**Alcohol Intake and Total Mortality in 142,960 Individuals from the MORGAM Project: a population based study**

**Supplemental methods**

*Study overview*

The MORGAM Project is a multinational follow-up study of population based cohorts. Briefly, the Cohorts were examined at baseline and followed up for death and cardiovascular events by the MORGAM Participating Centres (MPC) in different countries. Data from each cohort are transferred to the MORGAM Data Centre in Helsinki in a standardized format for joint analysis. Although similar data collection procedures were used by the MPCs - most of the cohorts were examined as part of the WHO MONICA Project (30)- there are differences in the details of the measurement procedures and questionnaires used, and in the availability of the data items between the MPCs. Consequently, conversion and combination of the local data items were sometimes needed to derive the standard MORGAM data items. The conversion was done locally in the MPC with advice from the MORGAM Data Centre. The baseline examinations took place mostly during the 1980s and early 1990s, although more recent cohorts are available for some populations (see supplemental Table 1). We invited each MORGAM Centre that had collected data on alcohol intake to participate to this project. Three accepting cohorts (DAN-MONICA Glostrup study, ATBC Cancer Prevention Study and MONICA/KORA Study) however did not separate between former drinkers and lifetime abstainers, and these cohorts were eliminated. At the end, the current analysis was based on 16 cohort studies recruited in 10 European countries, and 1 cohort from Australia. Statistical analyses were planned and conducted at the NEUROMED MORGAM Centre in Pozzilli, Italy.

*Alcohol intake assessment*

We asked the volume of alcoholic beverage and the alcohol pattern, the last one considering these alternatives: a) lifetime abstainer, b) ex-drinker, c) less than once a week, c) 1-2 days per week, d) 3-5 days per week, e) 6-7 days per week, f) unknown. Also we asked about the amount of alcoholic beverage consumed on average over a period of days, weeks or months. It was clear that individuals who coherently answered a) or b) did not drink, while subjects who offered responses c) to e) declared an amount >0. Individuals who responded f) (drinking pattern=unknown) and intake>0 have been classified as drinkers. There remains a group of individuals with unknown drinking pattern and intake=0 and this group is made up of lifetime abstainers and ex-drinkers, but we cannot distinguish them. We could have considered these individuals as lifetime abstainers but by doing so we would have included some ex-drinkers in the reference group. To avoid the bias of counting ex drinkers as abstainers, we combined individuals with unknown drinking pattern and intake=0 in a group per se, named “non-drinkers”. The following categories of alcohol intake were then constructed: lifetime abstainers, ex-drinkers, non-drinkers, light-moderate drinkers (0.1 to 10 gr/d), moderate drinkers (10.1 to 20 gr/d) and heavy drinkers (>20 gr/d). The cut offs of 10 and 20 gr/d were chosen because 10 gr/d is considered to represent the mean value of ethanol content in one “unit of alcohol drink”.

A small percentage of alcohol consumers had missing data on the question concerning frequency of drinking and this group was excluded from the analysis by frequency. In the FINRISK Study, alcohol consumption during the previous week was assessed. A person was classified as having a preference for wine, beer or spirits, when the alcohol consumption from the respective drink comprised 70% or more of the total alcohol consumption. When the average alcohol consumption from wine, beer or spirits did not add up to 70% of the total alcohol consumption, a person was classified as having no preference.

*Baseline risk factors assessment*

Data on daily cigarette smoking, history of hypertension (based on antihypertensive drug use or systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg) or diabetes were derived from measures at baseline, interviews or self-reported questionnaires. A positive history of CHD at baseline was defined as documented or self-reported history of myocardial infarction or stroke or unstable angina pectoris. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m2). Level of education was derived from the question "What is the highest level of education you have completed?" (university or college or equivalent; intermediate between secondary level and university (e.g. technical training); secondary school; primary school only (or less)).

