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Alcohol intake and total mortality in 142 960 individuals from the MORGAM Project: a population-based study

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ABSTRACT

Aim To test the association of alcohol consumption with total and cause-specific mortality risk. **Design** Prospective observational multi-centre population-based study. **Setting** Sixteen cohorts (15 from Europe) in the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) Project. **Participants** A total of 142 960 individuals (mean age 50 ± 13 years, 53.9% men). **Measurements** Average alcohol intake by food frequency questionnaire, total and cause-specific mortality. **Findings** In comparison with life-time abstainers, consumption of alcohol less than 10 g/day was associated with an average 11% [95% confidence interval (CI) = 7–14%] reduction in the risk of total mortality, while intake > 20 g/day was associated with a 13% (95% CI = 7–20%) increase in the risk of total mortality. Comparable findings were observed for cardiovascular (CV) deaths. With regard to cancer, drinking up to 10 g/day was not associated with either mortality risk reduction or increase, while alcohol intake > 20 g/day was associated with a 22% (95% CI = 10–35%) increased risk of mortality. The association of alcohol with fatal outcomes was similar in men and women, differed somewhat between countries and was more apparent in individuals preferring wine, suggesting that benefits may not be due to ethanol but other ingredients. Mediation analysis showed that high-density lipoprotein cholesterol explained 2.9 and 18.7% of the association between low alcohol intake and total as well as CV mortality, respectively. **Conclusions** In comparison with life-time abstainers, consuming less than one drink per day (nadir at 5 g/day) was associated with a reduced risk of total, cardiovascular and other causes mortality, except cancer. Intake of more than two drinks per day was associated with an increased risk of total, cardiovascular and especially cancer mortality.

Keywords Alcohol intake, cancer mortality, cardiovascular mortality, cohort study, HDL cholesterol, mortality.

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INTRODUCTION

Observational studies have reported that moderate alcohol drinkers live longer than both life-time abstainers and heavy drinkers [1–3]. In the absence of conclusions from randomized controlled trials [4] these findings have been scrutinized for confounding and bias [5, 6], and have been recently questioned [7–9]. The association of alcohol consumption with chronic diseases is complex, because of its distinct relationships with different chronic diseases, the potential for non-linear dose–response relationships, issues concerning setting, pattern of consumption, confounding, selection of the reference group and the varied roles of different types of alcoholic beverages [10–13].

Previous studies examining single diseases at a time provided contrasting results, making it difficult to assess the full burden of alcohol consumption [8, 14, 15]. Specifically, a lower risk of cardiovascular (CV) events among moderate drinkers has been repeatedly observed [11, 14–18]; however, at the same time, heavy alcohol intake was associated with increased risk of some cancers and other disorders [8, 11, 19]. As a consequence, a consensus has emerged on the fact that heavy alcohol consumption has a definite detrimental effect [11]. However, the existence of a healthy non-zero level of alcohol

consumption remains uncertain [7, 8, 20–24]. Important differences in terms of drinking cultures have been observed among countries [7, 8, 25], including: frequency and volume of drinking, drinking context (such as with meals), beverage preference, the way in which alcohol is culturally accepted and how alcohol-related policies operate. These differences may explain the heterogeneous results obtained in studies of alcohol.

To take simultaneously into account positive and negative effects of drinking, the association of different volumes with all-cause mortality needs to be analyzed, taking into account all the open issues mentioned above [11, 12, 23–25].

The primary aim of the present study was to examine the relationship between the volumes of alcohol consumed and total and cause-specific mortality in the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) [26] Project. Secondary aims were to investigate the role of frequency of consumption, to test the potential mediation by biomarkers of CV risk and to assess possible differences by country and by preferred beverage type.

METHODS

The MORGAM Project is a multi-national follow-up study of population-based cohorts. Details of MORGAM cohorts, data quality assessment for baseline and follow-up data are documented at http://www.thl.fi/publications/morgam [27–30], and accessible in Supporting information. The present analysis was based on 16 cohort studies recruited in 10 European countries and one cohort from Australia. Our study complies with the Declaration of Helsinki; all participating studies had been approved by local ethics review boards and informed consent was obtained from all individuals included.

Alcohol intake assessment and study outcome

Volume of ethanol in grams per day (g/day) from alcoholic beverages was obtained from a questionnaire for each cohort and assessed as follows: (a) as a component of the local questionnaire of eating habits, each person was asked for average quantity of drinks consumed; (b) the number of drinks was standardized to 1 day; (c) one-drink's ethanol content was assumed in the range of 10–12 g, according to country-specific references; (d) when available, the ethanol content was derived separately for each type of beverage and then summed; the percentage of ethanol ranged from 10 to 14 for wine, 3–5 for beer and 20–40 for liquor; (e) each person was also asked for frequency of consumption (fewer than 2 days/week, up to 5 and more than 5) and for their drinking habit (no, former, rare or common intake). Using this information, we were able to identify individuals who had stopped drinking anytime for any reason ('former drinkers') and those who declared they have never consumed, at occasion, as much as one drink ('life-time abstainers') [25].

Participants in each cohort were followed-up for death from any cause. Deaths were identified through record linkage with national or regional health information systems. In most centres the cardiovascular causes of death were adjudicated using MONICA diagnostic criteria [30]. The MORGAM Manual [27, 28] provides further information about the cause of death classifications.

Statistical analysis

Of the available 154 920 individuals, we excluded 11 960 (7.7%) due to missing data on alcohol. We estimated the hazard ratios [with 95% confidence intervals (CI)] for mortality across categories of alcohol intake from Cox proportional hazards models with age as the time-scale, and adjusting for sex, cohort, smoking and levels of education in a first model and further for body mass index (BMI), diabetes, CV disease, cancer and hypertension in a second model. Life-time abstainers were taken as the reference group. To test for a continuous relationship, we modelled alcohol as restricted cubic splines. For the mediation analysis, the Baron & Kenny approach-based %MEDIATE macro [31] was used. All statistical methods were implemented in SAS statistical software for Windows, version 9.4.

