Alcohol intake and long-term mortality risk after myocardial infarction in the Alpha Omega Cohort

Esther Cruijsen, Anne J de Ruiter, Leanne K Küpers, Maria C Busstra, and Johanna M Geleijnse

Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands

ABSTRACT

Background: Population-based studies generally show J-shaped associations between alcohol intake and mortality from cardiovascular disease (CVD). Little is known about alcohol and long-term mortality risk after myocardial infarction (MI).

Objectives: We examined alcohol intake in relation to all-cause, CVD, and ischemic heart disease (IHD) mortality in Dutch post-MI patients of the Alpha Omega Cohort.

Methods: The analysis comprised 4365 patients (60–80 years; 79% male) with an MI $\leq$ 10 years before study enrolment. We used a 203-item FFQ to assess alcohol (total ethanol) and dietary intakes over the past month. Patients were classified as nondrinkers (0 g/d; $n = 956$) or very light (>0 to 2 g/d; $n = 385$), light (M: >2 to 10 g/d; F: >2 to 5 g/d; $n = 1125$), moderate (M: >10 to 30 g/d; F: >5 to 15 g/d; $n = 1207$), or heavy drinkers (M: >30 g/d; F: >15 g/d; $n = 692$). HRs of mortality for alcohol intake were obtained from Cox models, adjusting for age, sex, education, smoking, BMI, physical activity, and dietary factors.

Results: Alcohol was consumed by 83% of males and 61% of females. During ~12 years of follow-up, 2035 deaths occurred, of which 903 were from CVD and 558 were from IHD. Compared to the (combined) reference group of nondrinkers and very light drinkers, HRs for all-cause mortality were 0.87 (95% CI, 0.78–0.98), 0.85 (95% CI, 0.75–0.96), and 0.91 (95% CI, 0.79–1.04) for light, moderate, and heavy drinkers, respectively. For CVD mortality, corresponding HRs were 0.80 (95% CI, 0.67–0.96), 0.82 (95% CI, 0.69–0.98), and 0.87 (95% CI, 0.70–1.08) for light, moderate, and heavy drinkers, respectively. Findings for IHD mortality were similar. HRs did not materially change when nondrinkers or very light drinkers were taken as the reference, or after exclusion of former drinkers or patients with diabetes or poor/moderate self-rated health.

Conclusions: Light and moderate alcohol intakes were inversely associated with mortality risk in stable post-MI patients. These observational findings should be cautiously interpreted in light of the total evidence on alcohol and health. The Alpha Omega Cohort is registered at clinicaltrials.gov as NCT03192410. *Am J Clin Nutr* 2022;115:633–642.

Keywords: alcohol, myocardial infarction, ischemic heart disease, cardiovascular disease, mortality, prospective cohort study, Alpha Omega Cohort, patients

Introduction

Alcohol use is a major contributor to the global burden of disease, causing substantial health loss (1). For many cancers and other disorders, a gradual rise in mortality risk is observed with higher alcohol intake, starting from 0 intake (1). For cardiovascular disease (CVD), however, an as-yet-unexplained J-shaped association between alcohol intake and mortality has been found in observational studies, suggesting that light or moderate drinking is beneficial compared to not drinking and heavy drinking (1–3). Whether alcohol indeed offers cardio protection at lower intake levels is highly debated because of potential confounding and other biases. Nondrinkers in cohort studies may not only include life-long abstainers, but also "sick quitters" who stopped drinking because of health problems and individuals who deliberately underreport their (heavy) alcohol use. The latter groups are generally at increased mortality risks, leading to biased risk estimates for 0 alcohol intake. Methods to deal with abstainer bias in observational studies are often not successful, also due to limitations of self-administered questionnaires (4). Randomized controlled trials of long-term alcohol use and clinical CVD endpoints are lacking because of ethical and feasibility constraints. Thus, despite extensive

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Supplemental Figures 1–8 and Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article at https://academic.oup.com/ajcn/.

Address correspondence to EC (e-mail: esther.cruijsen@wur.nl).

Abbreviations used: ATC, Anatomical Therapeutic Chemical; CBS, Statistics Netherlands; CVD, cardiovascular disease; IHD, ischemic heart disease; MET, metabolic equivalent task; MI, myocardial infarction; MR, Mendelian randomization; RCS, restricted cubic splines.

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research, the role of alcohol in the development of CVD is still not fully understood.

Patients already suffering from CVD are at an increased risk of recurrent events and premature mortality (5). Next to medical treatment, improvement of diet and lifestyle is a cornerstone of cardiovascular risk management (6). The European Society of Cardiology encourages patients with chronic coronary syndromes to limit their alcohol intake to less than 100 g/week (15 g/day) if alcohol is consumed (6). Cardiovascular organizations in Europe and the United States do not explicitly promote total abstinence for ischemic heart disease (IHD) patients who currently drink (6, 7).

Costanzo et al. (8) performed a meta-analysis of prospective cohort studies on alcohol use and mortality in CVD patients, mainly suffering from IHD. In 8 cohorts involving more than 16,000 patients from the United States, the United Kingdom, Sweden, and Japan (predominantly male), light and moderate alcohol intakes were consistently inversely associated with CVD and total mortality risks during a median follow-up of ∼5 years. In a subgroup analysis of post–myocardial infarction (post-MI) patients, risks were 19% lower for CVD mortality and 22% lower for total mortality for alcohol intakes around 12 g/d (9–12). Inverse associations were observed for all levels of intake up to 24 g/d for CVD mortality and 32 g/d for total mortality. Risk estimates for alcohol and mortality in these cohorts were adjusted for age, sex (if applicable), smoking, BMI, physical activity, socioeconomic factors, and diabetes, but not for diet.