High-density lipoprotein cholesterol (HDLc) was measured locally for each cohort. For the cohort studies FINRISK (Finland east/west), MONICA/Brianza (Italy), Moli-sani (Italy), Northern Sweden (Sweden) and Belfast study (United Kingdom), the variables C-reactive protein (CRP), hs troponin I (troponin) and N-terminal pro brain-type natriuretic peptide (NT-ProBNP) were centrally measured in frozen blood samples collected in the BiomarCaRE core laboratory (29). For the others cohort these variables were not available.

*Study outcome*

Participants in each cohort were followed-up for death from any cause. The follow-up continued until death or the end of a fixed follow-up period or, in some cases, loss to follow-up for another reason. Deaths were identified through record linkage with national or regional health information systems. In most centers, the cardiovascular causes of death were adjudicated using MONICA diagnostic criteria (30). CV mortality included deaths from coronary heart disease and stroke. Cancer death was considered when the underlying cause of death included ICD9 codes 140-209. Other causes of death were included in the ‘Mortality from other causes’ group. The MORGAM Manual (28) and the cohort descriptions (27) give further information about the cause of death classifications.

*Statistical analysis*

For 6.4% of the available population, one risk factor (history of hypertension or diabetes or myocardial infarction or stroke, categories of BMI or level of education) was missing; for 3.6% there were missing data for more than one covariate. We used multiple imputation techniques (SAS PROC MI, n=10 imputed datasets; and PROC MIANALYZE) to maximize data availability. History of cancer was missing for 26.3% of the population and adjustment for this variable was conducted including a dummy variable for missing data. We also performed analyses using all individuals (N=154920) and imputing missing values also for alcohol intake and history of cancer. Multiple imputation was repeated with n=10, 20 or 30 imputed datasets. To replace ex-drinkers and non-drinkers back in with drinkers, we assigned them a missing value for alcohol intake and then allowed multiple imputation to replace them back in with drinkers (n=10 imputed datasets).

With the exception of 150 individuals from other cohorts, history of cancer was always missing in the following cohorts: AUSTRALIA/Newcastle, FRANCE-Lille, Strasbourg and Toulouse, ITALY-Brianza and Pamela, LITHUANIA/Kaunas, RUSSIA/Novosibirsk and POLAND/Warsaw. We conducted a sensitivity analysis excluding these cohorts. Type of alcoholic beverage preferred was missing for 8.1% of drinkers; these individuals have been eliminated only in the analyses by type of beverage.

To test for a continuous relationship between alcohol intake and death, we used multivariable Cox regression analysis with alcohol modelled as restricted cubic splines (3 knots at 5%, 50% and 95% of the alcohol distribution); zero intake of alcohol was used as reference value. In spline analysis, because the distribution of alcohol intake was strongly right-skewed (mean 14.2 gr/d, standard deviation 31.3 gr/d; median 5.0 gr/d, coefficient of skewness 8.0), we transformed alcohol intake by using the formula: alcohol\_transformed=natural logarithm(alcohol+1); the distribution of alcohol\_transformed showed a negligible coefficient of skewness (0.3). Zero value of alcohol corresponds to zero value of alcohol\_transformed, and vice versa. The variable alcohol\_transformed was modeled as cubic spline, but dose-relationship curves were graphed after applying back transformation formula: alcohol = exponential (alcohol\_transformed) - 1. For these analyses, former drinkers and individuals for whom we failed to distinguish between abstainers and former drinkers were excluded.

For the mediation analysis, the %MEDIATE macro (31) in SAS was used which calculates the point and interval estimates of the percent of exposure effect explained by one or more intermediate variables, using the difference method. HDLc, CRP, troponin and NT-ProBNP were tested as possibly mediating the association of alcohol intake with mortality risk. Because of positive skewness, all these biomarkers, except HDLc, were natural log transformed before analysis. With the exception of HDLc, whose values were available for a very large proportion (92%) of the cohort, the other biomarkers were available only in some of the cohorts (total size ranged between 40301 to 43497, according to the biomarker). Mediation analysis was conducted on these subsets of cohorts.