Patient and public involvement

This research was conducted with no patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

Baseline characteristics for the study population (n = 142 960) according to alcohol categories are shown in Table 1; 49 801 individuals (34.8%) reported no alcohol consumption. Among these, 5486 (3.8%) individuals stopped drinking for any reason, 24.0% declared they were life-time abstainers and 7.0% had missing data on drinking pattern ('non-drinkers'); the latter group includes both ex-drinkers and life-time abstainers (see Supporting information for a detailed description of this group). A total of 93 151 individuals (65.1%) were alcohol consumers and were divided into three categories at increasing intake of alcohol (Table 1). Data are from 16 cohorts, 15 from Europe and one from Australia. The main characteristics of the cohorts are illustrated in Supporting information, Table S1. Overall, the prevalence of men was 53.9% and median age was 51 years [interquartile range (IQ) = 40–59 years]. The

Table 1 General characteristics of the studied population according to alcohol intake.

Baseline characteristics		*Alcohol intake categories*					
		Former drinkers	*Non-drinkers*[a]	*Life-time abstainers*	*Light–moderate 0.1–10 g/day*	*Moderate 10.1-20 g/day*	*Heavy > 20 g/day*
Number of individuals (%)		5486 (3.8)	10 013 (7.0)	34 310 (24.0)	51 471 (36.0)	16 885 (11.8)	24 795 (17.3)
Alcohol intake, mean (SD), g/day		0	0	0	4.5 (2.7)	14.6 (2.7)	53.6 (54.6)
Men, %		52.5	36.2	35.4	50.1	68.5	85.1
Age at baseline examination, mean (SD), years		55 (11)	47 (12)	51 (13)	48 (13)	51 (13)	52 (11)
Daily smoker, %		22.4	21.6	24.6	29.9	34.2	37.4
Diabetes, %		11.3	5.0	5.9	3.7	4.3	4.8
Previous CVD, %		10.7	4.2	7.7	4.3	4.8	4.0
Hypertension, %		50.0	49.9	44.7	39.8	46.8	51.6
Body mass index, %	≤ 18.5 kg/m^2	0.6	1.0	1.1	0.8	0.5	0.6
	18.5–24.9 kg/m^2	32.3	40.3	37.3	41.9	37.7	32.4
	25.0–29.9 kg/m^2	41.1	39.0	37.5	39.8	44.3	47.2
	≥ 30 kg/m^2	26.1	19.7	24.2	17.6	17.5	19.8
Level of education, %	primary school only (or less)	30.8	59.3	34.2	19.6	29.0	35.0
	Secondary school	49.9	20.5	35.1	33.3	35.8	41.2
	Intermediate between secondary and university	10.4	14.8	18.9	24.9	17.1	12.5
	University or college or equivalent	8.9	5.4	12.2	22.1	18.1	11.3

[a]Non-drinkers are individuals for which we failed to distinguish between teetotallers and former drinkers. Previous CVD means documented or self-reported history of myocardial infarction or stroke or unstable angina pectoris. CVD = cardiovascular disease; SD = standard deviation.

prevalence of men, smoking habit, hypertension, overweight and lower levels of education was higher in categories at increasing alcohol intake. The prevalence of history of CV disease or diabetes was higher in all three categories of non-alcohol consumers (Table 1).

Risk of death

During a median follow-up time of 11.8 years (IQ = 6.8–16.1), 16 907 deaths occurred (during 1 801 926 person-years of observation). Of these, 5547 were from a CV cause, 5511 were cancer deaths and 5849 were classified from 'other causes'.

Multivariable hazard ratios for mortality are reported in Table 2. In the fully adjusted model, in comparison with life-time abstainers, ex-drinkers and non-drinkers had a 19 and 13% higher risk of mortality, respectively; drinkers 0.1–10 g/day had an 11% (95% CI =7–14%) lower risk of death, whereas drinkers > 20 g/day had a 13% (7–20%) higher risk. Similar findings were observed for CV and 'other causes' deaths, whereas cancer mortality risk was higher in ex-drinkers, non-drinkers and in drinkers > 20 g/day (Table 2). Analogous results were observed after omission from the adjustment model of the factors that might be causally related to alcohol consumption (Table 2, Model 1) and after multiple imputations for missing data in all variables, including alcohol intake and history of cancer (Supporting information, Table S2).

Mortality risks according to drinking frequency are reported in Supporting information, Table S3. Irrespective of further adjustment for total alcohol intake, drinking on fewer than two occasions/week was associated with lower mortality for any cause but cancer. Drinking almost every day was associated with a 16% (1–33%) increase in the risk of cancer mortality, but this association disappeared [hazard ratio (HR) = 1.09; 95% CI = 0.94–1.26] when further adjusted for total alcohol intake.

Supporting information, Table S4 reports risks for alcohol after replacing ex-drinkers and non-drinkers with drinkers by use of multiple imputation. In comparison with life-time abstainers, light–moderate drinkers still had between an 8 and 18% lower total, cardiovascular and 'other causes' mortality, whereas heavy intake still was associated with an 8–20% higher risk for any type of mortality.

Mediation analysis

High-density lipoprotein cholesterol (HDLc), C-reactive protein (CRP), troponin and N-terminal pro brain-type natriuretic peptide (NT-ProBNP) were associated with alcohol categories (adjusted for age, sex and cohort). Supporting information, Fig. S1 shows the percentage of variation, in comparison to life-time abstainers. HDLc increases with alcohol intake, whereas CRP shows a J-shaped association. The percentage of the low intake effect mediated by HDLc was 2.9% (1.2–7.1%) for total and 18.7% (3.0–62.7%) for CV mortality, whereas the percentage of the heavy intake effect was 13.7% (6.4–27.0%) for 'other causes' deaths. No mediation role for CRP, troponin or NT-ProBNP was observed.