Since alcohol use is often linked to dietary habits (13), residual confounding in these studies cannot be excluded. Therefore, we set up an observational study of alcohol use and mortality risk in IHD patients, overcoming major shortcomings of previous studies, including short-term follow-ups, incomplete assessments of alcohol intake and dietary confounders, and a lack of investigation of abstainer bias. In 4365 post-MI patients of the Alpha Omega Cohort, we examined habitual alcohol intakes and risks of mortality during 12 years of follow-up, with extensive adjustments for diet, lifestyle, and other potential confounders. Alcohol use was studied in relation to all-cause, CVD, and IHD mortality, and sensitivity analyses were performed to gain insight into a potential abstainer bias.

Methods

Study design and participants

The Alpha Omega Cohort is a prospective cohort study of 4837 Dutch males and females aged 60–80 years with a verified history of MI for ≤10 years prior to study enrolment (2002–2006). During the first 3 years of follow-up, patients participated in a randomized controlled trial of omega-3 fatty acids, showing no effect on major cardiovascular events (14, 15). Follow-up research for cause-specific mortality started in 2002, and is still ongoing. Patients provided written consent, and the study was approved by a central ethics committee (Haga Hospital) and by the ethics committee of participating hospitals. Excessive habitual alcohol intake of ≥7 drinks per day was an exclusion criterion for the study. For the present analysis, we further excluded patients with missing data on alcohol intake ($n = 453$) or with implausible energy intakes (<800 or >8000 kcal/d for males and <600 or >6000 kcal/d for females; $n = 19$), leaving 4365 patients (**Supplemental Figure 1**).

Assessment of diet and alcohol intake

Dietary data were collected at baseline using a 203-item FFQ, aggregated in 24 food groups (16). This FFQ was an adapted and extended version of a reproducible and biomarker-validated FFQ. The Pearson correlation coefficient between the FFQ and the dietary history method was 0.83 for total energy intake (17). The FFQ contained questions on the frequencies and quantities of foods and beverages consumed during the previous month. All returned questionnaires were checked by trained dietitians who obtained additional information when data were missing or unclear. Double entry of the FFQ data was performed. Questionnaire data were linked to the Dutch Food Composition Database (NEVO 2006) to calculate nutrient and total energy intakes (18). Salt intake was only calculated from foods, since the FFQ did not include questions on discretionary salt use.

The FFQ included separate questions for intakes of beer (alcoholic, nonalcoholic), wine (red, rose, white, fortified), and liquor (e.g., whisky, rum, gin, cognac) and alcoholic long drinks. Patients could also indicate alcoholic drinks that were not mentioned as examples. For all alcoholic beverages, patients reported the number of glasses they consumed on a daily or weekly basis during the previous month (not this month, ≤1 per week, 2–3 per week, 4–6 per week, 1 per day, 2–3 per day, 4–5 per day, or ≥6 per day). Total alcohol intake (g/d) was calculated as the sum of ethanol from all alcoholic beverages, considering 10 grams of alcohol in a standard drink in the Netherlands. Additional information on alcohol use was obtained from a self-administered lifestyle questionnaire, where patients indicated whether they were a lifetime abstainer, former drinker, or current drinker and whether they had sometimes consumed >6 glasses of alcohol on 1 day in the past year, which we defined as binge drinking. The correlation for alcohol intake (g/d) from the FFQ and the lifestyle questionnaire was 0.81.

Alcohol intake was classified into sex-specific categories because females may have higher and more prolonged blood levels of alcohol than males for the same dose of alcohol per kg of body weight (19). In men, drinking categories were defined as 0 g/d (none), >0 to 2 g/d (very light), >2 to 10 g/d (light), >10 to 30 g/d (moderate), and >30 g/d (heavy). In women, the categories were 0 g/d (none), >0 to 2 g/d (very light), >2 to 5 g/d (light), >5 to 15 g/d (moderate), and >15 g/d (heavy). Nondrinkers are a heterogenous group that not only includes true abstainers but also "sick quitters" and alcohol use deniers. The additional category of very light drinking (>0 to 2 g/d) was used as an alternative reference group in the data analysis to avoid "abstainer bias," as described below.

Mortality follow-up

This study focuses on all-cause mortality as the primary endpoint and CVD and IHD mortality as secondary endpoints. The vital status of patients was monitored through linkage with municipal registries, from baseline through 31 December 2018. Follow-up for cause-specific mortality occurred in 3 phases.

From 2002–2009 (Alpha Omega Trial), information was obtained from the national mortality registry [Statistics Netherlands (CBS)], treating physicians, and close family members. Primary and contributing causes of death were coded by an independent Endpoint Adjudication Committee, as described previously (14, 15). After the trial through 2012, data on the primary and contributing causes of death were obtained from CBS. From 2013 onwards, CBS provided data on the primary cause of death only, and treating physicians were asked to fill out an additional cause-of-death questionnaire (response rate: 67%), which was coded by study physicians who were not involved in the current analysis. The endpoint of CVD or IHD mortality was allocated to all patients for whom it was a primary or contributing cause of death, based on any of the data sources.

Mortality coding was performed according to the International Classification of Diseases, Tenth Revision (20), where CVD mortality comprised codes I20–I25 (ischemic heart disease), I46 (cardiac arrest), R96 (sudden death, undefined), I50 (heart failure), and I60–I69 (stroke) and IHD mortality comprised codes I20–I25, I46, and R96.

