mediate alcohol consumption’s positive association with stroke and coronary disease excluding myocardial infarction.34-36 By contrast, pathways related to HDL-C (but not necessarily HDL-C itself37-39) could mediate alcohol consumption’s inverse association with myocardial infarction. Both blood pressure and HDL-C are known to increase in response to alcohol consumption.90 They have contrasting associations with cardiovascular disease outcomes: the inverse association of HDL-C with cardiovascular disease is substantially stronger for coronary disease than stroke,72-74 whereas the positive association of systolic blood with cardiovascular disease is considerably stronger for stroke than coronary disease.75 However, we did not find convincing evidence that other known risk factors were important mediators or confounders.

Our study’s access to individual-participant data avoided limitations of previous literature-based reviews.26 To limit reverse causality, our study focused on current drinkers without baseline cardiovascular disease and omitted the initial period of follow-up. To limit confounding, our study adjusted for a variety of risk factors. To correct for misclassification in alcohol consumption and covariates, our study also used extensive information on serial assessments. Our results were robust to a variety of sensitivity analyses. Generalisability of the findings was enhanced by inclusion of data from 83 prospective studies based in many different high-income countries recruited between 1964 and 2010. Although alcohol consumption levels declined during this period, HRs were similar over calendar time.

Nevertheless, our study has some potential limitations. Self-reported alcohol consumption data are prone to bias and are challenging to harmonise across studies conducted over different time periods that used varying instruments and methods to record such data.31,32 We did not, however, identify major differences in results across studies that used differing alcohol measurement instruments. Despite our study’s access to extensive serial alcohol re-surveys from mid-life, our study could not investigate alcohol consumption during the entire life course. Misclassification in outcomes would have diluted dose-response associations, suggesting that true underlying associations of alcohol consumption with cardiovascular disease subtypes are stronger and more divergent than we observed. Because we did not generally have access to additional alcohol-related adverse outcomes (eg, non-fatal liver disease, injuries, or psychiatric comorbidities), we probably underestimated potential benefits associated with lowering alcohol consumption. Because some individuals who reduced, but did not cease, alcohol consumption due to health complications were probably included in our analysis, we cannot exclude the effects of reverse causation (especially since some contributing studies did not record baseline chronic disease other than cardiovascular disease). Therefore, alternative study designs including randomised trials33 are needed, to control more completely for residual biases (including those related to studying ex-drinkers and never-drinkers).

In conclusion, our study shows that among current drinkers, the threshold for lowest risk of all-cause mortality was about 100 g per week. For cardiovascular disease subtypes other than myocardial infarction, there were no clear thresholds below which lower alcohol consumption stopped being associated with a lower disease risk. These data support adoption of lower limits of alcohol consumption than are recommended in most current guidelines.

Contributors
All the authors contributed to data collection, and to the design, analysis, interpretation, and re-drafting of this report. AMW and SK had full access to the combined data and did the statistical analysis. AMW, EDA, and JD drafted the manuscript and had responsibility for submission of the manuscript for publication.

Data management team
Thomas Bolton, Catherine Perry, Sarah Spackman, and Matthew Walker.

Coordinating centre

Declaration of interests
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Population Research Advisory Panel, outside the submitted work. M. L. reports grants from National Institutes of Health, during the conduct of the study; grants from National Kidney Foundation, outside the submitted work; and funding from the National Institutes of Health, Grant SU10A025286, to Johns Hopkins University. MS reports grants from the UK Medical Research Council, the British Heart Foundation, the National Institute for Health Research, European Commission Framework 7, and the European Research Council, during the conduct of the study. NW reports grants from the Netherlands Ministry of Health, Welfare and Sports, Directorate of Long-Term Care, during the conduct of the study. OHF reports grants from Nestle and Metagenics, outside the submitted work. PJ N. reports grants from the NIH, during the conduct of the study. STG reports grants from the UK Medical Research Council and the British Heart Foundation, during the conduct of the study. SKI reports grants from FFG COMET program: “Research Center of Excellence in Vascular Ageing—Tyrol. VASCare” (K-Projekt No. 841536) funded by the BMVIT, BWMAF, Wirtschaftsagentur Wien and Standortagentur Tirol, outside the submitted work. SKA reports grants from the UK Medical Research Council and the British Heart Foundation, during the conduct of the study. WK reports personal fees from AstraZeneca, Novartis, Pfizer, The Medicines Company, GSK, DaiCor, Sanofi, Berlin-Chernie, Kowa, and Amsen; grants and non-financial support from Roche Diagnostics, Beckmann, Sinyules, and Abbott, outside the submitted work. The other authors declare no competing interests.

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