Dose–response curves

The association with mortality of alcohol modelled as restricted-cubic splines is depicted in Fig. 1; former and non-drinkers were excluded and null intake served as the reference value. J-shaped curves were observed for total, CV and 'other causes' mortality (P-value for non-linearity < 0.0001), with the magnitude of the relative reduction ranging between 4 and 27% at nadir of 3–5 g/day and remaining lower than 1 up to 10–11 g/day (Fig. 1a,b,d); the relative risk becomes distinctly > 1 starting from 20 g/day, with the exception of CV mortality, for which the confidence intervals were somewhat wide (Fig. 1b). The association of alcohol with cancer mortality was null at low doses and became unequivocal at 15 g/day (Fig. 1c).

Subgroup analyses

In Supporting information, Table S5 we show how the choice of the reference group impacts our findings. If the reference category includes ex-drinkers and/or non-drinkers, the association of light/moderate intake with lower mortality rises from 11 to 13–15%, the negative association with moderate intake rises to 5–7% and the positive association of high intake drops from 13 to 7–9%. Conversely, the choice of light/moderate drinkers as reference group exacerbates the risk for drinking categories.

A J-shaped relationship between alcohol and total mortality was confirmed in different cohorts grouped by geographical location (Fig. 2), with the exception of Australia (Fig. 2d), in which no association was observed. The magnitude of the association at nadir varied slightly, ranging from 14 to 24%, and was greater in cohorts from Italy/France (Fig. 2a). The nadir varied from 3 g/day in eastern Europe to 8 g/day in Italy/France. The volume at which the protection vanishes was also different across countries, from 7 g/day in eastern Europe to 40 g/day in Italy/France.

Figure 3 depicts hazard ratios for total mortality in different subgroups. The magnitude of the association of light–moderate intake was stronger in the younger age group and among individuals with BMI < 25 kg/m^2, whereas it was lacking in CV patients. The role of heavy intake was marginally higher in younger people and in smokers.

After exclusion of cohorts from Australia, France, Lithuania, Russia, Poland and Italy (Brianza and Pamela), in which history of cancer was missing, the association of

Table 2 Hazard ratios for mortality, according to categories of alcohol intake.

Alcohol intake categories						
	Former drinkers	*Non-drinkers*[a]	*Life-time abstainers*	*Light–moderate 0.1–10 g/day*	*Moderate 10.1–20 g/day*	*Heavy > 20 g/day*
Number of individuals	5486	10 013	34 310	51 471	16 885	24 795
Person-year, years	57 893	204 659	401 755	690 658	189 365	257 596
Mortality for any causes (n = 16 907)						
Number of deaths	796	2412	4119	5473	1620	2487
Hazard ratio (1)	1.26	1.08	*1*	0.86	0.95	1.12
95% CI	1.16–1.36	1.01–1.14	Ref.	0.83–0.90	0.89–1.01	1.05–1.19
Hazard ratio (2)	1.19	1.13	*1*	0.89	0.98	1.13
95% CI	1.10–1.29	1.06–1.20	Ref.	0.86–0.93	0.92–1.05	1.07–1.20
Cardiovascular mortality (n = 5547)						
Number of deaths	250	989	1425	1762	484	637
Hazard ratio (1)	1.19	1.21	*1*	0.85	0.88	0.97
95% CI	1.03–1.37	1.09–1.33	Ref.	0.79–0.91	0.79–0.98	0.87–1.08
Hazard ratio (2)	1.08	1.30	1	0.90	0.94	0.99
95% CI	0.94–1.25	1.17–1.43	Ref.	0.83–0.97	0.84–1.05	0.88–1.10
Cancer mortality (n = 5511)						
Number of deaths	272	646	1230	1810	563	990
Hazard ratio (1)	1.35	1.11	1	0.99	1.03	1.21
95% CI	1.17–1.55	0.99–1.24	Ref.	0.92–1.07	0.93–1.15	1.09–1.33
Hazard ratio (2)	1.32	1.15	1	1.00	1.05	1.22
95% CI	1.14–1.51	1.02–1.29	Ref.	0.93–1.09	0.95–1.17	1.10–1.35
Mortality for other causes (n = 5849)						
Number of deaths	274	777	1464	1901	573	860
Hazard ratio (1)	1.24	0.92	1	0.78	0.95	1.20
95% CI	1.08–1.42	0.83–1.02	Ref.	0.73–0.84	0.86–1.06	1.09–1.33
Hazard ratio (2)	1.18	0.94	1	0.80	0.98	1.21
95% CI	1.03–1.35	0.85–1.05	Ref.	0.75–0.87	0.88–1.08	1.09–1.33

[a]Non-drinkers are individuals for which we failed to distinguish between teetotallers and former drinkers. (1) Hazard ratio adjusted for age at baseline, sex, smoking, level of education and stratified by cohort; (2) further adjusted for hypertension, diabetes, history of myocardial infarction or stroke, history of cancer and categories of body mass index. CI = confidence interval.