Other measurements

At baseline, data were collected on demographic and anthropometric factors, lifestyle, current health status, and medical history. BMI was calculated from the measured weight and height, and a BMI $\geq$ 30 kg/m^2 was classified as obese. Smoking status comprised 4 categories: current; former, quit $\leq$ 10 years ago; former, quit $>$ 10 years ago; and never. In current smokers, the daily amount of cigarettes (including rolling tobacco) was assessed. Pack years of smoking were calculated for current smokers by multiplying the number of smoking years with the daily amount of cigarettes, divided by 20. Pack years could not be calculated for former smokers, due to a lack of data. Physical activity was determined using the validated Physical Activity Scale of the Elderly (21), and divided into 3 categories: low [no activity or only light activity; $\leq$3 Metabolic Equivalent Tasks (METs)], intermediate [moderate or vigorous activity ($>$3 METs) on $>$0 to $<$5 days per week], and high [moderate or vigorous activity ($>$3 METs) on $\geq$5 days per week]. Educational level was divided into 3 categories: low (primary or lower secondary education), moderate (higher secondary or lower tertiary education), or high (higher tertiary education). Self-rated health was assessed with the question "how do you rate your overall health at this moment?," using a 5-point scale ranging from poor to excellent. Self-reported medication use was checked by research nurses and coded according to the Anatomical Therapeutic Chemical (ATC) classification system (22).

Serum lipids and plasma glucose were analyzed from nonfasting blood using standard kits and an automated analyzer (Hitachi 912; Roche Diagnostics). Blood pressure was measured twice using an automatic device and averaged (HEM-711; Omron). Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or use of an antihypertensive medication (ATC codes C02, C03, C07, C08, and C09). Diabetes mellitus was defined as fasting ($>$4 hours) plasma glucose $\geq$ 7.0 mmol/L, nonfasting plasma glucose $\geq$ 11.1 mmol/L, use of an anti-diabetic medication (ATC code A10), or a self-reported physician diagnosis of diabetes.

Statistical analysis

Patient characteristics at baseline are presented in alcohol categories as means $\pm$ SDs for normally distributed variables, medians (IQRs) for nonnormally distributed variables, and n (%) for categorical variables.

Cox proportional hazard models were used to estimate HRs with 95% CIs for all-cause, CVD, and IHD mortality in categories of alcohol intake, using the combined none and very light drinking categories (alcohol: 0 to 2 g/d) as the reference. Additional analyses were performed in which nondrinkers (0 g/d) and very light drinkers ($>$0 to 2 g/d) were studied as separate categories, using very light drinkers as the reference, to obtain insight into potential abstainer bias. The proportional hazard assumption was checked by log-minus-log plots and was met. Person-years were calculated as the number of years between the date of inclusion and the date of death, the censoring date, or the end of follow-up (31 December 2018), whichever occurred first. Patients who died due to a competing risk were censored, in addition to those who were lost to follow-up and survived until the end of follow-up. One patient was lost to follow-up and censored after 2.9 years.

HRs were adjusted for age and sex (Model 1). Model 2 additionally included obesity (yes/no), smoking (4 categories), physical activity (3 categories), and educational level (3 categories). Data on the amount of cigarettes and pack years were only available for current smokers, and the addition of these variables to the model did not impact the HRs. Therefore, these variables were left out of the model. Model 3 additionally included dietary factors: total energy intake (kcal/d, excluding energy from ethanol) and intakes of sugar-sweetened beverages (g/d), coffee (g/d), red and processed meat (g/d), fish (g/d), whole grains (g/d), and fruits and vegetables (g/d). Binge drinking (yes/no) was added to Model 3 (along with habitual alcohol intake categories) to examine whether this behavior was independently associated with mortality endpoints. Missing data (all at random) for BMI (n = 6), smoking (n = 1), physical activity (n = 25), and educational level (n = 24) were imputed with the age- and sex-specific median (for BMI) or mode (categorical covariates) to maintain these patients in the multivariable analysis.

Restricted cubic splines (RCS) were used to investigate associations between continuous alcohol intake and mortality and establish a potential threshold or nonlinear associations for males and females separately. For the RCS analysis, the reference value of 0 g/d was set and knots were placed at the 5th, 50th, and 95th percentiles. The Wald chi-square test was carried out for testing nonlinearity of the associations (23).

Effect measure modifications by sex, obesity, and smoking status were assessed by means of a stratified analysis, using the fully adjusted model. Sensitivity analyses were performed after exclusion of (1 by 1) 474 former drinkers, 1028 patients with poor or moderate self-rated health, and 883 patients with diabetes. Further sensitivity analyses were performed after excluding the first 2 years of follow-up, during which 155 deaths occurred, and excluding 633 patients with an MI $<$ 1 year prior to enrolment to investigate whether risk estimates could be biased by deteriorating health.

Two-sided P values $<$ 0.05 were considered statistically significant. All statistical analyses were performed using the statistical software SAS (version 9.4; SAS Institute Inc.). Forest

plots were created using R version 3.6.1 (R Foundation for Statistical Computing).

Results

Table 1 presents baseline characteristics for 4365 patients, overall and in categories of alcohol intake. Patients were 69.0 ± 5.6 years old on average, and 79% were male. At study entry, the median time since an MI was 3.7 years. Of the included patients, 16% were current smokers and 50% quit smoking ≤10 years ago, 20% had diabetes, 24% were obese, and 23% had poor or moderate self-rated health.

Alcohol was consumed by 83% of males and 61% of females (**Supplemental Table 1**). Males and females predominantly consumed wine (55% and 48%, respectively) and beer (52% and 7%, respectively). Of 956 nondrinkers, 384 patients (40%) were former drinkers. Those with a higher alcohol intake were slightly younger and more often men. They were more likely to be highly educated, to be physically active, and to have very good or excellent self-reported health, and were less likely to have diabetes or obesity. Among drinkers, the median alcohol intakes were 11.5 g/d in males and 5.8 g/d in females.