**Table S1. Characteristics of the cohort studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | **AUSTRALIA**  **Newcastle** | **FINLAND**  **East/West** | **SWEDEN**  **Northern** | **NORWAY**  **Tromsø** | **RUSSIA**  **Novosibirsk** | **POLAND**  **Warsaw** | **LITHUANIA Kaunas** |
| Number of individuals | 5 859 | 37 404 | 10 144 | 23 184 | 9 213 | 3 187 | 4 485 |
| Years of inclusion | 1983-1994 | 1982-2002 | 1986-2009 | 1994-1995 | 1985-1995 | 1983-1993 | 1983-1993 |
| Participation rate,% | 65 | 68-82 | 78 | 75 | 72 | 75 | 65 |
| End of follow up, y | 1998 | 2010 | 2011 | 2010 | 1998 | 1998 | 1998 |
| Age at baseline, y, mean (min-max) | 52 (24-71) | 46 (24-74) | 49 (24-75) | 46 (25-95) | 46 (23-66) | 50 (34-66) | 50 (33-65) |
| Biomarkers measured\*\* | No | Yes | Yes | No | No | No | No |
| Men, % | 49.6 | 48.2 | 49.2 | 49.8 | 69.4 | 52.8 | 49.9 |
| Daily smoker, % | 23.2 | 29.4 | 24.5 | 39.1 | 43.8 | 44.6 | 22.4 |
| Hypertension , % | 42.5 | 46.6 | 35.4 | 35.3 | 45.1 | 49.0 | 46.6 |
| Diabetes, % | 2.9 | 4.7 | 3.9 | 1.5 | 6.4 | 3.7 | 2.2 |
| Cardiovascular disease, % | 5.9 | 4.2 | 5.2 | 3.7 | 19.9 | 14.2 | 3.9 |
| Body Mass Index, kg/m² | 26.7 (4.5) | 26.5 (4.5) | 27.1 (4.9) | 25.0 (3.7) | 26.7 (4.7) | 27.3 (4.6) | 28.5 (4.8) |
| Low-intermediate education, % | 76.6 | 69.1 | 50.4 | 30.5 | 60.9 | 81.0 | 54.9 |
| **Alcohol intake** |  |  |  |  |  |  |  |
| Former drinkers, % | 19.3 | 3.0 | 0 | 0 | 4.1 | 0 | 5.4 |
| Non-drinkers\*, % | 0 | 26.1 | 0 | 0.1 | 1.4 | 0 | 0 |
| Lifetime abstainers, % | 6.0 | 18.5 | 33.1 | 24.5 | 51.4 | 26.2 | 9.9 |
| 0.1 to 10 g/d, % | 22.3 | 29.6 | 60.6 | 65.7 | 19.4 | 56.4 | 75.5 |
| 10 to 20 g/d, % | 12.9 | 11.9 | 5.12 | 8 | 12.0 | 10.0 | 5.4 |
| >20 g/d, % | 39.5 | 10.9 | 1.1 | 1.7 | 11.6 | 7.4 | 3.8 |
| **Events during follow up** |  |  |  |  |  |  |  |
| Person-year for total mortality | 59 053 | 636 340 | 137 127 | 345 627 | 84 883 | 32 729 | 100 069 |
| Total mortality, % | 8.6 | 16.0 | 12.3 | 12.3 | 11.6 | 14.0 | 34.1 |
| Cardiovascular mortality, % | 2.8 | 6.0 | 4.5 | 4.3 | 4.4 | 4.4 | 8.7 |
| Cancer mortality, % | 3.6 | 4.6 | 3.9 | 3.9 | 3.0 | 3.9 | 9.4 |
| Other causes mortality, % | 2.2 | 5.4 | 3.9 | 4.2 | 4.2 | 5.7 | 16.0 |