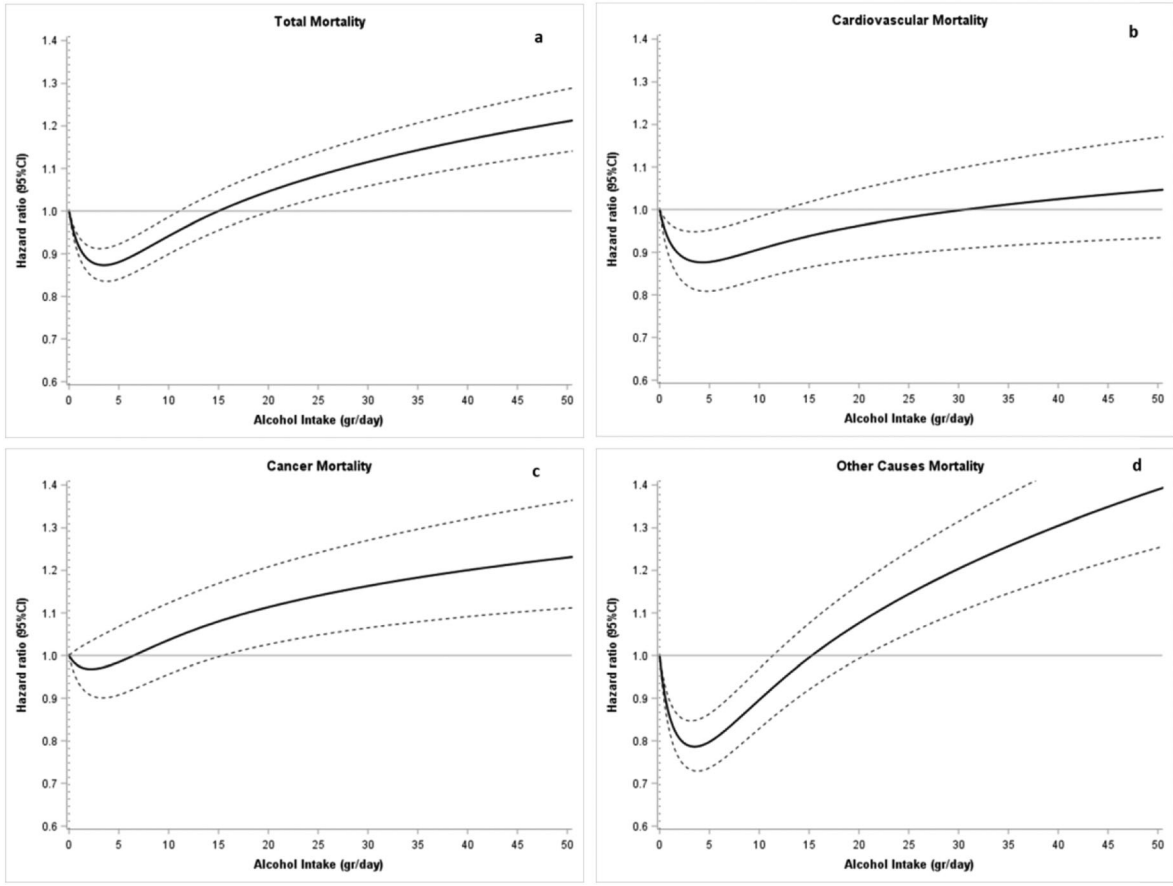

Figure 1 Dose–response relationship between alcohol dosing and total (a), cardiovascular (b), cancer (c) and other-causes mortality (d). Alcohol intake was modelled as restricted cubic splines (3 knots at 5, 50 and 95% of the alcohol distribution). For these analyses, former drinkers and individuals for which we failed to distinguish between teetotallers and former drinkers were excluded; zero intake of alcohol was used as reference value. Full line is hazard ratio adjusted for age at baseline, sex, smoking, hypertension, diabetes, history of myocardial infarction or stroke, history of cancer, categories of body mass index (BMI) and level of education, and stratified by cohort. Dashed lines are 95% confidence intervals

alcohol categories with mortality remained very similar (data not shown).

Subgroup analyses revealed that the association of light–moderate consumption with a reduced mortality risk was more apparent for individuals preferring wine or not having a beverage of preference (Table 3). Light–moderate intake was associated with a reduced risk of death for 'other causes' and was not associated with cancer mortality, irrespective of the type of beverage preferred. The detrimental effect of heavy intake was evident for individuals not having a preference and for beer or spirits drinkers.

Beverage preference was strongly dependent upon country. In Italy and France the preference for wine was very high (73.7%). Preference for beer was highest in northern Europe (28.1%) and that for spirits was highest in eastern Europe (56.5%) and very low in Italy/France (approximately 1.4%).

No difference was found between geographic locations in the association of specific types of beverage with mortality risk (Supporting information, Table S6).

DISCUSSION

In a large multi-country cohort, intake of > 20 g/day of ethanol was associated with a higher mortality risk (especially cancer-related), while light–moderate consumption (up to one drink per day) was associated with reduced risk of total, cardiovascular and 'other causes' mortality.

The observed higher risk over a certain amount is in line with a vast amount of literature [1–3, 5, 7–9, 15, 32]. Heavy drinking is associated with several adverse health effects. Although evidence from randomized clinical trials is lacking (very probably it will remain so for long time in the future), we can assert that alcohol intake above a certain volume is an unhealthy life-style to be firmly discouraged. Our data indicate that unsafe alcohol consumption is above 20 g/day of ethanol, nearly two drinks per day.

Conversely, 10–20 g/day intake of alcohol has a null association with mortality. Individuals who consume alcohol at these levels should be discouraged from increasing their consumption, but encouraged to reduce their consumption.