During a median follow-up of 12.4 years (48,473 person-years), 2035 deaths occurred, including 903 from CVD and 558 from IHD. **Table 2** presents HRs for all-cause, CVD, and IHD mortality in categories of total alcohol intake. Light and moderate alcohol intake compared to the reference (0 to 2g/d; i.e., nondrinkers or very light drinkers combined) was associated with a lower risk of all-cause, CVD, and IHD mortality in the fully adjusted models. For all-cause mortality, the lowest HR was observed for those with moderate alcohol intake (HR, 0.85; 95% CI, 0.75–0.96) compared to those with none or very light alcohol intake (**Supplemental Figure 2**). After excluding nondrinkers from the reference group, the HRs remained largely unchanged but the associations were no longer significant (**Supplemental Table 2**). For CVD mortality, the lowest HRs were observed for those with light alcohol intake (HR, 0.80; 95% CI, 0.67–0.96), which was also the case for IHD mortality (HR, 0.79; 95% CI, 0.63–0.99), compared to nondrinkers or very light drinkers (Table 2; Supplemental Figure 2). Also for these outcomes, excluding nondrinkers from the reference group yielded similar HRs, but the associations were no longer significant (Supplemental Table 2). For heavy alcohol intake, the associations were also inverse but nonsignificant for all endpoints.

When analyzed continuously, using RCS, alcohol intake was nonlinearly, inversely associated with all-cause, CVD, and IHD mortality (all P values < 0.05) in males with the lowest risk, observed at ∼ 20 g/d (**Figure 1**A–C). For the smaller group of females, no significant associations were observed for continuous alcohol intake and all endpoints (Figure 1D–F).

Subgroup analyses

In women, heavy drinking compared to the reference category (0 to 2g/d; nondrinkers or very light drinkers), was associated with an increased mortality risk, especially from IHD (HR, 1.89; 95% CI, 1.10–3.26; **Supplemental Figure 3**). Lower drinking categories were not associated with mortality in women. In men, HRs were similar as compared to the total cohort, but with inverse associations for heavy drinking reaching statistical significance for all-cause mortality (HR, 0.83; 95% CI, 0.70–0.97) and CVD mortality (HR, 0.77; 95% CI, 0.60–0.99) compared to the reference.

In patients with obesity, a trend towards an increased risk of all-cause, CVD, and IHD mortality was observed with heavy drinking, although it was not significant (**Supplemental Figure 4**). Moderate drinking was associated with lower risks of CVD and IHD mortality. In patients without obesity, associations were roughly similar compared to the total cohort and, additionally, heavy drinking was inversely associated with all-cause mortality (HR, 0.81; 95% CI, 0.68–0.96) and CVD mortality (HR, 0.73; 95% CI, 0.57–0.95).

HRs for alcohol intake with long-term mortality endpoints were not modified by smoking status, although associations in both smokers and nonsmokers were no longer significant (**Supplemental Figure 5**).

Sensitivity analyses

Excluding former drinkers from the none or very light reference group (0 to 2g/d) attenuated the inverse associations for light (HR, 0.93; 95% CI, 0.81–1.06) and moderate drinkers (HR, 0.90; 95% CI, 0.90–1.03) with all-cause mortality, but associations for CVD and IHD mortality remained comparable with HRs for the total cohort (**Supplemental Figures 6 and 7**). After excluding patients with poor or moderate self-rated health, light and moderate drinking were more inversely associated, with HRs for light drinking of 0.82 (95% CI, 0.71–0.95) for all-cause mortality, 0.72 (95% CI, 0.57–0.89) for CVD mortality, and 0.65 (95% CI, 0.49–0.86) for IHD mortality compared to the total cohort (Supplemental Figure 5). After excluding patients with diabetes, associations for light drinking but not moderate drinking were attenuated, with HRs of 0.95 (95% CI, 0.82–1.09) for all-cause mortality, 0.88 (95% CI, 0.72–1.09) for CVD mortality, and 0.86 (95% CI, 0.66–1.13) for IHD mortality compared to the total cohort (Supplemental Figure 5).

HRs for binge drinking in the fully adjusted model (including alcohol intake categories) were 1.02 (95% CI, 0.89–1.17) for all-cause mortality, 1.07 (95% CI, 0.87–1.31) for CVD mortality, and 1.09 (95% CI, 0.85–1.14) for IHD mortality. HRs did not essentially differ after excluding the first 2 years of follow-up and after excluding patients with an MI < 1 year before enrolment (**Supplemental Figure 8**).

Discussion

In the Alpha Omega Cohort of Dutch post-MI patients with ∼12 years follow-up, light or moderate alcohol intake was inversely associated with long-term risks of all-cause, CVD, and IHD mortality. In men, we observed nonlinear, inverse associations with these mortality endpoints, with the lowest HRs for alcohol intakes around 20 g/d. In the smaller group of women, associations for light and moderate alcohol intakes were also inverse, but weak and nonsignificant, with the lowest HRs around 10 g/d. For high alcohol intake, the mortality risk (especially from IHD) was increased in women.