continued

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | **GERMANY**  **ESTHER** | **UK**  **Belfast** | **FRANCE**  **Lil/Stra/Tou** | **ITALY**  **Pamela** | **ITALY**  **Brianza** | **ITALY**  **Moli-sani** |
| Number of individuals, No. | 8 983 | 2 745 | 7 855 | 2 039 | 4 838 | 23 024 |
| Years of inclusion | 2000-2002 | 1990-1992 | 1991-1993 | 1990-1993 | 1986-1994 | 2005-2010 |
| Participation rate; % | NA | 52 | 68-80 | 64 | 68 | 70 |
| End of follow up, y | 2010 | 1997 | 1998 | 1998 | 1998 | 2011 |
| Age at baseline, y, mean (min-max) | 62 (48-73) | 55 (50-60) | 55 (49-64) | 51 (26-75) | 46 (26-67) | 55 (35-99) |
| Biomarkers measured\*\* | No | Yes | No | No | Yes | Yes |
| Men, % | 46.8 | 100 | 100 | 50.4 | 49.2 | 48.2 |
| Daily smoker, % | 17.4 | 31.6 | 25.8 | 29.5 | 32.4 | 22.9 |
| Hypertension , % | 54.3 | 39.3 | 43.8 | 42.0 | 35.1 | 55.7 |
| Diabetes, % | 15.5 | 2.6 | 5.4 | 2.2 | 2.8 | 6.3 |
| Cardiovascular disease, % | 8.5 | 6.8 | 2.3 | 4.2 | 1.7 | 2.7 |
| Body Mass Index, kg/m² | 27.6 (4.3) | 26.2 (3.4) | 26.7 (3.5) | 25.6 (4.2) | 25.4 (4.1) | 28.0 (4.8) |
| Low-intermediate education, % | 73.7 | 50.6 | 80.4 | 90.3 | 72.1 | 87.2 |
| **Alcohol intake** |  |  |  |  |  |  |
| Former drinkers, % | 13.6 | 2.2 | 6.8 | 0 | 0.4 | 3.3 |
| Non-drinkers\*, % | 1.1 | 0.1 | 0 | 0 | 0.2 | 0 |
| Lifetime abstainers, % | 18.9 | 37.5 | 2.8 | 46.9 | 39.5 | 26.7 |
| 0.1 to 10 g/d, % | 38.7 | 12.1 | 16.1 | 0 | 0.4 | 24.5 |
| 10 to 20 g/d, % | 16.3 | 12.3 | 14.8 | 37.6 | 4.6 | 16.0 |
| >20 g/d, % | 11.4 | 35.7 | 59.5 | 15.5 | 54.9 | 29.4 |
| **Events during follow up** |  |  |  |  |  |  |
| Person-year for total mortality | 81 529 | 43 503 | 75 336 | 21 975 | 85 157 | 98 598 |
| Total mortality, % | 11.3 | 20.0 | 5.4 | 9.0 | 11.9 | 2.2 |
| Cardiovascular mortality, % | 3.1 | 4.8 | 1.1 | 2.1 | 2.6 | 0.3 |
| Cancer mortality, % | 4.6 | 9.0 | 2.9 | 4.5 | 6.2 | 0.8 |
| Other causes mortality, % | 3.6 | 6.3 | 3.1 | 2.4 | 3.1 | 1.1 |

Characteristics are presented as relative frequencies for categorical variables, and mean value (standard deviation) for continuous variables. \*Non-drinkers are individuals for which we failed to distinguish between lifetime abstainers and former drinkers. Lil/Stra/Tou means Lille, Strasbourg and Toulouse. \*\*Biomarkers measured for mediation analysis: C-reactive protein, troponin and N-terminal pro brain-type natriuretic peptide