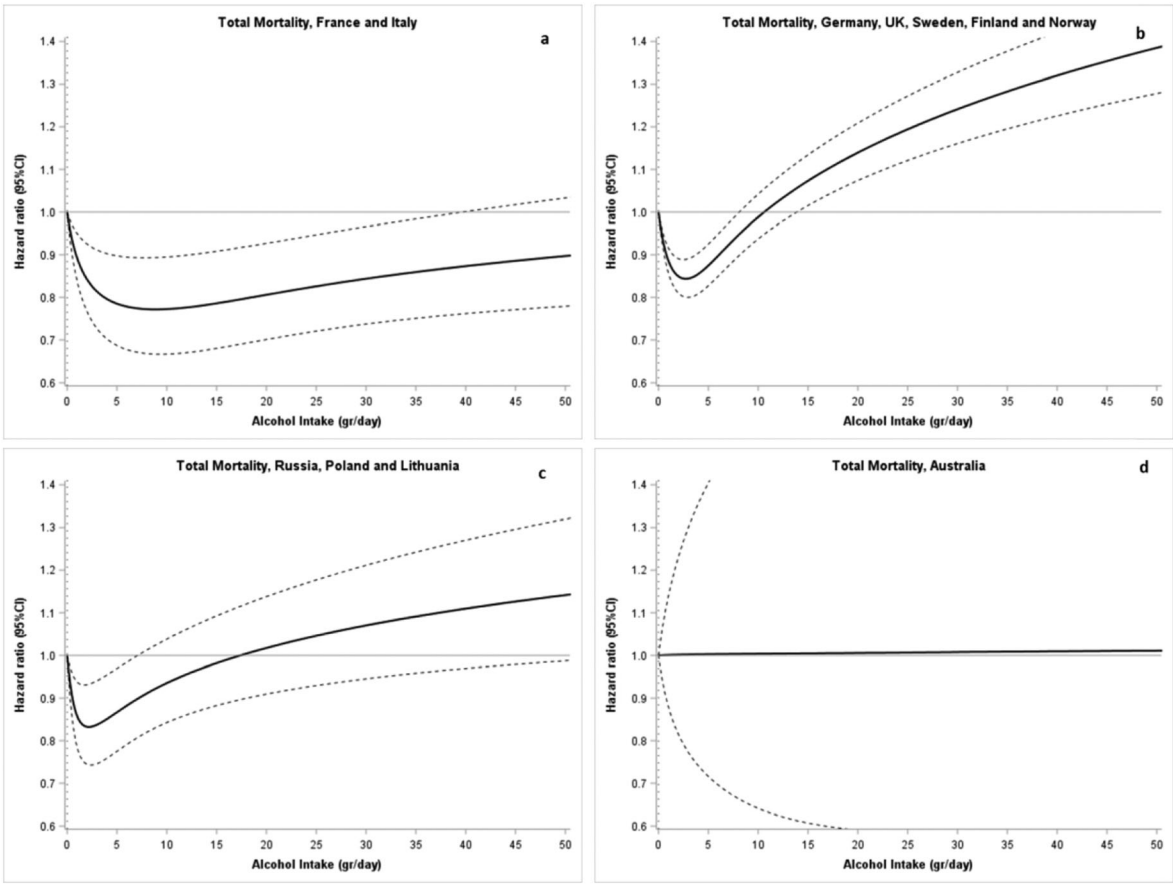

Figure 2 Dose–response relationship between alcohol dosing and total mortality in different cohorts grouped by geographical location. See Fig. 1 for the remainder

In comparison with life-time abstainers, individuals who consumed up to one drink a day have a 7–15% reduced risk of total mortality. The nadir of the association was observed at 5 g/day, a finding in agreement with a previous large meta-analysis [1]. The association was null for cancer deaths. These conclusions are in accord with a large amount of literature [1–3, 15, 32], but are not fully in line with the conclusions proposed by the Global Burden of Disease (GBD) study 2016 [8], suggesting that no level of alcohol consumption improves health. However, it is noteworthy that the GBD authors did not consider total mortality as an outcome; rather, they combined 23 relative-risk curves for as many different outcomes in a single dose–response curve; some of us have previously questioned the way in which the curves were combined [23].

An average consumption of 5 g/day corresponds to nearly three drinks per week; accordingly, we found that drinking up to 2 days per week is the only habit associated with a reduction in mortality (but not for cancer).

Epidemiological research findings should be only one input for making appropriate recommendations for individuals. For example, individuals with strong family history of alcohol use disorder or who take interacting medications may be best advised to abstain from alcohol.

Alcohol consumption seems to modify several vascular and biochemical factors that have potentially different health effects. Specifically, an increase in HDLc levels, decrease in platelet aggregation and changes in fibrinogen and fibrinolysis are thought to represent some mechanisms by which alcohol could reduce cardiovascular risk. Indeed, we observed that the inclusion of HDLc in risk models attenuated the inverse association between light–moderate intake and total and CV mortality while strengthening the association between heavy consumption and mortality, in line with other studies [7]. However, concern persists regarding whether HDLc is in the causal pathway to cardiovascular disease (medications to raise it have not succeeded) [33]. We also tested the role of a panel of biomarkers as potential mediators of alcohol action via different pathways—for example, regulation of inflammation, but failed to observe any role in mediating either the positive or the negative effect of alcohol.

The importance of the reference category

The 'sick quitter' hypothesis suggests that the inclusion of individuals who quit drinking alcohol because of health problems leads to an exaggeration of the poor health