In a meta-analysis by Costanzo et al. (4) of prospective cohort studies specifically in CVD patients, light and moderate

TABLE 1 Baseline characteristics of 4365 patients of the Alpha Omega Cohort, overall and in categories of alcohol intake[1]

		Alcohol intake, g/d				
Characteristics	Total ($n = 4365$)	None ($n = 956$) 0	Very light ($n = 385$) >0 to 2	Light ($n = 1125$) M: >2 to 10; F: >2 to 5	Moderate ($n = 1207$) M: >10 to 30; F: >5 to 15	Heavy ($n = 692$) M: >30; F: >15
Age, years	69.0 ± 5.6	70.0 ± 5.5	69.4 ± 5.6	68.7 ± 5.4	68.9 ± 5.6	68.0 ± 5.6
Females	933 (21)	364 (38)	126 (33)	142 (13)	197 (16)	104 (15)
Dutch ethnicity	4315 (99)	933 (98)	376 (98)	1,112 (99)	1,202 (100)	692 (100)
BMI,[2] kg/m^2	27.7 ± 3.8	28.2 ± 4.5	28.3 ± 4.0	27.7 ± 3.5	27.3 ± 3.4	27.6 ± 3.7
Obese	1032 (24)	281 (29)	114 (30)	261 (23)	231 (19)	145 (21)
Educational level[3]						
Low	2439 (56)	662 (70)	245 (64)	644 (58)	597 (50)	291 (42)
Moderate	1367 (31)	230 (24)	106 (28)	367 (33)	407 (34)	257 (37)
High	535 (12)	56 (6)	34 (9)	107 (10)	198 (16)	140 (20)
Smoking status[4]						
Never	722 (16)	227 (24)	80 (21)	182 (16)	174 (14)	59 (9)
Former, quit > 10 years ago	767 (18)	130 (14)	46 (12)	244 (22)	239 (20)	108 (16)
Former, quit ≤ 10 years ago	2162 (50)	427 (45)	191 (50)	534 (47)	605 (50)	405 (59)
Current	713 (16)	172 (18)	68 (18)	165 (15)	189 (16)	119 (17)
Cigarette use in current smokers, *n*/d	11 ± 7	11 ± 6	9 ± 6	10 ± 6	10 ± 6	13 ± 9
Pack years of cigarette smoking[5]	25 ± 17	24 ± 15	20 ± 16	24 ± 17	24 ± 15	31 ± 22
Physical activity[6]						
Low	1783 (41)	517 (54)	187 (49)	419 (37)	418 (35)	242 (35)
Intermediate	1635 (38)	279 (29)	118 (31)	448 (40)	499 (41)	291 (42)
High	922 (21)	154 (16)	76 (20)	250 (22)	286 (24)	156 (23)
Self-rated health[7]						
Poor or moderate	1010 (23)	322 (34)	110 (29)	225 (20)	234 (19)	119 (17)
Good	2827 (65)	569 (60)	247 (64)	745 (66)	795 (66)	471 (68)
Very good or excellent	510 (12)	61 (6)	27 (7)	151 (13)	173 (14)	98 (14)
Time since last myocardial infarction,[8] years	3.7 (1.7–6.3)	3.4 (1.5–6.2)	3.9 (1.7–6.0)	3.7 (1.7–6.5)	3.5 (1.7–6.3)	4.2 (1.8–6.5)
Prevalent diabetes mellitus[9]	883 (20)	279 (29)	91 (24)	228 (20)	177 (15)	108 (16)
Plasma glucose,[10] mmol/L	6.2 ± 2.1	6.4 ± 2.4	6.3 ± 2.2	6.2 ± 2.0	6.0 ± 2.0	6.1 ± 1.7
Blood pressure,[11] mmHg						
Systolic	141.9 ± 21.5	141.4 ± 22.7	140.3 ± 20.4	141.5 ± 20.6	141.8 ± 21.2	144.3 ± 22.6
Diastolic	80.2 ± 11.1	78.6 ± 11.7	78.9 ± 11.0	80.8 ± 10.8	80.4 ± 10.8	82.0 ± 11.4
Hypertension, *n* (%)	4161 (95)	920 (96)	368 (96)	1065 (95)	1147 (95)	661 (96)
Serum lipids, mmol/L						
LDL cholesterol[12]	2.6 ± 0.8	2.5 ± 0.9	2.5 ± 0.8	2.5 ± 0.8	2.6 ± 0.8	2.7 ± 0.8
HDL cholesterol[13]	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.3	1.4 ± 0.4
Triglycerides[13]	1.9 ± 1.0	2.0 ± 1.1	2.1 ± 1.2	1.9 ± 1.0	1.8 ± 0.92	1.9 ± 1.2
Use of cardiovascular medication, *n* (%)						
Antihypertensive medication	3919 (90)	881 (92)	348 (90)	1001 (89)	1077 (89)	612 (88)
Lipid-modifying medication	3785 (87)	808 (85)	326 (85)	975 (87)	1074 (89)	602 (87)

(*Continued*)

TABLE 1 (*Continued*)

Characteristics	Total ($n = 4365$)	Alcohol intake, g/d				
		None ($n = 956$) 0	Very light ($n = 385$) >0 to 2	Light ($n = 1125$) M: >2 to 10; F: >2 to 5	Moderate ($n = 1207$) M: >10 to 30; F: >5 to 15	Heavy ($n = 692$) M: >30; F: >15
Dietary factors						
Total energy,[14] kcal/d	1802 ± 500	1734 ± 500	1760 ± 521	1836 ± 501	1861.5 ± 500	1761 ± 469
Alcohol intake in drinkers, g/d	10.4 (4.5–23.1)	—	1.3 (1.1–1.8)	4.9 (3.4–7.4)	13.9 (11.3–20.5)	36.9 (32.5–46.5)
Beer drinker, *n*	1841 (42)	—	91 (24)	616 (55)	683 (57)	451 (65)
Beer in drinkers, g/d	72 (28–142)	—	28 (28–28)	72 (28–72)	72 (28–200)	72 (28–500)
Wine drinker, *n*	2324 (53)	—	160 (42)	694 (62)	910 (75)	560 (81)
Wine in drinkers, g/d	49 (31–124)	—	17 (14–17)	31 (17–45)	88 (45–124)	309 (76–323)
Binge drinking,[15] *n*	811 (19)	18 (2)	15 (4)	190 (17)	284 (24)	304 (44)
Coffee drinker, *n*	4164 (95)	885 (93)	362 (94)	1078 (96)	1165 (97)	674 (97)
Coffee, g/d	375 (375–563)	375 (188–563)	375 (375–563)	375 (375–563)	375 (375–563)	375 (375–563)
Tea, g/d	150 (45–450)	150 (21–450)	150 (54–450)	150 (26–450)	150 (54–450)	150 (21–450)
Milk, g/d	150 (21–150)	107 (0–150)	150 (21–150)	150 (21–150)	150 (21–150)	150 (21–150)
Sugar-sweetened beverages, g/d	128 (42–219)	115 (21–235)	128 (42–213)	138 (54–220)	146 (54–228)	108 (41–188)
Whole grains, g/d	113 (88–160)	99 (81–158)	106 (88–160)	122 (88–163)	118 (88–161)	101 (88–158)
Fruit and vegetables, g/d	219 (144–379)	213 (130–386)	226 (143–397)	222 (153–378)	223 (159–387)	215 (132–320)
Red and processed meat, g/d	68 (40–94)	61 (31–86)	65 (36–93)	67 (40–92)	70 (43–96)	72 (48–100)
Fish, g/d	14 (5–19)	11 (1–17)	11 (4–17)	12 (5–18)	15 (5–21)	16 (10–27)
Sodium,[16] g/d	2.1 (1.7–2.6)	2.0 (1.6–2,5)	2.1 (1.6–2.5)	2.2 (1.7–2.6)	2.2 (1.8–2.7)	2.2 (1.8–2.7)