**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=154920, deaths for any causes n=19139)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Former**  **drinkers** | **Non-**  **drinkers** | **Lifetime**  **abstainers** | **Light-Moderate**  **0.1 to 10 g/d** | **Moderate**  **10.1 to 20 g/d** | **Heavy**  **>20 g/d** |
| **Number of individuals** (mean\*) | 5 524 | 11 225 | 38 523 | 52 961 | 18 481 | 28 206 |
| **Number of deaths** (mean\*) | 796 | 2 412 | 4 119 | 5 473 | 1 620 | 2 487 |
| **Number of imputations = 10** | | | | | | |
| **Hazard ratio** | **1.16** | **1.09** | ***1*** | **0.86** | **0.95** | **1.09** |
| **95% CI** | 1.07 to 1.25 | 1.02 to 1.15 | reference | 0.83 to 0.90 | 0.90 to 1.01 | 1.03 to 1.15 |
| **Number of imputations = 20** | | | | | | |
| **Hazard ratio** | **1.16** | **1.08** | ***1*** | **0.86** | **0.96** | **1.09** |
| **95% CI** | 1.07 to 1.25 | 1.02 to 1.15 | reference | 0.83 to 0.90 | 0.90 to 1.01 | 1.03 to 1.15 |
| **Number of imputations = 30** | | | | | | |
| **Hazard ratio** | **1.16** | **1.08** | ***1*** | **0.86** | **0.96** | **1.09** |
| **95% CI** | 1.07 to 1.25 | 1.02 to 1.15 | reference | 0.83 to 0.90 | 0.90 to 1.01 | 1.03 to 1.15 |

\*mean values among imputations. 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. 95% CI means 95% confidence interval

**Table S3.** Hazard ratios for mortality, according to categories of frequency of alcohol intake

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Alcohol intake frequency** | | | | | | |
|  | **Former**  **drinkers** | **Non-**  **drinkers\*** | **Lifetime**  **abstainers** | **0.1 to 2**  **d/week** | **2.1 to 5**  **d/week** | **>5**  **d/week** |
| **Number of individuals** | 5 486 | 10 013 | 34 310 | 49 559 | 11 043 | 19 054 |
| **Mortality for any causes (n=14 964)** | | | | | | |
| **Number of deaths** | 796 | 2 412 | 4 119 | 5 303 | 1 189 | 1 145 |
| **Hazard ratio (1)** | 1.18 | 1.18 | *1* | 0.89 | 1.02 | 1.03 |
| **95% CI** | 1.11 to 1.26 | 1.08 to 1.27 | reference | 0.85 to 0.93 | 0.95 to 1.09 | 0.95 to 1.12 |
| **Hazard ratio (2)** | 1.18 | 1.19 | *1* | 0.88 | 0.99 | 0.94 |
| **95% CI** | 1.11 to 1.26 | 1.10 to 1.29 | reference | 0.84 to 0.92 | 0.92 to 1.06 | 0.86 to 1.03 |
| **Cardiovascular mortality (n=4 944)** | | | | | | |
| **Number of deaths** | 250 | 989 | 1 425 | 1 653 | 357 | 270 |
| **Hazard ratio (1)** | 1.37 | 1.08 | *1* | 0.87 | 0.96 | 0.91 |
| **95% CI** | 1.23 to 1.52 | 0.94 to 1.25 | *reference* | 0.80 to 0.94 | 0.85 to 1.08 | 0.78 to 1.07 |
| **Hazard ratio (2)** | 1.37 | 1.09 | *1* | 0.86 | 0.94 | 0.85 |
| **95% CI** | 1.23 to 1.52 | 0.95 to 1.26 | *reference* | 0.80 to 0.93 | 0.83 to 1.06 | 0.72 to 1.02 |
| **Cancer mortality (n=4 816)** | | | | | | |
| **Number of deaths** | 272 | 646 | 1 230 | 1 775 | 415 | 478 |
| **Hazard ratio (1)** | 1.18 | 1.30 | *1* | 1.00 | 1.09 | 1.16 |
| **95% CI** | 1.05 to 1.33 | 1.13 to 1.50 | *reference* | 0.93 to 1.09 | 0.97 to 1.23 | 1.01 to 1.33 |
| **Hazard ratio (2)** | 1.18 | 1.32 | *1* | 1.00 | 1.07 | 1.09 |
| **95% CI** | 1.05 to 1.33 | 1.15 to 1.52 | *reference* | 0.92 to 1.08 | 0.94 to 1.20 | 0.94 to 1.26 |
| **Mortality for other causes (n=5 204)** | | | | | | |
| **Number of deaths** | 274 | 777 | 1 464 | 1 875 | 417 | 397 |
| **Hazard ratio (1)** | 1.00 | 1.16 | *1* | 0.82 | 1.02 | 1.03 |
| **95% CI** | 0.89 to 1.11 | 1.01 to 1.33 | *reference* | 0.76 to 0.88 | 0.91 to 1.14 | 0.89 to 1.18 |
| **Hazard ratio (2)** | 1.00 | 1.19 | *1* | 0.81 | 0.97 | 0.89 |
| **95% CI** | 0.89 to 1.11 | 1.04 to 1.36 | *reference* | 0.75 to 0.87 | 0.86 to 1.09 | 0.76 to 1.04 |