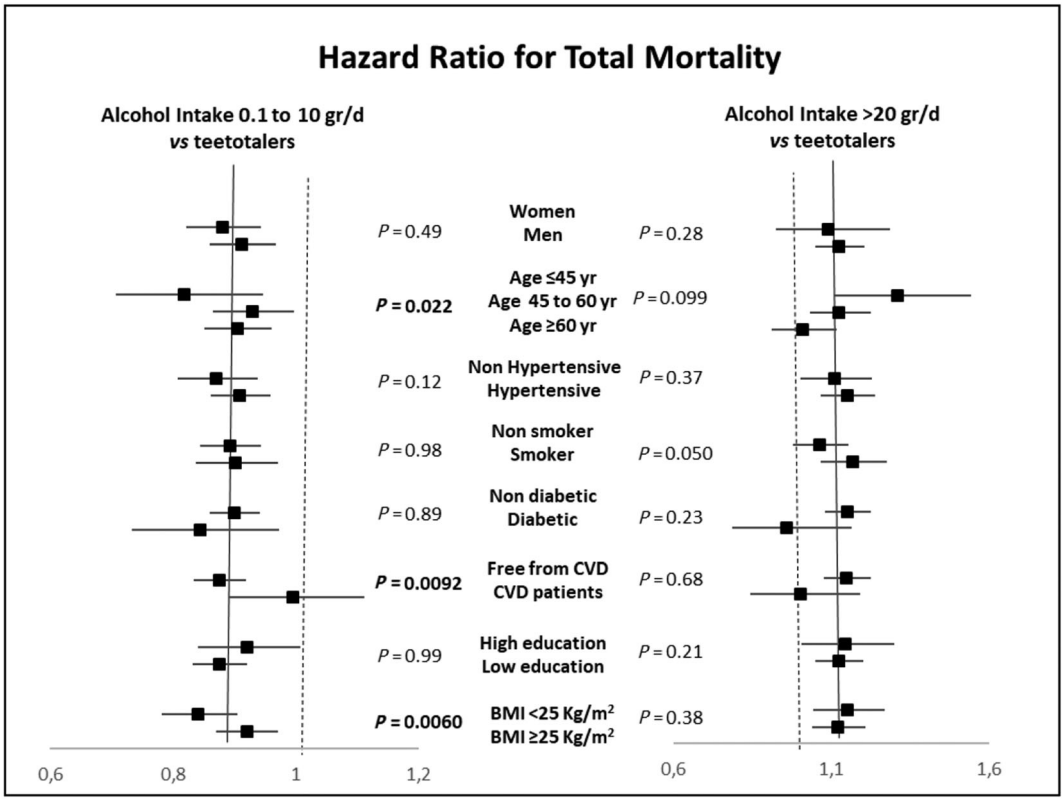

Figure 3 Hazard ratio for total mortality and 95% CI (adjusted as in Table 2) for alcohol intake 0.1–10 g/day (left) and for alcohol intake > 20 g/day (right) in comparison with life-time teetotallers, in subgroups with different risk factors; *P*-values are for the differences among hazard ratios across levels of the risk factor

profiles of non-drinkers [11, 34, 35]. Our data indicate that ex-drinkers have a poor health profile. The inclusion of ex-drinkers in the reference group induced non-negligible overestimation in the protective effect of light–moderate intake and also led to underestimation of the risk associated with heavy consumption. Our findings reveal the bias induced by combining life-time abstainers with former drinkers, and confirm that ex-drinkers must be excluded from the reference group [1]. Several investigators have even argued that ex-drinkers should be assigned to a drinking category based possibly on their previous alcohol consumption patterns [36]. We were not able to recover the prior levels of consumption of our ex-drinkers; however, we replaced them with drinkers by the use of multiple imputation and found very similar results to the main analyses with ex-drinkers as a sole group. Some worries remain, however, in using life-time abstainers as a reference group; life-time abstainers might be different in many ways from drinkers for reasons independent of alcohol consumption. As an example, young life-time abstainers already show health disparities with their drinking peers before any positive or negative effects of alcohol become relevant [37]. Wood *et al.* [7] chose moderate drinkers as reference group. As a consequence, their findings strengthened the risk for higher intake and put abstainers at higher risk, a result we replicated here when moderate drinkers were used as the reference group. We recognize that the communication of health policy messages may vary according to the choice of reference group and its interpretation [21].

Subgroup analyses

In our study, J-shaped association curves of alcohol intake with mortality were observed for all European countries. The magnitude, nadir and persistence of the association varied somewhat, with stronger values observed in Italy and France. This finding may be explained by the different patterns of alcohol consumption across countries [12, 16, 32, 38]. In Mediterranean countries alcohol is typically consumed during main meals, a pattern that has been recognized as a healthy habit [11, 39] and largely in the form of wine, whereas in non-Mediterranean countries alcohol is not usually consumed during meals; the preferred alcoholic beverage is not wine, and the practice of binge drinking, that is unequivocally an unhealthy habit [11, 40], is more frequent.

Accordingly, we found that intake of alcohol in moderation was associated more apparently with a reduced mortality risk in individuals preferring wine. This finding is in agreement with ample literature suggesting

Table 3 Hazard ratios for mortality, in subgroups with different alcoholic preferences.

		Life-time abstainers	*Light–moderate 0.1–10 g/day*	*Moderate 10.1–20 g/day*	*Heavy > 20 g/day*
No preferences		34 310	16 009	4836	5638
Mortality for any causes	Hazard ratio	1	0.85	0.92	1.22
	95% CI	Ref.	0.80–0.91	0.83–1.01	1.11–1.34
Cardiovascular mortality	Hazard ratio	1	0.84	0.92	1.01
	95% CI	Ref.	0.75–0.95	0.77–1.10	0.84–1.20
Cancer mortality	Hazard ratio	1	0.99	0.94	1.23
	95% CI	Ref.	0.88–1.11	0.78–1.12	1.05–1.44
Other causes	Hazard ratio	1	0.75	0.90	1.43
	95% CI	Ref.	0.67–0.84	0.76–1.06	1.24–1.66
Wine preferred (≥ 70%)		34 310	13 919	6588	10 855
Mortality for any causes	Hazard ratio	1	0.87	0.81	0.85
	95% CI	Ref.	0.81–0.93	0.71–0.91	0.76–0.95
Cardiovascular mortality	Hazard ratio	1	0.84	0.84	0.69
	95% CI	Ref.	0.74–0.96	0.66–1.05	0.54–0.89
Cancer mortality	Hazard ratio	1	1.00	0.88	1.04
	95% CI	Ref.	0.89–1.13	0.72–1.06	0.88–1.13
Other causes	Hazard ratio	1	0.77	0.74	0.79
	95% CI	Ref.	0.68–0.87	0.60–0.91	0.60–0.91
Beer preferred (≥ 70%)		34 310	10 938	2680	2907
Mortality for any causes	Hazard ratio	1	0.96	1.20	1.39
	95% CI	Ref.	0.90–1.03	1.06–1.34	1.25–1.55
Cardiovascular mortality	Hazard ratio	1	0.98	1.14	1.35
	95% CI	Ref.	0.87–1.11	0.92–1.41	1.11–1.64
Cancer mortality	Hazard ratio	1	1.02	1.26	1.44
	95% CI	Ref.	0.90–1.16	1.03–1.54	1.21–1.71
Other causes	Hazard ratio	1	0.89	1.21	1.40
	95% CI	Ref.	0.79–1.01	0.99–1.47	1.17–1.68
Spirits preferred (≥ 70%)		34 310	8135	1959	1720
Mortality for any causes	Hazard ratio	1	0.94	1.15	1.23
	95% CI	Ref.	0.88–1.00	1.03–1.29	1.09–1.38
Cardiovascular mortality	Hazard ratio	1	0.98	0.98	1.18
	95% CI	Ref.	0.87–1.09	0.80–1.19	0.97–1.44