[1]Values are means ± SDs for normally distributed variables, medians (IQRs) for skewed variables, or *n* (%) for categorical variables, unless otherwise indicated. MET, metabolic equivalent task.
[2]Missing data for 6 patients. Obesity was defined as a BMI ≥ 30 kg/m2.
[3]Missing data for 24 patients.
[4]Missing data for 1 patient.
[5]Calculation of pack years; pack years could not be calculated for former smokers due to a lack of data.
[6]Missing data for 25 patients. Low activity was defined as ≤3 METs, intermediate activity as >3 METs on >0 to <5 days per week, and high activity as >3 METs on ≥5 days per week.
[7]Missing data for 18 patients.
[8]Missing data for 38 patients. Myocardial infarction was based on a verified clinical diagnosis < 10 years before study enrolment.
[9]Defined as self-reported physician diagnosis, use of antidiabetic medication, or elevated plasma glucose (≥7.0 mmol/L if fasted >4 hours or ≥11.1 mmol/L if nonfasted).
[10]Nonfasted; missing data for 86 patients.
[11]Missing data for 6 patients.
[12]Nonfasted; missing data for 309 patients.
[13]Nonfasted; missing data for 111 patients.
[14]Minus energy from alcohol.
[15]Defined as sometimes drinking >6 glasses on 1 day.
[16]Sodium intake was only estimated from foods, since discretionary salt use could not be assessed by means of the FFQ.

TABLE 2 HRs for alcohol intake and all-cause, CVD, and IHD mortality in 4365 patients from the Alpha Omega Cohort

	Total alcohol intake, g/d			
	None or very light, 0–2 ($n = 1341$)	Light, M: >2 to 10; F: >2 to 5 ($n = 1125$)	Moderate, M: >10 to 30; F: >5 to 15 ($n = 1207$)	Heavy, M: >30; F: >15 ($n = 692$)
Male sex (%)	851 (63)	983 (87)	1010 (84)	588 (85)
Person-years	14,271	12,781	13,570	7852
Median intake, g/d				
Males	0	5.7	15.4	38.3
Females	0	3.2	10.0	30.9
All-cause mortality				
Cases	712	495	523	305
Model 1[1,2]	1.00	0.80 (0.72–0.91)	0.78 (0.70–0.88)	0.85 (0.74–0.98)
Model 2[1,3]	1.00	0.87 (0.77–0.98)	0.85 (0.75–0.95)	0.91 (0.79–1.04)
Model 3[1,4]	1.00	0.87 (0.78–0.98)	0.85 (0.75–0.96)	0.91 (0.79–1.04)
CVD mortality				
Cases	332	207	231	133
Model 1[1,2]	1.00	0.74 (0.62–0.88)	0.76 (0.64–0.90)	0.82 (0.67–1.01)
Model 2[1,3]	1.00	0.81 (0.67–0.97)	0.83 (0.70–0.99)	0.86 (0.70–1.06)
Model 3[1,4]	1.00	0.80 (0.67–0.96)	0.82 (0.69–0.98)	0.87 (0.70–1.08)
IHD mortality				
Cases	204	129	137	88
Model 1[1,2]	1.00	0.72 (0.57–0.90)	0.71 (0.57–0.88)	0.85 (0.66–1.09)
Model 2[1,3]	1.00	0.78 (0.62–0.99)	0.78 (0.62–0.98)	0.89 (0.69–1.16)
Model 3[1,4]	1.00	0.79 (0.63–0.99)	0.79 (0.63–0.99)	0.92 (0.70–1.20)

[1]HRs (95% CIs) were obtained from Cox proportional hazards models, using the lowest category as the reference. CVD, cardiovascular disease; IHD, ischemic heart disease.

[2]Adjusted for age and sex.

[3]Adjusted as in Model 1 plus obesity, smoking status, physical activity, and education level.