\*Non-drinkers are individuals for which we failed to distinguish between lifetime abstainers and former drinkers. (1) 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. 95% CI means 95% confidence interval. (2) further adjusted for total alcohol consumption. N=13495 drinkers (N=1943 deaths) with missing value for frequency of consumption have been excluded from this analysis.

**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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Alcohol intake categories** | | | | |
|  | **Lifetime**  **abstainers** | **Light-Moderate**  **0.1 to 10 g/d** | **Moderate**  **10.1 to 20 g/d** | **Heavy**  **>20 g/d** |
| **Number of individuals** (mean)\* | 34 310 | 54 535 | 20 225 | 33 890 |
| **Person-year, y** (mean) | 401 755 | 745 518 | 247 984 | 406 668 |
| **Mortality for any causes (n=16 907)** | | | | |
| **Number of deaths** (mean)\* | 4 119 | 6 102 | 2 328 | 4 358 |
| **Hazard ratio** | *1* | 0.91 | 1.02 | 1.12 |
| **95% CI** | reference | 0.87 to 0.95 | 0.96 to 1.08 | 1.07 to 1.18 |
| **Cardiovascular mortality (n=5 547)** | | | | |
| **Number of deaths** (mean)\* | 1 425 | 2 004 | 767 | 1 351 |
| **Hazard ratio** | *1* | 0.92 | 1.03 | 1.08 |
| **95% CI** | *reference* | 0.86 to 0.99 | 0.93 to 1.14 | 0.99 to 1.18 |
| **Cancer mortality (n=5 511)** | | | | |
| **Number of deaths** (mean)\* | 1 230 | 1 990 | 763 | 1 528 |
| **Hazard ratio** | *1* | 1.02 | 1.09 | 1.20 |
| **95% CI** | *reference* | 0.94 to 1.10 | 0.98 to 1.20 | 1.09 to 1.31 |
| **Mortality for other causes (n=5 849)** | | | | |
| **Number of deaths** (mean)\* | 1 464 | 2 108 | 7 98 | 1 479 |
| **Hazard ratio** | *1* | 0.82 | 0.97 | 1.11 |
| **95% CI** | *reference* | 0.76 to 0.88 | 0.88 to 1.07 | 1.01 to 1.21 |

\*Mean among N=10 imputations. Lifetime abstainers: N=34319; Light-Moderate drinkers: N=54482 to 54598 among n=10 imputations; Moderate drinkers: 20140 to 20286; Heavy drinkers: N=33766 to 33980. 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. 95% CI means 95% confidence interval.