(*Continues*)

Table 3. (Continued)

		Life-time abstainers	*Light–moderate 0.1–10 g/day*	*Moderate 10.1–20 g/day*	*Heavy > 20 g/day*
Cancer mortality	Hazard ratio	1	1.03	1.35	1.18
	95% CI	Ref.	0.91–1.16	1.11–1.66	0.94–1.47
Other causes	Hazard ratio	1	0.84	1.17	1.32
	95% CI	Ref.	0.75–0.93	0.97–1.41	1.09–1.59

Hazard ratio adjusted for age at baseline, sex, smoking, hypertension, diabetes, history of myocardial infarction or stroke, history of cancer, categories of body mass index and level of education and stratified by cohort; $n = 6967$ drinkers for which type of alcoholic beverage preferred was missing information have been eliminated in this analysis. CI = confidence interval.

that non-alcoholic components of wine may contribute to its health benefits [41–44].

Strengths and limitations

This study has a number of strengths. It is based on a large multi-national sample size of individuals followed-up during several years for hard end-points such as death. Measurements among cohorts have been harmonized. Assessment of alcohol drinking was based both on volume, frequency and pattern of consumption. Non-linear association was evaluated by splines modelling. Ex-drinkers were excluded from the reference group or re-added to drinkers using multiple imputation. Missing values have been dealt with multiple imputation. Mediation analysis of how a large panel of biomarkers could explain the alcohol association with mortality has been provided. Sensitivity analyses, including by type of alcoholic beverages, have been conducted.

We also acknowledge several study limitations. First, these findings did not derive from pre-registered analyses and the analyses should be considered exploratory. Alcohol consumption information was self-reported and was based on a single baseline ascertainment, although this is common in large population-based studies. Self-reporting can lead to the possibility of misclassification of exposure. Under-reporting by heavier drinkers is frequent [45]: the inclusion of 'real' heavier drinkers in 'apparently' lower intake categories may falsely lower the threshold for apparent harm. Other potential limitations include misclassification of former drinkers as never drinkers, not modelling heavy episodic drinking and the observational nature of the study, which cannot fully rule out residual confounding and confounding by unmeasured factors. Selection biases might also distort the relationship between alcohol intake and health [13]; however, self-selection bias related to an individual's alcohol consumption and study participation was negligible in our study because selection of individuals in the MORGAM cohorts was unrelated to alcohol intake [27, 28]. Several limitations of conventional epidemiological studies on alcohol might be overcome by genetic studies based on Mendelian randomization, which indicates that alcohol intake has no clear causal association either with myocardial infarction [9] or cancer [46]. However, use of the Mendelian randomization approach for studying alcohol has been questioned [47]. The cohorts included in our analysis were older than the age at which alcohol-related outcomes usually occur. However, we reported that the magnitude of the association of light/moderate intake with mortality was stronger in younger age groups, and the magnitude of the association of heavy intake was marginally higher in these younger people. Thus, we suppose that both positive and negative effects of alcohol would be more evident if our cohorts were

younger. Studies showing that alcohol consumption is associated with a reduced risk of cardiovascular death have been criticized, as disease-specific longitudinal studies might not take into account competing risks from other alcohol-linked causes of death, thus resulting in a survival bias [48]. This bias could have potentially occurred in our study among older heavy drinkers in regard to cardiovascular deaths. However, our main findings are focused upon light drinking and total mortality, so they are unlikely to have been influenced by a survival bias. A non-negligible percentage of non-drinkers had missing data regarding drinking habits, so we failed to distinguish them from ex-drinkers and life-time abstainers; to avoid the bias of counting ex-drinkers as abstainers, we did not include 'non-drinkers' in the group of life-time abstainers. There was some missing data for covariates, and we tried to deal with this issue by performing several multiple imputation analyses. History of cancer was not ascertained in some cohorts; however, we conducted a sensitivity analysis excluding these cohorts and conclusions did not change. Finally, because of missing values, mediation analysis (with the exception of HDLc) could only be performed on a small subsample.

Conclusions

With the known limitations of any observational study, alcohol consumption appears to be differently associated with total or cause-specific mortality depending upon the average in daily volume consumed. At excessive consumption levels (higher than two drinks per day), an excess of mortality risk is evident. At intermediate consumption (one to two drinks per day), the protection against CV diseases and the risk of dying from other disease appears to be balanced. At light–moderate but non-null intake (less than one drink per day), the balance is in favour of total, cardiovascular and 'other cause' mortality risk reduction, with no apparent increased cancer mortality risk. Thus, in our study any beneficial effect of light–moderate alcohol consumption on total mortality occurred at lower levels than those generally indicated in several guidelines.