[4]Adjusted as in Model 2 plus energy intake, excluding energy from alcohol, and intakes of sugar-sweetened beverages, red and processed meat, whole grains, fruits, vegetables, coffee, tea, milk, fish, and salt from foods.

alcohol intakes were associated with lower risks of all-cause and CVD mortality during a median follow-up of ∼5 years. In their subgroup analysis of post-MI patients from the United States and Europe, the maximum observed risk reductions were 19% for CVD mortality and 22% for total mortality for alcohol intakes around 12 g/d, corresponding to roughly 1 standard drink per day (24). These results were mainly driven by data in men, since women were not included or were underrepresented in the different cohorts. The present analysis in the Alpha Omega Cohort showed 15%–20% lower risks of CVD and all-cause mortality for light or moderate drinking. In our study of predominantly male patients (79%), the lowest mortality risks were observed for alcohol intakes around 20 g/d, corresponding to 2 drinks a day. Because of the relatively wide CIs around the HRs, our data would also be compatible with lower "optimal" doses of alcohol (e.g., 1 drink a day), in line with the meta-analysis by Costanzo et al. (4). In our subgroup analysis of women, the mortality risks were lowest for alcohol intakes around 10 g/d, but the HRs were not statistically significant due to small numbers.

The lower mortality risk in light and moderate drinkers, as observed in cohort studies, is highly debated (3, 4). Residual confounding may be present due to incomplete adjustments for socioeconomic status and lifestyle factors. In the present analysis of the Alpha Omega Cohort, we were able to adjust for many potential confounders, including dietary factors. Reporting bias may occur in cohort studies, with (heavy) drinkers being misclassified in the nondrinking reference category. We therefore repeated our analysis in drinkers only, using patients with the lowest alcohol intake (>0 to 2 g/d) as the reference group. This yielded similar inverse associations for all-cause, CVD, and IHD mortality, although the findings were no longer significant due to a smaller sample size.

Wood et al. (2) performed a population-based pooling study of almost 600,000 current alcohol users (i.e., nondrinkers and former drinkers excluded) from high-income countries. For incident CVD (fatal and nonfatal combined), a J-shaped association was observed, with the lowest risks (-10%) for alcohol intakes around 15 g/d. We obtained similar findings for light or moderate drinking in the Alpha Omega Cohort when excluding nondrinkers and former drinkers from the analysis, using very light drinkers (>0 to 2 g/d) as the reference group. For all-cause mortality, however, no protective associations were found in the pooling study among drinkers, while we still observed a 15% lower risk when comparing light and moderate drinking with very light drinking. This discrepancy may be due to our cohort of post-MI patients, in which all-cause mortality was largely driven by preexisting IHD. The impact of non-CVD mortality causes, such as cancer, may have been larger in the population-based pooling study.

Patients in the no-drinking category could have stopped drinking because of ill health ("sick quitters"), which may lead to biased risk estimates. Excluding former drinkers ($n = 384$; 40% of the no-drinking category), however, did not change the results, making this source of bias unlikely in our analysis. Furthermore, we did a sensitivity analysis excluding the first 2 years of