**Table S5.** Hazard ratios for total mortality using different reference categories

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Alcohol intake categories** | | | | | | |
|  | **Former**  **drinkers** | **Non-**  **drinkers\*** | **Lifetime**  **abstainers** | **Light-Moderate**  **0.1 to 10 g/d** | **Moderate**  **10.1 to 20 g/d** | **Heavy**  **>20 g/d** |
| **Number of individuals** | 5 486 | 10 013 | 34 310 | 51 471 | 16 885 | 24 795 |
| **Number of deaths** | 796 | 2 412 | 4 119 | 5 473 | 1 620 | 2 487 |
| **Reference category: lifetime abstainers** (as in Table 2) | | | | | | |
| **Hazard ratio** | 1.19 | 1.13 | *1* | 0.89 | 0.98 | 1.13 |
| **95% CI** | 1.10 to 1.29 | 1.06 to 1.20 | *reference* | 0.86 to 0.93 | 0.92 to 1.05 | 1.07 to 1.20 |
| **Reference category: lifetime abstainers + former drinkers + non-drinkers\*** | | | | | | |
| **Hazard ratio** | *1* | *1* | *1* | 0.85 | 0.93 | 1.07 |
| **95% CI** | *reference* | *reference* | *reference* | 0.82 to 0.88 | 0.88 to 0.98 | 1.01 to 1.13 |
| **Reference category: lifetime abstainers + former drinkers** | | | | | | |
| **Hazard ratio** | *1* | 1.09 | *1* | 0.87 | 0.95 | 1.08 |
| **95% CI** | *reference* | 1.03 to 1.16 | *reference* | 0.83 to 0.90 | 0.90 to 1.01 | 1.02 to 1.14 |
| **Reference category: lifetime abstainers + non-drinkers\*** | | | | | | |
| **Hazard ratio** | 1.14 | *1* | *1* | 0.87 | 0.95 | 1.09 |
| **95% CI** | 1.06 to 1.24 | *reference* | *reference* | 0.83 to 0.90 | 0.89 to 1.00 | 1.03 to 1.16 |
| **Reference category: light-moderate drinkers 0.1 to 10 g/d** | | | | | | |
| **Hazard ratio** | 1.33 | 1.26 | 1.12 | *1* | 1.10 | 1.27 |
| **95% CI** | 1.23 to 1.44 | 1.19 to 1.33 | 1.07 to 1.17 | *reference* | 1.04 to 1.17 | 1.20 to 1.34 |

\*Non-drinkers are individuals for which we failed to distinguish between lifetime abstainers and former drinkers. 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. 95% CI means 95% confidence interval.

**Table S6.** Hazard ratios for total mortality according to different alcoholic preferences and geographical location

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Lifetime**  **abstainers** | **Light-Moderate**  **0.1 to 10 g/d** | **Moderate**  **10.1 to 20 g/d** | **Heavy**  **>20 g/d** |
| **Wine preferred (≥70%)** |  |  |  |  |  |
| France and Italy | Hazard ratio | *1* | 0.91 | 0.79 | 0.79 |
|  | 95% CI | *reference* | 0.71 to 1.16 | 0.65 to 0.95 | 0.67 to 0.93 |
| Other countries | Hazard ratio | *1* | 0.86 | 0.79 | 0.90 |
|  | 95% CI | reference | 0.80 to 0.93 | 0.67 to 0.93 | 0.71 to 1.13 |
|  | P for difference |  | 0.48 | 0.49 | 0.93 |
| **Beer preferred (≥70%)** |  |  |  |  |  |
| Germany, UK, Sweden | Hazard ratio | 1 | 1.00 | 1.25 | 1.48 |
| Finland and Norway | 95% CI | *reference* | 0.93 to 1.08 | 1.11 to 1.42 | 1.32 to 1.66 |
| Other countries | Hazard ratio | *1* | 0.78 | 0.98 | 1.11 |
|  | 95% CI | *reference* | 0.62 to 0.97 | 0.65 to 1.48 | 0.86 to 1.42 |
|  | P for difference |  | 0.19 | 0.75 | 0.075 |
| **Spirits preferred (≥70%)** |  |  |  |  |  |
| Russia, Poland and Lithuania | Hazard ratio | *1* | 0.87 | 1.11 | 1.06 |
|  | 95% CI | *reference* | 0.78 to 0.98 | 0.94 to 1.30 | 0.88 to 1.28 |
| Other countries | Hazard ratio | *1* | 0.96 | 1.09 | 1.30 |
|  | 95% CI | reference | 0.88 to 1.04 | 0.92 to 1.30 | 1.12 to 1.51 |
|  | P for difference |  | 0.53 | 0.34 | 0.42 |

Hazard ratio adjusted for age at baseline, sex, smoking, hypertension, diabetes, history of myocardial infarction or stroke, history of cancer, categories of BMI and level of education, and stratified by cohort. 95% CI means 95% confidence interval. N=6 967 drinkers for which type of alcoholic beverage preferred was a missing information have been eliminated in this analysis. 95% CI means 95% confidence interval

**Figure S1**

Percentage of variation respect to lifetime 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.