Declaration of interests

S.C. and A.D.C. were the principal investigator and the co-applicant, respectively, of a study supported by a research grant from ERAB (the European Foundation for Alcohol Research; id. EA1767, completed in January 2020), outside the submitted work. A.D.C. reports personal fees as member of the Organizing Committee for the 7th European Beer and Health Symposium (2014), Beer and Health Initiative (The Dutch Beer Institute foundation—The Brewers of Europe), outside the submitted work. S.C. reports personal fees as member of the Organizing Committee and speaker for the 9th European Beer and Health Symposium (Bruxelles 2019) and for given lecture at the 13th European Nutrition Conference|FENS 2019 (Dublin), sponsored by the Beer and Health Initiative (The Dutch Beer Institute foundation—The Brewers of Europe), outside the submitted work. G.d.G. is a member of the International Scientific Forum on Alcohol Research (http://alcoholresearchforum.org), an independent organization of scientists that prepares critiques of emerging research reports on alcohol and health. The members of the Forum donate their time and effort to the review of papers and receive no financial support for their contributions to critiques. The Forum itself receives no support from any organization or company in the alcoholic beverage industry. However, whether the support for individual members is from governmental agencies, universities, private foundations or other groups, none of these organizations has any input into the conclusions presented in the critiques published on the forum web-site. A detailed disclosure statement signed by each member of the forum is available at: http://alcoholresearchforum.org/disclosure-statement. G.d.G. was also previously a consultant to the Web Newsletter of Assobirra, the Italian Association of the Beer and Malt Industries (until 2019) and is a corresponding member of the non-profit Accademia Italiana della Vite e del Vino; G.d.G. reports personal fees for a lecture at the 8th European Beer and Health Symposium (2017), Beer and Health Initiative (The Dutch Beer Institute Foundation—The Brewers of Europe), outside the submitted work. V.S. was supported by the Finnish Foundation for Cardiovascular Research and has received honoraria from Novo Nordisk and Sanofi and travel support from Novo Nordisk. V.S. also has ongoing research collaboration with Bayer Ltd (all unrelated to the present study). S.S. was supported by the Swedish Heart–Lung Foundation, the County Council of Västerbotten (ALF, VLL-548791) and Umeå University, and reports speakers' honoraria from Actelion Pharmaceuticals Ltd and from Astra Zeneca Ltd (unrelated to the present study). J.F. reports lectures fees from Amgen, MSD, Sanofi and Servier. B.S. is funded by the German Research Foundation.

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analysis, decision to publish or preparation of the manuscript. A.D.C. affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, and no important aspect of the study has been omitted.

Author contributions

Augusto Di Castelnuovo: Conceptualization; formal analysis; supervision. **Simona Costanzo:** Data curation; methodology; validation. **Marialaura Bonaccio:** Conceptualization; data curation. **Patrick McElduff:** Data curation; supervision. **Allan Linneberg:** Data curation; supervision. **Veikko Salomaa:** Data curation; supervision. **Satu Männistö:** Data curation. **Maria Moitry :** Data curation; supervision. **Jean Ferrières:** Data curation; supervision. **Jean Dallongeville:** Data curation; supervision. **Barbara Thorand:** Supervision. **Hermann Brenner:** Data curation; supervision. **Marco Ferrario:** Data curation; supervision. **Giovanni Veronesi:** Formal analysis; methodology; supervision. **Emanuela Pettenuzzo:** Data curation. **Abdonas Tamosiunas:** Data curation; supervision. **Inger Njølstad:** Supervision. **Wojciech Drygas:** Data curation; supervision. **Yuri Nikitin:** Data curation; supervision. **Stefan Söderberg:** Data curation; supervision. **Frank Kee:** Data curation; supervision. **Guido Grassi:** Data curation; supervision. **Dirk Westermann:** Data curation; supervision. **Benedikt Schrage:** Conceptualization; data curation; supervision. **Salim Dabboura:** Data curation; supervision. **Tania Zeller:** Data curation; methodology; supervision. **Kari Kuulasmaa:** Conceptualization; data curation; funding acquisition; methodology; project administration; supervision. **Stefan Blankenberg:** Conceptualization; data curation; funding acquisition; project administration; supervision. **Maria Benedetta Donati:** Conceptualization; data curation; funding acquisition; supervision. **Giovanni de Gaetano:** Conceptualization; methodology; supervision. **Licia Iacoviello:** Conceptualization; supervision.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Characteristics of the cohort studies.
Table S2 Hazard ratios for total mortality according to different alcoholic preferences after multiple imputation for missing data in all variables, including alcohol intake and history of cancer (total number of individual $n = 154\,920$, deaths for any causes $n = 19\,139$).
Table S3 Hazard ratios for mortality, according to categories of frequency of alcohol intake.
Table S4 Hazard ratios for mortality, according to categories of alcohol intake after replacing former drinkers and non-drinkers back in with drinkers by using of multiple imputation.
Table S5 Hazard ratios for total mortality using different reference categories.
Table S6 Hazard ratios for total mortality according to different alcoholic preferences and geographical location.
Figure S1 Percentage of variation respect to life-time abstainers for different categories of alcohol intake. Error bars are 95% confidence intervals. CRP means C-reactive protein and NT-ProBNP means N-terminal pro brain-type natriuretic peptide. CRP, troponin and NT-ProBNP were log transformed before analysis. P for association with alcohol categories <0.01 for each biomarker, adjusted for age, sex and cohort. Sample sizes were: $N = 116\,756$ for HDLc; $N = 42\,109$ for CRP; $N = 43\,497$ for troponin and $N = 40\,301$ for NT-ProBNP.