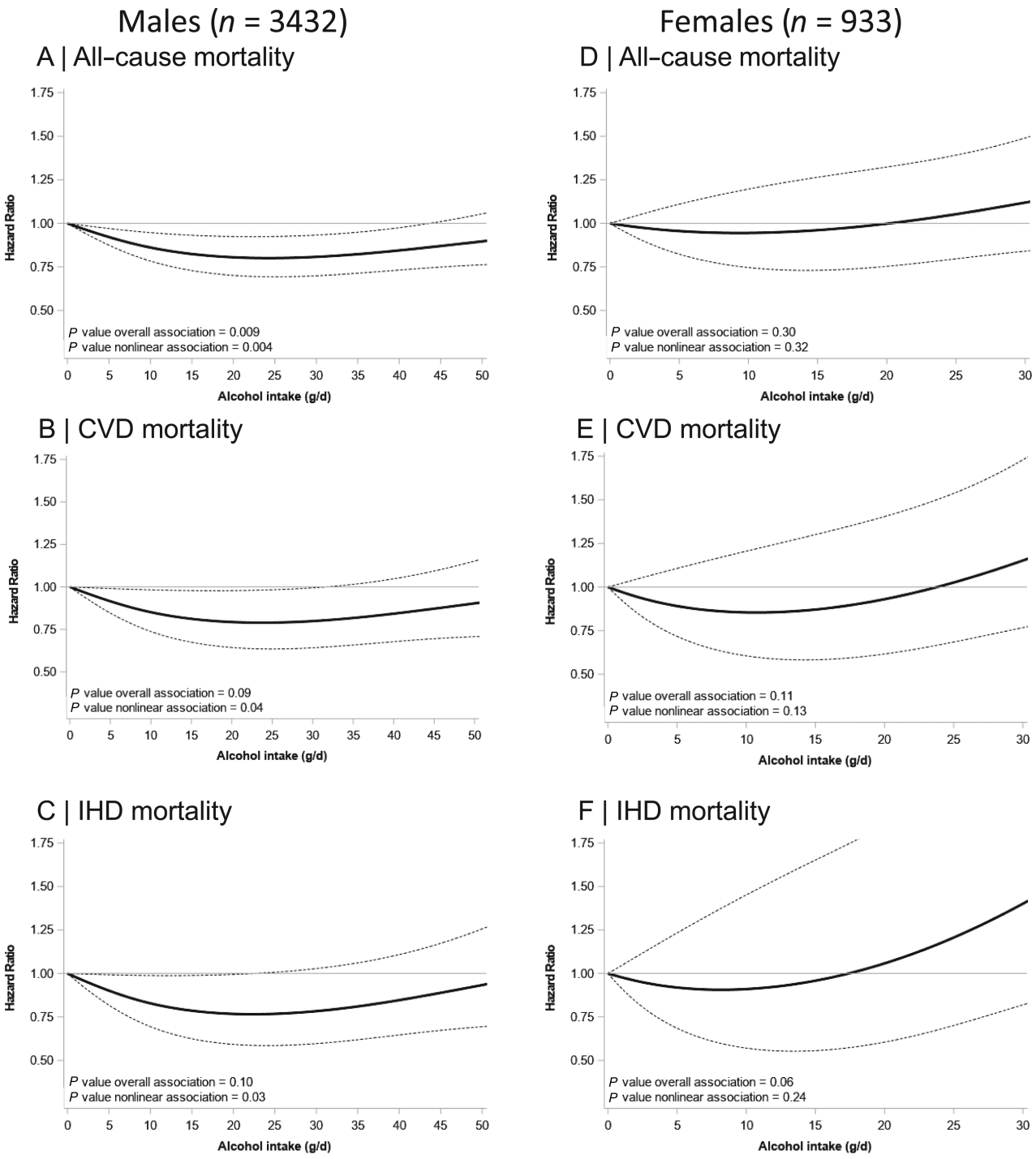

FIGURE 1 Associations of alcohol intake with all-cause, CVD, and IHD mortality in 4365 patients from the Alpha Omega Cohort. Lines are restricted cubic splines, showing continuous associations, with 3 knots located at the 5th, 50th, and 95th percentiles. The y-axis shows the predicted HRs for mortality for any value of alcohol intake, compared to the reference value set at 0 g/d. HRs are adjusted for age; sex; obesity; smoking; physical activity; education level; energy intake, excluding energy from alcohol; and intakes of sugar-sweetened beverages, red and processed meat, whole grains, fruits, vegetables, coffee, tea, milk, fish, and salt from foods. CVD, cardiovascular disease; IHD, ischemic heart disease.

follow-up. Patients who died during this period were more likely to have poor health at baseline. This did not change the results. Excluding patients who recently had an MI (<1 year prior to study enrolment) also yielded similar results. When stratifying our analysis for self-rated health, inverse associations with mortality for light or moderate alcohol intakes were observed in patients with both good/excellent health and poor/moderate health. These findings support the view

that our risk estimates were not influenced by deteriorating health.

Causal effects may be disentangled from associations in a Mendelian randomization (MR) study with genetically determined or predicted alcohol intake, which is not prone to abstainer bias and confounding factors (25). In a 10-year MR study of >500,000 healthy Chinese males and females with low habitual alcohol intake, no relationship was found between alcohol intake (as a continuous variable) and incident MI (fatal and nonfatal; RR, 0.96; 95% CI, 0.78–1.18; per 40 g/d) (26). This finding is against the hypothesis of a cardioprotective effect of light and moderate drinking. Results from the MR study, however, are hard to compare to the present study because of different populations (healthy Chinese individuals compared with Dutch post-MI patients), levels of alcohol intake, and outcomes (incident MI compared with mortality). Furthermore, the field of MR research is still advancing, and various underlying assumptions for MR studies have been questioned (27). MR studies across a wide range of alcohol intakes, accounting also for nonlinear relationships, are needed to further clarify the effect of genetically influenced alcohol use on mortality risks.

On one hand, alcohol intake may induce favorable changes in the cardiovascular system, such as improvement of the blood lipid profile, elevation of adiponectin, lowering of plasma fibrinogen, and a lower endocrine response to stress, which would support a cardioprotective effect (28, 29). On the other hand, alcohol raises blood pressure, which is a major risk factor for CVD (30, 31), and increases the risk of atrial fibrillation (32). Alcohol is harmful for the liver and brain and contributes to the development of cancers (1). It also increases the risk of injuries, and misuse of alcohol causes social harm (33). Therefore, even if a protective effect of alcohol intake against CVD were present, minimizing the intake of alcohol may be recommended.

Our study has several limitations. Misclassification of patients in alcohol categories could have occurred, because alcohol intake was only assessed at baseline, and seasonal variations in individual intake were not captured by our FFQ. This misclassification, which is likely to be nonsystematic, may have attenuated the HRs for alcohol in relation to mortality endpoints. Also, we were unable to examine drinking patterns or alcohol use in the context of meals. Heavy drinking could not adequately be studied, because patients with excessive alcohol intake (7 or more glasses per day) were not eligible for enrolment in the Alpha Omega Cohort. This also hampered the study of binge drinking, for which we found neutral associations, while other studies pointed at binge drinking as an independent risk factor for mortality and IHD risks (34, 35). The Alpha Omega Cohort comprises predominantly male, older, post-MI patients from the Netherlands. CVD risk factors were largely controlled by state-of-the-art drug treatment. Medication use and the underlying atherothrombotic disease process could have affected the sensitivity to alcohol in our patients. Findings from the present study cannot be generalized to healthy populations and IHD patients from non-Caucasian origin, and women were also underrepresented in our study. Sample sizes in the subgroup analyses were relatively small, and results in smokers and patients with obesity and diabetes should therefore be interpreted with caution. Strengths of our study include the unique cohort of post-MI patients, with ~12 years of follow-up for mortality endpoints and only 1 patient lost to follow-up. Detailed data collection enabled elaborate adjustments for dietary and lifestyle factors in the analyses. Alcohol intake was adequately assessed using a comprehensive FFQ and an additional lifestyle questionnaire. Sensitivity analyses were defined a priori to investigate potential biases.

In conclusion, we observed lower risks of all-cause, CVD, and IHD mortality in post-MI patients with light or moderate alcohol intakes compared to nondrinkers. These observational findings should be interpreted with caution in light of the total evidence on alcohol use and health, also taking into account the potential social harms of alcohol intake.

The authors' responsibilities were as follows – EC: conducted the research, interpreted the data, wrote the manuscript, and had primary responsibility for the final content; EC, AJdR, LKK: performed the data analysis; AJdR: drafted the first version of the manuscript; MCB: supervised the data analysis; MCB, LKK, JMG: critically reviewed the manuscript; JMG: conceived and designed the study, performed the data acquisition, and had primary responsibility for the final content; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

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